

Original Article

The Prevalence of Japanese Encephalitis in Taiwan and Adjacent Countries

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Abstract

The infection of Japanese encephalitis virus (JEV) is an important public health issue in Asia and Western Pacific regions with its infected area tending to enlarge. In tropical region, Japanese encephalitis (JE) is the main cause of acute encephalitis in children and adults. As long as clinical symptom appears, about 15% to 40% of cases die, and 30% to 50% of cases may have sequellae like permanent neural symptoms or mental disorders, bringing about poor prognosis. These will all greatly affect individuals, families and the society. Due to the JE vaccination program in children, the incidence rate has decreased apparently, and among all, Japan, Korea and Taiwan have shown the most remarkable effect. Japan and Korea have confirmed cases below ten in recent years, and Taiwan has 20 to 30 cases per year, which exceeds the two adjacent countries obviously. Though Taiwan, Japan and Korea's confirmed case numbers decreased with each passing year, they all face a problem that the main infected people have become adults and even elders, showing that in countries inoculating JE vaccine for a long period, their adults group becomes the newly high-risk group instead. This circumstance may be related to the group of people which had never been vaccinated, the decline of prolonged antibodies or the decrease of natural infection rate. Because that sequellae caused by the infection of JEV not only affect individual's living quality, but also reduce social productivity and waste huge amount of medical cost. Currently, there are no specific anti-virus drugs available but only supporting treatments, and vaccination is known as the most effective method of preventing JEV infection at the present time.

Keywords: Japanese Encephalitis, vaccination, sequellae

Introduction

Japan encephalitis (JE) is a zoonotic infectious disease, induced by Japanese

encephalitis virus (JEV) of Flavivirus of Flaviviridae, and it can be spread by vector mosquito stinging of carrying the virus, especially *Culex tritaeniorhynchus* [1-2]. Pig is the main amplification host while human beings and horses are the final hosts, and due to the low concentration and short period of viremia in human, there is no person-to-person transmission. This disease easily sickens children and elders, while in epidemic area, young groups have the highest disease rate, and it shows that the incidence rate of 3 to 15 years old people is five to ten times as the elders, reflecting the high immunity of adults [3]. The proportion of inapparent infection is quite high, and discrepancy exists in different regions or different groups of people in the same region, for instance, residents in JE epidemic area have higher inapparent infection rate, between 200:1 and 300:1, while non-local residents or foreign troops, like American soldiers in Southeast Asia, have lower rate at about 25:1. Because most people who are infected have no symptoms, though some countries have the monitoring procedure against JE, they still underestimate the exact burden of the viral infection [4]; there has been a research estimating that in the circumstance without vaccination, about 175,000 cases of JE occurs per year among children below 15 years old in Asia [1].

JEV infection is an important public health issue in Asia, Southeast Asia and Western Pacific area and the main cause of acute encephalitis in children and adults in tropical region. Among the world, about 3 to 40 billion people live in places raging of JE [2-3, 5-7], which has been estimated to have 30,000 to 50,000 cases per year, mainly from Mainland China, India and Southeast Asia region [8]. Of those people, 10,000 to 15,000 dies [1, 5, 9], with the death rate of 15 to 40%, and some cases will suffer serious clinical symptoms; while only one third can recover completely. In addition, about 30 to 50% of people will suffer permanent neural or mental sequellas among cases survived [1, 6-7, 9], including obstacles in aspects of exercise, language and cognition, while mental sequellae greatly affect and bear a burden on individual, family and society even more. Up until now, no specific anti-virus drugs but only supporting therapy can be used as treatment, and vaccination is known as the most effective method to prevent JEV infection to date [1, 3, 6, 9].

The epidemic pattern of JE can be divided to two. Temperate regions like north of South Korea, Japan, China, Nepal and north of India are prevalent of JE in summer, mainly from May to December every year; subtropical region like Taiwan is also prevalent in summer, mainly from May to August every year; tropical regions like Vietnam, south of Thailand, Indonesia, Philippines and Sri Lanka are classified as sporadic pattern, whose cases occur in the whole year. Because the rainy season causes the number of mosquito increased rapidly, which raises the infection rate, its prevalent peak is usually in rainy season [2, 7, 10]. In the past ten years, the countries with expanding and periodic outbreaks include Vietnam, Thailand, Nepal and India [3]. For instance, in 2005, JE broke out extensively in Uttar Pradesh region of India, resulting in 5,737 cases and 1,344 deaths, while it also had outbreak in Nepal in the same year [6]; regions with prevalence by small

scale include Philippines, Indonesia and north Queensland of Australia [3]. In recent years, prevalence has the trend to slightly expand to rising areas like Bangladesh, Cambodia, Indonesia, Laos and Myanmar [2, 6, 11], probably caused by the interaction of ecology, environment, climate and human-behavior factors. For example, the economic growth promotes the development of paddy irrigation system, attracts migratory birds and provides the environment beneficial for mosquito's reproduction, causing the virus has the ability to spread out. As in 1990s, virus spreads from Papua New Guinea to north of Australia [1, 7], meaning that it isn't restricted in Asian countries.

The prevalent circumstances in neighboring countries are different, like Japan and Korea have made their cases decreased and even totally controlled, owing to factors such as expanded implement of children immunization program, improvement of living qualities and mechanization of agriculture; and furthermore, the decrease of cases in China and India can also be contributed to implement of immunization program in part of region. However, cases of other countries in Asia like Bangladesh, Cambodia, Indonesia, Laos, Myanmar, North Korea and Pakistan have the tendency of increasing, because of factors such as increasing population, expansion of land planting paddy, farming of pigs and living environment too close to such places, while there are no immunization program and routine monitoring of diseases [2, 6]. The followings only discuss on the present situations of Japan, Korea, Hong Kong and China.

Japan's present prevalence and preventing strategy

Japan has already had records of Summer Encephalitis in 1870s. A big outbreak occurred in 1924, causing more than 6,000 cases and 60% of them dead [12]. During 1948-1966, about 1,000 to 5,000 cases occurred per year, while half of them died, as a result, Japan started to implement expanded JE immunization program in 1955. Since 1972, cases are below 100 per year, showing the reducing case numbers, during 1978-1991, the annual number of cases only 20-90, and between 1992 and 2004, cases were below ten per year [13-15].

As for the usage of vaccination, they adopted the inactivated Nakayama-NIH vaccine strain at first but replaced it with Beijing-1 vaccine strain which has broader antigenicity since 1989 [15]. According to statistics, among the 361 cases of JE between 1982 and 2004, most of them had not been vaccinated, while 18% of them died, 50% of them suffered neural or mental sequelae after recovery and 32% of them completely recovered; people over 40 years old account for 78%, which were mostly elders between 60-69 years old. However, the age group who has the lowest antibody against JE is the 45-49 group, and it was speculated that the virus damaged the immune system of the elders [14]. Because one child suffered from temporary ADEM (acute disseminated encephalomyelitis) symptoms after vaccine inoculation, Japan government announced to cease the inactivated Nakayama strain used in the routine immunization program [3, 6], causing the JE vaccination rate of

children at 3-4 years old to be only 10% in 2007 and the high susceptible individuals to increase, which may raise the probability of the occurrence of JE [13]. After the effort of all parties, the JE vaccine, BK-VJE, was developed by replacing the mouse brain with vero cell and obtained the permission from Japan government in 2009, and has resumed the expanded JE immunization program in the same year.

South Korea's present prevalence and preventing strategy

Korea had Summer Encephalitis spreading before 1933 too, and it was not until 1946 that JEV was isolated from American soldiers garrisoned in South Korea and was proved existed and dispersed extensively. In 1949, the outbreak of JE in Korea had more than 5,000 cases, while half of them died and more than 600 people were hospitalized. In early period of Korea, JE outbreak occurred every 2 to 3 year [15] with thousands of cases reported each time, and the most extensive epidemic was in 1958, summing up to 6,897 cases [12, 15]. As a result, Korean government started to implement JE immunization program in 1970s, but it was only at locals with the vaccination rate lower than 5%. It was not until the JE epidemic events which occurred twice in series between 1982 and 1983 that the government included JE on the list of National Immunization Program, which extensively inoculated mouse brain inactivated Nakayama strain aimed at children between 3 to 15 years old. Nevertheless, due to the problem of vaccine side-effects, causing the vaccination rate unable to increase, and thus, the inoculation number of the vaccine has gradually decreased from 14 doses in 1983 to 5 doses in 2000. Calculated from the 13 years from 1985 to 1998, there were only 21 confirmed cases [16], while there were 45 cases between 2007 and 2010, showing that the accumulated incidence rate was 0.013 to 0.055 per 100,000 population [17], moreover, cases were mainly adults [7, 12, 15, 17]. According to the calculated data from 2007 to 2010, the youth and middle-aged between 40 to 49 years old had the highest incidence rate, and the confirmed cases which were above 40 years old accounted for 86.7% of all cases. Because all the confirmed cases had no history of vaccination, this phenomenon may be resulted from the adults group who had not been vaccinated before on account of exceeding the vaccinating age during the period of immunization program and South Korea government's control of mosquito vector which lower the natural infection rate [17].

China and Hong Kong's present prevalence and preventing strategy

China has the most of JE cases in Southeast Asia with over one million cases from 1965 to 1975, even reaching up to 174,932 cases in 1971. China started to implement immunization program since 1968, greatly decreasing the case numbers. The case number has reduced to 20,000 to 40,000 cases per year in 1990s, and it even decreased from about 9,000 to about 5,000 per year between 2001 and 2005 [12, 18], however, China still has the most cases in the world. JE is one of 38 legal infectious diseases in China, except Qinghai, Xizang and Xinjiang provinces, all other regions have cases occurring, mainly centralized

in regions such as Sichuan (including Chongqing), Guizhou, Hainan, Shaanxi and Yunnan [18-19]. Take the example in 2002, JE cases in regions stated above accounted for 50% and 74.1% of the world and China, while the population of those regions only accounted for 26% of the world population [18]. As for the age distribution calculated from 1996 to 2005, children below six years old accounted for 68.1%, who were the mainly infected group, and children below 15 years old accounted for 90% of all cases [18-19]. China conducted the vaccination at people's own expense from 1981 to 2007. Though JE cases have been decreasing over the years since 2000, there were still 7,643 cases occurring in 2006, increasing by 50% compared to the former years. Because JEV infection is still the main cause of viral encephalitis, which is a problem of public health required to be solved necessarily, and consequently, except of Qinghai, Xizang and Xinjiang provinces, China central government classified JE as one of the targets of Expanded Program of Immunization (EPI) since 2008 to solve the problem of the numerous cases of JE [20]. The government offers vaccines to the residents for free, expecting to resolve the JE problem more critical with every passing day in rural or undeveloped areas. At the present time, China has produced three different kinds of JE vaccine, among them, inactivated vaccine is mainly Beijing-3 vaccine strain, separately produced by two kinds of cell strain, primary hamster kidney (PHK) cells and vero cells, usually inoculated by three doses; another one is attenuated vaccine, mainly using PHK cells to cultivate SA14-14-2 vaccine strain, usually inoculated only two doses.

Hong Kong had totally fifty JE cases from 1967 to 2004. Although Hong Kong government classified JE as the contagious disease required to be immediately informed, they considered that there is not necessary to implement expanded immunization program currently due to the small number of cases only, and only people staying in JE spreading regions for over a month have the need to be vaccinated [8].

Taiwan's present prevalence and preventing strategy

Taiwan had hundreds of cases each year in 1950s and 1960s and even up to 1,791 cases between 1966 and 1967, with the confirmed case incidence rate to be 2.05 per hundred thousand persons. The government started to implement expanded immunization program since 1968, leading to the decrease of the confirmed case numbers, and the incidence rate was reduced to 0.03 per 100,000 population in 1997 [21]. In the early stage, cases were mainly kids below ten years old and then teenagers between 10 and 19. Recently, though the cases have decreased, the age group infected has the phenomenon of rising. The main cases have shifted to adults from 20-29 years old since 1985 and even taken adults as the main invading target in recent years [21]. Calculated from 1998 to 2010, there were 335 confirmed cases in total, while the age group above 30 years old accounted for 76.13% (255/335), and among them, the middle-aged between 30-49 years old accounted for 45.67% (153/335) (Table). In recent ten years, the confirmed cases are between 20 and 30

people each year, higher than adjacent countries such as Japan and South Korea.

As for the investigation of sequellae, from 1975-1997, among the 277 living individual cases, 59.6% (165/277) of them were completely recovered, while 40% of the cases would suffer permanent neural or mental sequellae. And among them, people without being vaccinated had higher rate of suffering such diseases, about 43.2% (73/169), and the next would be people being vaccinated by one or two doses, about 38.2% (21/55), and finally, people being vaccinated by three doses had the lower rate, about 34% (18/53) [15]. Although there is no obvious difference in statistics between them, it is still clear to see the effect related to doses.

Taiwan started to produce inactivated Nakayama strain since 1967, implemented JE immunization program by two doses aiming at all kids from 2-4 years old in 1968 and increased the doses to three in 1974. In recent years, Taiwan conducts the vaccination from March to June every year, and the first dose is aimed at infants at 15 months old, while the second vaccination must be separated with the first by two weeks, and finally, the third is inoculated after a year. Moreover, the fourth dose was added after 1983 aiming at grade-one students in elementary school.

Previous researches pointed out that the most effective way to prevent JE is vaccination, and it has the best protective efficacy by inoculating four doses during childhood. Additionally, similar researches also proved that completing four doses has the higher seroconversion rate [10, 22]. Assessing and analyzing the vaccination's benefit using the confirmed JE cases from 1970 to 1994, it has been found out that affected by the immunization program, the generation born between 1970 and 1975 has only been vaccinated by three doses with the efficacy of vaccination to be 84.61%; the generation born between 1976 and 1994 has been vaccinated by four doses with a higher vaccination efficacy, which is about 86.5%. Overall, the efficacy of vaccination by over two doses is

Table The age distribution of Japanese Encephalitis confirmed cases in Taiwan,1998-2010

year	age group							Total
	0-9	10-19	20-29	30-39	40-49	50-59	>=60	
1998	0	3	8	4	5	0	2	22
1999	0	3	8	5	4	2	1	23
2000	2	0	4	1	1	2	3	13
2001	0	0	8	13	7	4	1	33
2002	0	2	4	2	6	4	1	19
2003	1	1	7	7	6	1	2	25
2004	0	1	4	6	10	9	2	32
2005	0	2	2	10	7	9	5	35
2006	0	1	0	5	10	10	3	29
2007	1	1	3	8	9	9	6	37
2008	1	2	2	2	7	3	0	17
2009	0	1	2	1	6	3	5	18
2010	1	0	5	4	7	10	5	32
total	6	17	57	68	85	66	36	335
% of confirm	1.79	5.07	17.01	20.30	25.37	19.70	10.75	

about 85% [21]. Another research analyzing the confirmed cases of JE from 1970 to 2000 has shown that the efficacy of vaccination by two doses is 88.1% and reaches to 95.54% by three doses [23] after adjusting the racial inoculation rate. The former conducts the efficacy assessment of inoculating or not by using confirmed cases, and the latter considered about the racial vaccination rate.

Conclusion

JE is a kind of zoonotic infectious disease which is spread by mosquito. Currently, it is classified as the third category of the legal infectious disease in Taiwan. As long as the suspected cases are detected, hospitals have to inform the health units according to law. Same as Japan, Taiwan started to implement the expanded immunization program of JE early in 1960s, and South Korea also kept up after 1983.

Taiwan started to implement JE immunization program on children since 1968. The confirmed cases of JE, 200-300 people per year in early stage, has decreased rapidly since 1971, mainly attributed to the immunization program, causing the cases to be controlled obviously and rapidly. In recent years, the decreasing incidence of JE in Mainland China and India are also attributed to the results of extensively implementing immunization program. On the other hand, the reduction of mosquito vectors, resulting from changes of the living environments like urbanization, decrease of paddy field surface area, usage of pesticide and enterprise of raising pigs is also considered as a probable cause of decreasing cases.

Currently, Taiwan has more JE cases than Japan and South Korea, and there are researches considering that no implement of pig's immunization program in Taiwan may be one of the reasons. However, vaccination doses, types of vaccine strains, types of vaccine, duration of inoculation, vaccination rate, climate and environments are also different among each country, and these may all be important factors that can affect prevention and care of JE. For instance, Japan totally implements five doses before 14-15 years old, and South Korea implements five doses before 12 years old after 2000, while Taiwan totally implemented four doses, adding one more dose after children enter elementary school.

In early stage, JE cases in Taiwan were mainly children below ten years old. Nevertheless, as the childhood expanded immunization program implemented, confirmed cases have appeared to be gradually turned from children to mainly adults, mainly contributed to the high vaccination rate in children. Adjacent countries also face the similar problem, for example, Japan calculated the confirmed cases of JE from 1982 to 2004, finding out that the elder group between 60-69 years old was the most, and the middle-aged from 40-49 years old accounted for the most in South Korea between 2007 and 2010. However, compared to the world, children below 14 years old still account for 75% of all JE cases at the present time.

Due to the comprehensive implementation of vaccination, the age group of JE confirmed cases occurrence in Taiwan, Japan and South Korea gradually turned from

children to adults and even mainly to the elder, and because of not being classified as vaccination targets and their advanced age, this group of people may never have been vaccinated. Since JE infection may lead to severe sequelae such as causing obstacles referred to language, cognition and exercise, which will induce great effect and burden on individuals, family and society, and since vaccine is the most effective and direct method of preventing JE, whether classifying adults as vaccination targets in the future deserved to be thoroughly discussed and assessed, anticipating to lower the incidence rate of adults cases.

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Outbreak Investigation Express

The First Case Report of Imported Rabies in 2012

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Abstract

A thirty-year-old male suspected infection by rabies virus was reported by a medical center in Taipei city on July 24, 2012. The Research and Diagnostic Center of Taiwan CDC

confirmed that he was the first rabies case over the last decade in Taiwan. This male started his business in China from February 2012, and he was bitten by his dog in June. However, the dog had a history of being bitten by a stray dog. The man did not seek any medical help, and received no preventive vaccination. On July 16, he experienced numbness, tingling feeling, and itching on his sole, and paresthesia on the lower part of his body. He was then sent to a local hospital in Wu-Han City on July 20 because of the symptoms of hydrophobia, ancaophobia, vomit, and difficulty of swallowing with a swollen throat. He was suspected infection by rabies virus due to these symptoms. On July 23, he was sent back to a medical center in Taiwan by a medical aircraft due to his critical condition. He has been receiving medical care in the ICU since back to Taiwan. The outbreak investigation revealed that his two nephews were also bitten by the same dog in China; nevertheless they sought medical help and received rabies vaccinations immediately, until now appeared no suspect symptoms. This case shows that it is important to seek immediate medical help when one is bitten or scratched by animals. One should clean wound, seek immediate medical help and receive recommended vaccinations and immunoglobulin under doctor's assessment in case she/he experiences any injury from cats, dogs, monkeys or bats in the rabies prevalent area such as India, China and Indonesia.

Keywords: Rabies, Imported disease, Rabies vaccine, Rabies Immunoglobulin.

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