

Meeting report

Japanese encephalitis vaccine development (Yokohama, 2006)

It is amazing that the Japanese encephalitis (JE) virus, which can be grown in most tissue culture systems, is still being manufactured using a “dinosaur” technology (suckling mouse brains) that was developed during and following the Korean War. This summary is derived from data presented at a conference held in Yokohama in 2006 with sponsorship of the Gates Foundation, US- and Japanese CDC.

Epidemiology and cost-benefit analysis of JE vaccination

Japanese encephalitis (JE) continues to spread throughout south and Southeast Asia, the Pacific Islands and Australia. Since suitable vector mosquitos are present virtually worldwide, it may soon appear in new regions as well. Moslem countries are also affected but regions with pig breeding have a greater prevalence. It is unclear whether increased recognition is not responsible for some of this increase. There is good evidence that other animals and birds can act as vectors though the pig remains the most effective amplifying host. JE is an “iceberg disease” where for each clinically recognized human case, there are hundreds that become infected and develop antibodies without having been significantly ill. Introduction of vaccination has clearly reduced the incidence of JE in China, Viet Nam, Malaysia and Thailand. Cost-benefit studies have shown that universal vaccination of children is cost effective. The Gates Foundation as well as the International Vaccine Institute in Seoul is now actively engaged in introducing new vaccines in Nepal and India where, just as in Thailand, nerve tissue derived JE suckling mouse brain vaccines were still the only available ones.

The JE situation in Japan

The vast number of Japanese receives inactivated suckling mouse brain derived JE (SMB-JE) vaccine before the age of 15 years. Clinically manifested annual JE nationwide cases have ranged around 10. Few booster vaccinations are given later in life. Pig farms have been moved away from population center and pigs are vaccinated. There are, nevertheless, an increasing number of older persons with neutralizing antibodies. This is unlikely due to persistent antibodies

from the SMB-JE vaccine which they had received as children. It has a relative short half life. “Booster infection” later in life is likely to play a role. Work is now in progress to develop an antibody test that measures naturally acquired immunity from actual infection. Antibody to the nonstructural NS1 protein can only be induced by natural infection. A population study in the Kobe region showed a natural infection rate of 5-10 % and in overall Japan studies it was 0.2-3.4 %. Among horses it was 15-67 %. This suggests that primary immunization with SMB-JE produces long lasting memory cells that are stimulated by natural infection which prevents disease even though the virus is still circulating.

Japanese efforts to develop a tissue culture JE vaccine

SMB-JE vaccine was licensed in Japan in 1965. Much of the work came out of the Biken Institute (Research Institute for Microbial Disease, Osaka University) though the US Army Lab in Tokyo had also contributed during the Korean War where JE proved to be a significant military medicine problem. The Biken continued to manufacture the “gold standard” JE vaccine for half a century and it is the only JE vaccine available in North America but only by special request from the US-CDC at Atlanta. It has a reputation of efficacy and a relatively low incidence of serious adverse side effects (though we know of at least 2 severe cases in Bangkok). SMB-JE is difficult to manufacture as thousands of suckling mice have to be raised. It also is not highly immunogenic and requires 3 injections and boosters are recommended by some authorities. The Biken Institute has now decided to make an inactivated tissue culture JE vaccine on the vero cell platform. It is now undergoing human studies.

The live attenuated JE vaccine from the Chinese JE-SA14-2S strain

This product was licensed in China in 1988. There are now 3 manufacturers and over 70 million doses are manufactured yearly. The virus is grown on hamster kidney cells, has been widely used and is displacing the SMB-JE and inactivated JE hamster

kidney cell vaccines in China. We were shown impressive data of reduction of clinical JE in China where this vaccine had been used. The attenuated vaccine is given as one dose and has long lasting immunity similar to the current yellow fever vaccines. The Gates Foundation, IVI and Program of Appropriate Technology in Health (PATH) are currently introducing to India. It is already in use in Nepal.

Inactivated SA14-14-2 JE vaccine

The basic research and technology for this product comes from the Walter Reed Army Institute in Washington, DC and is being advanced by the Intercell Company of Austria and in their plant at Livingston in the UK. It is grown on vero cells, inactivated and has shown great promise in early studies. The manufacturer hopes to introduce the product in India (Biological E Ltd, Hyderabad, India) and market on a “two tier pricing scheme” in developing JE endemic countries.

A flavivirus platform for an engineered JE vaccine

A Massachusetts research group (Acambia Inc, Cambridge, USA) is using the yellow fever virus which they have modified by insertion of a prM and E genes of JE SA 14-14-2. This vaccine is now undergoing

phase III trials and is called ChimeriVax. It was not clear who will be the eventual manufacturer and whether it will undergo technology transfer to a developing country and become available at an affordable price to JE endemic countries.

Conclusion

It would appear that at least 4 new modern JE vaccines are now in the pipeline and that the days of SMB-JE are numbered. The live attenuated vaccine from China is the most likely to succeed in Asia. An inactivated virus vaccine, that may be more stable under adverse conditions, may also have a place in the evolving JE vaccine market.

Just as this report is going to the printer, we received information that the attenuated JE vaccine favored by WHO, the International Vaccine Institute and Gates Foundation has been approved by the Thai government for commercial use in the Kingdom. It is the SA 14-14-2 strain virus grown in primary hamster kidney cell culture. The vaccine is manufactured by the Changdu Institute of Biological Products under WHO-GMP standards and has been used in China extensively for at least one decade with excellent safety and immunogenicity results. It confers long lasting immune memory with only one injection; similar to the commonly used Yellow Fever Vaccines.

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