



Immunol Allergy Clin N Am
23 (2003) 665–697

IMMUNOLOGY
AND ALLERGY
CLINICS OF
NORTH AMERICA

Allergic reactions to Japanese encephalitis vaccine

Anne-Marie Plesner, MD, PhD

*Department of Medical Officers of Health, Copenhagen County,
Islands Brygge 67 DK-2300 Copenhagen S, Denmark*

In Asia, an arbovirus, Japanese encephalitis (JE) virus, is the leading cause of viral encephalitis and accounts for more than 16,000 sporadic and epidemic cases and 5000 deaths reported annually. Although JE is a World Health Organization (WHO)-reportable disease, official notifications significantly underestimate the true incidence [1].

Most cases occur in China, India, Vietnam, Indonesia, and Thailand. The disease occurrence may vary, and during the first half of the 20th century, the disease mainly was seen in temperate areas of Asia (ie, Japan, Korea, China). After 1969, JE began to be a public health problem in Southeast Asia. Northern Australia has reported JE cases [1,2]. In countries where JE vaccine has been used widely, such as Japan and Korea, there are only sporadic JE cases [1,3]. Although most cases of JE are reported in China, a significant reduction in cases has been observed.

The disease is no longer seen in Singapore; the last case was reported in 1992, and a serosurvey demonstrated that no children younger than 15 years were seropositive. The eradication of transmission presumably is related to urbanization and mosquito control [4]. JE virus first was isolated in Japan in 1935 from the brain of a patient dying from encephalitis. Major epidemics have been reported in 1924, 1935, and 1948. The virus is transferred to humans by mosquitoes, with birds and mammals as reservoirs. JE infection of humans primarily is observed in rural areas. Rice paddies and pig farms may be situated near cities and imply a risk for the urban population.

In endemic areas, children younger than 15 years are the principal victims of JE, because they have not developed protective levels of antibodies. In one study, virtually 100% of nonimmune piglets that were exposed to JE seroconverted within 2 weeks, and parallel human seroprevalence studies indicate nearly universal exposure by adulthood in an unvaccinated population. In areas where children are protected by immunization, a secondary increase in the incidence of JE

E-mail address: apl@kbh.eli.dk

has been observed in the elderly, suggesting an increased JE risk with age because of waning immunity.

Disease occurrence in the Western population

Although the JE infection is primarily a problem for the Asian population, the disease also may occur in people from Western countries who work or travel in the region. People of all ages from nonendemic areas are not immune and are vulnerable to JE infection. Although the risk for JE is low for most travelers, individual risk is variable and depends on factors such as the location and duration of travel and the traveler's activities. Exposure in rural areas, especially for long periods, is the principal factor.

In 1969, at least 10,000 Americans were infected with JE in Vietnam, and 57 developed encephalitis [5]. After the deaths of two US citizens who had JE while staying in Beijing in the early 1980s, the JE vaccine was introduced for expatriates from the United States.

Asia is a popular destination for tourists, especially backpackers who often visit rural regions. No systematically collected data are available on cases in travelers from different countries. There were 24 case reports to the Centers for Disease Control and Prevention (CDC) from 1978 to 1992, including 11 US residents, of whom eight cases were military personnel or their dependents, and one case was a tourist [6].

Cases have occurred in the absence of obvious risk factors (eg, after a short vacation in Bali). A 10-year-old Australian girl who traveled on a 2-week vacation in Bali in 1988 and who only made a few excursions into rural areas developed JE [7]. A 60-year-old Swedish woman developed JE after a 10-day trip to Bali in 1994, where she stayed at a hotel by the coast and had a 1-day trip to the countryside without observing any mosquito bites [8]. A 51-year-old Danish man visiting Bali for 12 days in 1995 developed JE 1 week after his return from Bali and died within 2 weeks [9].

Clinical illness

Most infections are asymptomatic, and only 1 in 250 infections results in symptomatic illness. The principal clinical sign is encephalitis, but milder neurologic presentations, including aseptic meningitis and febrile illness with headache, may be manifestations of JE infection. The incubation period is 5 to 15 days. The attack usually starts with a high fever, a change in mental status, headache, and gastrointestinal symptoms. Speech disturbances and motor dysfunction, including paresis, may occur. Seizures are seen in as many as 75% of pediatric patients, whereas headache and meningism may be more common in adults. Extrapyrimal signs of involvement of the thalamic region with mask-like facies resembling parkinsonism can be seen [10]. Stupor, coma, and death may

follow. The mortality rate is as high as 25%, and neuropsychiatric sequelae are seen in up to 30% of survivors [11]. No specific treatment is available, but supportive treatment can reduce significantly the morbidity and mortality.

Vaccines

It has been estimated that in 25 years, approximately 500 million doses of JE vaccine (JEV) have been administered in China, Japan, Korea, and Taiwan [12]. Three types of JEV have been available worldwide, and more vaccines are being developed, including the following:

1. Inactivated mouse-brain–derived vaccine
2. Inactivated primary hamster-kidney (PHK)-cell–derived vaccine
3. Live attenuated JEV

Only the inactivated mouse-brain–derived vaccine is distributed commercially and is available internationally.

Inactivated mouse-brain–derived vaccine

The inactivated mouse-brain–derived vaccine was developed in the late 1930s in Japan and was tested in the United States during World War II [13]. The JEV was introduced in the childhood immunization program in Japan in 1954. In the 1960s, purification steps were introduced into the manufacturing process in Japan.

Manufacturing of inactivated vaccine is required to meet minimum standards published by the WHO [14]. Most manufacturers prepare the vaccine from the Nakayama strain that originally was isolated from the human case in 1935. In Japan, Nakayama vaccine is produced for export, whereas since 1989 the vaccine for the domestic market has been prepared from the Beijing strain that was isolated from infected human brain tissue in 1948 [11].

Since 1980, two inactivated purified products from Japan and Korea have been used in Western countries, and their use has increased with the increase of international air travel to endemic areas in Asia. The vaccine produced by the Research Institute of Osaka University (Biken) is the most widely used JEV [15], and a smaller amount from Korea (Green Cross) also is distributed [16,17]. In other parts of Asia (eg, Thailand, India), the same vaccine types are produced by other manufacturers [1,18,19].

The widely used product from Japan (Biken) is a mouse-brain–derived, formalin inactivated vaccine that is stabilized with gelatin, sodium glutamate, and preserved with thimerosal. The current vaccine contains less than 50 ng/mL of mouse serum protein, has undetectable levels of myelin basic protein (detection limit, 2 ng/mL), and is stabilized with 500 mg/mL of gelatin. All JEVs that are distributed in the Japanese market and are exported to the United States contain

gelatin of bovine or porcine origin. The vaccine initially was manufactured as a liquid preparation, but lyophilization and additional purification steps, such as ultracentrifugation, have been added to the process [13,20].

Since 1992, the vaccine has been licensed in the United States and has been recommended for travelers to Asia who will spend 1 month or longer in endemic areas during the transmission season. In most countries in Europe, the vaccine is only available through international pharmacies on an individual informed-consent basis.

In the United States, the vaccine was delivered from 1983 to 1987 on an individual basis, and 17,000 doses were distributed. After an outbreak in Okinawa, 10,000 doses were given to US military personnel and to more than 35,000 Navy personnel [21–23].

A placebo-controlled, randomized, blinded trial performed in Taiwan in 1965 included 240,000 children. Half of these subjects were vaccinated with two doses of a less refined mouse-brain–derived JEV product, and the other half received tetanus toxoid as placebo. Case detection was difficult because of the occurrence of other illnesses that resemble JE. The cases were seen by a number of health workers visiting health stations, hospitals, and private clinics twice a week. Suspected cases were persuaded to undergo serologic tests, and JE was confirmed serologically in 30 cases—24 placebo recipients and six vaccine recipients, indicating a protective efficacy of about 80% [24].

In 1985, an efficacy trial was conducted with the current purified JEV formulation. The randomized, double-blind trial involved more than 65,000 children in Thailand and compared two vaccines that were manufactured by Biken (monovalent Nakayama [$n = 21,628$] and bivalent Nakayama-Beijing-1 [$n = 22,080$]) with a placebo (tetanus toxoid; $n = 21,516$). Surveillance for encephalitis was performed at all facilities providing healthcare for this area, and suspected cases were transferred to a hospital and examined serologically and by spinal-fluid examination. The cumulative attack rate for JE in the placebo group was 51 cases per 100,000 persons as compared with 5 cases per 100,000 persons in both vaccine groups, indicating the efficacy of a two-dose regimen of both JE vaccines of 91% [25].

In Asia, the vaccine schedule differs, but a primary vaccination series for children often consists of two doses separated by 1 to 4 weeks, followed by booster doses at yearly intervals. For travelers from Western countries, a primary series usually consists of two or three doses, but booster doses may be needed for longer protection. Studies have shown that at least 3 years of protection is conferred after a three-dose series [26,27].

Side effects

In field trials, the inactivated mouse-brain–derived JEV has been found to be generally well tolerated with few and mild reactions. In the field study performed in Taiwan in 1965, 748 children were evaluated for side effects after two vaccine doses; fever was noted in less than 1%, and local reactions with redness or swelling were noted in 1% after the first dose and in 5% after the second dose. No case of allergic encephalitis was observed [24].

In 1983, 1137 British soldiers were immunized with three doses of Bikens JEV and were asked about side effects. Local side effects with discomfort at the injection site for a few hours were common and similar to the side effects that were experienced after tetanus vaccination. One subject complained of a rash after the first vaccination, but not after the second vaccination [28].

In a trial conducted in 1328 adults in 1983 in the United States, active follow-up on adverse reactions was performed after two doses of JEV in 59 subjects; 18% of subjects reported injection-site reactions, and 9% reported systemic symptoms, including headache. Of the 1328 participants with self-reported side effects, local reactions were reported in 12%, and systemic symptoms were reported in 2%. Two cases of anaphylaxis occurred after the first vaccine dose [29]. In a large, placebo-controlled field trial in Thailand from 1985, 21,000 children aged 1 to 14 years were vaccinated with monovalent JEV, and none developed anaphylaxis or vaccine-associated encephalitis. In a smaller sample of 490 children, local side effects were seen in less than 1%, and fever occurred in 2.9% [25].

In 1989, 7- to 9-year-old schoolchildren from Thailand were vaccinated twice with JEV from Biken (Nakayama strain or Beijing strain) or from a locally produced vaccine. Of 448 children receiving the Nakayama strain from Biken, 2% had a sore arm, 1.3% had fever, and 1.8% had headache. The data were comparable with those from the local vaccine and the Beijing-strain vaccine [19]. Another US follow-up trial from 1989 included 3573 soldiers who were vaccinated twice with Biken's vaccine and completed a questionnaire on side effects. No severe adverse reactions occurred. Local reactions, including arm soreness, were seen in 23%, and systemic side effects were seen in 10% to 14% [23].

In 1990, 538 US soldiers were vaccinated with three doses of Biken's monovalent vaccine. Subjects used a questionnaire to note the symptoms that occurred within 72 hours after each injection. Local side effects were seen in 21%, 12%, and 11% of subjects after the first, second, and third doses, respectively. Systemic symptoms were reported in 8%, 3.6%, and 3.2% of subjects after the first, second, third doses, respectively. One participant reported pruritus after the first dose, and two participants reported swelling around the eye. None sought medical attention [22].

The inactivated mouse-brain-derived vaccine has been used for more than 30 years, and studies have shown high efficacy and immunogenicity. Common side effects have been studied in Asian children and Western adults. Local side effects (erythema, swelling, tenderness) have been observed in up to 23% of vaccinees, whereas mild systemic side effects (fever, headache, malaise, dizziness) can be seen in up to 13% of vaccinees. The highest frequencies have been observed in the adults.

Inactivated primary hamster kidney-cell-derived vaccine

The safety of inactivated mouse-brain-derived vaccine has been the subject of renewed interest since the beginning of the 1990s after reports of allergic reactions. Cell-culture-derived vaccines have been used widely and exclusively in China [11]. The vaccine is a formalin-inactivated vaccine that is prepared in PHK cells

infected with the Beijing P-3 strain of JE virus. The vaccine is stabilized with 0.1% human serum albumin and is presented in a liquid formulation. The vaccine is not purified. Two doses should be administered and followed by a booster dose.

Rates of neutralizing antibodies, from 60% to 68%, have been found after vaccination in China with a two-dose regimen, and a booster dose may increase this response rate to close to 100% [11]. In extensive randomized field trials performed in China that included 480,000 children, vaccine efficacies ranged from 76% to 95% [11]. Approximately 70 million doses have been distributed annually in China, but the vaccine gradually is being replaced by the SA 14-14-2 live attenuated vaccine. These vaccines are not licensed in Western countries.

Side effects

Few side effects to the PHK-cell–derived vaccine have been reported. Local reactions, including swelling at the injection site, have been reported in 4% of vaccinees, and mild systemic symptoms with headache and dizziness have been reported by less than 1% of vaccine recipients. Fever was a complication in 12% of recipients, but this rate has been halved after a reduction in the amount of bovine serum in the vaccine. Allergic reactions, including urticaria, have been observed in 1 of 15,000 vaccinees [11]. More unspecified reactions with clusters of asthenia, syncope, and disorientation have been reported from some areas in People's Republic of China, and some of the features of the reactions suggest that the reactions might be of psychogenic origin.

Live attenuated Japanese encephalitis vaccine

The live attenuated JEV was developed in China and was licensed in 1988 [30]. The vaccine is derived from JE virus strain SA 14-14-2 and produced in PHK cell cultures that were infected with working seed virus. SA 14-14-2 vaccine is manufactured as a freeze-dried product and is stabilized with gelatin and sorbitol. A test for adventitious viruses and safety must be performed with each vaccine lot. One vaccine lot of 1 million doses requires kidneys from more than 3000 10- to 12-day-old hamsters (300 doses/hamster) [1].

More than 200 million doses of SA 14-14-2 vaccine have been delivered since 1988, and the vaccine is replacing the older inactivated PHK-cell–derived vaccine for routine immunization of children in PRC [13]. In China, SA 14-14-2 vaccine is given in a three-dose series to children aged 1, 2, and 6 years during large campaigns in the spring.

The vaccine has been licensed in Korea [31]. In other countries, local research is performed to develop a JEV from the SA 14-14-2 strain [1]. An obstacle for regulatory approvals outside of the PRC has been the PHK substrate, which is not accepted for vaccine production by the WHO. Significant issues need to be addressed to gain international approval of the product, including the safety profile [13]. In China, the SA 14-14-2 vaccine was safety-tested in 1026 children in 1985. A smaller group of seronegative children aged 6 to 7 years showed a seroconversion rate of between 83% and 100% 1 month after the first vaccine dose [32].

A trial that was performed in a nonendemic JE area in China in the mid-1990s included 12- to 15-year-old unvaccinated children. Two vaccine doses were given at intervals of 1 month (116 children) or 2.5 months (115 children) to evaluate this schedule, which would fit better with the Expanded Program on Immunization (EPI) than the usual two doses given 1 year apart. Seroconversion was observed in 94% to 100% of the children; however, according to the EPI, the vaccine preferably should be tested in 9- to 18-month-old children, the principal target groups for primary immunization [33]. In Korea, immunogenicity was measured in 1- to 3-year-old children in 1998. Among the children who received a single primary vaccination dose, 96% developed a neutralizing antibody response and high geometric titers [31].

Field studies in China between 1988 and 1993 involving 600,000 children compared JE incidence in vaccinated and unvaccinated children and indicated an overall efficacy of 98%. In one of these studies, good protection was observed through a second year after a booster dose [11]. A case-control study performed in 1993 in China included children younger than 15 years. Fifty-six JE cases were identified and were matched with 1299 controls. Previous vaccine exposures among cases and controls were registered. The effectiveness of one dose of the SA 14-14-2 vaccine was 80%, and that of two doses was 98% [34].

In an efficacy study performed in July 1999, 160,000 doses of JEV were given to children who were aged 1 to 15 years and were residents of Nepal. Several cases of JE were admitted to the hospital from early August. A matched case-control study was performed, and none of 20 children identified as JE cases had received the JEV. According to this study, the efficacy of a single dose of JEV was 99% when administered shortly before exposure to infection. Evidence of duration of protection was found to be at least 2 months, and long-term results remain to be presented [35].

Side effects

In a clinical trial in China that included 867 children, fever was monitored during a 21-day period after vaccination. Fever greater than 37.6°C was recorded in less than 0.5% of children. In the same study, symptoms were reported for 588,512 other vaccine recipients: Fever was reported in 0.046%, rash was reported in 0.01%, dizziness and nausea was reported in 0.0003% [11].

Common events after vaccination were studied in 1026 children aged 5 to 12 years who were living in China in a nonendemic JE area. Forty-seven children were examined for fever for 2 weeks after vaccination. Body temperature and local reactions were recorded in 47 children for 14 days, and none of these children developed fever or reactions. Physicians observed 944 children daily, and all of the subjects remained healthy. Of more than 1000 children, no adverse reactions were reported, and the attenuation seemed satisfactory [32].

In a postlicensure, randomized, cohort study, 13,266 vaccinated and 12,951 control children (median age, 1.9 years) were followed for 1 month. No cases of encephalitis, meningitis, or anaphylaxis occurred. The two groups had similar rates of hospitalization (risk ratio, 0.7; 95% confidence interval [CI], 0.43–1.15),

systemic illnesses with fever (risk ratio, 0.79; 95% CI, 0.56–1.11), and seizures (risk ratio, 0.91; 95% CI, 0.37–2.22). A subset of 266 vaccinated children was examined prospectively on days 1, 2, 3, and 7 after vaccination; local and systemic symptoms, including fever, occurred in 5% [30].

In Korea, in the first clinical evaluation of the vaccine outside China, side effects were monitored in 84 children aged 1 to 3 years during 1 month after vaccination. No immediate local or systemic reactions were observed. Seven percent of children had elevated temperatures, 1% had skin rash, and 1% had other systemic reactions. Using histories, the investigators found no significant adverse effects [31]. The rates of clinical encephalitis in field trials provide reassurance that the SA 14-14-2 virus in itself does not cause encephalitis at a detectable rate.

The live attenuated JEV has been reported to provide high efficacy rates with few side effects. Safety data are available after vaccination in China and from a small study in Korea reporting rates of mild side effects of a maximum of 7%. The cell substrate is not accepted by the WHO, and no reports of experience in Western countries are available.

New vaccines

Although the efficacies of the traditional vaccines are considered to be good, the vaccine constituents, including possible contaminating tissue products from the cultivation procedures, are suspected to be involved in the pathogenesis of adverse reactions. By consequence, newer vaccines are being developed to solve this problem using different principles [13].

A number of candidate vaccines are under development [14], and recombinant poxvirus vaccines have reached the stage of human trials [36]. Another future aspect involves the development of DNA vaccines. The high protection of the present vaccines, however, seems to depend on a broad spectrum of humoral and cellular immune mechanisms [27,37]. The choice of plasmids for the DNA vaccine may be one reason for the relatively low responses to some vaccines [37]. Animal studies of newer DNA vaccine candidates seem more promising [38], and adjuvants may be used for enhancing the efficacy [39].

A practical issue is based on the JE virus material that is harvested after amplification in *vero* cell cultures [40]. Animal studies have shown promising results for the immunogenicity of a vaccine that is produced on this basis [41]. Inactivated JEV made with the SA14-14-2 strain has a potential for use in human vaccinations, but clinical trials have not been published yet.

Allergic mucocutaneous reactions to Japanese encephalitis vaccine

Most of the information on allergic adverse reactions concerns the inactivated mouse-brain–derived JEV, which is the most widely used vaccine in Western countries. In 1947, Sabin reported 19 cases of allergy, including urticaria and angioedema, after JE vaccination of 53,139 persons and suggested that these reactions might be caused by sensitization to the solution of formaldehyde [42]. In 1990,

Poland reported that after vaccination of 1328 subjects, two persons had anaphylactic reactions after the first vaccine dose. Both cases were examined by a specialist in allergy, who determined one case to be exercise induced and not causally related, whereas the other person had generalized urticaria that was considered to be induced by the vaccination [29].

Since 1990, reports from several countries have described an apparently new pattern of allergic side effects to the inactivated mouse-brain–derived JEV. The first reports came from Australia, Canada, and Denmark. Hypersensitivity reactions have been encountered in other countries, including the United States, the United Kingdom, and Japan. Apart from an indication of an increased frequency of hypersensitivity reactions, the cases pointed at a delayed onset of urticaria or angioedema, which seemed to be the hallmark of at least some of these reactions.

During the 1990s, descriptive reports, including questionnaire studies and case-control studies, were performed to determine possible reactions to JEV. The aim was to describe the reactions meticulously and to clarify a cause of these reactions or a possible predisposition in the patients who develop these reactions. The publications, including the hypersensitivity reactions, are reviewed and are divided into descriptive reports, questionnaire studies, and case-control studies.

Descriptive reports

Denmark 1991

A mandatory, postmarketing adverse-event–reporting system in Denmark detected 15 reactions of allergic mucocutaneous character to Biken’s inactivated JEV during a 1-year-period from September 1989 to October 1990 (Table 1) [43]. In the preceding years, no side effects were registered, although a similar JEV from Biken had been used. In some patients, other vaccines had been given at the same time as the JEV. Allergic reactions to typhoid or cholera vaccine used in larger amounts and administered without JEV had not been reported.

Patients

Of 15 patients, 13 had urticaria all over the body, one had erythema multiforme, and one had a rash. Antihistamine was given to 12 patients with urticaria, and five patients also received prednisone.

Delay

Seven of 13 urticaria reactions began within 24 hours of vaccination, the remaining 6 reactions occurred within 72 hours. The patient with erythema multiforme developed symptoms 3 days after vaccination.

Frequency

All patients had received the same batch of vaccine (Biken, batch no EJN 016), and 35,000 doses had been distributed and given in a two-dose schedule. A

Table 1
Passive reporting of allergic, mucocutaneous reactions to inactivated Japanese encephalitis vaccine

Year, Country	Period of observation	No. of cases	Dose number	Type of reaction	Interval range before onset	Vaccine manufacturer	Batch no.	No. of doses or vaccinees (calculated frequency)
1991, Denmark [2]	1989–1990	15	1st (n = 1) 2nd (n = 14)	Urticaria (n = 13) Erythema multiforme (n = 1) Rash (n = 1)	72 h	Biken	EJN 016	35,000 (4/10,000 doses)
	1990–1991	2		Urticaria		Biken	EJN 032	15,000 (1.3/10,000 doses)
1991, Australia [52]	1990	3	2nd (n = 3)	Urticaria	72 h	Biken	EJN 017 EJN 042	1600 (20/10,000 doses)
	1990–1991	7	—	Urticaria/angioedema	—	Biken	—	4000 vaccinees
1995, United Kingdom [8]	1990	2	1st (n = 1) Booster (n = 1)	Urticaria	4 and 13 d	Biken	EJN 084 EJN 094A	—
	Before 1995	8	—	—	—	Biken (predominantly)	—	35,120 vaccinees (2.3/10,000 vaccinees)
1997, Denmark [48]	1989–1995	73	1st (30%) 2nd (62%) Booster (6%) Unknown (2%)	Urticaria/angioedema (n = 68), rash (n = 5)	Median, 2 d (range, 0–12 d; see Figs. 1 and 2)	Biken	See Table 3	(1–17/10,000 vaccinees)
1997, Japan [60]	—	3	—	Urticaria	20 min–2 h	Biken	—	—
2001, Japan [59]	1994–1996	9	—	Cutaneous/respiratory ^a	—	—	—	—
2000, Japan [67]	1996–1998	71	—	Systemic eruptions, urticaria/edema ^b	—	7 manufacturers of inactivated JEV	—	9.4 million doses (0.08/10,000 doses)
2000, United States [67]	1993–1998	51	—	Urticaria/edema	—	Biken	—	813,822 doses (0.6/10,000 doses)

^a Additional 10 cases developed anaphylaxis.

^b Additional 32 cases developed anaphylaxis.

frequency of 4 allergic reactions per 10,000 doses was calculated. From the batch EJV 032, which was delivered from November 1990 until January 1991 in 15,000 doses, two cases of urticaria were reported.

Discussion of the results

A cause for these reactions was not found, and several possibilities were considered. There had been an increase in thimerosal content from 0.0005% to 0.0067%, which was believed to be a possible influence on the reaction rate. At the same time, however, other vaccines were used that contained the same amount of thimerosal.

Australia 1991

From Australia, Ruff et al [44] reported an apparent increase in serious adverse events since June 1990 after the use of Biken's inactivated JEV. The cases were reported in a passive surveillance system, the Australian Adverse Drug Reactions Registry.

Patients

Three cases were reported:

1. Three days after receiving the second dose of JEV (batch EJV 017), an 18-year-old woman developed urticaria, dyspnea, and hypotension. She was hospitalized and treated for several days with adrenaline, corticosteroids, and intravenous fluids.
2. A 25-year-old woman developed a widespread rash and breathlessness 2 days after receiving her second JEV dose (batch EJV 017). She then developed edema of her lips and face. She improved after treatment with antihistamine and corticosteroid.
3. A 43-year-old woman developed urticaria 2 days after receiving her second dose of JEV (batch EJV 042). The following day she had nausea, vomiting, and uncontrollable chills and collapsed after an episode of vomiting. She had marked facial swelling. She improved over several days in the hospital, where she received antihistamine and corticosteroid therapy.

None of these patients had been given other vaccines, and symptoms occurred 24 to 72 hours after receiving the second dose of JEV.

Frequency

The report was based on 1606 doses that were dispensed in 601 persons in a 1.5-year period. In that area, from 1987 up to 1991, 4000 persons had been vaccinated, but all reactions that were reported occurred after June 1990. The three cases were part of a series of seven persons with allergic reactions (edema or rash, including urticaria), with an estimated frequency 7 cases per 601 vaccinees.

United Kingdom 1995

In the passive adverse-event–reporting system in the United Kingdom, two travelers were reported to have developed severe allergic mucocutaneous reactions [45].

Patients

A 26-year-old man received a booster dose of JEV (batch EJN 084); 13 days later, he developed a generalized, giant urticarial rash, sparing the face. He also had arthralgia. He had received primary vaccination in 1990 (batch EJN 084). He was hospitalized, and symptoms resolved over 4 days of treatment with antihistamine and 80-mg prednisolone daily. A 20-year-old woman received a single dose (batch EJN 094A); 4 days later, she developed a widespread urticaria and angioedema of the limbs.

Frequency

In the United Kingdom, 35,120 travelers have been immunized. Eight severe reactions have occurred, corresponding to two reactions per 10,000 vaccinees.

Denmark 1997

In a review of the adverse events reported in 1983 to 1995 in the nationwide mandatory notification system, 73 allergic mucocutaneous reactions were found. The first cases were reported in 1989 [46].

Table 2

Delivered doses of Japanese encephalitis vaccine and notified urticaria or angioedema reactions in Denmark, 1983 to 1995

Year	Delivered doses of JEV	Urticaria/angioedema		Rash
		No. of cases	No. per 10,000 vaccinees	No. of cases
1983	5535	—	—	—
1984	10,365	—	—	—
1985	16,875	—	—	—
1986	23,895	—	—	—
1987	29,585	—	—	—
1988	40,570	—	—	—
1989	41,505	2	1	—
1990	40,480	12	6	—
1991	25,675	18	14	2
1992	21,215	18	17	2
1993	23,945	8	7	—
1994	28,725	6	4	—
1995	41,925	4	3	1
Total	350295	68	6	5



Fig. 1. (A,B) 21-year old man with severe angioedema one day after the first JE vaccination.

Patients

Two thirds of the persons with reactions were females, and 40% were 20 to 29 years old. Of the 68 cases of urticaria, angioedema, or both, 21 had only urticaria, eight had angioedema, and 35 had urticaria and angioedema. Rash occurred in five patients who were noted by the system (Table 2). Angioedema primarily was located on the face, especially the eyelid and lips (Figs. 1, 2), but also on the hands and feet. One patient had difficulty eating and talking. Four patients complained of difficulty when breathing or swallowing. One patient developed erythema multiforme after the first dose and was hospitalized for 8 days.

Treatment

Medical treatment was given to 67% of subjects, and antihistamine or prednisone was given separately or in combination (19%). Ten patients were hospitalized, with a median duration of symptoms lasting 7 days.



Fig. 2. (A,B) 20-year old woman with urticaria and angioedema one day after the first JE vaccination.

Dose and delay

Two thirds of the reactions were observed after the second dose. The mean duration from vaccination until occurrence of reactions was 2 days (range, 0–12 days). Eight percent of subjects reacted 1 to 2 weeks after vaccination.

Frequency

A total of 350,000 doses of the vaccine had been distributed. The first notified case of urticaria, angioedema, or both was observed in 1989. From 1989 to 1995, 73 subjects had allergic reactions, of which 68 were classified as urticaria or angioedema. The highest estimated frequency of allergic reactions (17 cases per 10,000 vaccinees) was seen in 1992 and declined in 1995 to 3 cases per 10,000 vaccinees. The frequency of urticaria or angioedema was 6 cases per 10,000 vaccinees (Table 3).

Considerations

Different batch numbers were involved with varying rates of reactions. The highest frequencies and the most serious reactions, including hospitalization, occurred with the batches EJN 012, 016, 032, 033, and 048, which were delivered in 1990 to 1991 (see Table 3). Meetings with the Japanese producer, Biken, did not clarify any changes in the manufacturing process, although a new production line had been started. Whatever might have been the cause of the increased frequency in these years, the later part of the period included in the study seemed to indicate a decreasing incidence of allergic reactions to JEV. The incidences in Denmark and several other countries were high in the early 1990s, and this finding may have

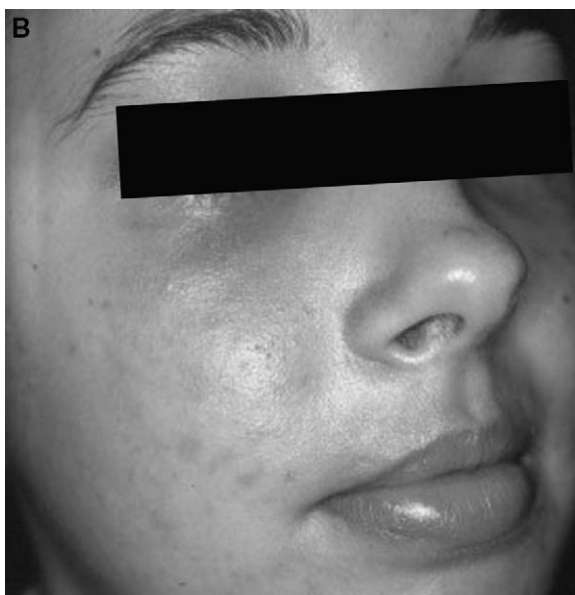


Fig. 2 (continued).

Table 3

Notified reports of urticaria or angioedema in 68 patients according to batch number in Denmark, 1989 to 1995

Batch no.	Year of delivery	No. of vaccinees	Reactions ^a	
			No. of reactions	No. per 10,000 vaccinees
012	1990	6500	10	15
016	1989	17,500	13	7
032	1990	7500	4	5
033	1990	10,000	14	14
048	1991	10,000	11	11
071	1992	12,400	3	2
074	1992	4000	1	3
084	1994	7500	3	4
094a	1995	4325	2	5
Unknown	—	—	7	—

^a χ^2 -test for difference in proportion of reactions according to batches distributed before and after 1992 ($P < 0.0001$).

been a transient phenomenon; however, a later report from another source indicated that such reactions still occur, with a total frequency of 1 case per 100,000 vaccinations [20].

Japan 1997

Cases

Three children had systemic immediate reactions to JEV [47]:

1. One patient developed mild anaphylaxis (systemic urticaria and pruritus) 30 minutes after receiving JEV.
2. One patient developed systemic urticaria 1 hour after JE vaccination. He received treatment, and symptoms disappeared after 2 hours.
3. Another patient had mild anaphylaxis, systemic urticaria, pruritus, and wheezing 20 minutes after receiving JEV. He recovered fully after treatment.

The patients and 50 controls were examined for antigelatin IgE. The patients had antigelatin IgE, whereas the controls did not.

Japan 1998 to 2001

In extended reports, the Japanese observations were specified further [48]. Two different patterns of systemic immediate-type reactions were seen after JEV containing gelatin as the stabilizer was administered. The following reactions occurred within 1 hour of the vaccination:

Systemic cutaneous signs or respiratory symptoms

Anaphylactic shock with cardiovascular symptoms without cutaneous symptoms

In support of the importance of antigelatin IgE, it was observed that these antibodies were found only in the first group (1998: six patients presumably immunized against gelatin by previous MMR vaccination) [49]. The hypothesis was substantiated further in the 2001 study of 10 children with an immediate-type reaction within 2 hours of receiving JEV. All of these children had antigelatin IgE [50].

Frequency

From 1994 to 1996, reports included 19 children with anaphylaxis caused by JE vaccination (mean age, 5 years and 5 months). The frequency of cutaneous and respiratory symptoms seen in these studies (nine children; mean age, 4 years and 1 month) corresponded to the frequency of 2 cases per 1 million doses. This frequency was lower than those for similar reactions after measles, mumps, rubella, and varicella vaccine, for which 8 to 10 cases per 1 million doses occurred [48].

Considerations

All JEVs that are produced in Japan contain 0.05- to 0.1-mg gelatin (liquid type for general use in Japan) or 0.5-mg gelatin (freeze-dry type for export) per dose. In comparison, some of the other vaccines used in children's vaccination program (eg, measles, mumps, and varicella vaccine) contain up to 15-mg gelatin per dose. Presumably, larger amounts of gelatin result in more severe systemic reactions. To prevent systemic allergic reactions to gelatin on vaccination, alternative stabilizers that have no antigenicity to humans must be explored.

Japan and United States 2000

Postmarketing, passive surveillance data from Japan and the United States have shown that the rate of total adverse events per 100,000 doses is 2.8 in Japan and 15.0 in the United States. Rates for systemic hypersensitivity reactions were 0.8 and 6.3 per 100,000 doses, respectively [20].

Japan

From 1996 to 1998, 9.4 million doses were given, delivered from seven different manufacturers. Prefixed criteria included time limits: Neurologic reactions should occur within 7 days, anaphylaxis should occur within 1 day, and urticaria should occur within 2 days. Thirty-two cases of anaphylaxis and 71 cases of systemic eruption occurred. Urticaria and edema was seen with an estimated frequency of 0.8 cases per 100,000 vaccinations.

United States

Annually, 180,000 to 200,000 doses are given mostly to adult travelers, adding to the more than 813,000 doses distributed between 1993 and 1998. The Biken JEV has been in investigational use since 1983 and used by licensure since 1992. Between 1993 and 1998, 122 reports were submitted to the Vaccine Adverse Events Reporting System (VAERS). Fifty-one cases (42%) were hypersensitivity reac-

tions, urticaria, or edema. Eighteen cases (37%) had onset on the day of vaccination, and 25 (51%) experienced onset within 1 to 3 days after vaccination. For 42 reports, detailed information was available, and of these patients, 23 (55%) developed systemic urticaria or angioedema on receiving the first dose. Twenty-two (52%) patients required an emergency room visit, and six patients required hospitalization for 1 to 2 days. Three vaccinees had bradycardia, cyanosis, or hypotension without urticaria or edema on the day of vaccination. Two of these reactions occurred after the first dose of JEV.

Considerations

Passively collected VAERS surveillance data indicate that characteristic hypersensitivity reactions with delayed onset continue to occur among JEV recipients.

Questionnaire studies

Canada 1991

In a prospective study, information was obtained by questionnaire from 96 vaccinees (Table 4). One patient developed urticaria [51].

India 1993

A trial with the Biken vaccine involved 113 schoolchildren [52]. Minor complaints were registered in 55% of subjects, but only one case had a definite allergic reaction: This girl had itching all over the body on the second day after the first dose and for 4 days. On the third day, she had puffiness of the face, which subsided after 2 days. She was treated with antihistamine, and no further vaccination was given.

United Kingdom 1994

In a short letter, the reactions were described to two unlicensed formalin inactivated JEVs (from Biken and Green Cross), which have been used in the United Kingdom. Green Cross is a liquid formulation obtained from Korea.

Cases

A questionnaire was sent to 501 recipients of each vaccine. Answers were obtained from 314 recipients of the Biken JEV and 246 recipients of the Green Cross JEV [16].

Reactions

Many respondents reported minor allergic reactions; however, with a case definition of reactions developing within 10 days of the JE vaccination, the rate of systemic allergic reaction was calculated to be 0.6% (0.1%–2.3%) after receiving the Biken vaccine and 0% (0%–1.5%) after receiving the Green Cross

Table 4

Questionnaire studies of allergic, mucocutaneous reactions to inactivated Japanese encephalitis vaccine

Year, Country	Period of observation	Type of study	No. of respondents	No. of cases	Type of reaction	Interval before onset	Vaccine manufacturer	Estimated rate per 10,000 vaccinees
1991, Canada [51]	1989–1990	Prospective, cohort	96	1	Urticaria	2 d after 3rd dose	Biken, EJA 032	104
1993, India [37]	—		113	1	Universal itching, puffy eyes	2–3 d	Biken	—
1994, United Kingdom [40]	—	Retrospective, postal survey	314 (of 501)	2	Puffy eyes (n = 1), arthralgia (n = 1)	2 d and 24 h	Biken	60 (95% CI, 10–230)
			246 (of 501)	—	—	—	Green Cross	0 (95% CI, 0–150)
1996, Germany [41]	—	Prospective, cohort	509 (of 860)	8	Generalized rash	—	Biken	—
1999, United States [14]	1990	Prospective, cohort	538	2	Eye swelling	Within 72 h	Biken, EJA 029–031	—

vaccine. In two recipients of the Biken vaccine, systemic reactions were seen (ie, puffy eyes, swollen joints). Neither patient was admitted to hospital or needed treatment. This report also mentioned that five other allergic reactions were seen after 68,000 vaccine doses were administered in 1988 to 1992. Three reactions were cases of urticaria or angioneurotic edema that were associated with the Biken vaccine. A case of rheumatism was reported after receiving the Biken vaccine, and a case of delayed hypersensitivity with arthralgia, joint swelling, and rash was reported after receiving the Green Cross vaccine.

Germany 1996

In Germany, 860 travelers vaccinated twice with inactivated JEV (Biken) were recruited over a 16-month period to participate in a prospective questionnaire study [53]. The vaccinees only received JEV and did not receive any other vaccine 3 days before or after JE vaccination. A total of 509 questionnaires could be evaluated, and eight persons reported a generalized rash. The rash was not specified further. No subject was admitted to hospital.

United States 1999

The safety of the Biken vaccine was studied in 538 healthy soldiers in Hawaii in 1990 before the soldiers traveled to countries where JE infections occur [22]. Three doses of JEV were given on days 0, 7, and either 14 or 30 (total number of injections, 1605).

Questionnaire study

Symptoms occurring within 72 hours were detected by questionnaire, which asked subjects to report local and systemic reactions (fever, headache, rash) and severity (eg, ability to work). Symptoms occurring 72 hours after vaccination were not included. Two persons reported periorbital swelling: One person experienced this symptom after a single dose and received no more vaccines, and the other person completed the vaccination regimen without further symptoms. No subjects sought medical attention.

Case-control studies

Australia 1995

A case-control study was performed in Australia (Table 5) [54]. The subjects had developed an allergic reaction (rash or edema) within 1 week after receiving a dose of the Biken JEV; the reactions had been reported to the Adverse Reactions Advisory Committee. Hypersensitivity was defined as rash, angioedema, or a generalized reaction. Participants completed a questionnaire.

Table 5
Case-control studies of allergic, mucocutaneous reactions to inactivated Japanese encephalitis vaccine (Biken)

Year, Country	Period of observation	No. of cases	No. of controls	Dose number	Risk factors	Comment
1995, Australia [52]	1992–1993	5	15	2 nd (n = 4); booster (n = 1)	Alcohol consumption Other vaccinations No contact with dogs	Small number of cases
1997, United States [5]	1991	25	64	—	Previous urticaria (OR, 11; 95% CI, 2.4–62.1) Asthma and/or rhinitis (OR, 6.5; 95% CI, 2.1–20.8) Any allergy (OR, 5.7; 95% CI, 1.8–18.1)	Batches: EJM 049 and EJM 059
2000, Denmark [45]	1989–1993	49	148	1st dose (31%); 2nd dose (65%); 3rd dose (4%)	Previous urticaria (OR, 5.02; 95% CI, 1.18–22.4) Allergy to nickel (OR, 4.53; 95% CI, 1.43–14.58) Any previous allergy (OR, 2.1; 95% CI, 1.1–4.2) Younger age (OR, 0.45; 95% CI, 0.23–0.89)	See Table 3

Cases

Five cases (three males) and 15 matched controls participated in the study. Four patients developed the reaction after the second dose, whereas the fifth patient had the reaction after a booster dose. The patients were seen in hospital settings, and two patients were admitted, one of whom was treated in an intensive care unit because of swelling of the throat and larynx and respiratory distress.

Cases and controls had similar histories of allergy and had received a variety of vaccines. More-than-usual consumption of alcohol soon after receiving the JEV was associated with an increased risk for allergic reaction. A history of contacts with dogs was associated with a reduced risk for allergic reactions to the JEV. Cases were more likely than controls to have received other vaccines 1 to 9 days before JE vaccination.

Considerations

Because of the small number of cases, further studies should look into the possible association between allergic reactions to the JEV and alcohol consumption.

United States 1997

In 1991 to 1992, 20,000 marines stationed in Okinawa were vaccinated with Nakayama-National Institute of Health (NIH) strain from Biken and were given subcutaneous doses on days 0, 7, and 30 [21]. The marines were informed of symptoms of hypersensitivity reactions to the vaccine and were instructed to report such reactions. The reactions were described as (1) urticaria or angioedema, or (2) wheezing and pruritus. Thirty-eight persons reacted, and the reaction rate was 26.7 reactions per 10,000 vaccinees. If only urticaria and angioedema were included the frequency dropped to 18 reactions per 10,000 vaccinees.

Patients

Sixteen reactions per 10,000 vaccinees were observed after the first dose, 10 per 10,000 were observed after the second dose, and 2 per 10,000 were observed after the third dose. A striking feature was the prolonged latency and the difference in latency for dose 1 compared with that for dose 2. A clustering was seen after dose 1 (74% of the reactions occurred within the first 48 hours). Reactions to dose 2 occurred later, with a median interval of 96 hours.

Of the subjects with reactions, 68% had urticaria or angioedema, 29% had pruritus alone, and one subject had wheezing alone. Eleven subjects had facial angioedema, and four had wheezing. Six subjects, four of whom had urticaria or angioedema, experienced paresthesias (tingling) of the extremities, which resolved after a few days. Three subjects complained of localized joint pain, and two were mildly febrile.

In a case-control study, 25 reactors were compared with 64 controls according to self-reported history of previous allergic reactions. The study results showed that four variables were associated with an increased likelihood of reacting to the JEV:

urticaria (odds ratio [OR], 11.4; 95% CI, 2.4–62.1), asthma or rhinitis (OR, 6.5; 95% CI, 2.1–20.8), and any allergy (OR, 5.7; 95% CI, 1.8–18.1).

Denmark 2000

A case-control study was performed using Danish reports of allergic reactions to JEV to evaluate possible risk factors [55]. Questionnaires were sent to 62 cases from the Danish mandatory passive surveillance system from 1989 until 1993. Forty-nine cases (response rate, 79%) answered the questionnaire. A total of 240 travelers were recruited as controls from the vaccination center at Statens Seruminstitut. Overall, 154 travelers answered the questionnaire (response rate, 64%). Because six controls answered that they had had some kind of rash, they were excluded, and 148 controls were eligible for the analysis. The median age was 23 years (range, 1–58) for the cases and 31 years (range, 2–79) for the controls.

Results

The multivariate analysis showed that the main risk factors among adults were younger age, female gender, and previous allergic reaction of any kind (Table 6). Cases more often had reacted to nickel and had more severe edema after mosquito or other insect bites. Administration of other vaccines at the same time as use of the JEV was not a risk factor.

Discussion of studies

A few cases of allergic mucocutaneous reactions have been noted before 1990. In the subsequent decade, a marked increase in observations of such reactions has been reported from many countries, especially among Western adult travelers. No explanation for these reactions has been found. The gelatin component of the vaccine has been proposed as cause of the immediate-type reactions. Other factors associated with the production process cannot be excluded, as indicated by a significant decline after the mid-1990s.

Neurologic reactions to Japanese encephalitis vaccine

Neurologic complications after immunizations constitute a pathologic spectrum and may involve any part of the central and peripheral nervous systems. The reactions are of different pathogenesis, among which immunoallergic mechanisms are probably the most important. Cases of neurologic complications occurring after vaccination have been reported with different vaccines. Studies performed to try to clarify a causal relationship of such observations mostly have been negative.

The JEV contains material from infected mouse brain. Accordingly, postvaccination acute disseminated encephalomyelitis (ADEM) might occur because of an

Table 6

Comparisons of characteristics and exposures registered by cases (n = 49) and controls (n = 148) in a case-control study in Denmark

	Cases % (n = 49)	Controls % (n = 148)	OR	95% CI
Male sex	35	51	0.50	(0.24–1.03)
Age (cutoff, 30 y)	37	56	0.45	(0.22–0.93)
Reason for traveling				
Tourist	82	80	1.08	(0.44–2.70)
Business	4	8	0.48	(0.07–2.40)
Other	14	12	1.28	(0.45–3.58)
Destination				
Urban	31	32	0.95	(0.44–2.01)
Rural	25	33	0.66	(0.29–1.44)
Both rural and urban	43	35	1.43	(0.70–2.90)
Duration of stay in JE endemic-area				
≤ 3 wk	36	38	0.95	(0.46–1.96)
4 wk	12	13	0.73	(0.24–2.11)
5–8 wk	24	20	1.28	(0.55–2.91)
> 8 wk	24	29	0.79	(0.35–1.76)
Other medicine	18	8	2.80	(0.98–7.96)
Hormone use (women)	10	2	4.30	(0.95–19.00)
Chronic disease	14	10	1.48	(0.51–4.20)
Disease history				
Asthma	2	2	—	—
Hay fever	12	14	0.89	(0.30–2.56)
urticaria	12	3	5.02	(1.18–22.40)
Eczema	8	5	1.56	(0.37–6.07)
Dry skin	20	8	2.91	(1.07–7.90)
Previously tested for allergy	27	18	1.62	(0.71–3.68)
Previous reactions to:				
Medicine	20	11	2.12	(0.81–5.41)
Food	10	9	1.18	(0.34–3.83)
Insects	22	14	1.85	(0.75–4.51)
Nickel	18	5	4.53	(1.43–14.58)
Other	33	16	2.64	(1.17–5.91)
Familiar disposition:	16	12	1.41	(0.52–3.76)
General allergic indicator	63	43	2.26	(1.11–4.65)

Data from Plesner A, Ronne T, Wachmann H. Case-control study of allergic reactions to Japanese encephalitis vaccine. *Vaccine* 2000;18(17):1830–6.

immune-mediated process. Postvaccination ADEM may be seen within 1 month after vaccination. Ohtaki et al [56] first reported two children with ADEM after use of the Beijing strain of the JEV and later noted additional cases [57].

United States 1947

Of 5403 persons vaccinated with two doses of JEV in Okinawa in 1945 [42], three developed significant neurologic reactions that were evaluated as neuritis

and possibly related to the vaccination. No cases were suggestive of demyelinating encephalopathy.

Japan 1972

In Japan, a committee of 12 experts who are interested in the neurologic complications related to JE vaccination has been finding and confirming cases since 1965. It was considered that neurologic complications appearing within 1 month after vaccination might be related to an allergic reaction caused by the vaccine. From 1957 to 1966, 26 possible cases were reported, including two cases of the demyelination type [58].

Japan 1997

After vaccination with the highly purified JEV derived from the Beijing strain, a 14-year-old boy developed acute disseminated myelitis (ADM) [59]. He was vaccinated in May 16, 1996, and 2 weeks later he suddenly developed right-shoulder pain and muscle weakness in the right arm and leg. Temperature and pain sensation were diminished below the C-3 level on the left side. Deep tendon reflexes were absent on the right upper limb. MRI of the cervical spine revealed two high-intensity areas in the white matter of the right half of the spinal cord at C1-2 and C3-4 with T₂-weighted images. Electroencephalographic (EEG) results were normal, and the myelin basic protein level was not elevated in the cerebrospinal fluid (CSF). The boy showed improvement after 3 days of treatment with intravenous methylprednisolone, followed by 50 mg of oral prednisolone daily.

Japan 2002

A 4-year-old girl was vaccinated with the highly purified JEV derived from the Beijing strain [60]. Two weeks later, she developed acute transverse myelitis. The girl had a high fever a few days after the vaccination that lasted 2 days but did not develop further signs of inflammation. Fourteen days after the vaccination, she developed pain around her lumbar region and knees that was associated with muscle weakness of the lower limbs. She was admitted to a hospital, and the weakness worsened to complete flaccid palsy. She developed nuchal rigidity and severe paraplegia. She was conscious without involvement of cranial nerves. Temperature and pain sensation was absent below thoracic segment (Th) 11. Myelin basic protein level was elevated in the CSF. Brain MRI results were normal, but MRI of the spinal cord showed diffuse swelling between the cervical and lumbar cords. High-dose gammaglobulin was given for 2 days without improvement. Steroid pulse therapy (30 mg/kg) was started with improvement in back pain and neck stiffness. Diplegia and urinary retention persisted, and after 3 months, severe atrophy of the spinal cord between Th10 and Th11 could be seen on MRI. Investigators noted that the reaction probably was elicited by vaccination because of a cellular autoimmune mechanism.

Japan 1992

Two case reports of ADEM [56] were observed after vaccination with the Beijing strain of the JEV, and a follow-up study published in 1995 included additional cases.

Japan 1995

In one study from Japan, investigators analyzed mailed questionnaires covering the period from 1968 to 1993 and a collection of previous reports of neurologic complications to JEV. Questionnaires were sent to 162 medical institutions to screen for patients who developed neurologic complications (ADEM) within 1 month after JE vaccination. ADEM was defined as an acute inflammatory disease with perivenous lymphocyte infiltration and scattered demyelinating foci in the white matter of the CSF confirmed by CT or MRI. Cases from the literature also were included [57].

Seven cases were identified as ADEM (age range of patients, 1–7 years). Apart from the ADEM cases, seven patients with other neurologic complications were registered, and two patients with encephalitis, one patient with encephalopathy, one patients with transient hemiplegia, and three patients with aseptic meningitis were reported.

Denmark 1998

In 1982 to 1996, 10 adult travelers were reported in the mandatory nationwide surveillance system with moderate-to-severe neurologic symptoms within a few weeks of JE vaccination [61,62]. Three patients had symptoms that varied from severe encephalitis-like illness to paresthesia, double vision, or Parkinsonian gait disturbance. MRI results showed severe atrophie of the corpus callosum with altered signal intensity indicating gliosis in one patient. Another patient had hyperintensive spots located periventricularly in the white matter, and a third patient had spots with increased signals in the pons, right substantia nigra, and occipital region. ADEM was a possible explanation for the MRI changes, although multiple sclerosis was an alternative diagnosis in one or two patients.

United States 1999

A 21-year-old white man received his first does of JEV together with his first dose of typhoid vaccine. He also took pseudoephedrine for weight loss. Seventy-five minutes after the vaccinations, while on a 3-mile run in mild temperature, he collapsed. The rectal temperature was 42.2°C. Resuscitative efforts were unsuccessful. The coroner's report did not find any evidence of heart failure or thrombosis, and it was considered likely that the combined pyrogenic effects of the two vaccines, pseudoephedrine, exercise, and mild obesity contributed to a failure in thermoregulation [63].

Korea 2000

In Korea, a reporting system for adverse effects was in place before the mid-1990s. An overview of the Green Cross JEV was produced by the CDC in 2000 [17]. Two sudden deaths were attributed to anaphylactic reactions to the vaccine, and four cases of severe neurologic illness, including encephalopathy and ADEM, were observed. Since 1994, seven cases have been filed with the Advisory Committee of the National Immunization Program. Five children died: Two of these children were aged 5 years and had anaphylactic shock, and one child aged 15 years developed headache, seizures, stupor, and encephalopathy after her ninth dose of JEV and her third dose of hantavirus vaccine (also made in mouse brain). A causal relationship could not be ruled out. A 9-year-old girl developed fever, headache, and seizures and died; her CT scan showed diffuse brain edema 17 days after receiving her third dose of JEV. A 10-year-old boy developed headache and seizures and died 31 days after receiving the JEV. An 8-year-old girl had high fever and seizures 12 days after JE vaccination. EEG results were compatible with encephalopathy, and CSF protein levels were elevated; this girl recovered. A 2-year-old girl developed urinary incontinence, high fever, and cranial nerve palsy and had MRI results that were compatible with ADEM. She remained retarded.

As a consequence of these reports and the undocumented need for annual boosters, the Korean authorities changed the schedule to a biannual interval for JEV booster administration. A governmental initiative was taken to reevaluate the safety of the vaccines produced in Korea.

Japan and United States 2000

Japan

From 1996 to 1998, 9.4 million doses inactivated JEV from seven manufactures were used in Japan. Prefixed criteria, including time limits for neurologic reactions, should occur within 7 days [20]. There were 17 neurologic cases (age range, 1–15 years; 51% female), including 16 patients with meningitis or meningoencephalitis and five patients with ADEM (0.2 cases per 100,000 vaccinees). Median onset was after 1 day. One 3-year-old boy developed fever, became comatose, and died from brain edema 4 days after vaccination.

United States

Of the 122 reports to VAERS since 1990 after more than 813,000 doses of JEV had been distributed to adult travelers between 1993 and 1998 (discussed earlier in article), there were only two reports of neurologic reactions: A 55-year-old man developed Guillain-Barré syndrome (GBS) and recovered completely, and a 22-month-old child developed febrile seizures after inadvertent administration of an overdose of 1.0 mL of JEV instead of 0.5 mL. Both patients had concurrent infections [20].

Discussion of neurologic reactions

A raised myelin basic protein concentration in the CSF is suggestive of ADEM. The pathogenesis of transverse myelitis is unknown. Acute transverse myelitis (ATM) is an uncommon disease in childhood. ATM can be divided into parainfectious, post-vaccination and presumably is developed by way of an autoimmune reaction against the myelin sheath of the central tract. ATM also may be caused by direct infection by the pathogen of the spinal cord and may be associated with collagen disease [64].

Case definitions for neurologic events should include an observation period of 1 month, and if neurologic complaints occur within this period after vaccination, the patient should be seen by a neurologist, and a MRI should be considered [61]. As reviewed, the evidence of an association between JEV and these neurologic events is only circumstantial and based mostly on case reports. Further epidemiologic studies are needed to clarify this matter.

Summary

The JEV widely is used in Asian countries each year and is an important vaccine for travelers to the East from other parts of the world. JE virus is a zoonotic disease with natural reservoirs and cannot be eliminated. Although a declining incidence of JE has been observed in Asia because of reduced transmission by agricultural approaches and vaccination, the most important control measure now, and in the future, is vaccination of humans against JE [12].

The inactivated vaccine, produced from infected mouse-brain–derived tissue, is the only commercially available vaccine. There are several concerns with the use of this vaccine. It is expensive, requires two or three doses to achieve protective efficacy, and, in practice, requires further booster doses to maintain immunity. The apparent increase in allergic reactions in the first part of the 1990s has set focus on the safety of the JEV.

A cheap, live attenuated SA 14-14-2 vaccine is used almost exclusively in China and parts of Korea, but there have been no trials of SA 14-14-2 vaccine outside JE endemic countries. The vaccine seems to be highly efficient, and few adverse events have been observed; however, PHK cells are used for the production of this vaccine, and these cells are not approved by the WHO. A satisfactory cell substrate is needed. A committee under the WHO has proposed that for the live JEV, there should be validity of the assays for retrovirus when applied to PHK cell substrate and validity of the mouse assays for neurovirulence. Further information should be reviewed on the long-term follow-up of recipients of the vaccine [65].

Several new types of vaccines have reached the phase of clinical trials; however, studies remain to be completed. Until a new vaccine is available, the priority of surveillance of adverse events and the continuous reporting of such events to the users of the vaccines must be of importance. This fact is highlighted by the possibility of the varying frequency of adverse events with different batches over the years.

The WHO offers information and recommendations for vaccines in the EPI and issues a series of updated papers on other vaccines that are of international public health importance (eg, JEV). The development of alternative efficient, safe, and appropriately priced JEVs is recommended, as is intensified surveillance of adverse events [66].

Prospective vaccine studies of safety may be limited because of sample size and because rare adverse events may not be detected. Several new initiatives have been taken to improve surveillance of adverse events to vaccines within the past 10 years. In Japan, there is an increasing awareness of the importance of efforts taken to improve vaccine safety, and surveillance of adverse events and possibilities of compensation for vaccine-related injuries are in place [67]. In Vietnam, a database to detect adverse events after vaccination has been established; the project involves active visits to data collectors at the vaccination sites [68].

Comparative studies of adverse events, such as one recent study from Japan and the United States, are important for the evaluation of the reporting systems [20]. The reporting rate for JEV adverse events from Japan was approximately one order of magnitude lower than that in the United States. Japan had strict predefined reporting criteria and time limits for observations. If time limits for the observation are too strict (eg, defining a possible neurologic reaction to occur within 1 week after vaccination), later reactions will not be included (eg, if ADEM is elicited by a vaccine, the symptoms cannot be expected to occur until weeks after the vaccination).

The passive surveillance systems have limitations with an underreporting of adverse events, depending on clinical seriousness, temporal proximity to vaccination, awareness of healthcare workers, and tradition of reporting particular events [69]. In developed countries, surveillance of adverse events is formalized, although not necessarily optimal. An increase in reporting would be expected when the reporting of adverse events is mandatory. Reports have been sent to VAERS, the Vaccine Safety Datalink Project [70,71], and the European Union Pharmacovigilance System. A Brighton collaboration has been implemented to enhance comparability of vaccine safety data [72,73]. Public health authorities in specific countries, such as the CDC in the United States and the National Advisory Committee in Canada, regularly have published information on the JE situation in Asia and the preventive measures to be taken, including information on the vaccines and adverse reactions [6,66,74,75].

The conventional recommendation is that travelers should be vaccinated if they will spend more than 1 month in a JE endemic area or in areas with epidemic transmission with even shorter periods [76]. Although the risk for JE for short-term travelers is considered small (1 case per 1 million travelers per year), sporadic cases, including deaths, have been reported among tourists traveling to endemic areas. Risk for travelers in rural districts in the season of risk is considerably higher (range, 1 case per 5000 travelers to 1 case per 20,000 travelers per week) [6]. Doctors who advise travelers should be updated on the latest JE occurrences in Asia. Updates on the JE situation can be found on bulletins at <http://www.promedmail.org> or are available from the WHO or CDC.

The allergic reactions primarily described after vaccination with the inactivated mouse-brain–derived JEV have been observed in several countries during the 1990s. Allergic reactions, including the mucocutaneous and neurologic reactions reported after JE vaccination, may vary in frequency, and these reactions should be evaluated meticulously yearly. This step enables recommendations, including information on possible side effects, to be given in an optimal way.

References

- [1] Tsai TF. New initiatives for the control of Japanese encephalitis by vaccination: minutes of a WHO/CVI meeting, Bangkok, Thailand, 13–15 October 1998. *Vaccine* 2000;18(Suppl 2):1–25.
- [2] Hanna J, Barnett D, Ewald D. Vaccination against Japanese encephalitis in the Torres Strait. *Commun Dis Intell* 1996;20(8):188–90.
- [3] Igarashi A. Control of Japanese encephalitis in Japan: immunization of humans and animals, and vector control. *Curr Top Microbiol Immunol* 2002;267:139–52.
- [4] Goh KT. Vaccines for Japanese encephalitis. *Lancet* 1996;348(9023):340–1.
- [5] Ketel WB, Ognibene AJ. Japanese B encephalitis in Vietnam. *Am J Med Sci* 1971;261(5):271–9.
- [6] Centers for Disease Control and Prevention. Inactivated Japanese encephalitis virus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1993;42(RR-1):1–15.
- [7] Macdonald WB, Tink AR, Ouvrier RA, Menser MA, de Silva LM, Naim H, et al. Japanese encephalitis after a two-week holiday in Bali. *Med J Aust* 1989;150(6):334–9.
- [8] Wittesjo B, Eitrem R, Niklasson B, Vene S, Mangiafico JA. Japanese encephalitis after a 10-day holiday in Bali. *Lancet* 1995;345(8953):856–7.
- [9] Buhl MR, Black FT, Andersen PL, Laursen A. Fatal Japanese encephalitis in a Danish tourist visiting Bali for 12 days. *Scand J Infect Dis* 1996;28(2):189.
- [10] Misra UK, Kalita J. Movement disorders in Japanese encephalitis. *J Neurol* 1997;244(5):299–303.
- [11] Tsai T, Chang G-JJ, Yu YX. Japanese encephalitis vaccines. In: Plotkin SA, Orenstein WA, editors. *Vaccines*. Philadelphia: WB Saunders; 1999. p. 672–710.
- [12] Vaughn DW, Hoke Jr CH. The epidemiology of Japanese encephalitis: prospects for prevention. *Epidemiol Rev* 1992;14:197–221.
- [13] Monath TP. Japanese encephalitis vaccines: current vaccines and future prospects. *Curr Top Microbiol Immunol* 2002;267:105–38.
- [14] Barrett AD. Current status of flavivirus vaccines. *Ann N Y Acad Sci* 2001;951:262–71.
- [15] Jelinek T, Nothdurft HD. Japanese encephalitis vaccine in travelers: is wider use prudent? *Drug Saf* 1997;16(3):153–6.
- [16] Nazareth B, Levin J, Johnson H, Begg N. Systemic allergic reactions to Japanese encephalitis vaccines. *Vaccine* 1994;12(7):666.
- [17] Sohn YM. Japanese encephalitis immunization in South Korea: past, present, and future. *Emerg Infect Dis* 2000;6(1):17–24.
- [18] Rao Bhau LN, Singh G, Goyal D, Saxena SN, Kobayashi M, Oya A, et al. Safety and efficacy of Japanese encephalitis vaccine produced in India. *Indian J Med Res* 1988;88:301–7.
- [19] Rojanasuphot S, Charoensuk O, Kitprayura D, Likityingvara C, Limpinthien S, Boonyindee S, et al. A field trial of Japanese encephalitis vaccine produced in Thailand. *Southeast Asian J Trop Med Public Health* 1989;20(4):653–4.
- [20] Takahashi H, Pool V, Tsai TF, Chen RT. Adverse events after Japanese encephalitis vaccination: review of post-marketing surveillance data from Japan and the United States: the VAERS Working Group. *Vaccine* 2000;18(26):2963–9.
- [21] Berg SW, Mitchell BS, Hanson RK, Olafson RP, Williams RP, Tueller JE, et al. Systemic

- reactions in US Marine Corps personnel who received Japanese encephalitis vaccine. *Clin Infect Dis* 1997;24(2):265–6.
- [22] Defraites RF, Gambel JM, Hoke Jr CH, Sanchez JL, Withers BG, Karabatsos N, et al. Japanese encephalitis vaccine (inactivated, BIKEN) in US soldiers: immunogenicity and safety of vaccine administered in two dosing regimens. *Am J Trop Med Hyg* 1999;61(2):288–93.
- [23] Sanchez JL, Hoke CH, McCown J, Defraites RF, Takafuji ET, Diniega BM, et al. Further experience with Japanese encephalitis vaccine. *Lancet* 1990;335(8695):972–3.
- [24] Hsu TC, Wei HY, Chen CL, Hsu ST, Huang CT, Kitaoka M, et al. A completed field trial for an evaluation of the effectiveness of mouse-brain Japanese encephalitis vaccine. In: Hammon W, Kitaoka M, Downs W, editors. *Immunization for Japanese encephalitis*. Amsterdam: Excerpta Medica; 1972. p. 258–65.
- [25] Hoke CH, Nisalak A, Sangawhipa N, Jatanasen S, Laorakapongse T, Innis BL, et al. Protection against Japanese encephalitis by inactivated vaccines. *N Engl J Med* 1988;319(10):608–14.
- [26] Gambel JM, DeFraites R, Hoke Jr C, Brown A, Sanchez J, Karabatsos N, et al. Japanese encephalitis vaccine: persistence of antibody up to 3 years after a three-dose primary series. *J Infect Dis* 1995;171(4):1074.
- [27] Kurane I. Immune responses to Japanese encephalitis virus. *Curr Top Microbiol Immunol* 2002; 267:91–103.
- [28] Henderson A. Immunisation against Japanese encephalitis in Nepal: experience of 1152 subjects. *J R Army Med Corps* 1984;130(3):188–91.
- [29] Poland JD, Cropp CB, Craven RB, Monath TP. Evaluation of the potency and safety of inactivated Japanese encephalitis vaccine in US inhabitants. *J Infect Dis* 1990;161(5): 878–82.
- [30] Liu ZL, Hennessy S, Strom BL, Tsai TF, Wan CM, Tang SC, et al. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. *J Infect Dis* 1997;176(5):1366–9.
- [31] Sohn YM, Park MS, Rho HO, Chandler LJ, Shope RE, Tsai TF. Primary and booster immune responses to SA14-14-2 Japanese encephalitis vaccine in Korean infants. *Vaccine* 1999;17(18): 2259–64.
- [32] Xin YY, Ming ZG, Peng GY, Jian A, Min LH. Safety of a live-attenuated Japanese encephalitis virus vaccine (SA14-14-2) for children. *Am J Trop Med Hyg* 1988;39(2):214–7.
- [33] Tsai TF, Yu YX, Jia LL, Putvatana R, Zhang R, Wang S, et al. Immunogenicity of live attenuated SA14-14-2 Japanese encephalitis vaccine—a comparison of 1- and 3-month immunization schedules. *J Infect Dis* 1998;177(1):221–3.
- [34] Hennessy S, Liu Z, Tsai TF, Strom BL, Wan CM, Liu HL, et al. Effectiveness of live-attenuated Japanese encephalitis vaccine (SA14-14-2): a case-control study. *Lancet* 1996;347(9015): 1583–6.
- [35] Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. *Lancet* 2001;358(9284): 791–5.
- [36] Kanasa-athan N, Smucny JJ, Hoke CH, Marks DH, Konishi E, Kurane I, et al. Safety and immunogenicity of NYVAC-JEV and ALVAC-JEV attenuated recombinant Japanese encephalitis virus-poxvirus vaccines in vaccinia-nonimmune and vaccinia-immune humans. *Vaccine* 2001; 19(4–5):483–91.
- [37] Ashok MS, Rangarajan PN. Evaluation of the potency of BIKEN inactivated Japanese encephalitis vaccine and DNA vaccines in an intracerebral Japanese encephalitis virus challenge. *Vaccine* 2001;19(2–3):155–7.
- [38] Tanabayashi K, Mukai R, Yamada A, Takasaki T, Kurane I, Yamaoka M, et al. Immunogenicity of a Japanese encephalitis DNA vaccine candidate in cynomolgus monkeys. *Vaccine* 2003;21(19–20): 2338–45.
- [39] Nukuzuma C, Ajiro N, Wheeler CJ, Konishi E. Enhancing effect of vaxfectin on the ability of a Japanese encephalitis DNA vaccine to induce neutralizing antibody in mice. *Viral Immunol* 2003;16(2):183–9.

- [40] Sugawara K, Nishiyama K, Ishikawa Y, Abe M, Sonoda K, Komatsu K, et al. Development of vero cell-derived inactivated Japanese encephalitis vaccine. *Biologicals* 2002;30(4):303–14.
- [41] Srivastava AK, Putnak JR, Lee SH, Hong SP, Moon SB, Barvir DA, et al. A purified inactivated Japanese encephalitis virus vaccine made in Vero cells. *Vaccine* 2001;19(31):4557–65.
- [42] Sabin AB. Epidemic encephalitis in military personnel. *JAMA* 1947;133(5):281–93.
- [43] Andersen MM, Ronne T. Side-effects with Japanese encephalitis vaccine. *Lancet* 1991;337(8748):1044.
- [44] Ruff TA, Eisen D, Fuller A, Kass R. Adverse reactions to Japanese encephalitis vaccine. *Lancet* 1991;338(8771):881–2.
- [45] Bonington A, Harbord M, Davidson RN, Cropley I, Behrens RH. Immunisation against Japanese encephalitis. *Lancet* 1995;345(8962):1445–6.
- [46] Plesner AM, Ronne T. Allergic mucocutaneous reactions to Japanese encephalitis vaccine. *Vaccine* 1997;15(11):1239–43.
- [47] Sakaguchi M, Yoshida M, Kuroda W, Harayama O, Matsunaga Y, Inouye S. Systemic immediate-type reactions to gelatin included in Japanese encephalitis vaccines. *Vaccine* 1997;15(2):121–2.
- [48] Sakaguchi M, Nakashima K, Takahashi H, Nakayama T, Fujita H, Inouye S. Anaphylaxis to Japanese encephalitis vaccine. *Allergy* 2001;56(8):804–5.
- [49] Sakaguchi M, Inouye S. Two patterns of systemic immediate-type reactions to Japanese encephalitis vaccines. *Vaccine* 1998;16(1):68–9.
- [50] Sakaguchi M, Miyazawa H, Inouye S. Specific IgE and IgG to gelatin in children with systemic cutaneous reactions to Japanese encephalitis vaccines. *Allergy* 2001;56(6):536–9.
- [51] Robinson HC, Russell ML, Csokonay WM. Japanese encephalitis vaccine and adverse effects among travellers. *Can Dis Wkly Rep* 1991;17(32):173–4, 177.
- [52] Mohan Rao CV, Risbud AR, Dandawate CN, Umarani UB, Ayachit VM, Rodrigues FM, et al. Serological response to Japanese encephalitis vaccine in a group of school children in South Arcot district of Tamil Nadu. *Indian J Med Res* 1993;97:53–9.
- [53] Nothdurft HD, Jelinek T, Marschang A, Maiwald H, Kapaun A, Loscher T. Adverse reactions to Japanese encephalitis vaccine in travelers. *J Infect* 1996;32(2):119–22.
- [54] Robinson P, Ruff T, Kass R. Australian case-control study of adverse reactions to Japanese encephalitis vaccine. *J Travel Med* 1995;2(3):159–64.
- [55] Plesner A, Ronne T, Wachmann H. Case-control study of allergic reactions to Japanese encephalitis vaccine. *Vaccine* 2000;18(17):1830–6.
- [56] Ohtaki E, Murakami Y, Komori H, Yamashita Y, Matsuishi T. Acute disseminated encephalomyelitis after Japanese B encephalitis vaccination. *Pediatr Neurol* 1992;8(2):137–9.
- [57] Ohtaki E, Matsuishi T, Hirano Y, Maekawa K. Acute disseminated encephalomyelitis after treatment with Japanese B encephalitis vaccine (Nakayama-Yoken and Beijing strains). *J Neurol Neurosurg Psychiatry* 1995;59(3):316–7.
- [58] Kitaoka M. Immunization for Japanese encephalitis. Tokyo: Igaku Shoin; 1972.
- [59] Fukuda H, Umehara F, Kawahigashi N, Suehara M, Osame M. Acute disseminated myelitis after Japanese B encephalitis vaccination. *J Neurol Sci* 1997;148(1):113–5.
- [60] Matsui M, Kawano H, Matsukura M, Otani Y, Miike T. Acute transverse myelitis after Japanese B encephalitis vaccination in a 4-year-old girl. *Brain Dev* 2002;24(3):187–9.
- [61] Plesner AM, Arlien-Soborg P, Herning M. Neurological complications and Japanese encephalitis vaccination. *Lancet* 1996;348(9021):202–3.
- [62] Plesner AM, Arlien-Soborg P, Herning M. Neurological complications to vaccination against Japanese encephalitis. *Eur J Neurol* 1998;5(5):479–85.
- [63] Franklin QJ. Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine. *Mil Med* 1999;164(2):157–9.
- [64] Knebusch M, Strassburg HM, Reiners K. Acute transverse myelitis in childhood: nine cases and review of the literature. *Dev Med Child Neurol* 1998;40(9):631–9.
- [65] WHO expert committee on biological standardization. WHO Technical Report Series 2002;904:7.
- [66] Japanese encephalitis vaccines. *Wkly Epidemiol Rec* 1998;73(44):337–44.

- [67] Nakatani H, Sano T, Iuchi T. Development of vaccination policy in Japan: current issues and policy directions. *Jpn J Infect Dis* 2002;55(4):101–11.
- [68] Ali M, Canh do G, Clemens JD, Park JK, Seidlein L, Thiem VD, et al. The vaccine data link in Nha Trang, Vietnam: a progress report on the implementation of a database to detect adverse events related to vaccinations. *Vaccine* 2003;21(15):1681–6.
- [69] Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *Am J Public Health* 1995;85(12):1706–9.
- [70] Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, et al. Vaccine Safety Datalink project: a new tool for improving vaccine safety monitoring in the United States: the Vaccine Safety Datalink Team. *Pediatrics* 1997;99(6):765–73.
- [71] Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12(6):542–50.
- [72] Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). *Vaccine* 2002;21(3–4):298–302.
- [73] Kohl KS, Bonhoeffer J, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: enhancing comparability of vaccine safety data. *Pharmacoepidemiol Drug Saf* 2003;12(4):335–40.
- [74] National Advisory Committee on Immunization (NACI): statement on Japanese encephalitis vaccine. *Can Commun Dis Rep* 1993;19(19):160–4.
- [75] An Advisory Committee Statement (ACS): Committee to Advise on Tropical Medicine and Travel (CATMAT): statement on Japanese encephalitis vaccine. *Can Commun Dis Rep* 1998;24:1–8.
- [76] Shlim DR, Solomon T. Japanese encephalitis vaccine for travelers: exploring the limits of risk. *Clin Infect Dis* 2002;35(2):183–8.