Objectives. To review past and present patterns of occurrence of Japanese encephalitis in Hong Kong and across Asia. A better understanding of the disease should facilitate the formulation of an effective strategic plan to prevent a future epidemic.

Data sources. Report of local cases, and literature search of MEDLINE up to November 2004.

Study selection. Literature and data related to Japanese encephalitis.

Data extraction. Relevant information and data were reviewed by the authors.

Data synthesis. Since 16 July 2004, under the ordinance of Hong Kong, Japanese encephalitis has been a notifiable disease. In the past, Japanese encephalitis has reached epidemic proportions in Japan, South Korea, and some areas in China. It has spread globally and has a worldwide incidence of 35 000 to 50 000 cases per year with 10 000 deaths. Mortality is about 30% and survivors often suffer serious long-term morbidity. In 2004, there were five local cases of Japanese encephalitis in Hong Kong. Subsequent serological surveillance of serum samples from 1547 local inhabitants revealed that 37 were positive, ie 2.4% of local inhabitants had been exposed to the Japanese encephalitis virus in the past. Most local inhabitants are immunologically naive to Japanese encephalitis virus. Most infections in endemic areas are asymptomatic. Patients with symptomatic Japanese encephalitis usually present with fever, headache, and confusion. Other signs include neurosis, poliomyelitis, and convulsion. Investigations including magnetic resonance imaging, electroencephalography, and single photon emission computed tomography are not specific. A definitive diagnosis depends on serological studies. Treatment is mainly supportive.

Conclusions. The control of Japanese encephalitis in Hong Kong relies on an accurate surveillance system, vector control, vector avoidance, and vaccination of the at-risk population. At present, vaccination should be limited to travellers to endemic areas who would stay for longer than 1 month.
Introduction

In 2004 five patients resident in Hong Kong were diagnosed with Japanese encephalitis (JE), two of them died. Between 1967 and 2003, 45 cases of JE were reported; of these, six were reported between 1994 and 2003 (Fig). During this time, reporting of JE cases was voluntary. After 16 July 2004, under the ordinance of Hong Kong, JE became a notifiable disease. Many other viruses can cause vector-borne encephalitides, such as West Nile virus, St Louis encephalitis virus, Rocio virus, and Murray Valley encephalitis virus. Nonetheless JE is the most important mosquito-borne viral encephalitis in terms of numbers and is endemic almost exclusively to Asia. This article reviews the occurrence of JE in the past and the current trend, global epidemics, and the situation in Hong Kong. It is hoped that this will enable a better understanding of the disease and thus facilitate the planning of an effective strategy to prevent JE reaching epidemic proportions.

Epidemics—the problem

Globally, JE is a major health problem with an annual incidence of about 30 000 to 50 000 cases and associated mortality in 10 000 cases. Epidemics of JE were first reported in 1871 in Japan. Major epidemics occurred in 1924, 1935, and 1948. An epidemic occurred in Korea in 1949 and recurred every 2 to 3 years, reaching a peak in 1958 with 6897 cases. China reported over 1 million cases between 1965 and 1975, with a peak annual incidence of 175 000 cases in 1971. Japanese encephalitis was first recorded in northern Thailand in 1964; a large epidemic occurred in 1969. In 1998 the first case of JE was reported in mainland Australia. Another case was recently reported in New Zealand. National immunisation programmes have now been introduced in the most severely affected countries: Japan, South Korea, northern Thailand, and some areas of China. The World Health Organization has also introduced measures to control the spread of JE. Nevertheless, despite all these efforts, JE continues to spread globally.

Previous studies of the JE virus suggest that there are four genotypes across Asia that may cause different epidemiological patterns. This may explain why JE occurs in epidemics in northern Asia but causes endemic disease in southern Asia. The most recent available data suggest that the distribution is best explained in terms of the virus’ origin in the Indonesia-Malaysia region (where all genotypes have been found), and the spread of the more recent genotypes to new geographical areas. A natural diversity of JE viral strains has been demonstrated in minor antigenic differences and in biological characteristics. There is however no evidence of corresponding differences in human pathogenicity and no evidence that immunity to one strain would not protect against the disease caused by another.

Mortality and morbidity of Japanese encephalitis

The mortality of JE is about 30%. Although intensive care support can reduce the mortality rate, patients often suffer significant long-term morbidity. Some effects, such as learning difficulties and behavioural problems, can be subtle and may remain undetected for several years.

Clinical features, investigations, and diagnosis of Japanese encephalitis

In endemic areas, infection with JE is often asymptomatic. The signs and symptoms of encephalitis are non-specific and the physician must maintain a high index of suspicion if a clinical diagnosis of JE is to be made. Common features include fever (generally >41°C), headache (bi-frontal, retro-orbital, and intense), and confusion. Children often have a staring eye-look, fever, and convulsions that may be misdiagnosed as febrile. Multiple seizures, prolonged seizures, and status epilepticus are associated with poor outcomes. Subclinical manifestations of status epilepticus can be subtle and signs may be just twitching of a digit, eyebrow, or lip. Without electroencephalographic monitoring, the diagnosis of JE can be easily missed. A decreased conscious level at pre-
sentation is also associated with a poor outcome.\textsuperscript{16-18} Confusion may be mistaken as neurosis.\textsuperscript{19} Some patients can present atypically as poliomyelitis.\textsuperscript{20} Other patients may present with abnormal movements.\textsuperscript{21,22} Japanese encephalitis during the first and second trimester of pregnancy may lead to foetal death and abortion.\textsuperscript{23} Neuro-imaging including magnetic resonance imaging reveals T2-weighted increased signal over the thalamic region in most patients.\textsuperscript{24} Haemorrhagic lesions are found in 70\% of patients; similar lesions are less commonly found over the cortex, midbrain, cerebellum, and spinal cord.\textsuperscript{24} Electroencephalography can show diffuse delta activity in early infection, spikes and seizure discharges are rare. Burst suppression as well as generalised slow wave with alpha coma are late findings.\textsuperscript{25} These electroencephalographic findings can provide non-invasive diagnostic clues although they are neither specific nor diagnostic. Single photon emission computed tomography shows hot spots over the thalamic regions in the acute phase.\textsuperscript{26}

The JE virus is rarely isolated in clinical specimens because viraemia is transient and titres are low.\textsuperscript{13} When isolated from cerebrospinal fluid (CSF), it indicates immuno-insufficiency and is associated with a high mortality rate.\textsuperscript{27} The virus may be identified from CSF by reverse transcriptase–polymerase chain reaction.\textsuperscript{28} Definitive diagnoses rely on serological and molecular studies although the latter are performed only at the research level. Serological tests can be performed on serum or CSF. Serological tests by haemagglutination inhibition, complement fixation, and indirect fluorescent antibody test on paired sera 14 days apart can confirm the diagnosis. Early diagnosis can be made by immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (MAC ELISA) from a single CSF or serum specimen.\textsuperscript{2} The sensitivity and specificity of this assay are higher than 95\% when samples are collected a few days after disease onset. An alternative means of diagnosis is IgM dot enzyme immunoassay (JEV MAC DOT).\textsuperscript{29} This assay is derived from MAC ELISA and requires no specialised skills or equipment, thus it may be appropriate for rural hospitals.\textsuperscript{29} Despite the advances in diagnostics, cross-reactivity with other flaviviruses, such as dengue virus, yellow fever virus, and West Nile virus may still occur in both acute and chronic stages.\textsuperscript{30} During the acute stage when immunofluorescent assay (IFA) is used to detect flavivirus-specific IgM antibody, the cross-reactivity with flaviviruses is between 4\% and 10\%.\textsuperscript{30} During the chronic stage, when IFA is used to detect IgG antibody, the cross-reactivity with other flaviviruses is between 16\% and 71\%.\textsuperscript{30} Flaviviruses contain cross-reactive epitopes that cause problems in confirming a serological diagnosis, especially in areas where there are several

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\includegraphics[width=\textwidth]{fig.png}
\caption{Reported Japanese encephalitis in Hong Kong, 1967-2004}
\end{figure}
flaviviruses. To avoid this and to enable an accurate diagnosis, specimens should be tested against different flaviviruses. Diagnostic accuracy is further improved if the physician considers the patient’s clinical presentation, country of origin of the sample, the vaccination status, and the travel history. Prior infection with dengue fever seems to protect against severe JE infection. Certain genotypes of JE virus appear to cause large outbreaks of encephalitis: this may be related to the ability of the JE virus to enter the central nervous system, and is related to certain amino acids in some critical regions.

**Treatment of Japanese encephalitis**

There is no cure for JE and treatment is mainly supportive. Patients are not infectious, but should avoid further mosquito bites. Some patients may require intensive care support. In 1985 an open-label trial of interferon alpha-A in four patients with JE showed promising results. A subsequent randomised double-blind placebo-controlled trial (RCT) among 112 Vietnamese children showed no such promise. There is no anti-viral treatment and dexamethasone is not beneficial.

**Vaccination for Japanese encephalitis**

Two vaccines are available: the formalinized vaccine (used since the 1930s) and the live-attenuated vaccine. The new generation live-attenuated vaccine is highly purified and is available in Asia and Japan. In 1984 and 1985, a highly purified monovalent vaccine derived from mouse brain, BIKEN vaccine (Nakayama-Yoken strain) and a bivalent vaccine consisting of Nakayama-Yoken and Beijing-1 strains were tested in northern Thailand. In an RCT of 65 224 children, the efficacy of both vaccines was 91%. There were no major side-effects apart from some headache, rash, sore arms, and local swelling. Similar side-effects were seen in the placebo arm of the study. In another series, several cases of acute disseminated encephalomyelitis temporarily associated with JE vaccination were reported with an estimated rate of 0.2 per 100 000. Other major adverse effects included anaphylactic shock with collapse and cardiac arrest. The vaccine has been widely used among different regions including Hong Kong, but its cost prohibits mass immunisation. Another live-attenuated vaccine, SA 14-14-2, has been developed in China and follows the success of the SA 14-3 vaccine. It is immunogenically effective and safe and has been used in at least 5 million Chinese children. It is used primarily within China.

**The current situation of Japanese encephalitis in Hong Kong**

The factors that govern clinical presentation and outcome of flavivirus infection are poorly understood. Transmission of JE is influenced by three factors: the prevalence of JE cases, the density of Culex tritaeniorhyncus, and the presence of infected pigs in the vicinity of human habitation. Among the 45 patients infected with JE between 1967 and 2003, 70% were below the age of 19 years with males and females equally affected. Nine patients were believed to have been infected elsewhere in Asia. Five patients died and the case fatality ratio was 11.1%. Following confirmation of five local cases in 2004, massive serological screening was undertaken. In 1547 serum samples collected from people living close to the five index patients, 37 (2.4%) were positive: 36 (97.3%) of the samples were from individuals over the age of 40 years. Such findings have several implications for future planning. The fact that most seropositive patients were aged older than 40 years suggests that their exposure to the JE virus might have been several years earlier. In many Asian countries where JE remains endemic, most local habitants will acquire JE antibodies by the time they reach adulthood. In these countries, JE mainly affects young children.

The situation differs in Hong Kong. First, most residents have not been exposed to the virus, so JE can affect people of all age-groups. Future strategic planning should target the whole population, not just children. Second, the ratio of symptomatic to asymptomatic JE commonly quoted as 1:300 has not been verified in Hong Kong; the ratio varies in different studies from 1:25 to 1:1000. It appears that the number of asymptomatic JE infections in Hong Kong is unknown. Third, pigs are natural hosts for JE and are an important factor in JE transmission. Abattoirs or pigsties were identified within 2.6 km of the residence of two patients diagnosed this year, but in the remaining cases neither abattoirs nor pigsties existed nearby. The possibility of other domestic and wild animals as natural hosts should be considered.

**The control of Japanese encephalitis in Hong Kong**

The control of JE in Hong Kong depends on vector control, vector avoidance, and vaccination of travellers to endemic or epidemic areas. Vector control in the form of spraying insecticide is costly, and mosquito numbers return to almost 80% within 4 days of intensive spraying. This method thus appears to
have a minimal effect. Continuous use of a larvicide may encourage the emergence of resistant strains. Avoidance of mosquito bites, zoo-prophylaxis, use of insecticides, placement of larvivorous fish in rice paddies, and intermittent irrigation of rice paddies to control mosquito breeding are probably the most effective deterrents.

Other methods of vector control, such as maintaining clean sewers and avoiding collection of stagnant water, are effective. Vector avoidance includes avoiding travelling to the jungle especially at dawn and at dusk when mosquitoes are actively feeding, wearing long sleeves and trousers, and using bednets. These are all effective measures although they are inconvenient. Mosquito repellents with at least 30% active ingredient of N,N-diethyl-m-toluamide (DEET) on exposed skin surfaces have been suggested before outdoor activities.

Vaccination of the natural host including pigs is theoretically sound but difficult to achieve in practical terms. There are about 280 pig farms with 400,000 heads of pigs in Hong Kong. The government has imposed a strict demerit point scheme on farms in an attempt to alleviate the environmental problems posed by livestock farming. With the issue of JE and the competition of chilled pigs from China, pig farmers are very pessimistic about their future. Many of them hope the government will buy back their licenses. The pig farming industry in Hong Kong has been shrinking over the last few years, so vaccination of a small and diminishing pig population may be the most efficacious, sustainable, and cost-effective measure to prevent the spread of JE. Nevertheless, most investigators who have tried to vaccinate pigs agree that it is fine in theory but difficult in practice.

The experience of South Korea

The South Korea Government introduced a voluntary immunisation programme in the 1970s, but the coverage rate was below 5%. In 1983, a mandatory national immunisation programme (NIP) was implemented for children under the age of 15 years. By the mid-1990s, more than 97% of the target population had been immunised. At this time, living standards also improved as did the environment and agricultural practices were modernised. In 1975, the South Korea Government implemented an epidemic forecast programme. The health authority regularly checks for the virus from the vector mosquito, C. tritaeniorhyncus. In addition, blood of sentinel piglets less than 6 months old is screened weekly at slaughterhouses for IgM antibody. When JE virus is detected from the vector, a mosquito alert is issued to encourage JE vaccination. When JE IgM antibody titre is found raised in piglets, the public is warned and an aggressive mosquito control programme implemented. A few index cases of JE are often identified after the alarm. Such methods have resulted in a significant decrease in the number of cases of JE. Between 1985 and 1998, there were only 21 serologically confirmed JE cases.

The strategic elements in the future

An NIP has been implemented in areas prone to epidemics of JE, such as Japan and South Korea, but this has not been considered necessary in countries that see only sporadic cases. A good surveillance system with reliable data is nonetheless essential. In areas where JE is endemic, certain groups who may be at high risk of acquiring JE should be closely monitored. This includes preschool and young school-aged children who like to play outdoors. People who live close to porcine husbandry or rice-growing areas are also at high risk of mosquito contact and hence are at high risk of acquiring JE.

Conclusions

Hong Kong sees only a few sporadic cases of JE, thus it is unwise and perhaps not necessary to advocate a universal vaccination programme. An important element of a successful JE control programme is to develop an effective surveillance system. Since July 2004, JE has been classified a notifiable disease and all cases must be reported to the Centre for Health Protection. Vaccination should be restricted to persons who are intending to stay in an endemic area or an area where there is an epidemic for more than 1 month. A combination of travel advice, vigilant selection of those at risk for vaccination, and improved living standards may reduce the number of JE cases in Hong Kong and the rest of Asia.

References


45. Two recent cases of Japanese encephalitis in Hong Kong. Centre for Health Protection website: http://www.chp.gov.hk/


