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Safety profile comparison of chimeric live attenuated and Vero cell-derived inactivated Japanese encephalitis vaccines through an active surveillance system in Australia

Nazmul Islam[a], Colleen Lau[b,c,d], Alan Leeb[e], Deborah Mills[c,d], and Luis Furuya-Kanamori[f]

[a]Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar; [b]School of Public Health, Faculty of Medicine, The University of Queensland, Herston, Australia; [c]Dr Deb The Travel Doctor, Travel Medicine Alliance, Brisbane, Australia; [d]Research School of Population Health, College of Health and Medicine, Australian National University, Canberra, Australia; [e]Illawarra Medical Centre, Perth, Australia; [f]UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, Australia

ABSTRACT

Limited information is available about post-marketing safety of Japanese encephalitis (JE) vaccines. Using data from SmartVax, an active surveillance system for monitoring vaccine safety, adverse events following immunizations (AEFIs) were compared between the two JE vaccines available in Australia (a chimeric live attenuated vaccine [Imojev] and a Vero cell-derived inactivated vaccine [JEspect]). Data from 2756 patients (1855 Imojev and 901 JEspect) were included. Overall (7.0%), systemic (2.8%), and local (1.9%) AEFIs were uncommon. There were no significant differences in the odds of overall (OR = 1.27; 95%CI: 0.91–1.77), systemic (OR = 1.23; 95%CI: 0.74–2.06), or local (OR = 1.20; 95%CI: 0.65–2.22) AEFIs with Imojev compared to JEspect. There was an increase in odds of overall AEFI in patients aged <5 years (OR = 2.39; 95%CI: 1.10–5.19) compared to those aged >50 years. Both JE vaccines available in Australia are safe and well tolerated. Odds of AEFIs were age-dependent, young children should be carefully observed for AEFIs after vaccination.

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KEYWORDS
Immunization; tolerability; safety; SmartVax; vaccination

Introduction

Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the main cause of viral encephalitis in Asia.[1] Japanese encephalitis (JE) has a high case-fatality rate of around 30% among hospitalized patients, and more than half of individuals who survive the acute illness develop neurological sequelae.[2] JE is of public health concern in numerous countries in Asia where JEV transmission is endemic.[3] Although there is no specific treatment for the disease, effective JE vaccines are available,[4] and are included in the national immunization programs in many JE-endemic countries (e.g. Thailand[5] and Vietnam[6]).

In Australia, sporadic JE cases have been reported in the Torres Strait Islands (Far North Queensland) in the 1990s[7,8] and more recently among unvaccinated returned travelers.[9–11] Currently, two JE vaccines are licensed and available in Australia; Imojev® (Sanofi-Aventis Australia), a chimeric live attenuated vaccine,[12] and JEspect® (Seqirus), a Vero cell-derived inactivated vaccine based on the attenuated SA 14–14-2 strain.[13] These vaccines are recommended for laboratory workers exposed to JEV, travelers spending ≥1 month in an endemic area, and residents and visitors to the Torres Strait Islands in northern Australia.[14]

Both vaccines are equally immunogenic and shown to be safe in children and adults during the development and testing phases of Imojev[15,16] and JEspect.[17,18] However, post-marketing surveillance is critical for identifying uncommon adverse reactions following immunization (AEFIs), and these data are scarce for JE vaccines in non-endemic areas. Given that the minimum recommended age (2 months and 9 months for JEspect and Imojev, respectively) and contraindications for both vaccines are similar, immunocompetent individuals aged ≥9 months are eligible to receive either vaccine. Post-marketing surveillance data could assist with identifying subgroups of individuals at higher risk of AEFIs with JE vaccines. In this study, we therefore investigated AEFIs in vaccinees who received Imojev or JEspect at Australian primary health-care centers and specialist travel medicine clinics. We also compared differences in AEFIs between the two vaccines and between subgroups based on age, sex, and number of other vaccines received.

Methods

Ethics approval

The study was approved by the Australian National University Human Research Ethics Committee (protocol: 2020/662). All personal information was removed, and only de-identified data were received for the study.

Data source

Data were retrieved from SmartVax (www.smartvax.com.au),[19] an active surveillance system for monitoring vaccine safety utilized by more than 450 clinics and other immunization providers

CONTACT Nazmul Islam nislam@qu.edu.qa Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar, P.O. Box 2713
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in major cities and regional areas, in all states and territories throughout Australia including general practices, travel medicine clinics, and other immunization clinics (public, council, and hospital).[20] A key strength of SmartVax data is the high response rate from vaccine recipients or their parents/guardians (>70%).[21] SmartVax sends an automated short message service (SMS) message to patients, parents, or guardians 3 to 5 days after vaccination. If an AEFI is reported via SMS, a link is sent to an online survey to ask further questions about the adverse event. Clinics are automatically alerted through their practice software if any of their patients report a medically attended AEFI.

Patients who received Imojev or JEspect between 1 May 2015 and 4 December 2020 at clinics in Australia that used SmartVax were included in the study. Patients who did not respond to SmartVax's SMS message or where the type of JE vaccine (i.e. Imojev or JEspect) administered was not specified in SmartVax were excluded from the analysis. Two doses (28 days apart) are recommended for JEspect; to not violate the assumption of independent observations, data on the second dose of JEspect were excluded from the analysis. There was no difference in the proportion of patients who reported AEFIs between the first and second dose of JEspect (result not shown). Only one dose is recommended for Imojev.

Statistical analysis

AEFIs were the outcome of interest. SmartVax collects data on a range of AEFIs, and for the analyses these were classified into i) overall (i.e. any AEFI reported), ii) local (i.e. pain, swelling, or rash), and iii) systemic (i.e. fever, tiredness, irritability, sleep disturbance, headache, vomiting, diarrhea, convulsions, rigor, or hypotonia). Chi-squared test (or Fisher's exact test if 20% of cells had expected count of <5) were utilized to compare patient demographics and AEFIs reported between those who received Imojev or JEspect. To estimate the odds of AEFIs (overall, local, and systemic) with Imojev compared to JEspect, multivariable logistic regression models were built and adjusted for demographic factors and the number of other vaccines received during the same encounter. Interactions between predictor variables were assessed, and interaction terms were added into the regression models if appropriate. Sensitivity analysis was done by restricting the analysis to patients who only received Imojev or JEspect (i.e. no other vaccines received on the same day). The proportion of patients who reported AEFIs and received other vaccines on the same encounter were examined by sex for combination of vaccines with more than 10 records in the dataset.

All statistical analyses were two-sided and a p-value of less than 0.05 was considered statistically significant. The analyses were conducted in Stata MP version 16 (Stata Corp, College Station, TX, USA).

Results

Summary characteristics of the dataset

A total of 5389 immunization records of JE immunizations from 184 clinics across Australia were identified and retrieved from SmartVax. The number of JE immunization records in SmartVax steadily increased over the years as the number of clinics participating in SmartVax increased, except for 2020 when the number of JE vaccines sharply declined due to international travel restrictions related to the COVID-19 pandemic (Supplementary material S1). The median number of JE vaccines administered in each clinic per month was 1 (interquartile range [IQR 1–3]). The states/territories with most JE vaccine records were New South Wales (n = 1925) followed by Queensland (n = 1898), Western Australia (n = 654), and Victoria (n = 566).

Of the 5389 records, 1739 (32.3%) did not receive a response to the SmartVax automated SMS enquiring about AEFI, 69 (1.3%) did not contain information about the type of JE vaccine used, 816 (15.1%) corresponded to the second dose of JEspect, 9 (0.2%) did not contain information about the sex of the patient and were excluded from the analysis. Overall, 2756 patients (1855 Imojev and 901 JEspect) were included in the analysis. A subset of 637 patients (429 Imojev and 208 JEspect) who received only a JE vaccine were included in the sensitivity analysis (Figure 1). Of the 2756 patients, 1449 (52.6%) were females, the median age was 34 years (IQR 22–51). The median number of other vaccines received during the same encounter was 1 (IQR 1–2).

Comparison of patient's characteristics between those who received Imojev and JEspect

When comparing characteristics between patients who received Imojev and JEspect, the proportion who were female (51.9% [Imojev] versus 53.9% [JEspect]) was similar (p-value = 0.318); however, the age distribution was different (p-value < 0.001). Among patients who received Imojev, 3.0% were aged <5 years and 31.1% aged 16–30 years; whereas in patients who received JEspect, only 1.1% were aged <5 years and 40.8% aged 16–30 years. No significant difference was observed in the number of other vaccines received (p-value = 0.526) (Table 1).

Rate of adverse events following immunization

Overall AEFI were reported by 193 (7.0%; 95%CI 6.0–8.0%) patients; among these, 77 (2.8%; 95%CI 2.2–3.4%) and 52 (1.9%; 95%CI 1.4–2.4%) reported systemic and local AEFIs, respectively, while 103 (3.74%, 95% CI 3.1–4.5%) patients did not specify the type (i.e. local or systemic) of AEFI. The proportion of patients who reported overall, systemic, or local AEFIs with Imojev (7.6%, 3.0%, 2.0%) were not statistically significantly different compared with JEspect (5.9%, 2.3%, 1.7%) (Table 1 and Figure 2). Tiredness (2.3% Imojev, 1.9% JEspect) and headache (1.7% Imojev, 1.1% JEspect) were the most common systemic reactions reported; while the most common local reactions reported were pain (1.4% Imojev, 1.3% JEspect) and swelling (1.6% Imojev, 0.7% JEspect) (Table 1).

Among the 193 patients who reported an AEFI, 87 (45.1%) reported the time to onset of signs/symptoms post-immunization. Most patients reported AEFIs on day 1 post-immunization (88.5%), followed by day 2 (6.9%) (Supplementary material S2).

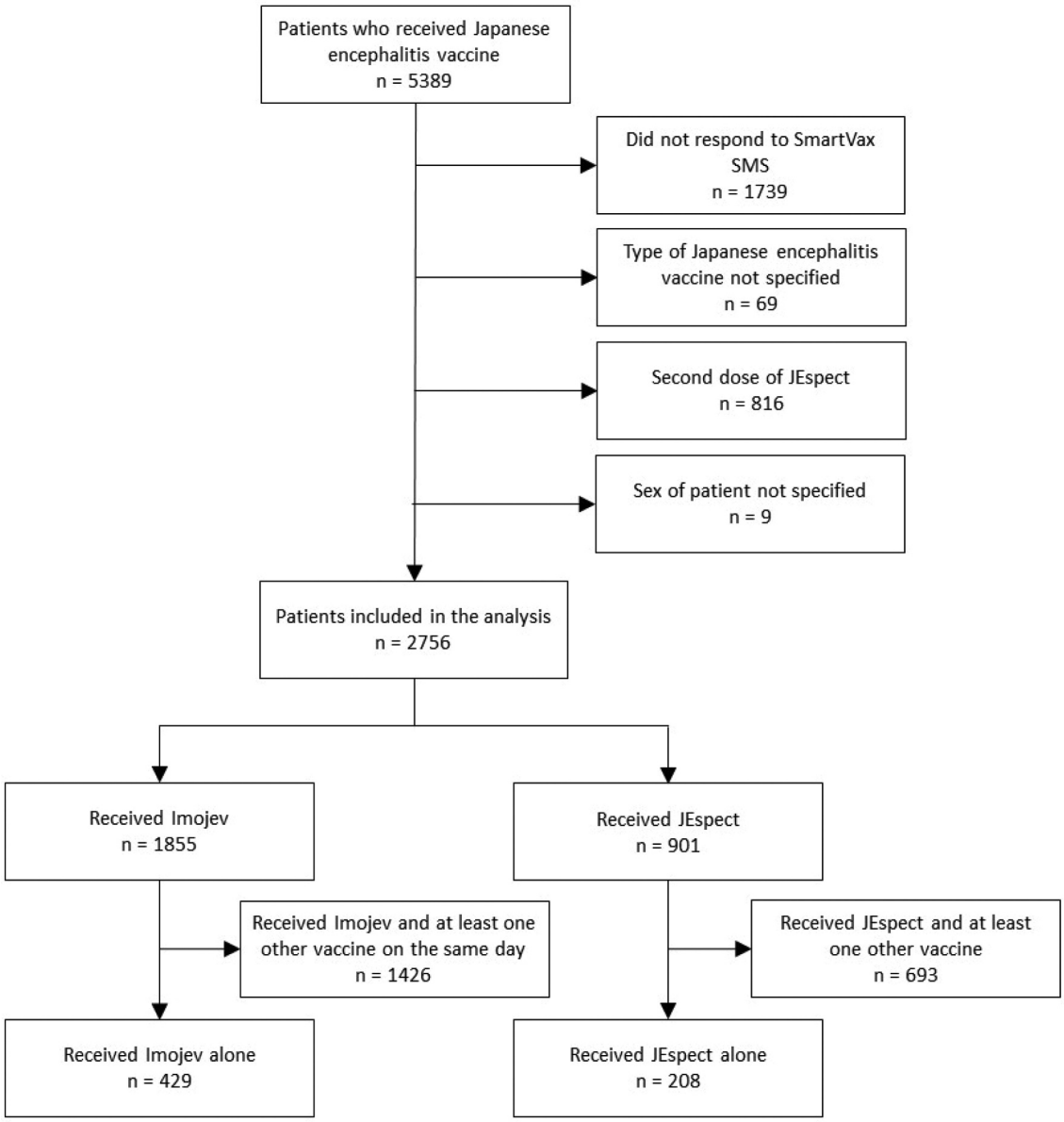

Figure 1. Flowchart of the selection of patients for comparison of local adverse events following immunization between Japanese encephalitis vaccines.

Predictors for adverse events following immunization

After adjusting for demographic characteristics and number of other vaccines received, there were no significant differences in the odds of overall (OR = 1.27; 95%CI: 0.91–1.77), systemic (OR = 1.23; 95%CI: 0.74–2.06), or local (OR = 1.20; 95%CI: 0.65–2.22) AEFIs in patients who received Imojev compared to those who received JEspect. Higher odds of overall (OR = 2.39; 95%CI: 1.10–5.19) and local (OR = 4.13; 95%CI: 1.08–15.74) AEFIs were observed in patients aged <5 years (n = 9 overall and 3 local AEFIs) compared to those aged >50 years (n = 47 overall and 11 local AEFIs). There was an interaction between sex and number of other vaccines received and an interaction term was added to the multivariable logistic regression models. There was a trend, though not statistically significant, of differential effect between sex and the number of vaccines – the odds of AEFI increased in females when the number of concomitant vaccines increased, while the odds remained stable in males (Table 2).

When the regression analysis was restricted to patients who did not receive other vaccines, the sample size substantially decreased (n = 637). The odds of AEFI were higher with Imojev (overall AEFI OR = 2.16, 95%CI 0.93–5.01; systemic AEFI OR = 3.27, 95%CI 0.73–14.67; local AEFI OR = 1.98, 95%CI 0.22–17.87), though not statistically significant different than with JEspect (Supplementary material S3).

Concomitant vaccines

There were no statistical differences in AEFI by sex due to the small number of patients who received each combination of vaccines. However, it was observed that the proportion of females who reported AEFIs was equal or higher than males for most vaccine combinations except for measles, mumps, and rubella (MMR) (33.3% in males versus 25.0% in females), rabies + typhoid (18.8% in males versus 0.0% in females) and hepatitis B + rabies (9.1% in males versus 0.0% in females) (Figure 3).

Table 1. Characteristics of patients and adverse events following immunization by type of Japanese encephalitis vaccine received.

	Imojev N= 1855 n (%)	JEspect N = 901 n (%)	*p*-Value
Female patients	963 (51.9)	486 (53.9)	.318
Age group			<.001
<5 years	54 (3.0)	10 (1.1)	
5 to 15 years	129 (7.0)	55 (6.1)	
16 to 30 years	577 (31.1)	368 (40.8)	
31 to 50 years	613 (33.1)	251 (27.9)	
>50 years	482 (26.0)	217 (24.1)	
Number of other vaccines received on the same day			.526
0	429 (23.1)	208 (23.1)	
1	621 (33.5)	295 (32.7)	
2	420 (22.6)	225 (25.0)	
≥3	385 (20.8)	173 (19.2)	
Overall AEFI	140 (7.6)	53 (5.9)	.108
Systemic AEFI	56 (3.0)	21 (2.3)	.304
Tiredness	42 (2.3)	17 (1.9)	.521
Headache	31 (1.7)	10 (1.1)	.254
Fever	16 (0.9)	8 (0.9)	.946
Irritability	13 (0.7)	4 (0.4)	.419
Sleep disturbance	11 (0.6)	3 (0.3)	.368
Diarrhea	10 (0.5)	4 (0.4)	.742
Vomiting	2 (0.1)	2 (0.2)	.460
Rigors	1 (0.1)	1 (0.1)	.602
Convulsions	0 (0.0)	0 (0.0)	-
Hypotonia	0 (0.0)	0 (0.0)	-
Local AEFI	37 (2.0)	15 (1.7)	.551
Pain	26 (1.4)	12 (1.3)	.883
Swelling	29 (1.6)	6 (0.7)	.048
Rash	5 (0.3)	5 (0.6)	.242
Other reactions	15 (0.8)	6 (0.7)	.686
Unspecified type of AEFI	74 (4.0)	29 (3.2)	.317

Unspecified type of AEFI refers when the patient indicated that he/she presented an AEFI, but did not specify the symptom/sign (e.g. tiredness, pain).
None of 'Other reactions' were severe e.g. anaphylaxis.
AEFI adverse event following immunization.

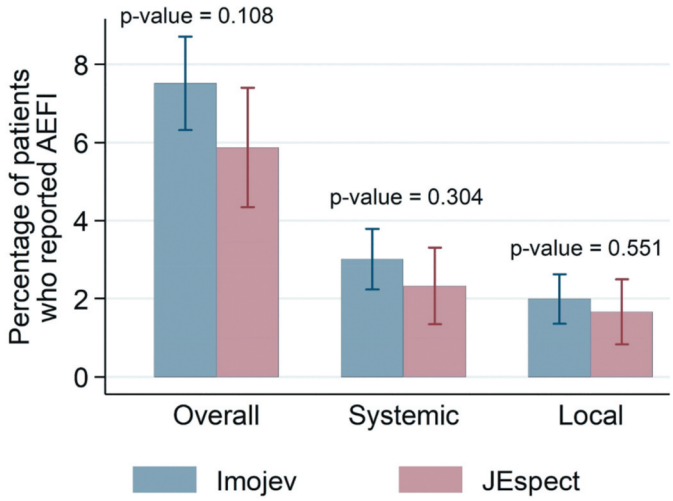

Figure 2. Percentage of patients who reported overall, systemic, and local adverse events following immunization (AEFIs) by the type of Japanese encephalitis vaccine received. 103 patients did not specify the type AEFI. The percentage of patients with unspecified AEFI with Imojev (4.0%) and JEspect (3.2%) were not different (*p*-value = 0.317).

Discussion

Using a large active surveillance system for AEFIs, our study confirmed that both JE vaccines currently available in Australia have good post-marketing acute safety profile,[22,23] with only 7% of patients reporting an AEFI in the first five days post-vaccination. No previous interventional or observational study had examined AEFI of chimeric (Imojev) and Vero cell-derived inactivated (JEspect) vaccines in the same population. Our findings of the most common AEFIs (i.e. tiredness, headache, and pain) were consistent with studies examining the safety profile of only one type of JE vaccine.[23,24] When comparing Imojev and JEspect, the former presented ~30% higher odds of AEFI, though the difference was not statistically significant and unlikely to be of any clinical significance. Our study also support findings from previous JE vaccine clinical trials[15,16] as well as smaller post-marketing studies with passive[25] and active[26] surveillance systems that AEFIs are age-dependent and more frequent among children aged <5 years.

In JE non-endemic countries, like Australia, the large majority of JE vaccines are administered to travelers, who are often given multiple vaccines (e.g. hepatitis A, typhoid, and rabies) at the same encounter during pre-travel consultations.[27] Previous surveillance studies have found that individuals who received concomitant vaccines were more likely to report AEFIs compared to those who only received JE vaccine.[25,26,28] The evidence on AEFIs after receiving specific combinations of vaccines is sparse. Capeding et al. found that infants (aged 9–10 months) who received concomitant live attenuated SA 14–14-2 JE and MMR vaccines compared to JE vaccine alone were twice as likely to develop fever, rash, diarrhea, and irritability.[29] However, Huang et al. did not find a difference in the proportion of toddlers (aged 12–18 months) with AEFI who received concomitant chimeric live attenuated JE and MMR vaccines compared to JE vaccine alone.[30] Kaltenbock et al. found no difference in safety profile between concomitant administration of Vero cell-derived inactivated JE with hepatitis A vaccines and the administration of one of the vaccines in healthy adults.[31] Cramer et al.[32] and Jelinek et al.[33] did not find an increase in risk of AEFI in

Table 2. Univariate and multivariable logistic regression models for predictors of overall, local, and systemic adverse events following Japanese encephalitis immunization.

	Overall AEFI		Systemic AEFI		Local AEFI	
	Univariate OR (95% CI)	Multivariable OR (95% CI)	Univariate OR (95% CI)	Multivariable OR (95% CI)	Univariate OR (95% CI)	Multivariable OR (95% CI)
Vaccine type						
JEspect (reference)	1	1	1	1	1	1
Imojev	1.30 (0.94–1.81)	1.27 (0.91–1.77)	1.30 (0.78–2.16)	1.23 (0.74–2.06)	1.20 (0.66–2.20)	1.20 (0.65–2.22)
Age group						
<5 years	**2.27 (1.06–4.88)**	**2.39 (1.10–5.19)**	1.96 (0.66–5.85)	2.01 (0.66–6.09)	3.08 (0.83–11.32)	**4.13 (1.08–15.74)**
5 to 15 years	0.80 (0.40–1.61)	0.83 (0.41–1.68)	0.32 (0.08–1.38)	0.33 (0.08–1.42)	1.04 (0.29–3.75)	1.14 (0.31–4.19)
16 to 30 years	1.01 (0.68–1.49)	0.98 (0.66–1.45)	0.70 (0.39–1.27)	0.66 (0.36–1.20)	1.35 (0.65–2.85)	1.22 (0.58–2.60)
31 to 50 years	1.09 (0.74–1.62)	1.08 (0.73–1.61)	0.91 (0.52–1.62)	0.92 (0.52–1.63)	1.11 (0.51–2.43)	1.06 (0.48–2.34)
>50 years (reference)	1	1	1	1	1	1
Sex						
Male (reference)	1	-	1	-	1	-
Female	**1.64 (1.21–2.22)**	-	**2.16 (1.32–3.54)**	-	**3.43 (1.76–6.70)**	-
Number of other vaccines received						
0 (reference)	1	-	1	-	1	-
1	1.34 (0.89–2.02)	-	1.40 (0.75–2.62)	-	2.53 (0.93–6.84)	-
2	0.90 (0.55–1.46)	-	0.72 (0.33–1.58)	-	1.99 (0.68–5.86)	-
≥3	**1.67 (1.08–2.58)**	-	1.62 (0.83–3.18)	-	**4.46 (1.65–12.01)**	-
Interaction between sex and number of other vaccines received						
Male and no other vaccine (reference)	-	1	-	1	-	1
Male and 1 additional vaccine	-	1.00 (0.53–1.91)	-	1.05 (0.39–2.80)	-	1.19 (0.28–5.03)
Male and 2 additional vaccine	-	0.69 (0.33–1.44)	-	0.37 (0.09–1.47)	-	0.29 (0.03–2.87)
Male and ≥3 additional vaccine	-	0.82 (0.40–1.69)	-	0.40 (0.10–1.56)	-	0.67 (0.11–4.12)
Female and no other vaccine	-	0.89 (0.46–1.75)	-	0.89 (0.32–2.50)	-	0.50 (0.08–3.01)
Female and 1 additional vaccine	-	1.69 (0.73–3.94)	-	1.76 (0.49–6.36)	-	4.03 (0.50–32.18)
Female and 2 additional vaccines	-	1.79 (0.68–4.71)	-	3.38 (0.63–18.27)	-	**19.68 (1.26–306.09)**
Female and ≥3 additional vaccines	-	**3.62 (1.45–9.05)**	-	**8.75 (1.75–43.65)**	-	**21.06 (2.06–215.69)**

AEFI adverse event following immunization; *OR* odds ratio; *CI* confidence interval.

healthy adults who received concomitant Vero cell-derived inactivated JE and rabies vaccines compared to those who either received JE or rabies vaccine. It is not clear if the reason for the increase in AEFIs reported with multiple vaccines is due to an additive effect of the concomitant vaccines or due to the most reactogenic vaccine. Therefore, future studies are required to investigate the mechanism, identify combinations of vaccines that should be avoided, and examine whether these combinations differentially affect males and females.

There were some limitations that need to be considered when interpreting the findings of the study. AEFIs were more common in children aged <5 years; however, the sample size in this age group was small (n = 64) and it is unknown whether patients in this age group experienced more severe AEFIs as the severity of symptoms was not recorded in the system. Additionally, we acknowledged that intensity of AEFIs may be difficult to ascertain in young children, and parents may be more likely to report AEFIs (even if they are mild) due to concerns about their child's health following vaccination; thus, age-dependent AEFI requires further exploration in future research. AEFIs were more commonly reported in the first day post-immunization, though it was not possible to ascertain differences between vaccines, future studies need to investigate onset of sign/symptoms. SmartVax sends automated SMS messages to patients 3 to 5 days after immunization, thus we were not able to examine adverse events that may have occurred beyond 5 days post-immunization. This is especially important with live vaccines for which AEFIs often occur later and may not capture late onset AEFIs such as cardiovascular or neurologic complications. For example, myocardial infarction[34] and vaccine-associated Guillain-Barré syndrome[35]) have been reported three and six weeks, respectively, after JE immunization, thus future studies should examine longer follow-up periods. Despite the relatively large number of vaccinees (n = 2756) for the whole study, the sample size for some subgroups (e.g. specific combination of vaccines and by sex) were small, and statistical analyses were not possible. Although our analyses identified higher risk of AEFIs in females who received ≥3 vaccines in addition to JE vaccine, the results should be verified by further studies specifically designed to compare differences in AEFIs between sexes, after receiving different combinations of vaccines. Studies are also required to determine whether AEFIs after concomitant vaccines are determined by the combination of vaccines or the most reactogenic vaccine.

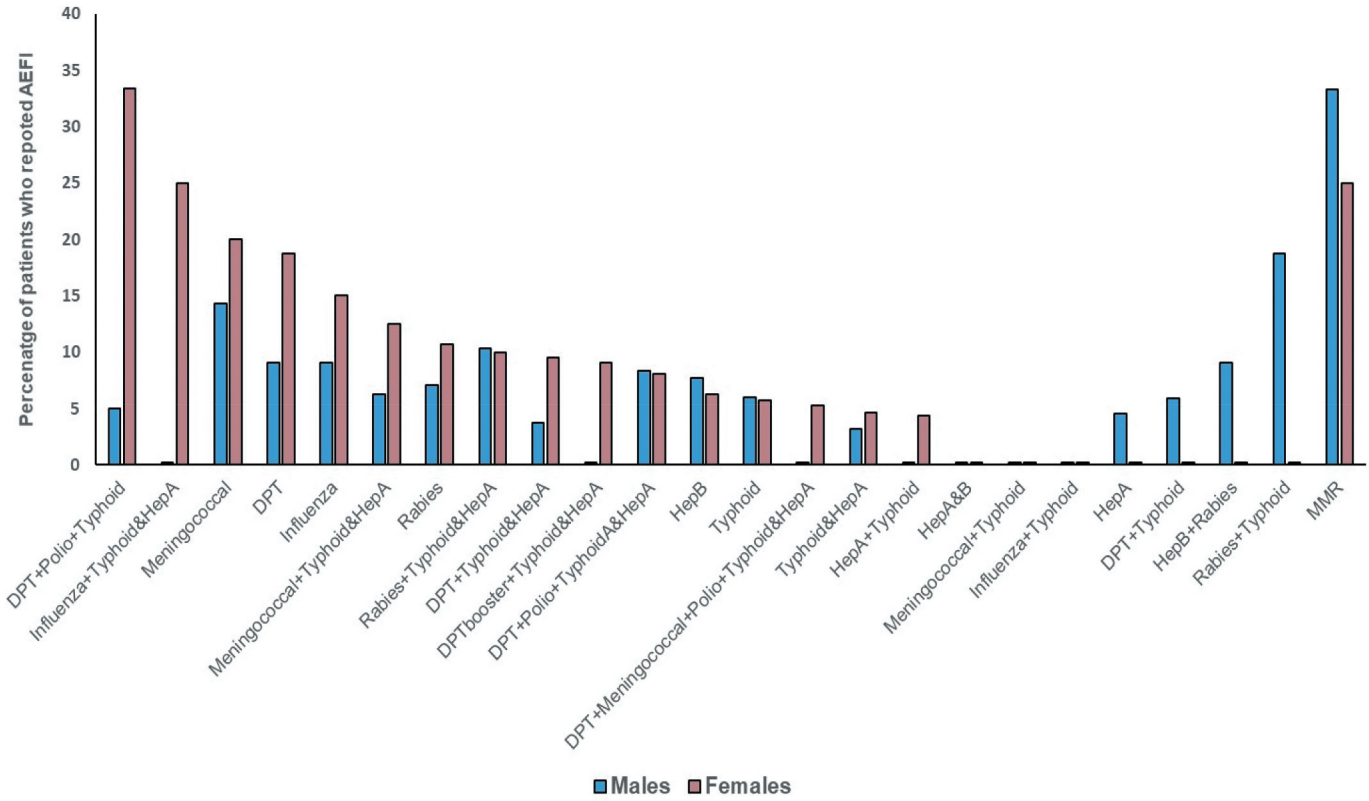

Figure 3. Percentage of patients who reported adverse events following Japanese encephalitis immunization by sex and other vaccines received on the same day. *DPT* diphtheria, pertussis, and tetanus; *MMR* measles, mumps, and rubella; *HepA* hepatitis A; *HepB* hepatitis B.

The main strengths of this study were the use of active vaccine safety surveillance data, and the large sample size. As opposed to passive surveillance systems which are prone to underreporting of mild and moderate AEFIs,[36] SmartVax actively surveys for AEFIs (irrespectively of the intensity), and has a vast network of sites throughout Australia and a high response rate (~70%).[21] SmartVax can provide early safety signals of vaccines to health-care providers, regulatory bodies (e.g. Therapeutic Goods Administration [TGA]), pharmaceutical companies, and patients. Therefore, it is reassuring that both JE vaccines had low rates of AEFIs, in particular Imojev, which is more widely used in Australia likely because of its one-dose schedule and long-term immunity.

In conclusion, both Imojev and JEspect had low rates of AEFIs and were well tolerated. Additional consideration should be taken with children aged <5 years, young children should be carefully observed for AEFIs after vaccination.

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Disclosure statement

AL is the Director and creator of SmartVax. The other authors do not have any conflicts of interest to declare.

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Authors' contribution

Conception and design of the study: CLL, DJM, LFK
Collection and assembly of the dataset: AL
Analysis of the dataset: NI, LFK
Interpretation of results: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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