Conference Paper

A Systematic Review: Prevention of Japanese encephalitis in Asia

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Abstract

Japanese encephalitis (JE) is one of the vector-borne diseases caused by infection with Japanese encephalitis virus, through the Culex tritaeniorrhynchus mosquito bites. Pigs and birds are the main reservoirs of JE viruses. JE is an important cause of encephalitis in most of Asia, with high case fatality rates and often significant neurologic sequelae among survivors. This study aimed to describe the prevention of JE in some countries in Asia. This study is a systematic review of 29 studies in Asia conducted in 2010 - 2017. It found that the most prevalent of JE prevention program in Asia is vaccination. It was recommended by the World Health Organization (WHO) to integrate JE vaccinations in national immunization programs and to prioritize in endemic areas. Some countries have well established or developing JE vaccination programs; those are Cambodia, China, India, Japan, Taiwan, Korea, Malaysia, Nepal, Sri Lanka, Thailand, and Vietnam. While some other countries in Asia have minimal or no JE vaccination programs, that are Bangladesh, Philippines, and Indonesia. JE prevention measures in some countries in Asia are the establishment of guidelines and service improvements, diseases and vectors/hosts surveillance, implementation of immunization programs, local vector control, education, and health promotion campaigns, and community engagement and environmental management that should focus on high-risk areas. The incidence of JE is decreased significantly in countries that have implemented JE vaccination programs.

Keywords: Japanese encephalitis, prevention, Asia

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1. Introduction

Japanese encephalitis (JE) is one of the vector-borne diseases caused by viral infection of *Japanese encephalitis*, a virus from a member of the JE serogroup of the genus *flavivirus*, and family *Flaviviridae* [1]. JE virus transmitted through the bite of *Culex tritaeniorrhynchus* mosquito, with birds and pigs as the main hosts. JE virus is one of the most important causes of viral *encephalitis* in Asia based on epidemiological and severe disease data, where rice cultivation and pigs farming are considered a significant risk factor [2].

JE disease in humans is the last resort in a dead-end cycle because *viremia* in humans occurs only a few hours so that it is difficult to transmit to others. Humans infected by

this disease can result in death if they not appropriately treated. According to Hills S, Marfin A, Fischer M (2013) and Chen, H., Chang, J.K., Tang, R.B. et al. (2015), JE is a virulent disease with a high fatality rate (20-30%) and among those living experiencing neurological sequelae (30-50%) as well as endemic to almost all countries in Asia [3, 4]

The genetic study estimates that this virus is originated from Malaya archipelago and has evolved since several thousand years ago into five genotypes spreading across Asia. The clinical case was first reported in Japan in 1871 [1, 5]. Then, there was a JE virus infection of about 6000 people in 1924, and the disease-causing agent of the brain tissue of dead *encephalitis* patients successfully isolated in 1983. The first time happened outbreak in 1935, and almost every year there is an outbreak, from 1946 to 1950 [6].

The global JE incident is unknown because the intensity and quality of JE supervision, as well as the availability of diagnostic laboratory testing, varies worldwide. Although JE cases have reported to the World Health Organization (WHO), the reporting is highly variable and incomplete. In the late 1980s, Burke and Leake estimated 50.000 new JE cases occur annually among 2.4 billion people living in 16 Asian countries. In 2000, with the annual assumption, the incidence of specific age groups was 25 cases per 100000 [7]. According to Hills (2014), every year, an estimated 67,900 JE cases occur. Approximately 75% of these cases occur in children <15 years old with an annual incidence of 5.4 cases per 100.000 children [3].

Due to the absence of medication for JE and the recent expansion of the geographic outbreak of disease, the WHO recommends integrating JE vaccine into routine immunization programs. JE is a public health problem and vaccination is considered the most critical measure of control for JE [8]. In this research, it will find out how JE prevention program conducted by several countries in Asia, using a meta-synthesis – systematic review approach based on the studies that have been undertaken previously by other researchers.

A systematic review is a literature review designed to find, assess and synthesize the best available evidence, related to specific research questions to provide information and evidence-based answers [9]. The process consists of identification of research questions, development of research protocols, determination of research database location as a search area, selection of relevant research results, selection of quality research results, data extraction from individual studies, synthesis of results by meta-analysis method or meta-synthesis method and presentation of results [10].

The advantage of using this systematic review is to obtain valid and applicable findings from several previous types of research on a specific phenomenon [10]. It expects that from this systematic review, it can identify JE prevention efforts in several countries in Asia, based on the results of previous researches.

2. Methods

This research is a systematic review, by following the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement*) guidelines. Sources of research data are the literature obtained through the database of international journal database of

University of Indonesia subscriptions, namely *Proquest* and *Ebsco.* Also, the data also collected through a database of journals on the internet such as *Google scholar* and publications of the World Health Organization (WHO).

Population in this research is the journal literature in the form of research results on JE which have been published in international journals and can access via the internet. The search process performed by writing keywords relevant to the topic, namely *Japanese encephalitis, prevention,* and *Asia.* Determination of some samples is through inclusion and exclusion in the process of identification, screening, and eligibility to determine the journals to be reviewed (journal inclusion). The first inclusion criteria in this research are the journals that have the object of study on JE prevention in several countries in Asia. The first exclusion criteria in this research are the journals that have a research object other than JE prevention in several states in Asia. The second inclusion criteria are the year of journal publication in the range from 2010 to 2017. The second exclusion criteria are the year of journal publication other than the range from 2010 to 2017. The determination of this second inclusion and exclusion criteria is performed to maintain the updated writing based on the latest research results.

The number of journal samples used to find out the election results based on inclusion and exclusion criteria has determined. The unit of analysis in this research publish journals. Data collection is performed from March to April 2017. After the data collected, then it performs data processing in the form of editing and entry. Editing is to examine the literature under the research by looking for variables to be considered, namely JE prevention while data *entry* is the data entry from the sample literature into the computer software with Microsoft office word and excel program.

This research uses a meta-synthesis – systematic review method so that the data analysis performed quantitatively and the research result presented in the textual form.

3. Results

Total results of journal finding through the identification process in several electronic journals database are 170 journals from *Proquest,* 159 journals from EBSCO, 41 journals from *google scholar* and eight publications from WHO. After the screening, 76 relevant journals obtained. Furthermore, it is conducted eligibility process to get 25 relevant journals. From 8 WHO publications, one relevant publication obtained. So as scientific data, it used 29 articles. It can see in Figure 1 Flow Chart of Data Reduction.

Based on the journal search result, it obtained the data on JE prevention program in 14 countries in Asia. From 14 states, there are differences of development in JE prevention program in the country (see Table 1). In Bangladesh, Philippines, and Indonesia, prevention program through immunization is still in the introductory stage and has not been included in the national immunization program to human being. Notably Bangladesh showed that a reduction of JE cases had occured probably due to vaccination to pigs program. [11] In the Philippines, the JE routine immunization program was still under planning. [8] While in Indonesia, JE vaccination are recommended for travellers. [33] The use of imported JE vaccine for national program was still a debate. [32]

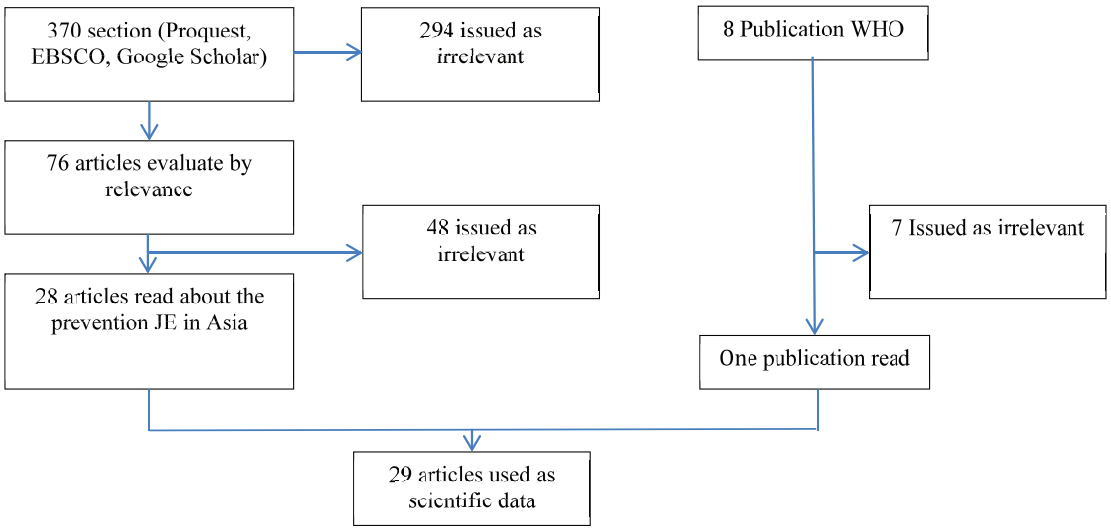

Figure 1: Flow Chart of Data Reduction.

Cambodia, Japan, China, Taiwan, Korea, India, Malaysia, Nepal, Sri Lanka, Thailand, and Vietnam were countries that have introduced JE vaccines gradually, starting in JE endemic areas, expanding the coverage of immunization areas and finally incorporating JE immunization in national immunization programs. Of them, five countries (Sri Lanka, Thailand, Korea, Taiwan and Vietnam) had already started earlier, i.e before the year 2000, in incorporating JE vaccine program into national program. Clearly the decrease of JE cases after the program were shown in all studied countries those have started the immunization program, except in India (see Table 2). India recorded an increase of cases after program introduction, and it needs for further assessment whether it was due to former underreported cases or other reason [39]. More details on JE prevention programs in several countries in Asia can see in Table 1.

TABLE 1: Characteristics of Journals and Study Results.

LOCATION	REFERENCE	RESULT OF STUDY (JE PREVENTION PROGRAM)
Bangladesh	Khan SU, et al. (2014) [11]	There is no plan to introduce JE vaccine into the immunization program. Vaccinating 50% of pigs each year results in an 82% annual incidence in pigs. The rate of JE can substantially reduce through the scope of pig vaccination that may lead to a reduced impact in humans.
Cambodia	Touch S, et al. (2010) [12]	The introduction of JE vaccine conduct in 2008, and 2009 became an immunization program for children aged 1-10 years.
	Julien Cappelle, et al. (2016) [13]	Understanding the transmission of JE viruses in different environments is essential for long-term planning of JE virus control and also an attractive model for studying the complexity of vector-borne diseases. Collecting quantitative data such as infection strength will help calibrate epidemiological models that can be used to understand the epidemiological cycle of vector-borne disease better.

LOCATION	REFERENCE	RESULT OF STUDY (JE PREVENTION PROGRAM)
China	Wang LY, et al. (2013) [14]	Immunization programs were undertaken in the early 1970s. Preventive measures: establishing guidelines and service improvements, disease and vectors/hosts surveillance, implementation of immunization programs, local vector control, education, and health promotion campaigns, community involvement and environmental management should focus on High-risk areas.
	Li X, et al. (2014) [15]	Recommendations for children vaccinated at eight months and two years of age. After 2000, with the help of WHO and the Program for Appropriate Technology in Health (PATH), as well as other international organizations, other JE endemic countries in Asia have begun implementing JE vaccination programs.
	Gao X, et al. (2014) [16]	Since 2008, nearly 100% of JE vaccine (live attenuated vaccine) has improved in China after being incorporated into the national Expanded Program of Immunization (EPI). China produces its vaccine, from 2007-2011, not only meet domestic demand but also abroad
	Xiaolong Li, et al. (2016) [17]	In 2008, children aged 0-15 get free JE vaccinations. People's living standards have been rapidly increasing, bringing positive changes in stopping the spread of JEV, for example: Improving water and sanitation in rural areas, transforming poor toilets into clean and separate restrooms to clean up mosquito breeding environments, relocating pig farms from villages' A place away from the town.
Phillipines	Lopez AL, et al. (2015) [8]	The Philippine government has developed a plan to expand sentinel JE supervision with laboratory confirmation to collect systematic data from all regions of the country and to provide a basis for measuring the effects of vaccines. The introduction of JE vaccine into the country's routine immunization program is still under planning.
India	Borah J, et al. (2013) [18]	Prevention of JE: reducing mosquito exposure, vector control, sanitation, health education and early diagnosis and care, as important as controlling acute encephalitis syndrome. Pig vaccination is an alternative strategy for controlling JE.
	Kumari R, Joshi PL. (2012) [19]	In 2006, the Government of India launched a JE vaccination campaign for children between 1 and 15 years old in endemic areas. The 2007-2009 JE vaccination program gradually expands to other endemic districts.
	Sarika Tiwari, et al. (2012) [20]	The prevention of JE is based mainly on two interventions; Mosquito control, and by an immunization system.
Japan	Ishikawa T, Konishi E. (2010) [21]	The use of vaccines has been carried out since 1954, Recommendations for vaccination were withdrawn in 2005 and restore in 2009. April 2010, the Japanese government restarted their recommendations for regular immunization of the limited population with new Vero cell vaccines

LOCATION	REFERENCE	RESULT OF STUDY (JE PREVENTION PROGRAM)
China Taiwan	Hsu L, et al. (2014) [22]	The main issue for JE control in Taiwan is reducing adult JE cases through cost-effective analysis of various immunization strategies. The Taiwan government launched a comprehensive vaccination campaign against JE in the 1960s, where all children younger than three years received two doses of JE vaccine. After 1980, the target population for JE vaccination is mainly children older than 15 months.
	Chang Y, et al. (2017) [23]	JE control in Taiwan: JE monitoring through diagnostic testing and determining the best vaccination programs to reduce adult JE cases. The national vaccination program implement in Taiwan in 1968.
Korea	Seo H, et al. (2013) [24]	The mandatory vaccination program in children began in 1967. Additional studies that measured the impact of vectors in JEV transmission and which incorporated environmental factors (e.g., weekly rainfall) were needed to determine the role of Culex species in viral pathogenesis during outbreaks and non- Outbreak. Furthermore, longitudinal vector surveillance required to understand the dynamics of JEV transmission in ROK better and to characterize the role of potential secondary vectors, in the maintenance and communication of JEV humans.
	Lee EJ, et al. (2016) [25]	The Korean government initiated mandatory vaccinations of all children aged 3-15 years annually until 1994. After that, the vaccination schedule was changed twice in 1995 and 2000
Malaysia	Impoinvil DE, et al. (2013) [26]	The JE vaccine was provided free of charge under the Malaysian National Immunization Program, in 2001
Nepal	Impoinvil DE, et al. (2011) [27]	From 2004 to now, Nepal has been actively detecting JE cases through a nationwide preventable vaccine surveillance network for Acute Encephalitis Syndrome (AES) conducted by the Nepalese government, with technical and financial support from WHO, under the Ministry of Health and Population of Nepal. Massive JE vaccination campaigns have been conducted annually, targeting 1 to 8 endemic districts each year, beginning in 2006. Critical strategies for JE prevention and control include vector education, vector control, and immunization of people and pigs.
	Access O, et al. (2015) [28]	Prevention: expanding vaccine coverage, improving agricultural practices, raising public awareness, supporting the use of mosquito-avoidance practices and regional collaboration on the border against JE.
Sri Lanka	Jeewandara C, et al. (2015) [29]	In Sri Lanka, immunization against JEV began gradually, and since 1988 it has been included in the national routine immunization program.
Thailand	Anderson KB, et al. (2011) [30]	JEVAX began slowly being incorporated into the EPI in Thailand in 1988, and a vaccination program began in 1990.
Vietnam	Marks F, et al. (2012) [31]	In 1997, the Vietnamese government initiated an immunization campaign targeting all children aged 1-5 years in high-risk areas

LOCATION	REFERENCE	RESULT OF STUDY (JE PREVENTION PROGRAM)
Indonesia	Hadisoemarto PF, et al. (2016) [32]	JE has identified since 1972. The 2-year hospital-based surveillance results in Bali published in April 2006. The JE vaccine from China is planned to use in Indonesia through the JE PATH Program (International Vaccine Institute 2009). However, the plan was rejected by the Minister of Health, because the minister did not want to use import vaccines
	Gunardi H, et al.(2017) [33]	JE vaccine recommends for travelers who will stay for more than one month in endemic areas during the JE virus transmission period.

4. Discussion

The prevention of JE mainly based on two interventions; mosquito control, and an immunization system. WHO recommends integrating JE vaccine into routine immunization. [8] The use of JE vaccine has implemented since 1954 in Japan. Several countries have also conducted JE immunization campaigns and blended JE vaccine in national immunization program, with the support and assistance from WHO and Program for Appropriate Technology in Health (PATH), as well as other international organizations.

The successes of JE prevention program in several countries in Asia include the initiation of free immunization program for children aged 0-15 years. Importantly, vaccine production by China that can meet the needs in the country and vaccine needs for abroad, and also positive change that can inhibit the spread of JEV such as improving water and sanitation in rural areas, converting poor toilets into clean and separate restrooms to clean up mosquito breeding environments, and relocating pig farms from village residence areas to places far from the village. [...] Another thing is that the importance of understanding about JE virus transmission in different environments can help to plan the control of JE virus in the long-term. Collecting quantitative data such as infection strength may help calibrate epidemiological models that can be used to understand the epidemiological cycle of vector-borne disease better. [...] Additional studies that measure the impact of the vector in JEV transmission and which combine environmental factors (for example, weekly rainfall) are needed to determine the role of Culex species in viral pathogenesis during outbreaks and non-outbreak diseases. Furthermore, long-term longitudinal vector surveillance is necessary to understand the dynamics of JEV transmission better. The implementation of mass JE vaccination campaign is conducted regularly every year. [...] JE's preventive measures are the establishment of guidelines and service improvements, diseases and vectors/hosts surveillance, the implementation of immunization programs, local vector control, education campaigns, and health promotion, community involvement and environmental management that should focus on high-risk areas.[...]

Several countries in Asia that have not integrated JE immunization in national immunization programs are Bangladesh, Philippines, and Indonesia. Although these countries are aware of JE and JE prevention programs but based on the literature obtained by the researcher, there has been no regular JE immunization program. Bangladesh is still in

Table 2: The Estimated Incidence of Japanese encephalitis (JE) in Asia.

Country	Time of immunization program	Estimated JE Incidence		Reference
		Before immunization program	After immunization program	
Bangladesh	-	Rajshahi was 2.7 per 100.000, Khulna was 1.4 per 100.000, Chittagong was 0.6 per 100.000 (2011)		[34]
Cambodia	2008	11.1 cases per 100.000 children under 15 years (2007)	-	[13]
China	1970	20.58 per 100.000 (1966) 20.92 per 100.000 (1971)	3.24 per 100.000 (1990) 0.4171 per 100.000 (2004) 0.16 per 100.000 (2013) 0.068 per 100.000 (2014)	[17]
Philippines	-	600 - 900 cases per year (2011-2014)		[8]
India	2006	6061 cases and 1500 death (2005)	5-fold increase in the number of cases (2010-2014)	[35]
Japan	1954	More than 1000 cases per year (before 1967)	Less than 10 cases per year (1992)	[21]
China Taiwan	1968	1.65 - 2.04 cases per 100.000 (1966-1970)	0.233 cases per 100.000 (1975 – 1991) 0.066 cases per 100.000 (1992 – 1997) 0.188 cases per 100.000 (1998) 0.118 cases per 100.000 (2002-2012)	[22]
Korea	1967	6.04 per 100.000 (1961-1967)	0.67 per 100.000 (1968-1983) 0.004 per 100.000 (1984-2009)	[25]
Malaysia	2001	84 cases per year (1997-2001)	49 cases per year (2001-2006)	[27]
Nepal	2006		1.648 per 100.000 (2010) 0.289 per 100.000 (2012)	[36]
Sri Lanka	1988	4.7 per 100.000 (1987)	0.1 per 100.000 (2006)	[37]
Thailand	1990	1500 - 2500 cases per year (1970-1980)	297-418 cases per year (2002-2008)	[38]
Vietnam	1997	5-15 per 100.000 (before 1997)	3.4/100.000 was observed among children less than ten years of age (after 1997)	[31]
Indonesia	2001-2003	In Bali, JE incidence is 7 per 100.000 children younger than ten years		[2]
	2005-2006	A study involving 15 hospitals in 6 provinces against children younger than 15 years found 28 cases of JE		

the stage of introducing JE vaccine to endemic areas of the country, and there is no plan to enter JE vaccine into immunization programs in Bangladesh. While in the Philippines, the introduction of vaccines into routine immunization program is still under planning, and Indonesia has been conducting hospital-based surveillance in Bali in 2006, but

there has been no approval from the Minister of Health to use the imported vaccines. In 2017, according to immunization program of Indonesian Pediatric Society (IDAI) 2017, JE vaccine is recommended for tourists who will stay for more than one month in endemic areas during the JE virus transmission period. Moreover, WHO suggests that JE vaccine should integrate into national immunization program and a priority in JE endemic areas. [...] The success of Asian countries in conducting JE prevention program should be an example for countries that have not implemented the program. By seeing at JE incidence data in several countries in Asia, it can look that JE incidence has declined significantly in states that have implemented JE vaccination programs.[...]

The limitation of this research is that the researcher only observes JE prevention program in several Asian countries, regardless of whether JE incidence occurs in urban or rural areas. The researcher also does not discuss immunization program provided in these countries, either the type of immunization or the dosage and the procedure of its administrations. The number of incidences obtained in each state is not entirely complete from year to year; even some countries only get the number of cases that occurred in several cities in the country. [...]

5. Conclusion

The most critical JE prevention program in Asia is the provision of JE vaccination and mosquito control. WHO recommends integrating JE vaccination into national immunization program in all countries. JE prevention measures are the establishment of guidelines and service improvements, diseases and vectors/hosts surveillance, implementation of immunization programs, local vector control, education, and health promotion campaigns, and community engagement and environmental management that should focus on high-risk areas. JE incidence declined significantly in countries that have implemented/provided JE vaccination programs.

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