衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Supporting Document for Pig Vaccination as a Control Strategy to reduce Japanese Encephalitis in Humans in Hong Kong

Hong Kong is an enzootic area for Japanese encephalitis (JE) as shown by the continued seroconversion of pigs and birds in Hong Kong throughout the year. There are a large number of pig farms situated close to residential estates in the New Territories West area e.g. Yuen Long and *Culex tritaeniorhynchus* is found in considerable numbers near these farms. In general, *Culex* mosquitoes prefer feeding on pigs and birds rather than humans.

2. In a review of 45 cases of JE reported to Department of Health from 1967 to 2003, the annual incidence ranged from 0 to 0.1 per 100 000 population, with an average of 0.01 per 100 000 population. Male and female were equally affected. Over 70% of the patients were below the age of 19. Nine out of the 45 were classified as imported cases and almost all were reported after the 1980s. About 80% of the local cases resided in the New Territories where migratory bird roosts, local pig farms and rice fields were found. There were five deaths resulting in a case-fatality rate of 11.1%.

3. Hong Kong recorded five human local JE cases in 2004, a pattern markedly different from that in the past ten years. Since pigs are the major amplifying hosts for JE, the Scientific Committee on Vector-borne Diseases (SCVBD) has discussed in depth the subject of pig vaccination as a control strategy to reduce the risk of Japanese encephalitis in humans in Hong Kong. The discussions took into account local epidemiology, pig farming practices, published literature, correspondence with and experience of overseas experts. Meanwhile

the Health, Welfare and Food Bureau had issued a press release on 19 November 2004 stating that the Government was actively considering implementing a trial vaccination program for pigs against JE to reduce the risk of the virus threatening public health. Pigs infected with JE virus have no apparent disease except for stillbirth or abortion amongst pregnant swine. Infected pigs have a high level of viraemia lasting up to four days. The SCVBD concluded that pigs played a major role in the spread of JE to humans as evidenced by the following overseas references:

(a) seroconversion in sentinel farm animals was followed by seroconversion and illness in humans 1;
(b) seroprevalence of JE antibodies in humans correlated with the pig population 2;
(c) in Taiwan human cases often followed 2-3 weeks after seropositivity rates in pigs reached 50% and in Japan human cases increased as the number of infected pigs increased 3 ; and
(d) the elimination of pig farms in Singapore resulted in a dramatic reduction in the incidence of JE in Singapore 4.

4. The Committee noted that pig vaccination was not being used in any country, except for the purpose of preventing abortion and miscarriage in breeding swine. Pig vaccination was not considered in endemic places such as Japan, Taiwan, Mainland China, Korea and Thailand because their major control strategy was human vaccination, which was highly effective and was, in some cases, part of the national expanded program on immunization.

5. The SCVBD reviewed several studies on pig vaccination conducted in Japan from 1960-1985. [Annex] These studies can be criticized on several grounds including insufficient controls, no accounting for the human vaccination rates which could have a confounding effect on the results and no comparison made with vector numbers in the years of study. They did however show that –

(a) pig vaccination lowered the mosquito infection rate (MIR);
(b) two doses at monthly intervals produced only low titres of antibodies;
(c) there was conflicting evidence of a boosting effect due to natural infection;
(d) despite (c) viraemia was prevented in one small study; and
(e) pig vaccination was associated with a reduction in human cases in the 1985 Kumamoto study.

6. It should be remembered that these studies were conducted in Japan and there were basic epidemiological differences in JE transmission between Japan and Hong Kong. In Japan pigs were infected between the months of April to October while pigs that were not infected during the warmer months would remain seronegative the rest of the year. In Hong Kong pigs

could become infected throughout the year and, theoretically, human cases could occur in the winter. In Japan piglets can be vaccinated November to February after maternal antibodies have disappeared without the worry of natural infection. The lack of such distinct seasonality in Hong Kong forbids a swine vaccination programme that can be carried out in defined months for effectively preventing natural viraemia after maternal antibodies have disappeared.

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8. In our deliberations on the subject of pig vaccination, practical difficulties including sustainability of the program and the timing of pig vaccination were revealed. Following vaccinations using the currently available pig vaccines, the level of antibody would fall to non-protective titre over time. Therefore once the pig vaccination was implemented, annual booster vaccination is needed to maintain immune levels of antibody. Unless a vaccination program is sustainable, breeding sows may lack maternal antibody resulting in large numbers of susceptible piglets, with potential for a JE epidemic. It is estimated that about 10% of the pigs in Hong Kong are breeding sows, i.e. approximately 30,000 sows need to be given boosters twice each year. This approximates 7 to 10% of the local swine population. Due to the high turnover of pigs that need to be vaccinated, this would be a costly program.

9. The SCVBD has discussed vaccination and maternal antibodies. In essence there is only a short period during which piglets can be effectively vaccinated, i.e. between the time when maternal antibodies disappear and the pigs becoming naturally infected. The timing for pig vaccination was crucial. Given too early, the vaccine would be ineffective and given too late, natural infection with consequent viraemia was likely.

[1] Pig vaccination is ineffective in the presence of maternal antibody. All piglets in Hong Kong have maternal antibody at birth. Piglets lose maternal antibody between 8-14 weeks at variable, litter dependent, times. This means that the optimal time to vaccinate is difficult to determine and that not all pigs will be optimally vaccinated.

[2] Two vaccinations one month apart are required to produce protective antibody levels and it takes two weeks after the second vaccination before pigs became protected. There is thus a window period of six weeks during which natural infection can occur.

[3] It could be argued that the first dose of vaccine would prime the pig to develop antibodies in the presence of natural infection and would minimize/ prevent any viraemia. The evidence for this is, however, conflicting [5,6,7].

10. The SCVBD noted that a large number of pigs were imported into Hong Kong from Mainland China. Records show that over 1.87 million pigs were imported in 2004. These pigs usually stayed in the slaughterhouse for two days before being slaughtered. Imported pigs showed about the same degree of seropositivity as locally raised pigs. It had been shown that pigs could become viraemic within one day of infection [8, 9, 10]. The SCVBD believes that there is therefore some opportunity for a certain proportion of imported pigs to pose a public health risk. Moreover although the pigs may only remain in the slaughterhouse for two days, such pigs may be viraemic in transit from China or become viraemic in transit, thus contributing an additional risk factor. Since it is not known what percentage of imported pigs will become viraemic the SCVBD proposes that further studies are done to determine the exact significance of the risk. Meanwhile the SCVBD would propose that measures be taken to protect imported pigs whilst in the slaughterhouse from mosquitoes.

11. Even if pigs were vaccinated in Hong Kong (and indeed even if pig farming ceased in Hong Kong) it would not eliminate JE. Singapore ceased pig farming in the 1980's. Two cases were reported in 2001. Serology showed that about 50% of chickens and dogs were seropositive. This demonstrated that JE was still circulating in Singapore despite the absence of pig farming, suggesting that migratory birds were significant in the continuing circulation of JE in Singapore. Migratory birds pass through Hong Kong on their way south August – November and return through Hong Kong February – May. Of the five cases in Hong Kong in 2004, three did not live near pig farms. The SCVBD concluded that even if pig vaccination were effective in reducing the mosquito infection rate, and subsequently human cases, it would not eliminate JE in Hong Kong.

12. The SCVBD considers the evidence inconclusive as to whether or not the five cases diagnosed in 2004 represented a genuine increase. Disease awareness was high since the diagnosis of one case of JE in June 2004 among a cluster of three patients with initially unknown cause of severe systemic illness with a neurological component. Two additional JE cases were subsequently diagnosed under the heightened surveillance for "Encephalitis of Unknown Origin" cases which took place in June and July 2004. Testing for JE in these patients would not normally have been performed in previous years. The remaining two cases in 2004 might have been diagnosed due to the enhanced

index of suspicion and recognition by clinicians. A heightened disease surveillance and awareness might have detected an increase in cases although there was no increase in the number of imported cases. We would therefore be concerned that a decision to vaccinate pigs would be made on the basis of an increase in cases in Hong Kong whereas in fact the evidence for a real increase was inconclusive.

13. High pig turnover means that pig vaccination would involve an enormous number of immunizations. Such vaccination would need to be given directly by the pig farmers as the government did not have resources for such a program. Moreover even if resources existed, farmers would resist the idea of traveling inoculators who could spread infectious diseases from one farm to another. It also seems likely that some farmers would inadvertently vaccinate themselves. The adverse effects of inadvertent human vaccination with pig vaccine are unknown.

14. Finally the SCVBD note that available pig vaccines are live attenuated vaccines. Live flaviviral vaccines pose a theoretical risk of viral recombination to produce a new, possibly virulent virus 11. However the Committee noted that this problem had not emerged in China where over 180 million doses of the live-attenuated human vaccine SA14-14-2 have been given.

15. In summary, while pig vaccination might be expected to slow the spread of the JE virus and reduce the challenge to human population, practical considerations such as timing of the vaccination to account for maternal antibodies, rapid turnover of pig populations, sustainability and the cost of the vaccine would make effective vaccination of pigs difficult to achieve 12. Appropriate clothing, the use of insect repellants and insect screens could help prevent human JE cases. The SCVBD feels that the overall benefit of pig vaccination as a control strategy remains to be demonstrated. We advise that pilot studies in selected farms in the Yuen Long area may generate useful information to guide risk assessment and decision making. An evaluation framework should be planned ahead of the implementation of a pig vaccination program in Hong Kong.

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A summary of the pig vaccination studies conducted in Japan from 1960-1985

Nagasaki Prefecture study performed in Karako and Aite in 1966 [13]: A specially made inactivated veterinary vaccine containing three times the normal titer of JE antigen was given two to three times to swine. 70% seroconverted. An MIR of 25% was documented in the vaccinated areas (Karako) compared to 60% in unvaccinated control areas (Aite). The following year swine were not vaccinated and the MIR was 100% in Karako and 80% in Aite. The data indicated that pig vaccination can reduce the MIR

2. Nagasaki Prefecture study performed in Iki Island 1967-1972 [6, 5] . A single dose of live-attenuated vaccine was given to all swine. This failed to produce 100% seroconversion and from 1971 onwards two doses at monthly intervals were given. A control area was not set up in this study. Results showed that relatively low-titer antibodies persisted among vaccinated swine indicating the absence of a booster effect due to natural infection. There was a reduction in the MIR in 1972 and a probable reduction in human cases (however the number of field caught Cx. tritaeniorhynchus caught in 1971-1972 was significantly lower than in the preceding 4 years).

3. Osaka Prefecture study performed in Takatsuki City and Ibaraki City in 1967 [14]. Swine were given two or three doses of inactivated vaccine with very high titers of viral antigen. The MIR was 16.6% in the control area versus 5.1% in the vaccinated area. No mention was made on whether or not there was a reduction in human cases. There was a reduction in the MIR.

4. Kyoto City study 1968-1970 7. Swine were immunized with a live-attenuated vaccine. The MIR in mosquitoes caught in pig-pens housing vaccinated swine was lower than the control group by 50-75%. There was no mention of a reduction in human cases. Vaccinated swine produced relatively low titres of HI antibodies (1:20 to 1:40) which were significantly augmented by natural infection.

5. Osaka Prefecture study performed in Yokosyoji, Higashi-Osaka City in 1975 [15]. A single dose of live-attenuated vaccine was given to litter mates bred together in the same pen at 4 months old. This was a small study with five pigs in the vaccinated group and four in the control group. Vaccinated pigs developed antibodies 7 days after vaccination and no viraemia was ever detected in this group. All the pigs in the control group developed antibodies shortly after viraemia which occurred at variable time-points after entering the study. The mean antibody titre in the control group was higher than that in the vaccinated group. The duration of viraemia in the controls was 1-4 days. The data indicates that pig vaccination reduces or prevents viraemia in pigs.

6. Kumamoto prefecture study in 1985 [16, 17]. This prefecture had 10-57% of all cases of JE in Japan in the period 1978-1984 with around 10-25 cases a year. In 1985 25,000 swine in Kumamoto City were vaccinated with a live-attenuated vaccine. In 1984 there were 10 human cases. In 1985 after pig vaccination there was only one human case. Whether this was due to pig vaccination or to the cumulative effect of human vaccination is unclear. Moreover the total number of human JE cases in the Prefecture was reduced from 16 in 1984 to 4 in 1985, possibly reflecting a general downtrend in transmission in these years. The appearance of IgM antibodies in swine was delayed and reduced in the vaccinated areas compared with the unvaccinated areas.

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