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Neurologic disease associated with 17D-204 yellow fever vaccination: A report of 15 cases

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Abstract

Yellow fever (YF), can be prevented by an attenuated vaccine (YEL). We reviewed neurologic adverse events (AE) following YEL that were reported to the national Vaccine Adverse Events Reporting System (VAERS). VAERS is a passive reporting system with inherent limitations for causality assessment. Based on defined criteria, five cases of encephalitis were classified as 'definitely' and one of acute disseminated encephalomyelitis (ADEM) as 'probably' caused by YEL. Six cases of Guillain-Barre Syndrome (GBS), one of encephalitis, and two of ADEM, were classified as 'suspect' vaccine-associated disease. Laboratory and epidemiological evidence suggests that YEL caused encephalitis. Additional studies will be required to confirm whether YEL can rarely result in GBS and/or ADEM.
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1. Introduction

Yellow fever (YF) is an acute febrile illness caused by a mosquito-borne flavivirus, found in tropical South America and sub-Saharan Africa. Case-fatality rates of YF are 20–50% [1–3]. Wild type yellow fever virus (YFV) infrequently causes encephalitis or other neurologic illness [4]. YF can be prevented by immunization with an attenuated vaccine derived from the 17-D YFV strain. In the United States, vaccine type 17D-204, manufactured by Sanofi Pasteur as YF-VAX®, is the only commercially available yellow fever vaccine (YEL).

YEL-associated encephalitis was first described in the 1950s, when children less than 10 years of age were vaccinated with the live French neurotropic vaccine (FNV, no longer used) [5]. Encephalitis occurred in some children 7–23 days following immunization and had a 39% case-fatality rate in infants [5]. Encephalitis also has occurred in young infants receiving the 17D-based vaccines [6]. Since limiting YEL administration to persons age ≥6 months in 1969 [7], there have been few reports of encephalitis and other neurologic illnesses temporally associated with YEL. Two fatalities have been individually reported over the past 40 years: a previously healthy 3-year-old from whose brain a mutated variant of the vaccine virus was isolated [8] and a 53-year-old man with HIV infection, who died from encephalitis 9 days following YEL [9]. During a 1993 YF vaccination campaign in Kenya, an active hospital-based surveillance system for postvaccinal encephalitis was established during a vaccination campaign in response to a yellow fever epidemic. There were three fatalities out of four people with postvaccinal encephalitis;

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the estimated crude incidence of postvaccinal encephalitis was 5.8 per million vaccinees [6].

Recently, cases of neurologic disease after YEL have been reported to the Vaccine Adverse Event Reporting System (VAERS) [10]. For the purpose of this analysis the "reporting rate" is defined as the number of people with neurologic adverse events occurring within 30 days of YEL vaccination that were reported to VAERS during the study period divided by the number of doses of YEL distributed to the U.S. civilian population during the same study period. In 2005, the reporting rate of severe neurologic disease, including encephalitis, Guillain-Barre Syndrome (GBS), and acute disseminated encephalomyelitis (ADEM) following YEL was estimated to be 4 reported cases/10^6 doses distributed in the U.S. [10,11]. There was a similar reporting rate from the United Kingdom [12] where another 17D-204-based vaccine is used. The reporting rate of encephalitis following YF-VAX® in the U.S. is highest among older vaccine recipients; 14 reported cases within 30 days of vaccination/10^6 doses in persons 59 years and older, compared to 4 cases within 30 days of vaccination/10^6 doses/in persons 1–18 years of age, and zero in persons aged 19–39 years of age [11].

We summarize the cases of neurological illness after YEL reported to VAERS in the U.S. over the past 15 years and discuss the likelihood that these illnesses were caused by YEL; describe the clinical features of three neurological illnesses—encephalitis, ADEM, and GBS; and estimate the reporting rates of neurological disease following YEL.

2. Methods

2.1. Yellow fever working group

In 2001, the Yellow Fever Working Group (YFWG), a group of vaccine safety specialists from academia, government, and the private sector, was formed by the Centers for Disease Control and Prevention (CDC) to review YEL-associated adverse events (AEs), assess the risk for serious AEs, and define important areas for future research [13].

2.2. Case definition

Three YEL-associated neurologic syndromes were defined: encephalitis, ADEM, and GBS (Tables 1A and 1B).

ADEM was defined by the presence of disseminated demyelination on neuroimaging in a clinically compatible case (recognizing that multiple sclerosis could not be definitively excluded without longitudinal clinical data). GBS was defined by the presence of signs of peripheral neuropathy or electrodiagnostic findings consistent with acute demyelinating or axonal polyneuropathy. AEs classified as encephalitis were considered to be definitely caused by vaccine if 17D-204 YFV was isolated from CSF, 17D-204 YFV RNA was amplified from CSF by nucleic acid-amplification testing, or YFV-specific IgM antibody was found in CSF by IgM-capture ELISA [14]. ADEM and GBS are thought to be due to autoimmune mechanisms, in which pathogenic autoantibodies are generated to an antecedent stimulus. Since other stimuli in the setting of YF vaccination could not definitely be excluded in these cases, the association between all ADEM or GBS cases and YEL was considered either "suspect" or "probable", but not "definite".

2.3. Case finding

VAERS is a passive surveillance system jointly managed by the CDC and Food and Drug Administration (FDA) for monitoring AEs following vaccination. VAERS accepts all reports without limitations on the type or extent of data submitted. AEs reported to VAERS following YEL have been followed up as part of an enhanced surveillance program since July 2001. We searched VAERS for reports received from January 1, 1990 to April 30, 2005; 15 of 97 reports that were assigned neurologic coding terms (see Appendix) had enough clinical information in the report or accompanying medical records to determine case status AND fit one of the three case definitions. We also searched the VAERS database for possible cases that occurred outside the defined 30-day window.

2.4. Reporting rates of adverse events

The reporting rate of YEL-associated neurological AEs was calculated by dividing the number of cases of each neurologic condition reported within 30 days of vaccination during the study period and by the number of YEL doses distributed to U.S. civilians 1990–2004 (personal communication, Dr. Rachel Eidex, Centers for Disease Control and Prevention). Military cases were clinically described but neither military vaccinees nor military cases were included in the reporting rate calculations.

2.5. Background incidence of neurological disease

The background incidence rates of encephalitis and GBS were calculated assuming a 30-day window of observation since that was the window used to define the neurologic AEs following YEL. The incidence rates of GBS [15] and encephalitis [16–18] used in calculation of background incidence rates were taken from adult populations from the U.S. [15,17,18] and the United Kingdom [16]. For encephalitis, "adults" were defined as >16 years of age in data taken from one reference [16] or >19 years of age in data taken from others [17,18]. The population-based incidence rate of GBS in adults was extrapolated for a 30-day observation period from a table of annual incidence rates included in a meta-analysis by Hughes and Rees [15]. We excluded the estimates outside the U.S. to enhance comparability with the U.S. VAERS data. To our knowledge, a background population-based estimate of the incidence rate of ADEM in adults in the U.S. was not available.

Table 1A
Case definitions of neurologic disease

Level 1 neurologic disease	One or more of the following signs and symptoms: • Fever (≥100.5 F >24 h) and headache (>24 h duration) • Focal neurologic dysfunction (including but not limited to: ataxia, aphasia, and paresis) • Mental status change (confusion, lethargy, or personality change >24 h) • New onset seizure or recurrence of previously controlled seizures • CSF pleocytosis (≥5 WBC/mm^3) • Elevated CSF protein (>1.5 times the normal limit)
Level 2 encephalitis	Level 1 neurologic disease AND one or more of the following: • Neuroimaging consistent with inflammation, (with or without demyelination) • EEG finding consistent with encephalopathy
Level 2 acute disseminated encephalomyelitis (ADEM)	Level 1 neurologic disease AND: • Neuroimaging consistent with multifocal or disseminated areas of demyelination
Level 2 Guillain-Barre Syndrome (GBS)	Level 1 neurologic disease (does NOT require presence of altered mental status, or seizures) AND two or more of the following signs and symptoms: • Limb weakness with decreased or absent tendon reflexes • Cranial nerve abnormalities • Autonomic dysfunction (including but not limited to: postural hypotension, arrhythmias, abnormal sweating, gastric motility abnormalities) • Numbness or paresthesias • Electromyography finding consistent with GBS • Neuromuscular respiratory failure as suggested by ancillary testing (e.g. pulmonary function testing, arterial blood gas, diaphragmatic elevation on chest X ray) or the use of ventilatory support

Table 1B
Criteria for levels of causal relationship to yellow fever vaccine by neurologic condition

Encephalitis	
Suspect	• Onset of symptoms occurs within **1–30 days** of vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations AND • Level 1 neurologic disease or Level 2 encephalitis AND • No evidence of other diagnoses causing disease
Probable	Suspect encephalitis AND one or more of the following: • Vaccine type yellow fever viral isolation from blood (>7 days post-vaccination) • Yellow fever 17D[a] virus concentration in serum on any day exceeds 3log 10 pfu/ml
Definite	Suspect Encephalitis AND one or more of the following signs: • YF specific IgM in CSF • Yellow fever 17D[a] virus isolation from CSF • Amplification of vaccine type virus[a] from CSF
Acute disseminated encephalomyelitis (ADEM)	
Suspect	• Onset of symptoms occurs within **1–30 days** of vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations AND • Level 2 ADEM AND • No evidence of other diagnoses causing disease
Probable	Suspect ADEM AND one or more of the following: • YEL given alone
Guillain-Barre Syndrome (GBS)	
Suspect	• Onset of symptoms occurs within **1–30 days** of vaccination with yellow fever vaccine (YEL), either given alone or in combination with other vaccinations AND • Level 2 GBS AND • No evidence of other diagnoses causing disease
Probable	Suspect GBS AND one or more of the following: • YEL given alone

[a] Confirmed as 17D virus by monoclonal antibody analysis or nucleotide sequencing where possibility of wild-type YF infection exists, inclusive of all 17-D derived vaccines.

3. Results

3.1. Clinical presentation

Fifteen reports to VAERS had adequate data in VAERS or medical records for case determination and fit the case definition (Tables 1A and 1B) of encephalitis ($N=6$), ADEM ($N=3$), or GBS ($N=6$) (Table 2, case numbers 2–5 previously reported [19]). The median age of these 15 vaccinees was 49 years (range 16–78 years). Four (27%) were female, and three (20%) were in the military. Two of the military cases were diagnosed with ADEM, and one with GBS; all 3 were male between the ages of 19 and 37 years. Sex distribution varied by diagnosis: whereas 3 of 6 persons with GBS were women, only 1 of 6 with encephalitis and 0 of 3 with ADEM were women. The median age in years was lower (19 years) in the ADEM group than the other two groups (52.5 [GBS] and 54 years [encephalitis]) (Table 3). Since we only had information on the number of doses of vaccine distributed and not on persons vaccinated, we were not able to compare the age and gender distributions of the neurologic cases with the same among vaccinees as a whole. All 11 patients with information regarding previous YEL vaccination were primary YEL vaccinees. No deaths among these 15 persons were reported.

The six vaccine recipients reported with encephalitis presented with fever and pleocytosis; of five who had neuroimaging, two had acute findings (cases 4 and 6 in Table 2). A brain magnetic resonance imaging scan (MRI) in case 4 showed nonspecific lesions of unclear clinical significance. MRI spectroscopy performed one day following the initial MRI was normal. An MRI in case 6 reported showing "mild increased enhancement of the right parietal dura". Five of the six cases had YF-specific IgM detected in the CSF. In 4 cases, serologic tests for other North American flaviviruses and other arboviruses were performed. All were negative, with the exception of case 6 who had a weakly positive IgM antibody to St. Louis encephalitis virus thought to be due to cross-reactivity with antibody to YFV. By discharge, all patients had improved.

Six vaccine recipients reported with GBS presented with peripheral neurological deficits including paresthesias, extremity weakness, numbness, and decreased deep tendon reflexes. Other signs/symptoms included blurred vision, diplopia, fecal or urinary incontinence, and/or slurred. Results of electrophysiologic testing, performed at unspecified times after symptom onset, were consistent with GBS in two of the three cases in which they were performed, and normal in the other. Three patients were treated with intravenous immunoglobulin (IVIG); one with high-dose solumedrol; one with plasmapheresis; and one with both IVIG and plasmapheresis. At the time of discharge, five clinically improved but had mild neurological residua; the sixth person continued to have diplopia at discharge, but was otherwise normal (Table 2).

Three vaccine recipients reported with ADEM presented with focal neurological signs. MRI of the brain and/or spinal cord showed acute demyelinating disease in 2 patients and retrobulbar optic neuritis in 1 patient. All patients were treated with steroids, and had improved by discharge (Table 2).

The period between vaccination and symptom onset was by definition between 1 and 30 days. There was no clustering in the number of days from vaccination to onset of symptoms for any of the adverse event types when plotted by individual day (Fig. 1) or by week of onset. Persons with encephalitis had symptom onset ranging from 5 to 24 days after vaccination; GBS, 7–27 days after vaccination; and ADEM, 7–20 days after vaccination. There was one additional U.S. case of GBS in a 53 year old man reported to VAERS during the study period that clinically met the case definitions but had symptom onset 32 days after vaccination with YEL, hepatitis A vaccine, and typhoid vaccine.

We compared the clinical and laboratory features of the encephalitis, GBS, and ADEM groups (Table 3), but the small number of cases limited statistical power to infer differences among the groups. There was little difference between the three groups with respect to interval between vaccination and onset of symptoms, peak blood WBC count, or peak CSF protein. The median peak WBC count in the CSF was lower in the GBS group (1 cell/mm^3) than in the other groups

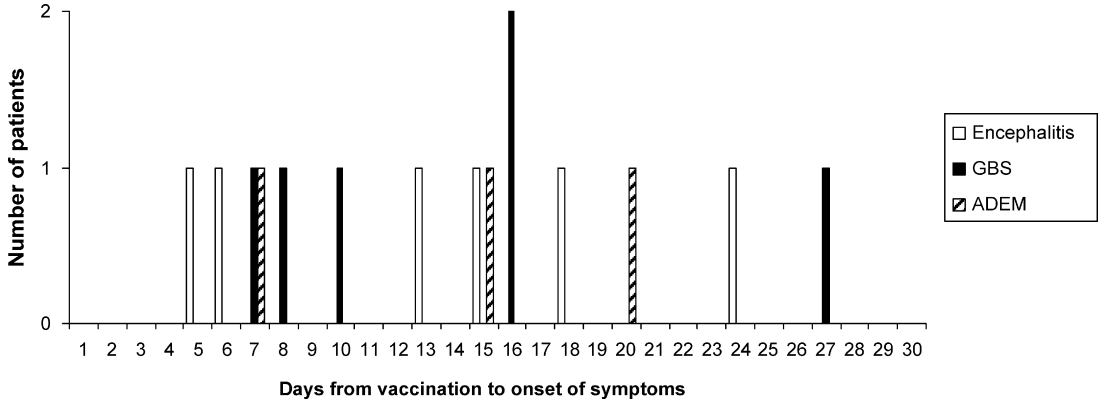

Fig. 1. Number of days from vaccination to onset of symptoms among patients with three groups of neurologic adverse events following yellow fever vaccination: encephalitis, Guillain-Barre Syndrome (GBS), acute disseminated encephalomyelitis (ADEM).

Table 2
Cases of neurologic disease following yellow fever vaccine

Case number	YFWG case classification (diagnosis/relationship to YEL)	Other vaccines	Days to onset from vaccine	Age (years)	Gender	Presentation	Peak CSF WBC (ml^{-1})	Peak CSF protein (mg/dl)	CSF YF IgM	Treating physician's diagnosis	Status at discharge
1 (216736)	Encephalitis/suspect	Td, Typhoid, Hepatitis A, Hepatitis B	15	67	F	Confusion, lethargy, weakness, headache, temperature 102.6 F	77	142	Neg[a]	Encephalitis	Afebrile, mental status improved, increased energy
2 (181929)	Encephalitis/definite	Hepatitis A	5	41	M	Temperature 104.5 F, headache	63	82	Pos[b]	Meningitis	Full recovery
3 (176386)	Encephalitis/definite	Hepatitis A, Hepatitis B	13	36	M	Headache, temperature 106 F	406	59	Pos	Encephalitis	Afebrile, occasional headache, persistent fatigue
4 (186467)	Encephalitis/definite	None	24	16	M	Dysarthria, aphasia, dysphasia, afebrile	0	70	Pos	Encephalitis	Neurological exam returned to normal
5 (185825)	Encephalitis/definite	Typhoid, Hepatitis A	6	71	M	Headache, temperature 101.1 F, confusion, slurred speech	137	64	Pos	Encephalitis	Mental status returned to normal
6 (200548)	Encephalitis/definite	None	18	78	M	Fever 104.5 F, altered mental status, urinary tract infection	18	64	Pos	Encephalitis	Improved mental status, afebrile
7 (39772)	GBS/suspect	Mening, IPV, Td, Typhoid	10	49	M	Severe headache, horizontal diplopia		80	ND[c]	Guillain-Barre Syndrome, Fisher variant	Continued to have diplopia
8 (120262)	GBS/suspect	Hepatitis B, Mening, Td	16	37	M	Headache, dizziness, blurred vision, paresthesias	1	239	ND	Guillain-Barre Syndrome	Able to walk independently, was regaining his strength
9 (217755)	GBS/suspect	Typhoid vaccine, Hepatitis A vaccine, DT	7	17	F	Weakness, shortness of breath	1	24	Neg	Guillain-Barre Syndrome variant	Improved respiratory function, but more peripheral weakness, decreased reflexes
10 (225211)	GBS/suspect	HepAHepB, Typhoid, Mening	27	56	M	Numbness, unable to stand	3	63	ND	Guillain-Barre Syndrome	Symptoms improved in hospital, required inpatient physical therapy at rehabilitation facility
11 (96427)	GBS/suspect	Hepatitis A	16	63	F	Headache, numbness and tingling, unstable gait. BP 240/118	0	40	ND	Guillain-Barre Syndrome	Blood pressure near baseline, but more difficult to control than before illness, motor function returned to near normal
12 (162449)	GBS/suspect	Td, Hepatitis A, Typhoid	8	68	F	Pains and weakness in thighs and calves, tingling and numbness in hands and feet, afebrile	2	73	ND	Guillain-Barre Syndrome	Did better with feeding, but little improvement in legs. Transferred to intermediate care facility
13 (198551)	ADEM/probable	Typhoid, IPV, Influenza, Hepatitis A, Hepatitis B, MMR, Anthrax	15	19	M	Headache, temperature 102 F, weakness, numbness, unable to ambulate, bladder dysfunction	159	73	Pos	Acute disseminated encephalomyelitis	Ambulated without assistance, regained sensation in lower extremities, voided without assistance
14 (214072)	ADEM/suspect	DT, MMR	20	18	M	Bilateral eye pain, blurry vision, leg numbness, arm tingling, difficulty urinating	465	117	ND	Devic's disease	Visual acuity restored almost to baseline, voided successfully, unsteadiness improved, numbness unchanged
15 (193603)	ADEM/suspect	Hepatitis A, Td	7	61	M	Left foot and left leg drag	ND	ND	ND	Undefined demyelinating disease of the central nervous system	Continued left sided hemiparesis, transferred to the rehabilitation program

[a] Neg, negative.
[b] Pos, positive.
[c] ND, not done.

Table 3
Clinical features of three groups of neurologic disease following yellow fever vaccine

Case classification	Encephalitis ($N=6$)	GBS ($N=6$)	ADEM ($N=3$)
Median age in years (range)	54 (16–78)	52.5 (17–68)	19 (18–61)
% female	16.7	50	0
Median onset interval in days (range)	14 (5–24)	13 (7–27)	15 (7–20)
Median temperature (F) on admission (range)	101.9 (98.3–105)	97.85 (96.7–99.0)	99.54 (98.78–103)
% with confusion	50	17	0
Median (range) blood WBC peak ($\times 10^3/mm^3$)	11.95 (6.3–15.0)	9.15 (2.4–15.1)	12.7 (10.2–15.2)
Median (range) creatinine peak (mg/dl)	1.4 (0.9–1.6)	0.9 (0.5–1.1)	1.35 (1.3–1.4)
Median (range) WBC in CSF peak ($/mm^3$)	41.5 (0–406)	1 (0–3)	246 (27–465)
Median (range) % lymphocytes in CSF peak	27 (0–73)	0 (0–68)	92.5 (85–100)
Median (range) CSF protein peak (mg/dl)	67 (59–142)	69 (24–239)	85 (53–117)
Summary of CSF IgM (# positive/# tested)	5/6	0/1	1/1

($41.5/mm^3$ for encephalitis and $246/mm^3$ for ADEM). The median percent lymphocytes in the CSF of the ADEM group was 92% compared to 27% in the encephalitis group.

3.2. Case classification

The causality classification by the YFWG for each case is shown in Table 2.

3.3. Reporting rate of adverse events compared to estimated background incidence of neurologic disease

The six cases of encephalitis following YEL vaccination among U.S. civilians correspond to a reporting rate of 2.3 encephalitis cases in the 30 days after vaccination per 10^6 distributed YEL doses. The estimated incidence of encephalitis from all causes in the U.S. is 0.9–2.8 cases/30 days/10^6 population. The five cases of GBS following YEL vaccination among U.S. civilians corresponds to a reporting rate of 1.9 reported cases of GBS within 30 days of vaccination/10^6 distributed YEL doses. The estimated incidence of GBS from all causes in the U.S. is 0.8–3.3/30 days/10^6 population. There was only one case of ADEM reported following YEL vaccination among U.S. civilians corresponding to a reporting rate of 0.4 reported ADEM cases within 30 days of vaccination/10^6 distributed YEL doses.

4. Discussion

We identified 15 cases of encephalitis, GBS, and ADEM temporally associated with YEL administration. After review, five encephalitis cases were considered to have been caused by YEL based upon the presence of YFV-specific IgM in CSF. One case of ADEM with YFV-specific IgM in CSF was thought to be probably caused by YEL, with YEL serving as the possible antigenic stimulus. All 6 GBS cases, 2 ADEM cases, and 1 encephalitis case were considered suspect; all had received other vaccines on the day that they also received YEL.

Usually VAERS data do not allow evaluation of causality due to incomplete information, absence of control or comparison data, and inadequate denominator data [20]. In contrast, this report reviews cases which had appropriately detailed clinical work-ups, and in which the diagnoses of GBS, encephalitis and ADEM were made with relative clinical certainty. Moreover, the assessment of causality for neurologic AEs following YEL was based on the diagnostic finding of YEL-specific IgM in the CSF. Since IgM does not normally cross the blood–brain barrier, the presence of IgM antibodies in CSF suggests intrathecal antibody production in response to a nervous system infection. For some encephalitides, detection of CSF IgM antibodies is the diagnostic standard [21]. A limitation to this approach in our study is that there is no published information on YEL-specific IgM in CSF in a series of YEL recipients without AEs. Also, although other flaviviral infections were excluded when possible and although such infections are relatively uncommon in the U.S., tests for YFV-specific IgM can cross-react with antibodies to other flaviviruses. Nevertheless, the YFWG considered the presence of YFV-specific IgM in CSF in these cases with clinically compatible illness and a temporal association with YEL vaccination to be sufficient evidence for concluding that the illness was caused by YEL [22], particularly when there was neither clinical, epidemiological, nor serological evidence of concurrent infection with a different flavivirus, and when there was no apparent alternative etiology.

The reporting rates of ADEM, GBS, and encephalitis after YEL vaccination were low; roughly 0.5–2 reported cases of each per 10^6 doses of vaccine distributed. The denominator used in this calculation is the number of vaccine doses distributed to the U.S. civilian population, which likely overestimates the true number of individuals actually vaccinated, thus lowering our estimate of the reporting rate of neurologic AEs. While we may overestimate the number of vaccinated persons, we also underestimate the incidence of these neurologic events due to underreporting associated with a passive surveillance system. The degree of underreporting is unknown. However, YEL-associated neurologic AEs may have been reported at a higher rate than AEs following other vaccines due to heightened awareness of YEL-associated AEs following a published report [19], and due to the fact that reporting is more complete for serious outcomes [23]. A study

in both the civilian and military [24,25] sectors is underway to estimate the population-based incidence of encephalitis attributable to YEL.

The population-based incidence rates of encephalitis [16–18] and GBS [15] were similar to the VAERS reporting rates of encephalitis and GBS after YEL vaccination. However, the comparability of these two estimates is limited for several reasons. Population-based estimates of disease incidence based on active surveillance systems are higher than reporting rates derived from passive surveillance systems [26]. This concept is especially important in this case, since the population-based incidence rates theoretically encompass all etiologies of encephalitis and GBS, and the passive surveillance system, VAERS, captures only cases that are thought by a reporter to be vaccine-associated. Use of distributed doses instead of administered doses inflates the denominator of the reporting rate. Finally, the use in this study of a 30 day window could underascertain cases, since other studies, particularly of vaccine-associated GBS, use 6–8 week windows of observation [27], though our search of VAERS found only 1 case of GBS and no cases of encephalitis beyond the 30-day period. Thus, the combination of these 3 effects almost certainly results in underascertainment of vaccine-associated neurologic events. Another limitation is that the populations in the reference studies may not represent that reporting to VAERS or receiving YEL.

Given the difficulties in assessing the comparability of population-based estimates of neurologic disease and vaccine-associated estimates, another approach to assessing the safety of YEL is to compare the AEs of this vaccine with the AEs of another live viral vaccine. In the 1960s, it was estimated that smallpox vaccination resulted in 2–9 encephalitis cases/10^6 vaccinees over 2 years old [28]. In a summary of the 2002–2004 neurologic AEs following smallpox vaccine [29], with passive reporting, 3 cases of encephalitis were detected, for a reporting rate of 5 encephalitis cases/10^6 doses of vaccine administered—more than twice the reporting rate observed for YEL. However, unlike the YEL-associated AEs identified here, these cases did not have formal causality assessments; vaccinia was not isolated from the CNS; vaccinia-specific antigen, nucleic acid, and IgM were not assayed in the CSF. In the earlier reports of post-vaccinial encephalomyelitis (PVE), many reported PVE cases appeared more likely to be ADEM than acute viral encephalitis on more detailed review. In addition, the studies of neurologic AEs following smallpox vaccination did not restrict to a 30-day observation period and used the actual number of vaccinated persons rather than distributed doses. In addition, the surveillance during the smallpox vaccination campaign was considerably more enhanced than typical "passive" surveillance [30], as compared to the ongoing surveillance of AEs after YEL and other vaccines, despite the fact that AEs after all these vaccines are reported to VAERS. These factors may have resulted in an over-estimated reporting rate for PVE. Despite these difficulties with direct comparison, the reporting rates of encephalitis following YEL and smallpox vaccine were on the same order of magnitude.

This review suggests that YEL can very rarely cause encephalitis after vaccination. In healthy adults identified in this very small series with limited power to detect associations, recovery without residual deficit appears to be common, but the acute disease can be severe. It is possible that ADEM and GBS are rarely associated with antecedent YEL, but this relationship cannot be definitely determined through this review because of the concurrent administration of multiple vaccines, the presumed autoimmune mechanism of these diseases and absence of standardized laboratory tests linking YF vaccination to these diseases, and the many assumptions made in the epidemiological assessment. Although the risk of neurological disease after YEL appears small, it is important that people receive YEL only when there is a risk of exposure to wild type YFV [10]. The YFWG will continue ongoing surveillance for neurologic AEs, and collect clinical specimens when possible. Clinicians who observe neurological symptoms or any other illness following YEL are encouraged to report to VAERS at: http://www.vaers.org/, Tel.: 1 800 822 7967, fax: 1 877 721 0366, email: info@vaers.org.

Despite what appears to be a small risk after YEL of severe neurological disease, YEL is indicated in the event of risk of exposure to wild type YFV. The risk of YEL-associated neurologic AEs has been considered in the current package insert for the US-licensed product, YF-VAX®. The low reporting rate and absence of reported fatalities are reassuring, and thus, changes in vaccine indications have not been made.

Appendix A. Conditions searched in VAERS for neurologic disease following yellow fever vaccine

Condition
Aphasia
Apraxia
Ataxia
Cerebellar ataxia
Positive babinski sign
Blind
Cerebellar syndrome
Cerebrovascular accident
Cerebrovascular disease
Central nervous system depression
Central nervous system stimulation
Coma
Confusion
Convulsion
Grand mal convulsion
Cerebrospinal fluid abnormality
Delirium
Delusions
Dementia
Dysarthria
Dystonia
Electroencephalogram abnormality
Encephalitis

Appendix A (*Continued*)

Eye disease
Eyes gaze upward
Febrile seizure
Fever
Guillain-Barre Syndrome
Hallucination
Vascular headache
Intracranial hypertension
Cerebral ischemia
Myelitis
Paralysis
Extraocular paralysis
Facial paralysis
Flaccid paralysis
Spastic paralysis
Photophobia
Psychosis
Decreased reflexes
Increased reflexes

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