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A Stamaril Vaccine Expanded Access Investigational New Drug Program Prevented a Yellow Fever Vaccine Shortage in the United States, 2017-2020

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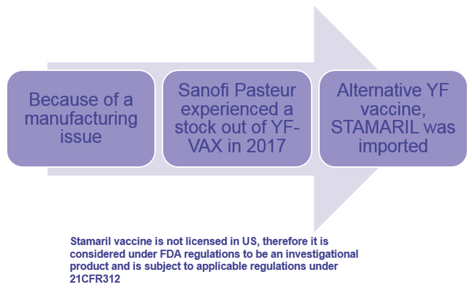
BACKGROUND

YF-VAX

- A yellow fever (YF) vaccine licensed by the United States (US) Food and Drug Administration (FDA), YF-VAX® (Sanofi Pasteur Inc., Swiftwater, PA), is a live attenuated vaccine based on strain 17D-204. It is the only YF vaccine licensed in the United States
- Due to a manufacturing disruption beginning in 2017, YF-VAX supply was not available to US civilian travel clinics. Another widely distributed YF vaccine, STAMARIL® (Sanofi Pasteur, France), was imported into the US to fulfil the public health need for YF vaccination

STAMARIL Expanded Access Investigational Program (EAP)



Yellow Fever

- YF is a mosquito-borne hemorrhagic disease that is caused by a single-stranded RNA virus belonging to the genus Flavivirus. The virus is transmitted primarily by infected Aedes aegypti mosquitoes
- YF is widespread in sub-Saharan Africa and tropical South America and is a significant health problem to residents of endemic countries and non-vaccinated travellers entering endemic areas. There are ~200,000 cases and ~30,000 deaths due to YF worldwide each year. The case-fatality ratio varies widely in different studies but is typically 20% or higher
- Because no specific treatment exists, prevention through vaccination is critical to reduce morbidity and mortality

STAMARIL

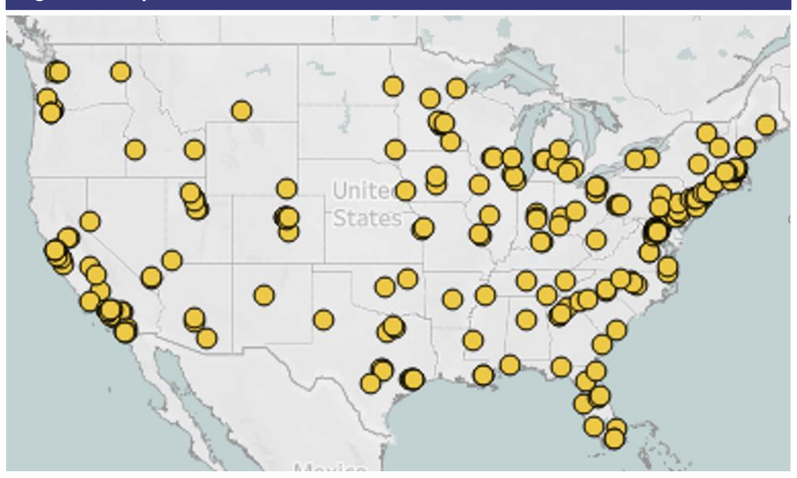
- STAMARIL has been licensed since 1986 in more than 100 countries. Over 500 million doses have been distributed globally
- Like YF-VAX, STAMARIL is a live attenuated vaccine prepared by culturing the 17D-204 strain of yellow fever virus in chicken embryos. Vaccination provides strong and long-term protection against YF
- Safety and efficacy of STAMARIL and YF-VAX vaccines are comparable; and like all yellow fever vaccines currently available, there are three rare but important identified risks: YF vaccine-associated acute viscerotropic disease (YEL-AVD), YF vaccine-associated neurotropic disease (YEL-AND), and anaphylaxis

METHODS

EAP

- To meet the public health need for a safe and effective YF vaccine for the US civilian population, in conjunction with the CDC and FDA, the EAP was implemented, allowing the importation of STAMARIL vaccine
- Typically, ~500,000 doses of YF-VAX are distributed in the US annually, with two thirds of the doses being provided to ~4,000 civilian travel clinics
- Due to the requirements of the EAP, only a limited number of clinics could participate. Approximately 250 YF vaccine clinics were enrolled as STAMARIL EAP sites based on the volume of YF-VAX previously ordered and geographic location (**Figure 1**). The goal was to ensure YF vaccine was available at large volume clinics and still provide geographic access to remote areas

Figure 1: Map of STAMARIL EAP sites



Not shown on this map are STAMARIL EAP sites in Alaska, Guam, Hawaii, Puerto Rico and the US Virgin Islands.

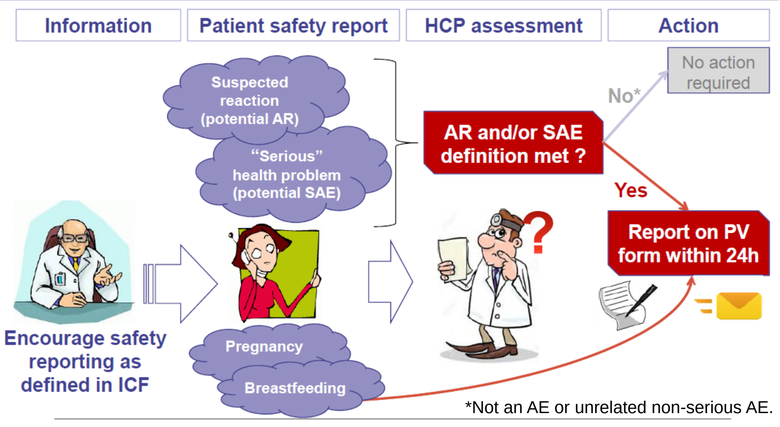
- Site participation required IRB approvals and adherence to protocol requirements (**Table 1**). Each site designated a principal investigator (YF vaccine-certified Healthcare Provider) responsible for the activities at the site and all personnel involved in the EAP completed training
- Before STAMARIL could be administered, inclusion and exclusion criteria were reviewed **(Table 2),** and informed consent was obtained. Participants were informed about benefits and risks of vaccination, early symptoms indicative of potential adverse reactions and instructed on how to report safety events

Table 1: EAP sites' protocol requirements & participant process flow

Determine eligibility	By review of inclusion/exclusion criteria and precautions
Document	If eligible, document the review in the vaccinee's medical chart
Consent	The vaccinee, file the original in the medical chart, provide a copy to the vaccinee
Assign	Patient ID: (5 digit, in sequence. First patient = 00001): *xxxxx*
Vaccinate	The patient
Record	Vaccine on the Vaccine Accountability Form
Record	Vaccinee demographics and vaccine administration details on the cumulative list of doses administered
Observe	Vaccinee for 20 minutes
Instruct	The vaccinee on which medical events that may occur after vaccination must be reported back to the HCP
Report	Within 24 hours to Sanofi Pasteur relevant adverse events and exposure in pregnancy/breastfeeding

- Sites were required to report doses administered, and vaccinee demographic information
- Safety reporting required sites to inform Sanofi Pasteur within 24 hours the following: suspected adverse reactions, serious adverse events (SAEs), vaccination during pregnancy and vaccination of women who breastfed infants during the 14 days after vaccination (**Figure 2**)

Figure 2: Summary of Safety Reporting for the STAMARIL EAP



RESULTS

EAP

- From May, 2017 through June, 2020, 609,010 doses of STAMARIL were administered by the EAP sites. No case of YF disease has been reported in a returning US traveler during the EAP
- As of December, 2020, there were seven cases of YF vaccine-associated acute neurotropic disease (YEL-AND) and two cases of YF vaccine-associated acute viscerotropic disease (YEL-AVD) reported (reporting rate: 1.1 and 0.3/100,000 vaccinees, respectively), which, with the exception of one suspect case of YEL-AND, all occurred in individuals at increased risk (age ≥ 60 years) (**Tables 2-3**)
- One vaccinee developed an anaphylactic reaction (reporting rate: 0.16/100,000 vaccinees)
- No safety concerns were identified from inadvertent vaccine exposure during pregnancy (41 pregnant women) or potential neonatal exposure via breast milk (4 exposed infants)
- Other relevant events included 11 reports of neurologic events not meeting the definition of YEL-AND, classified as "Level 1 neurologic disease" as per ACIP criteria. Clinical picture mainly included symptoms of aseptic meningitis, paresthesia or seizure, which started between 4 and 32 days post-vaccination. In 3 of these cases, the cerebrospinal fluid was positive for YF IgM which supported the causal association with the vaccine. These events were mainly reported in young adults, suggesting that the severity and extent of vaccine-associated neurologic reactions may be age-related

Table 2: STAMARIL EAP participant enrollment criteria

Inclusion Criteria	Exclusion Criteria	Precautions
✓ Persons at high risk for YF, including researchers, laboratory workers, vaccine production staff, and those who are traveling to a YF-endemic area requiring proof of YF vaccination under IHRs.	× Age < 9 months	Pregnancy
✓ ≥9 months of age on the day of vaccination	× Breastfeeding, if the nursing cannot be discontinued for at least 14 days following vaccination.	Age ≥ 60 years
✓ A signed ICF, indicating that Stamaril vaccine (non-US-licensed) is being administered in place of YF-VAX, by persons ≥ 18 years of age.	× Immunosuppression, including for example, leukemia, lymphoma, other malignancies, and patients who are receiving immunosuppressant medications or radiation therapy, or organ transplantation.	Asymptomatic HIV infection with moderate immune suppression or no evidence of immune suppression
✓ A signed assent form by persons 7 years to < 18 years of age, and ICF signed by parent(s) or guardian(s) for persons ≥ 9 months to < 18 years of age.	× Symptomatic HIV infection	
	× Known hypersensitivity to the active substance or to any of the excipients of Stamaril vaccine or to eggs or chicken proteins	
	× Asymptomatic HIV infection when accompanied by evidence severe immune suppression.	
	× History of thymus dysfunction (including myasthenia gravis, thymoma, thymectomy).	
	× Moderate or severe febrile illness or acute illness	

Table 3: Cases of Suspect, Probable and Definite YEL-AND reported during the EAP

Case	Age Gender	Signs and symptoms	Latency	YFV testing/relevant investigations	Comment	Classification
1	70 Y M	Ataxia, headache, diplopia, weakness. Reported as YEL-AND	15 days	D17 post-vaccination: CSF YFV PCR (-), IgM (+) MRI brain normal	Medical history: pulmonary embolism, allergy (unspecified). Recovered	**Definite YEL-AND (autoimmune)**
2	67 Y F	Dizziness, fall, diplopia, seizure, difficulty speaking, mental status change (reported as YEL-AND)	2 weeks	D54 post-vaccination: CSF : YF IgM(+) [PRNT90 = 1:256] Serum: PRNT90 =1:640	Medical history of atrial fibrillation, migraine, hyperlipidemia, herpes zoster. Brain MRI signal abnormality. Encephalopathy confirmed by EEG. Suspected underlying neoplasia Not recovered	**Definite YEL-AND**
3	64 Y M	Fever, headache, diplopia, confusion (reported as neurotropic disease)	11 days	CSF : YF IgM(+)	Hospitalized for 1 night. Concomitant vaccines: Tdap, hepatitis A, meningococcal and oral typhoid. Recovered	**Definite YEL-AND**
4	64 Y M	Bilateral progressive weakness. Reported as GBS	13 days	Not reported	Medical history: Myocardial infarction, hypercholesterolemia. No known immunocompromising conditions. Recovering, then lost to follow up	**Probable YEL-AND (autoimmune)**
5	62 Y F	Headache, limb weakness, areflexia, ataxia, cranial nerve abnormalities. Reported as YEL-AND. Diagnosed as Miler-Fisher syndrome	17 days	CSF (drawn at onset): YFV PCR (-), IgM (-). MRI brain normal	Medical history: hyperthyroidism. Recovered, with sequelae of facial nerve palsy	**Suspect YEL-AND (autoimmune)**
6	61 Y F	Headache, fever, photophobia, hemiparesis	4 days	Lumbar puncture not done. MRI normal Laboratory data not provided.	Medical history: polymyalgia rheumatica, asthma (treated with omalizumab), irritable bowel syndrome. Recovered	**Suspect YEL-AND**
7	37 Y F	GBS	7 days	Not reported	History of asthma and hyperthyroidism. Event occurred 7 days after Stamaril given with other vaccines, and 6 weeks after suspected influenza infection. Recovering then lost to follow-up	**Suspect YEL-AND**

CSF: Cerebrospinal Fluid; IgM: Immunoglobulin M; YEL-AND: Yellow Fever-Associated Neurotropic Disease; YFV: Yellow Fever Virus; GBS: Guillain Barré Syndrome; EAP: Expanded Access Program; PCR: polymerase chain reaction; PRNT: plaque reduction neutralization test; MRI: Magnetic Resonance Imaging; EEG: Electroencephalography

Table 4: Cases of Probable YEL-AVD Reported during the EAP

Case	Age Gender	Signs and symptoms	Latency	YFV testing/relevant investigations	Comment	Classification
1	68 Y M	Nausea, vomiting, diarrhea, abdominal pain Laboratory: -Liver enzymes >3xULN -Platelets <100 000/µL	4 days	YF testing in blood: -D7 post-vaccination: IgM(-), PRNT(-), PCR(+), YFV: 2-3 $\log_{10}$ pfu/mL -D11 post-vaccination: IgM(+), PRNT(+), PCR(+), YFV: < 2 $\log_{10}$ pfu/mL	Medical history: splenectomy for autoimmune hemolytic anemia (2002) Concomitant vaccination with MenB, Hib, MCV4, IPV, oral typhoid Recovered	**Probable YEL-AVD**
2	65 Y M	Nausea, vomiting, myalgia, fever (103.7F), chills, diarrhea Laboratory: -Liver enzymes >3xULN -Platelets <100 000/µL -Urine output <500 mL/24 h	5 days	YF testing in blood: -D5 post-vaccination: IgM(+), PRNT(-), PCR(+), YFV: 2-3 $\log_{10}$ pfu/mL -D13 post-vaccination: IgM(+), PRNT(+), PCR(-)	Medical history: thrombocytopenia, obesity, systemic inflammatory response syndrome, chronic kidney disease (with kidney atrophy), coronary artery disease, elevated troponin, essential hypertension, mixed hyperlipidemia and gouty arthropathy Concomitant *Clostridium difficile* infection Recovered	**Probable YEL-AVD** in a subject with concomitant infection

Hib: *Haemophilus influenzae* type B; Ig: immunoglobulin; IPV: inactivated polio vaccine; MCV: meningococcal conjugate vaccine; MenB: meningococcal B; PCR: polymerase chain reaction; pfu: plaque-forming unit; PRNT: plaque reduction neutralization test; ULN: upper limit of normal range; YF: yellow fever; YFV: Yellow Fever virus

LIMITATIONS

- The EAP did not include immunogenicity assessment
- EAP safety data collection was based on stimulated safety reporting (enhanced passive safety surveillance). There was no active follow-up of vaccinees for adverse events. However, underreporting of serious adverse reactions was unlikely given, the informed consent process and instructions given to all vaccinees for reporting of safety events
- Not all US travel clinics were included in the STAMARIL EAP and clinics were not randomly enrolled, thus not all travelers had similar ease of access to YF vaccination. Despite this, no cases of YF have been reported in US travelers during the EAP

CONCLUSIONS

- The STAMARIL EAP supported the public health need for YF vaccination by making an internationally licensed vaccine available to civilian travelers during the time when the US-licensed YF-VAX supply was insufficient
- For the duration of the EAP, May 2017 to present, no case of YF disease has been reported in a returning US traveler. Over 600,000 doses of STAMARIL were administered during the EAP
- No new safety concerns were identified. Serious adverse reactions remained very rare and consistent with the known safety profile of STAMARIL
- With the increase in YF-VAX manufacturing capacity and the resulting ample supply available to civilian travel, the STAMARIL EAP is anticipated to end in June 2021

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DISCLOSURES

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All authors are Sanofi Pasteur employees

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