

REVIEW



## Use of the live attenuated Japanese Encephalitis vaccine SA 14–14–2 in children: A review of safety and tolerability studies

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### ABSTRACT

Japanese encephalitis (JE) is the leading cause of viral neurological disease and disability in Asia. Some 50–80% of children with clinical JE die or have long-term neurologic sequelae. Since there is no cure, human vaccination is the only effective long-term control measure, and the World Health Organization recommends that at-risk populations receive a safe and effective vaccine. Four different types of JE vaccines are currently available: inactivated mouse brain-derived vaccines, inactivated Vero cell vaccines, live attenuated SA 14–14–2 vaccines and a live recombinant (chimeric) vaccine. With the rapidly increasing demand for and availability and use of JE vaccines, countries face an important decision in the selection of a JE vaccine. This article provides a comprehensive review of the available safety literature for the live attenuated SA 14–14–2 JE vaccine (LAJEV), the most widely used new generation JE vaccine. With well-established effectiveness data, a single dose of LAJEV protects against clinical JE disease for at least 5 years, providing a long duration of protection compared with inactivated mouse brain-derived vaccines. Since 1988, about 700 million doses of the LAJEV have been distributed globally. Our review found that LAJEV is well tolerated across a wide age range and can safely be given to children as young as 8 months of age. While serious adverse events attributable to LAJEV have been reported, independent experts have not found sufficient evidence for causality based on the available data.

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### Background

Japanese encephalitis (JE)—a mosquito-borne, neglected tropical disease—is the leading cause of viral neurological disease and disability in Asia.<sup>1,2</sup> Approximately 3 billion people living in Asia, including 700 million children, are at risk for JE, with an estimated 67,900 JE cases occurring annually in JE-endemic countries.<sup>2</sup> The burden due to death and disability is often underestimated, while determinants for developing overt neurologic disease following infection are not fully understood.<sup>3</sup> JE primarily affects children and confers lifelong immunity to those infected.<sup>4</sup> There is no cure for JE; about 20–30% of JE cases are fatal and of those who survive, 30–50% have long-term neurologic sequelae.<sup>5</sup>

Human vaccination is the only effective long-term control measure against JE, and the World Health Organization (WHO) recommends that at-risk populations receive a safe and effective vaccine through the national immunization program.<sup>1</sup> The 15 JE vaccines currently in use fall into 4 classes: inactivated, mouse brain-derived vaccines; inactivated, Vero cell culture-derived vaccines; live, attenuated SA-14-14-2 vaccines; and a live, recombinant (chimeric) vaccine.<sup>6</sup> Thus far, the inactivated, mouse brain-derived JE vaccine has successfully reduced JE disease in several countries; however, barriers to wider use have included a complex multi-dose schedule, a difficult production process and uncertain supply, high vaccine

price, and safety concerns.<sup>7,8</sup> Due to these concerns, in 2005, the Japanese government withdrew its recommendation for routine immunization with the inactivated, mouse brain-derived JE vaccine.<sup>9–11</sup> In reviewing this decision, the WHO Global Advisory Committee on Vaccine Safety (GACVS) determined there was no causal link suggesting an increased risk for acute disseminated encephalomyelitis associated with the inactivated mouse brain-derived JE vaccine.<sup>9–11</sup> However, the WHO recommended that the inactivated mouse brain-derived JE vaccine be gradually replaced by new-generation JE vaccines.<sup>1,9,10</sup>

The newer JE vaccines, available in several endemic countries, fall into 3 classes. First, there are inactivated Vero cell culture-derived JE vaccines developed from various JE strains (e.g., Beijing-1, Beijing P-3, Kolar strain [(JEV 821564 XY)].<sup>6</sup> Each vaccine strain follows different schedules for doses and boosters; for example, the Vero cell culture-derived JE vaccine derived from an attenuated SA 14–14–2 strain generally requires a primary immunization of 2 intramuscular doses administered 4 weeks apart for children 2 months of age or older in endemic regions.<sup>6,12</sup> A second class includes a live, attenuated SA 14–14–2 JE vaccine (LAJEV), derived from the SA 14–14–2 viral strain of a genetically stable, neuro-attenuated JE virus, which requires a single dose for children 9 months of age or older and confers protection against clinical JE disease

for at least 5 y.<sup>13</sup> A third class consists of a novel live, attenuated, recombinant (chimeric) JE vaccine (JE-CV) comprising the structural genes of SA 14-14-2 virus and nonstructural genes of yellow fever 17D virus, which has been licensed for children 9 months of age or older as a 2-dose vaccine given subcutaneously, and confers 5 y of protection against clinical JE disease.<sup>14</sup> The WHO recommends a single-dose of JE-CV over a 2-dose schedule.<sup>6</sup> Furthermore, the WHO has underscored the continued importance of rigorously monitoring all JE vaccine failures.

Of these 3 classes, LAJEV has become the most widely used vaccine in endemic countries in Asia.<sup>6,8,15,16</sup> The vaccine was first licensed in China in 1988 after initial trials showed no significant local reactions, systemic reactions, nor serious adverse events (SAEs) in follow-up periods ranging from 14 to 21 d after vaccination.<sup>17,18</sup> Since licensure, approximately 700 million doses of LAJEV have been produced in China (personal communication between S. Halstead and Dr. Yu, July, 2016). It is the first Chinese vaccine to be used internationally on a large scale. In 2013, LAJEV became WHO-prequalified at the Chengdu Institute of Biological Products, Chengdu, China. In 2014, Global Alliance for Vaccines and Immunization (GAVI) invited eligible countries to apply for financial support to conduct national JE vaccine catch-up campaigns and to introduce JE vaccine into their routine national immunization programs.<sup>19,20</sup>

As countries face the decision to introduce or update JE vaccines in their national immunization schedules, a comprehensive review of the available safety literature for LAJEV is warranted, especially as results from more methodologically rigorous safety studies have been recently published. In this paper, we reviewed published data on LAJEV since 1988 and synthesized the available evidence to determine vaccine safety according to the following topics: a) local reactions; b) systemic reactions; and c) serious adverse events (SAEs).

## Materials and methods

### Search strategy

We searched for all articles in the English language in PUBMED, EMBASE, and Web of Science using the following indexed and free-text search terms: “Japanese encephalitis,” “live attenuated,” “SA 14-14-2,” “vaccine,” and “safety” in multiple combinations. Snowball searching through the references of retrieved articles supplemented our search results. We also reviewed PMS reports, 2 from China (2005–2012 and 2009–2012)<sup>21</sup> and one from South Korea (2002–08).<sup>21-23</sup> In addition, we contacted Chengdu Institute of Biological Products for other vaccine safety data that may not be publicly accessible.

### Study selection

Titles and abstracts identified through the search strategy were screened for inclusion if: 1) children received primary immunization with the licensed, LAJEV produced by Chengdu Institute of Biological Products containing titers of at least 5.4 log PFU per 0.5 ml dose; and 2) children were monitored for local (e.g., erythema, swelling, induration, pain) and/or systemic (e.g.,

fever, lethargy, insomnia, irritability, seizure, anorexia, nausea, vomiting, diarrhea, cough, and rash) reactions following vaccination. Studies were excluded if they: 1) examined other versions of LAJEV produced by other manufacturers; 2) were conducted before 1988 (when a standardized vaccine titer was not mandated post-licensure); 3) included less than 30 study participants; 4) were primarily immunogenicity studies and did not include safety data; and/or 5) lacked or had limited details on methodology. Disagreements about the inclusion of an article were collectively discussed by the authors before a decision was reached. Appendix Figure A1 provides additional information on the study selection process.

### Data extraction

Articles were screened and data abstracted by the first 2 co-authors, and discrepancies were reviewed to reach agreement. The following data were extracted from included articles: author, publication year, country, study design, number and age of subjects, episodes of AEs and/or SAEs experienced post-vaccination, duration of follow-up and any other vaccines delivered concomitantly or before the administration of LAJEV.

## Findings

### Overview of included studies

An overview of the 16 studies that met the inclusion criteria are summarized in Table 1. The studies, which were conducted between 1995 and 2015 in various Asian countries, consist of 7 prospective cohort studies,<sup>8,24-29</sup> 3 PMS studies,<sup>21-23</sup> 2 open-label, nonrandomized single arm trials,<sup>30,31</sup> one prospective randomized trial with a control group,<sup>32</sup> 2 observer-blind, randomized controlled trials (RCT) comparing LAJEV to JE-CV,<sup>33,34</sup> and one 4-arm, double-blind RCT assessing lot-to-lot consistency of LAJEV.<sup>35</sup>

### Study subjects and vaccination

Study participants were healthy male or female children ranging from 8 months to 15 y of age. LAJEV was administered subcutaneously as a single 0.5 ml dose. In most of the studies,<sup>22,24-26,29,30,35,36</sup> children were administered only one dose of LAJEV with the exception of 5 studies.<sup>8,27,28,31,32</sup> In 2 RCTs, children were randomized 1:1 to receive either LAJEV or JE-CV.<sup>33,34</sup> One study that administered a single dose of LAJEV required children to have previously received the inactivated mouse brain-derived vaccine.<sup>30</sup> All studies, except one<sup>29</sup> which did not clearly specify, excluded children from vaccination if they had visible signs of sickness (e.g., a fever, cough or cold); however, the stringency of the exclusion criteria applied varied by study.

### Assessment of safety

Local and/or systemic reactions were monitored across all trials at various time intervals. Most studies monitored children for local reactions or AEs for at least 30 minutes after each

Table 1. Overview of clinical studies providing safety data on the live attenuated SA 14–14–2 JE vaccine in children.

Year	Authors	Study country	Study design	Number of vaccinated children	Age of children	Number of vaccine doses on age	Concomitant vaccines	Duration of follow-up per child	Children with serious adverse events related to vaccine
1997	Liu <sup>32</sup>	China	Prospective randomized trial with control group, block randomization, of primary immunization in Chengdu, Sichuan province; 1995	13,275	1, 2, 6 years	1 or 2 depending on age	None	30 d (subsample of 266 subjects were examined at days 1, 2, 3 and 7)	None
1999	Sohn <sup>24</sup>	South Korea	Prospective cohort study of primary immunization in 3 private chronic care facilities in Seoul (2) and Kyungki province (1); 1998	68	1–3 years	1	None	30 days	None
2008	Glovax <sup>22</sup>	South Korea	Post-marketing surveillance study of primary immunization in 8 research centers across South Korea; 2002–2008	606	10 months–13 years	1	None	30 days	None
2008	Gatchalian <sup>8</sup>	Philippines	Prospective cohort study of primary immunization in a single center in Manila; 2005–2006	571	8–10 months	1	Measles	28 days	None
2011	Chotpitayasunondh <sup>25</sup>	Thailand	Prospective open-label single center trial of primary immunization in a single center in Bangkok; 2006–2007	150	9–15 months	1	None	28 days	None
2012	Ranganath <sup>26</sup>	India	Prospective cohort study of immunization campaign in Kolar, Karnataka; 2007	1,640	10–15 years	1	None	28 d	None
2013	Choi <sup>27</sup>	South Korea	Prospective cohort study of booster immunization in 3 tertiary level hospitals in South Korea; 2009–2010	68	5–7 years	1 booster (already received 1 or 2 doses previously at ages 1–2 years)	None	28 days	None
2014	Wijesinghe <sup>31</sup>	Sri Lanka	Prospective randomized open-label trial of primary immunization in a single center in Colombo; 2007–2008	278	9 months	1	Measles	1 y	None
2014	Liu <sup>23</sup>	China	Post-marketing surveillance study of 2- or 3-dose series in Guangdong, China; 2005–2012	23 million doses	8 months, 18–24 months, 6 years	3 dose series before 2009; 2 dose series post-2009 (ages 8 months 18–24 months)	Largely administered alone; some cases concurrently administered with measles-rubella, or diphtheria-tetanus-pertussis (acellular) vaccines	3 month reporting period via passive surveillance	36, including 2 deaths (difficult to assess causality)

Year	Author	Country	Study Design	62.39 million doses released (number of doses administered is unknown)	1–3 years	N/A	None	1 y	70, including 4 deaths (difficult to assess causality)
2014	Wang <sup>21</sup>	China	Post-marketing surveillance study of primary immunization throughout 26 provinces in China; 2009–2012			N/A	None	1 y	
2014	Zaman <sup>35</sup>	Bangladesh	Lot-to-lot consistency randomized controlled trial of primary immunization in Matlab and Mirpur; 2012	818	10–12 months	1	None	28 days	None
2014	Feroldi <sup>33</sup>	Thailand	Observer-blind randomized controlled trial of primary immunization with LAJEV or JE-CV in 3 sites in Thailand; 2010	300	9–18 months	1	None	6 months	None
2014	Kim <sup>34</sup>	South Korea	Observer-blind randomized controlled trial of primary immunization with LAJEV or JE-CV in 10 sites in South Korea; 2011–2013	274	12–24 months	1	None	6 months	2
2015	Kwon <sup>28</sup>	South Korea	Prospective cohort study of 2-dose primary immunization in 5 centers across South Korea; 2007–2009	90	1–3 years	2 (1 y interval)	None	42 d after each vaccination	None
2016	Sanchayan <sup>29</sup>	Sri Lanka	Prospective cohort study of primary immunization in Jaffna district; 2012–2015	3,041	9 months	1	None	45 days	15
2016	Wijesinghe <sup>30</sup>	Sri Lanka	Open-label nonrandomized single arm study of primary immunization in children previously vaccinated with inactivated mouse brain-derived JE vaccine in Colombo district; 2007	305	2–5 years	1	None; Children who previously received 2 or 3 doses of inactivated mouse brain-derived JE vaccine, were again vaccinated with LAJEV	10 months	None

LAJEV = live, attenuated SA 14–14–2 JE vaccine; JE-CV = live, attenuated, recombinant (chimeric) JE vaccine.

vaccination.<sup>8,22,24,25,28,30,31,33-36</sup> After vaccination, subjects were generally followed for SAEs at least 28 d and some up to one year following the last study vaccination. In addition to clinic and home visits, parents were encouraged to record and/or report any local and systemic symptoms following vaccination in some studies.<sup>8,24,28,29,31,35,36</sup>

In contrast, the 2 PMS studies in China<sup>21,23</sup> tracked AEs following immunization (AEFI) using a national passive surveillance system, the Chinese Center for Disease Control (CDC) database, which includes AEFI report card data submitted by health staff, manufacturers and patients.<sup>37</sup> A PMS study in South Korea actively assessed the occurrence of AEs and SAEs following LAJEV vaccination by administering a series of 6 surveys annually over a 6 y period across 19 hospitals and clinics.<sup>22</sup>

### Local reactions

Local reactions such as erythema (0.2%–1.1%), swelling (0.4%–1.54%), pain (0.9–17%) and signs and/or symptoms at the injection site (3%) were reported across studies that administered only one LAJEV dose,<sup>22,25,26,35</sup> except in a prospective cohort study among South Korean children,<sup>24</sup> in which neither local nor systemic reactions were reported. In a study in Sri Lanka, a local reaction at the injection site or induration was reported in 12 out of 2878 infants over a 14 day follow-up period.<sup>29</sup> In another study from Sri Lanka, all solicited local reactions (including erythema, induration, and pain) were non-severe in children 2 y of age (74 children with local reactions out of 151 children) and 5 y of age (106 out of 154) who were previously vaccinated with the inactivated, mouse brain-derived JE vaccine before being vaccinated with a single dose of LAJEV.<sup>30</sup>

In 2 RCTs conducted in Thailand and South Korea where LAJEV and JE-CV were compared, solicited reactions at the injection site were common.<sup>33,34</sup> In Thailand, tenderness, erythema and swelling were the most common local reactions reported in both LAJEV (37.5%, 23.0%, 7.9%) and JE-CV (30.1%, 17.8, 6.2%) vaccination groups.<sup>33</sup> Similarly, in South Korea, pain and erythema followed by swelling were the most common local reactions reported in LAJEV (27.7%, 24.1%, 7.3%) and JE-CV (25.5%, 16.8%, 4.4%) vaccination groups.<sup>34</sup> In both studies, one child vaccinated with LAJEV experienced severe injection site pain or tenderness, which spontaneously resolved.<sup>33,34</sup>

Solicited local reactions following immunization were also observed in 2 South Korean studies which administered a 2 dose primary LAJEV series<sup>28</sup> and a booster dose of LAJEV.<sup>27</sup> Children that received the 2 dose primary LAJEV series reported solicited local reactions such as erythema (24.6% vs 13.3%), pain/tenderness (20.3% vs 8.9%), and swelling (11.6% vs 7.8%) more frequently after the second dose versus the first dose.<sup>28</sup> Interestingly, this study reported a higher frequency of local reactions following the second dose of LAJEV compared with the first, but also noted that the geometric mean titer increased by 6.5-fold in the second dose compared with the first dose.<sup>28</sup> Solicited local reactions, such as, erythema (4.8%), pain (4.8%) and swelling (3.2%) were also observed at the 4 week follow-up, among children that received a booster dose.<sup>27</sup> In a

large prospective study in China, local reactions such as injection site tenderness (0.4%), hives (0.4%), and rash (2.2%) were reported over 7 d in a closely observed sub-sample of 266 children who received either their first or second LAJEV dose.<sup>32</sup>

Two studies in which both LAJEV and measles vaccine (MV) were administered found most solicited local reactions among children to be mild and transient.<sup>8,31</sup> A study from the Philippines, which randomized infants to one of 3 study groups (group 1: receive LAJEV at 8 months and MV at 9 months; group 2: receive both LAJEV and MV at 9 months; or group 3: MV at 9 months and LAJEV at 10 months), found that 12.1–27.0% of infants across the groups experienced a solicited local reaction (e.g., erythema, pain, swelling, or induration) within 7 d of vaccination.<sup>8</sup> However, none of these local reactions were classified as severe, and only 2.1–8.0% reactions were considered moderately severe. A study from Sri Lanka which co-administered LAJEV and MV to children, similarly reported solicited local reactions (e.g., erythema, induration or pain) among 12.2% of children within 0–3 d and 0.7% of children between days 4–7; however, no reactions were classified as severe.<sup>31</sup> Neither study reported safety issues associated with the co-administration of the 2 vaccines.<sup>8,31</sup>

The occurrence of local reactions following LAJEV immunization was also documented in the 3 PMS studies we reviewed. A PMS study in Guangdong, China examining 23 million LAJEV doses between 2005 to 2012 recorded a total of 1,426 AEFIs, of which 1,390 were classified as non-serious.<sup>23</sup> Though 3% of these cases were classified as location reactions (e.g., erythema, swelling, and local or sterile abscess), most of the remaining cases were attributed to systemic reactions including fever or allergic reactions. A 2009–2012 national PMS study in China found erythema and swelling (13.73%), rash (7.17%), and induration (5.76%) were the most commonly reported local reactions among 6,024 AEFIs cases; in this study “the reported rate of AEFI with 6,024 cases was 96.55 per million doses using lot release data as denominator” (62.39 million LAJEV doses).<sup>21</sup> In comparison, only 3 cases out of 606 vaccinated children in a PMS study in South Korea reported local reactions, which included erythema or swelling.<sup>22</sup>

### Systemic reactions

A majority of studies we reviewed using a single dose administration of LAJEV reported mild and time-limited systemic reactions following immunization regardless of follow-up time.<sup>25,26,35</sup> For example, in a prospective cohort study in Bangkok, Thailand during the first week following immunization, cough (16%), rhinorrhea (10.7%) and fever >38.0°C (9.3%) were commonly reported systemic reactions.<sup>25</sup> Similarly, in a lot-to-lot consistency study in Bangladesh, solicited systemic reactions, such as fever (3.2%), but also diarrhea (2.2%), drowsiness (0.7%) or vomiting (1.8%) were reported among vaccinated children within 7 d of the vaccination.<sup>35</sup> In a study in Sri Lanka, fever (> 37.8°C) was noted among 133 infants immunized with a single dose of LAJEV, of whom 39% and 44% reported recovering within one day and 2 days, respectively.<sup>29</sup> Fifty infants sought care and 6 infants were hospitalized, though, the specific circumstances of the hospitalization were not described. In addition, irritability (41%) was the most



commonly reported systemic reaction, which mothers noted was likely related to pain and fever from the vaccination.<sup>29</sup>

Over a longer follow-up period of 30 days, fever (4.9%–11.3%), cough (3.4%–12.6%) and irritability (1%–3.8%) remained the most commonly reported systemic reactions across 3 single dose studies from South Korea, India and Bangladesh, and a Chinese PMS study that documented systemic reactions following either one or 2 LAJEV doses.<sup>24,26,32,35</sup> Less reported systemic reactions included headache (2.6%),<sup>26</sup> nausea/vomiting (1%–1.1%),<sup>24,26</sup> as well as self-limited skin rashes (1%) and loss of appetite (1%).<sup>24</sup>

Fever (3.2%) was the most commonly solicited systemic reaction reported among South Korean children that received a booster dose, followed by unsolicited reports of systemic reactions including upper respiratory tract infection (9.67%) and pneumonia (1.61%) over the 4 week follow-up period.<sup>27</sup> Similarly, in a 2 dose LAJEV safety evaluation in South Korea, fever was common after the first dose (4.4%) and second dose (7.2%), but no fever  $\geq 40^{\circ}\text{C}$  was reported.<sup>28</sup> All other events reported after each dose were considered mild and self-limiting.<sup>28</sup> Among children who were previously vaccinated with inactivated, mouse brain-derived JE vaccine and then vaccinated with a single dose of LAJEV in Sri Lanka, solicited systematic reactions were largely non-severe.<sup>30</sup> Among 151 2 and 154 5 y old children, anorexia ( $n = 28$ ;  $n = 16$ ), fever ( $n = 12$ ;  $n = 16$ ), crying ( $n = 15$ ;  $n = 8$ ), and insomnia ( $n = 13$ ;  $n = 5$ ) were reported. Only 2 severe systemic reactions (irritability and diarrhea) were reported overall.

In 2 studies which administered both LAJEV and MV, solicited systemic reactions were also reported.<sup>8,31</sup> Specifically, in a study in the Philippines, of those vaccinated first with LAJEV, 34% of infants experienced a mild systemic reaction (including anorexia, crying, diarrhea, drowsiness, insomnia, irritability, vomiting, and fever).<sup>8</sup> Moderate (22%) and severe (2%) reactions were reported less frequently. Within 7 d of receiving LAJEV dose alone, mild ( $37.5\text{--}38.6^{\circ}\text{C}$ ) and moderate ( $38.7\text{--}39.9^{\circ}\text{C}$ ) fevers were noted in 6.0% and in 18.0% of infants, respectively. Similarly, in a study in Sri Lanka in which LAJEV and MV were co-administered, fevers were noted in 7.6% of infants within 3 d of receiving the vaccines, and 5.0% within 4 to 7 d of the vaccines.<sup>31</sup> However, no cases of severe fever were reported in either study.

Fever was also a commonly reported systemic reaction in PMS studies in China.<sup>21,23</sup> Fever was the most reported AEFI in Guandong in 2005–2012<sup>23</sup> and nationally in 2009–2012.<sup>21</sup> In a Guandong PMS study, the reported rates were provided by temperatures  $37.1\text{--}37.5^{\circ}\text{C}$  (1.20 per million),  $37.6\text{--}38.5^{\circ}\text{C}$  (6.74 per million), and  $\geq 38.6^{\circ}\text{C}$  (22.37 per million).<sup>23</sup> In a national PMS study, a single reported rate of fever per 76.76 per million dose distributed was provided.<sup>21</sup> By comparison, a PMS study in South Korea found that upper respiratory infections (8.91%) and cough (6.60%) were the most commonly reported systemic reactions among vaccinated children.<sup>22</sup> Systemic allergic reactions including generalized rash, urticaria, and angioedema were also observed in the 2005–2012 PMS study in Guandong, China.<sup>23</sup>

Solicited systemic reactions were observed in 2 RCTs conducted in Thailand and South Korea.<sup>33,34</sup> In Thailand, irritability and loss of appetite were the most commonly reported in

both LAJEV (38.2%, 35.5%), and JE-CV (28.1%; 21.9%) groups.<sup>33</sup> Fever was more commonly reported in LAJEV (21.7%) than JE-CV group (16.4%). In South Korea, similar trends were observed in solicited systemic reactions in LAJEV and JE-CV groups: irritability (26.3% vs. 22.6%), loss of appetite (29.2% vs. 27.7%), and fever (25% vs. 24.6%).<sup>34</sup>

### Serious adverse events

Many studies that documented SAEs determined that all reported SAEs were unrelated to LAJEV administration.<sup>8,25,26,28,30,31,33,35</sup> One study reported no “significant” AEs,<sup>24</sup> but others did not fully describe or address the issue of causality,<sup>22,27</sup> or were unable to make strong assessment due to study design<sup>23</sup> or the use of a passive surveillance system.<sup>22</sup> However, SAEs associated with LAJEV vaccination were noted in 2 studies.<sup>29,34</sup>

A RCT study conducted in 1995 in China observed SAEs such as encephalitis, meningitis or hospitalizations due to all causes, but noted that they were no more commonly observed among vaccinated children compared with non-vaccinated children.<sup>32</sup> Diarrhea (0.8%) was reported in a closely observed subsample.<sup>32</sup> Acute diarrhea or severe pneumonia was also documented among 10 of 818 vaccinated children in a lot-to-lot consistency study in Bangladesh, but none of the cases were determined to be vaccine-related.<sup>35</sup>

In a 2005–2012 PMS study in Guandong, China, out of a total of 1,426 AEs (61.24 per million doses) reported, there were 36 SAEs (2.5%), including 2 deaths, 11 hospitalizations, 19 life-threatening events, and 4 cases of severe disability.<sup>23</sup> The 2 deaths following vaccination were reported as due to viral hypothalamic encephalitis and viral hemorrhagic encephalitis. Thirty-one neurological events were reported, including febrile convulsion (14 cases), asphyxia ( $n = 4$ ), seizure ( $n = 3$ ), viral encephalitis ( $n = 3$ ), encephalopathy ( $n = 2$ ), acute disseminated encephalomyelitis ( $n = 2$ ) among others ( $n = 3$ ). Most of the febrile convulsion cases were reported on the day of vaccination, which the study noted was “closely associated” with high fever; the study also noted that “in most cases, high fever was correlated with infection.” Due to the design of this PMS study, a strong assessment of causality was not possible. Another Chinese 2009–2012 national PMS study recorded 70 SAEs over 366 d following vaccination which included central nervous system damage ( $n = 34$ ), serious immunological reactions ( $n = 13$ ), blood system diseases ( $n = 12$ ), peripheral nervous system disease ( $n = 2$ ), serious infection ( $n = 3$ ), and other diseases ( $n = 6$ ).<sup>21</sup> In 14 SAE cases, LAJEV was co-administered with another vaccine. Of the 70 SAEs, 4 resulted in deaths, which were reported in children 8 months to 1 y of age. These deaths were due to (1) viral encephalitis and serious pneumonia, (2) serious pneumonia, respiration-circulation failure, (3) serious infection, and (4) malnutrition and severe dehydration. In the death due to malnutrition and severe dehydration, the child was co-vaccinated with other vaccines (meningococcal A conjugate vaccine, hepatitis B vaccine, diphtheria-tetanus-acellular pertussis vaccine, and oral polio vaccine). Due to the use of a passive surveillance system in this PMS study, causality was assessed largely by reviewing clinical symptoms and signs and laboratory examinations.

In a RCT in Thailand comparing LAJEV and JE-CV, SAEs were reported in both groups; however, none were determined to be associated with either vaccine.<sup>33</sup> Among children previously vaccinated with inactivated, mouse brain-derived JE vaccine, 26 SAEs were observed in 22 two year old children and 9 SAEs in 8 five year old children; however, none were determined to be related to LAJEV vaccination.<sup>30</sup> SAEs were also observed in a study from Sri Lanka when LAJEV was co-administered with MV.<sup>31</sup> Overall, 16.2% (n = 45) of infants experienced a non-vaccine-related SAE, most commonly resulting from gastroenteritis (4%), viral infections (2.9%) and lower respiratory tract infections (2.5%). No deaths or life threatening illnesses occurred and illnesses were resolved without any serious sequelae. Study investigators determined no SAEs were related to either vaccine.

SAEs associated with LAJEV vaccination were noted in 2 studies. A study in Sri Lanka assessing the safety of LAJEV noted that 15 out of 2,878 infants followed for 14 d experienced SAEs which were “consistent with causal association” to LAJEV.<sup>29</sup> These infants had fever (n = 2), febrile convulsions (n = 6), papular urticaria (n = 1), acute gastroenteritis (n = 2), and diarrhea (n = 4). The study reported “no deaths” or “life threatening AEFIs.” In a RCT in South Korea comparing LAJEV and JE-CV, SAEs were reported in both the LAJEV group (13.1%) and the JE-CV group (12.4%).<sup>34</sup> The SAEs included 2 cases of fever which required hospitalization and were determined to be associated with LAJEV vaccination; the 2 cases were treated and the children continued in the study. The study authors did not specifically comment on whether these cases fully resolved.

## Discussion

Our review indicates that LAJEV is a safe vaccine. While SAEs attributable to LAJEV administration have been reported, independent experts have not found sufficient evidence for causality based on the available data. In some studies, AEs and SAEs were reported without an assessment of causality, and thus, it is important to note that AEs and SAEs can be due to chance. Our review found that LAJEV is well tolerated across a wide age range (8 months to 15 years) and may be safely administered to children as young as 8 months of age. A recent study reported that a single dose of LAJEV also can be safely administered to adults, generating immunity among both seronegative and naturally seropositive adults.<sup>38</sup> Furthermore, data on the co-administration of LAJEV with MV shows an acceptable short-term safety profile,<sup>15</sup> which may encourage endemic JE countries to revise their national immunization programs to reflect a co-administration of the 2 vaccines as in Sri Lanka.<sup>39</sup> An immunogenicity study examining the co-administration of LAJEV and MV just completed in China,<sup>40</sup> and an immunogenicity and safety study is underway in the Philippines to evaluate the co-administration of LAJEV and the measles-mumps-rubella (MMR) vaccine which pending the results, may turn into an official recommendation for interested countries.<sup>41</sup>

Limitations to our review included the small number of eligible studies for analysis as well as several differences between studies that prevented clear comparisons. The differences occurred in the areas of monitoring and measurement of local

and systemic reactions following immunization, data collection methods, frequency of study visits, the types of outcomes documented, and reporting mechanisms (active vs. passive). Those studies with active safety monitoring following immunization with LAJEV while smaller, allowed more rigorous evaluation of AEs; those studies with passive safety reporting and surveillance also helped establish LAJEV’s safety. Both types of studies were used to inform decisions around LAJEV recommendations and regulatory action.

Additional limitations also encompassed differences in the level of investigator and clinical trial site experience. We suspect some studies may have under-reported AEs and SAEs, which may have resulted from less recognition and/or reporting of AEs and SAEs by study participants over prolonged time periods, especially when there was no active surveillance. The PMS studies in China also recognized the limitation of under-reporting due to incomplete or erroneous documentation of cases. In spite of these limitations, the safety profile of LAJEV has been consistent and acceptable across the studies, and the risk-benefit ratio remains favorable.

In China, where JE vaccines have been included in the national childhood immunization programs since 2008, PMS data generated by the Chinese national surveillance system from 2009–2012 determined that LAJEV had a reasonable safety profile.<sup>21</sup> A 2005–2012 PMS study in Guangdong, China reinforced this finding; AEs were most commonly mild, occurring within 3 to 5 d following LAJEV, and neurologic events were observed rarely.<sup>23</sup> It is important to note that the rates of AEs reported with LAJEV are comparable to those reported with other JE vaccines.<sup>42,43</sup> A recent review quantifying the benefits of LAJEV vaccination concluded that since the inclusion of LAJEV in the national Chinese immunization program that provides all immunizations at no cost, the nationwide JE incidence has declined considerably and yielded significant economic and social benefits.<sup>44</sup> In 2001, South Korea was the first country outside of China to license LAJEV and since then, its national regulatory agency has conducted PMS studies<sup>22</sup> and concluded that LAJEV has an acceptable safety profile.<sup>23</sup>

Through JE vaccination campaigns, India has successfully immunized over 62 million (78.8%) children between one to 15 y of age with LAJEV without evidence of vaccine-related serious illnesses or deaths.<sup>45</sup> After a 2006 campaign reached greater than 9.3 million children in India, a PMS study documented no SAEs following immunization, but was unable to reconcile the reports of 65 hospitalizations, including 22 deaths.<sup>46</sup> These reports prompted an evaluation by an independent expert committee, which concluded that no direct causality had been established between these events and the administration of LAJEV. After reviewing this report, the WHO GACVS recommended that future immunization campaigns be accompanied by strengthened monitoring and investigation of AEFIs. When the GACVS reconvened in 2007 and 2008 to review the available safety data, including new reports from South Korea and the Philippines, it concluded that the short-term safety profile of LAJEV is satisfactory and that LAJEV could safely be co-administered with MV to children 9 months of age.<sup>8,22</sup>

India and Nepal have seen a significant reduction in JE cases and deaths post-introduction of LAJEV.<sup>47,48</sup> Both countries

have seen an improvement in acute encephalitis syndrome and JE lab surveillance systems as well as increased awareness about JE disease prevention through vaccination. In Sri Lanka, due to increasing reports of AEs associated with the inactivated mouse brain-derived JE vaccine, and the desire to keep costs down while expanding the target population to include vulnerable adults in high-risk areas in addition to children, the Sri Lankan Ministry of Health transitioned from the inactivated mouse brain-derived JE vaccine to LAJEV after conducting a safety study.<sup>31</sup> Other countries in the region have also implemented strategies to scale up LAJEV immunization efforts. In 2015, Lao People's Democratic Republic became the first GAVI-eligible country to conduct catch-up campaigns for children 9 months to 15 y of age with Cambodia and Nepal following suit in 2016.<sup>49</sup> Cambodia has also launched a national JE vaccination campaign following which the vaccine will be included in the national routine immunization program.<sup>50</sup> Having conducted surveillance showing active circulation of JE virus and learning from the experiences of regional partners, Bangladesh and Indonesia are planning or expanding their national JE immunization programs, potentially first through vaccination campaigns and then routine immunization programs.

A JE control target has been supported by the 2005 World Health Assembly resolution on disability, and is consistent with the goals and objectives of WHO, United Nations Children's Fund (UNICEF), GAVI, and World Bank as well as several countries that face a high risk of JE infection. Through safe and effective JE immunization, JE control is feasible. Safety data and introduction experiences summarized in this review strengthen the evidence base for LAJEV safety, and may inform the decision-making of countries considering introducing a vaccine for JE control.

## Disclosure of potential conflicts of interest

The authors report no conflict of interest.

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## Appendix

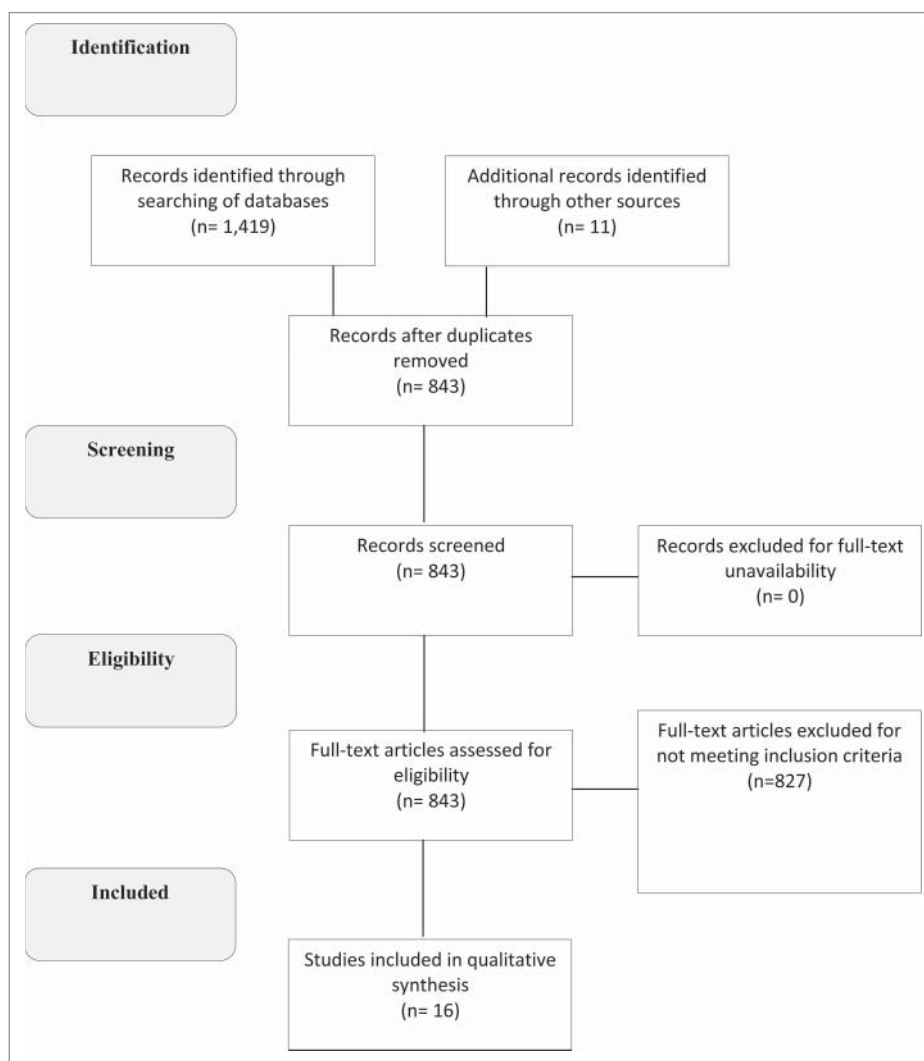


Figure A1. Source: Authors' review of published articles from peer-reviewed and gray literature.