第 45 回日本小児感染症学会招待講演

Japanese Encephalitis in South Korea

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Introduction

Japanese encephalitis (JE) is endemic in Asian countries. In tropical regions, JE occurs year round, whereas in temperate areas it is mainly encountered from May to June and is uncommon between September and March.

Due to vaccination programs against Japanese encephalitis virus (JEV), changes in climate, agricultural practice, and animal husbandry the incidence of JE in South Korea, Japan, and Taiwan has declined substantially to near zero levels over the past two decades. In addition, its incidence is declining in China, Taiwan, and Vietnam, but remains high in India, Nepal, and Sri Lanka. In addition, the disease has become endemic in regions of Papua New Guinea and Northern Australia. Moreover, the incidence of JE has increased recently in South Korea, albeit, to much lower levels than those recorded in the past, and although, many studies have been undertaken to explain why, no satisfactory explanation has been offered.

Ⅰ. Epidemiology

In South Korea, JE has been reported through passive surveillance since 1949. 5,616 cases and 2,729 consequential deaths were attributed to JE in 1949. In the epidemic of 1958, 2,177 mortalities were reported among 6,897 incidences. Between 1960 and 1968, the annual incidence of JE was 1,000-3,000 cases per year (**Figure 1**)[1~2], with an annual mortality of 300-900. After the introduction of JE vaccination in 1971, its incidence substantially decreased in South Korea. Furthermore, excepting the 1982 epidemic, during which 1,197 cases and 10 consequential deaths were reported, its incidence has dramatically decreased than 1960s in South Korea.

From 2000 to 2013, the cumulative incidence and mortality of JE in South Korea declined to a level of 96 reported incidences and 17 reported deaths. However, the incidence of the disease and associated deaths increased from 2010 (**Table 1**)[2~3]. However, the precise reason for this increase remains unclear.

Ⅱ. Immunization program

A mouse brain-derived inactivated JE vaccine (Nakayama strain : JE-MB) introduced in 1971 substantially contributed in the prevention of JE. However, safety issues concerning the vaccine have been aroused by deaths after JE vaccination in 1994. These deaths led to the modification of JE vaccination schedules as detailed in the National Immunization Program (NIP) in South Korea. The primary vaccination schedule still consists of two doses with an interval of 1-2 weeks, and a third

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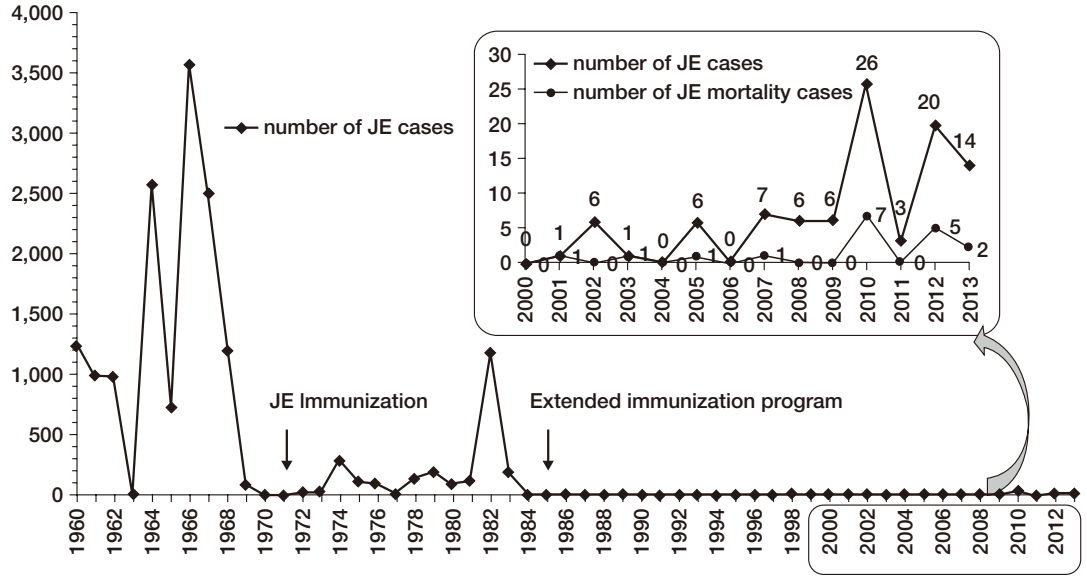

Figure 1 Reported annual incidences of JE in South Korea (KCDC*statistics, 2014)
*Korea Centers for Disease Control and Prevention

Table 1 Cases of JE reported to the KCDC, South Korea, 2007～2013

Characteristic	2007	2008	2009	2010	2011	2012	2013	Total
Cases	7	6	6	26	3	20	14	82
Age group								
＜20	0	0	0	1	0	2	0	3
20～29	0	0	1	1	0	0	0	2
30～39	1	0	1	1	1	1	0	5
40～49	3	4	3	10	1	5	3	29
50～59	2	1	1	8	0	9	5	26
＞＝60	1	1	0	5	1	3	6	17
Age median	50.6	52.3	40.3	50.4	46.3	47.6	57.7	
Death	0	0	0	7	0	5	2	14

dose 1 year after the second. In 1995, the recommended JE vaccination schedule was changed from the injection of booster doses annually until 15 years of age after the primary schedule (total 11 booster doses) to the injection of booster doses biennially after the primary schedule. More recent studies have revealed that neutralizing antibodies are present at 3 years after primary schedule, and have recommended the JE vaccination schedule be changed to booster doses at 6 and 12 years of age after the three-dose primary schedule administered between 1 to 3 years of age (**Table 2**).

However, recommended JE vaccination schedules of other countries consist of only one booster dose after the primary schedule. For example, in Japan the vaccination schedule was modified to one booster dose after the primary schedule in 2005. The issue of whether the booster dose should be continued at 12 years of age is currently under debate in Korea. Over past years, studies conducted in Korea have identified sufficient seropositive rates of neutralizing antibodies (NTab) and geo-

Table 2 Inactivated JE vaccination schedule recommended by the NIP

Primary schedule	Booster doses	Interval of booster doses after the primary schedule
3 years-old	11 doses (until 1994)	1 year
3 years-old	6 doses (1995～1999)	2 years
1～3 years-old	2 doses (from 2000)	6 years-old, 12 years-old

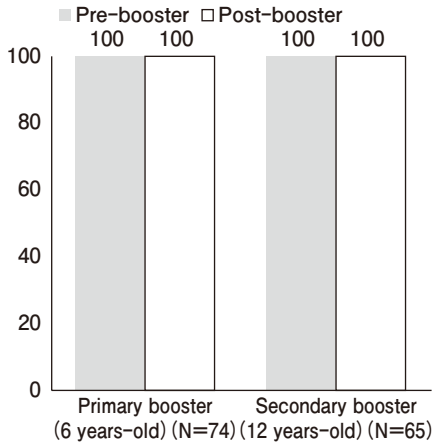

Figure 2 Seropositive rate of NTAb after booster doses of inactivated JE vaccine

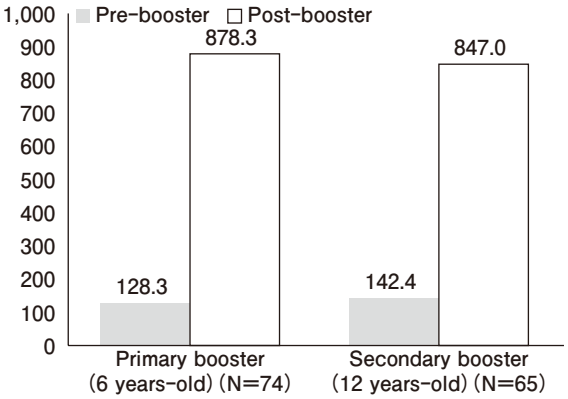

Figure 3 Geometric mean titers of NTAb after booster doses of inactivated JE vaccine

metric titers of neutralizing antibodies after both primary and booster schedules. In particular, antibody tests conducted before and after booster schedules at 6 and 12 years of age showed antibodies were sufficient (**Figure 2**)[4,5], and that geometric titers of neutralizing antibodies showed a rapid increase after the booster dose (**Figure 3**). This indicates that immune memory has developed before booster dose administration. However, more discussion is required on the topic, because most cases reported recently in South Korea have occurred in individuals older than 40 years.

Ⅲ. Vaccines

1. Vaccine types

The currently approved and used JE vaccines for immunization in South Korea are JE-MB and a primary hamster kidney cell derived live-attenuated SA 14-14-2 vaccine (CD.JEVAX®). A vero cell-derived inactivated vaccine (ENCEVAC®) and a Yellow fever 17D vectored live-attenuated chimeric vaccine (IMOJEV®) have also been recently approved and commercialization is now underway (**Table 3**).

JE-MB, which was introduced in 1971, has a played a major role in the JE the NIP. However, due to concerns over adverse reactions, the cost of vaccine production, and ethical issues regarding animal utilization, circumstances indicating its use are under discussion. Nevertheless, JE-MB is still the major vaccine used by the NIP for JE prevention, and is expected to be continuously used until a better substitute becomes available.

CD.JEVAX® is a live-attenuated vaccine produced in China and has been used in the private sector in South Korea since 2002. However, due to safety concerns regarding its development from pri-

Table 3 Summary of JE vaccines approved for use in South Korea

Vaccines	Virus Strain	Common Name	Manufacturer
Inactivated vaccines			
Mouse brain	Nakayama	JE-MB	Korea
Live-attenuated vaccines			
Primary hamster kidney	SA14-14-2	CD. JEVAX®	China
Newly developed vaccines			
Inactivated			
Vero cell	Bejing-1	ENCEVAC®	Japan, Kaketsuken
Live-attenuated chimeric			
Yellow fever 17D vectored	SA14-14-2	IMOJEV®	Acambis

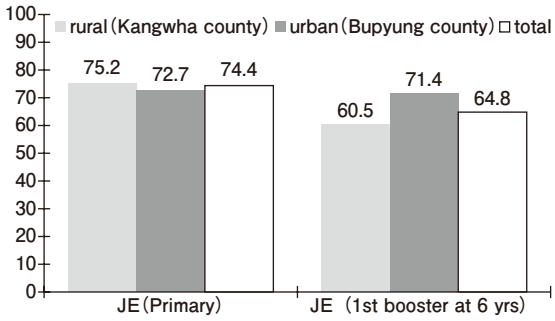

Figure 4 Vaccination rate against JE in South Korea (questionnaire survey, 2006)

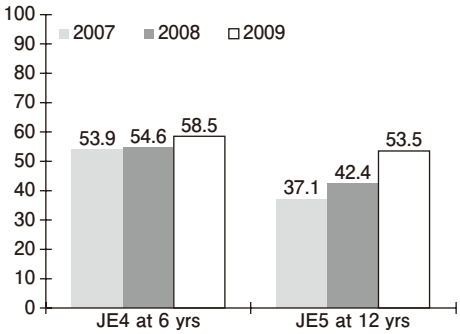

Figure 5 Booster vaccination rate (JE4, JE5) in South Korea (National Immunization Registry Statistics, 2010)

mary cells, it was excluded from the JE NIP. However, in 2013, CD. JEVAX® was prequalified (approved?) by the World Health Organization (WHO) and has now been included in the NIP.

ENCEVAC® and IMOJEV® have been approved by Korean National Institute of Food and Drug Safety Evaluation for usage in 2013, but for cost reasons, it has not been included in the NIP.

2. Vaccination rate

According to a previous questionnaire survey conducted in two counties (Kangwha and Bupyung) in 2006, which included rural and urban regions, the vaccination rate for the primary and first booster schedules were ～75% and 60-70%, respectively (**Figure 4**)[6]. However, recent reports have claimed higher vaccination rates. According to the National Immunization Registry Statistics, the rate of booster doses in South Korean children was around 55% in 2009 (**Figure 5**)[6]. Furthermore, as children are required to submit documents confirming previous vaccination in South Korea since 2012, the rate of JE vaccination is believed to have increased substantially.

3. Severe adverse reactions

Despite its long-term use since 1971 and its recommendation use in all children over 3 years old by the NIP since 1994, no severe adverse reactions related to JE-MB were reported until 1995. However, in 1995, four children died after JE-MB vaccination, and social awareness regarding its safety was aroused. Accordingly, the South Korean government started paying compensation for adverse events associated with vaccines included in the NIP, and since, many compensation claims

Table 4 Numbers of compensatory claims for adverse events associated with vaccinations in South Korea

	Total	BCG	HepB	DTP	DTP +others	Td	Var	Polio	MMR	MR	JE	Flu	Else	Pandemic H1N1 (2009)
1994	10	3									7			
1995	4	3	1											
1996	3	2									1			
1997	0													
1998	13	1			11				1					
1999	6			1	5									
2000	29	3	2	5	13				2		4			
2001	141	5		2	2				2	129			1	
2002	22	5	1		5				3		4	4		
2003	25	14							2		5	4		
2004	45	10	2	3	8			1	4		4	7	6	
2005	364	239	7	27	15	1		1	1		11	56	6	
2006	635	400	14	38	48	3	5	4	17		34	65	7	
2007	515	262	13	20	43		9		16		46	53	53	
2008	407	143	17	31	62	2	3		9		38	49	53	
2009	2,384	35	23	21	44	4	4		11		32	66	31	2,113
2010	18	1	2	3							1	11		
Total	4,621	1,126	82	151	256	10	21	6	68	129	187	315	157	2,113

associated with JE-MB vaccines have been settles (**Table 4**)[6]. However, the government has paid compensation based on only temporal associations between vaccinations and adverse events in the absence of proven causal relationships (**Table 5**). After four deaths were in South Korea reported in 1995, only one mortality associated with JE vaccination was reported to 2010. Although compensation has been paid in 15 cases, which included mortalities, no causal relationship has been identified in any case (**Table 6**). Since 2010, 5 claims resulted in compensatory payments in 2012 and 4 in 2013.

Summary

Due to the efficient JE prevention afforded by the NIP, the incidence of JE has substantially decreased in South Korea since 1982. However, the incidence of JE increased in 2010, 2012, and 2013, and investigations are being undertaken to determine reasons for these increases. Over past years, the immunogenicity of JE-MB has been well characterized. Furthermore, the rate of vaccination against JE has increased by improved government tracking of vaccination status in children. However, JE-MB has aroused social concerns regarding its safety after reported deaths, regardless of evidence-based indications of its safety. Thus, due to limitations imposed by vaccine production and by concerns over adverse reactions, the time has come to taper its use and make decisions regarding its discontinuation. Because vaccines can be used immediately after passing clinical trials in South Korea, it is important that matters raised by its replacement and issues regarding the management of vaccination records be resolved. Furthermore, we need to decide upon the necessity for second booster doses, which currently are only administered in South Korea.

Reference

1) Korea Centers for Disease Control and Prevention (KCDC) : Infectious Diseases Surveillance Year-

Table 5 Numbers of successful compensatory claim cases for adverse events associated with vaccination in South Korea

	Total	BCG	HepB	DTP	DTP +others	Td	Var	Polio	MMR	MR	JE	Flu	Else
1995	4										4		
1996	1										1		
1997	0												
1998	4				4								
1999	1				1								
2000	4			1	3								
2001	19			1						17	1		
2002	13									13			
2003	3									2	1		
2004	6		1	1			1				1	2	
2005	12			3	5						2	2	
2006	15	1		2	6						1	5	
2007	13	2		1	2						2	5	1
2008	6	1			4			1					
2009	5			2		1					1	1	
2010	5	1		1							1	2	
Total	111	5	1	12	25	1	1	1	0	32	15	17	1

Table 6 Numbers of successful compensatory claim cases for adverse events associated with JE vaccination in South Korea

Year	Age/Sex	Vaccination Institution	Vaccine	Side effect/Outcome
1995	5/F	Hosp. /Clinic	JE (inactivated)	Death (anaphylaxis)
1995	4/M	Hosp. /Clinic	JE (inactivated)	Death (anaphylaxis)
1995	15/F	Health care center	JE (inactivated) +EHF	Death (anaphylaxis)
1995	2/F	Hosp. /Clinic	JE (inactivated)	Acute disseminated encephalomyelitis
1996	9/F	School	JE (inactivated)	Death (anaphylaxis)
2001	3/F	Hosp. /Clinic	JE (inactivated)	Acute transverse myelitis
2003	3/F	Health care center	JE (inactivated)	Cellulitis
2004	4/M	Health care center	JE (inactivated)	Osteomyelitis
2005	2/M	Health care center	JE (inactivated)	Convulsion
2005	3/M	Health care center	JE (inactivated)	Encephalopathy
2006	2/M	Health care center	JE (inactivated)	Convulsion
2007	1/M	Health care center	JE (inactivated)	Convulsion
2007	1/F	Hosp. /Clinic	JE (inactivated)	Cellulitis
2009	3/F	Health care center	JE (inactivated)	Cellulitis
2010	3/F	Health care center	JE (inactivated)	Myositis

book 2012. Japanese encephalitis, pp93–95, 2012
2) KCDC：Public Health Weekly Report 7(2)：38, 2014
3) KCDC：Public Health Weekly Report 6 (11)：1–4, 2013
4) Hong YJ, Kim NH, Kim HM, et al：The Assessment of Japanese Encephalitis Vaccine Effectiveness. National Institute of Food and Drug Safety Evaluation (NIFDS), pp18–20, 2010
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6) Hong YJ, Lee HJ：Analysis of vaccine development and current policy of Japanese Encephalitis Vaccine. KCDC, pp49–56, 2009