

COMPARISON OF THE IMMUNOGENICITY AND SAFETY OF TWO 17D YELLOW FEVER VACCINES

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Abstract. As part of the clinical validation process of a new working seed of a licensed yellow fever vaccine (new working seed PV26, Stamaril[®]; Pasteur Mérieux Connaught, Lyon, France), the immunogenicity and safety of two batches of this vaccine (PM-YF) were compared with those of another commercially available vaccine (Arilvax[®]; Evans Medical-Wellcome, Liverpool, United Kingdom) in 211 healthy adults. While the geometric mean titer values at days 10–14 and day 28 after vaccination were higher in the PM-YF group, the vaccines provided equivalent seroprotection (titers $\geq 1/10$) one month after a single vaccine dose (100% PM-YF versus 99% W-YF; $P = 0.001$, by one-sided equivalence test). Both vaccines were safe. There were no serious local or systemic reactions reported, nor any clinically significant hepatic function abnormalities associated with the use of either vaccine. These two 17D yellow fever vaccines from different European vaccine manufacturers were highly immunogenic and safe, and provided equivalent seroprotection.

Yellow fever is a viral tropical disease, occurring endemically, with periodic epidemics, in the Americas and Africa. The yellow fever virus, a member of the Flavivirus family, is mosquito borne, and in humans produces a clinical disease characterized by sudden onset of fever, followed by hepatorenal dysfunction and hemorrhage. Epidemics can be associated with attack rates of 33% and mortality rates of more than 75%.^{1,2} Since 1980, there has been a sudden re-emergence of this disease in Africa and South America, with a total of 18,735 cases and 4,522 deaths reported world-wide between 1987 and 1991. This represents the highest level of yellow fever activity reported to the World Health Organization (WHO) over any five-year period since reporting began in 1948,³ and emphasizes the continued need for effective control through vaccination and other public health measures. The Advisory Committee on Immunization Practice of the Centers for Disease Control and Prevention (Atlanta, GA) and the WHO now recommend that yellow fever vaccine be administered to all persons ≥ 9 months of age if they are living in or travelling to areas of South America and Africa where yellow fever is officially reported.^{4,5}

The history of the yellow fever vaccine is extensive; yellow fever was the third human disease (after small pox and rabies) to be controlled by vaccination. A live, attenuated virus (17D), derived from a human isolate (Asibi), and attenuated by serial passage in mouse brain and chick embryo cells^{6,7} has been used safely and effectively as a vaccine for more than 50 years. Due to some early problems with this vaccine, such as overattenuation or reversion to virulence, that were related to inconsistent manufacturing processes,^{8,9} in 1945 WHO proposed the use of a seed-lot system in which a primary seed is used to generate secondary seeds that are then used by the different laboratories to produce vaccine batches.¹⁰ Twelve institutes around the world manufacturing yellow fever vaccine from one of three different 17D vaccine strains (17D-204, 17DD, and 17D-204-WHO) are approved by WHO for certification for international travel.¹¹

Since the addition of heat-stabilizing components to the 17D vaccine preparations in 1991, very few evaluations of

the immunogenicity and safety of the different yellow fever vaccines have been performed according to Good Clinical Practice (GCP) guidelines and using thorough statistical methodology. This is all the more worrisome in face of recent reports showing some 17D yellow fever vaccines to have suboptimal immunogenicity.¹² The same concerns were recently voiced during a Yellow Fever Steering Committee on Epidemiology and Field Research held in May 1998 by WHO in Geneva, Switzerland.¹³

Numerous factors are known to influence the immunogenicity of a yellow fever vaccine, including handling conditions, particularly a poor cold chain, dose (possibility of a prozone effect in which too high a dose of yellow fever attenuated virus may lead to reduced immunogenicity), injection site, route of administration, and subject characteristics.¹⁴ It would thus seem worthwhile to verify the immunogenicity of these vaccines on a regular basis using rigorous clinical trial methodology.

The yellow fever vaccine (Stamaril[®]) manufactured by Pasteur Mérieux Connaught (Lyon, France) is a thermostable, lyophilized, avian-leukosis-free, live, attenuated virus obtained by multiplication of the 17D–204 strain in embryonated chicken eggs. From 1983 to 1994, approximately 65 million doses of this vaccine were distributed worldwide. The vaccine has been proven safe and efficacious during long-term experience in the field and is currently licensed in 51 countries. Recently, a new working seed of this vaccine (PV26) was adopted for vaccine manufacture because the old seed (IP/F2) had been used up. As part of the clinical validation of the new seed, the immunogenicity and safety of two batches of this vaccine (PM-YF) were compared with those of another commercially available vaccine (Arilvax[®]; Evans Medical, Liverpool, United Kingdom; licensed to Glaxo Wellcome, Greenford, United Kingdom) (W-YF) in this large-scale randomized trial.

The primary objective of our study was to demonstrate that the immunogenicity of yellow fever vaccine derived from the new working seed was equivalent to that of the reference vaccine in terms of the percentage of subjects who achieved seroprotective levels of yellow fever virus neutral-

izing antibodies one month after a single vaccine dose. In addition, the study aimed to confirm the validity of using serologic assessments performed 10–14 days after vaccination as an early control for seroprotection against yellow fever. Finally, the consistency of two different batches of PM-YF was verified in the setting of this GCP-compliant trial.

MATERIALS AND METHODS

Study design and ethical considerations. This was a multicenter, randomized, modified-double-blind study performed in 211 healthy adult volunteers in the United Kingdom. Due to differences in vaccine color, a nurse or pharmacist independent from the investigational team reconstituted the vaccine into masked syringes. Neither the investigator nor the subject was aware of the nature of the vaccine used, and all clinical and serologic assessments were performed under double-blind conditions.

Subjects were randomized to receive a single subcutaneous injection of either PM-YF or W-YF. Venous blood samples were drawn just before immunization (day [D]0), as well as 10–14 days (D10–14), and one month (D28) after vaccination. Local and systemic reactogenicity were monitored up to 28 days after injection. Venous blood samples for a series of hepatic function tests were taken on D0 and D28.

This trial was conducted in accordance with the latest revision of the Declaration of Helsinki (1989) and European GCP guidelines. The protocol was approved by the Ethics Committees of the Royal Free National Health Service Trust and School of Medicine (London, United Kingdom) and that of East Berkshire, United Kingdom prior to the commencement of the study. Each subject gave written informed consent before being included in the study.

Selection of subjects. Subjects were recruited from one travel clinic in the United Kingdom (British Airways Travel Clinic, London), one hospital travel medicine unit (Academic Unit of Travel Medicine and Vaccines, Royal Free Hospital School of Medicine, London), and one Contract Research Organization healthy volunteer clinical trial center (Chiltern International, Limited, Buckinghamshire). Subjects were at least 18 years old, had never received yellow fever vaccine, and had a state of health compatible with vaccination. Subjects with hepatosplenomegaly or with fever (axillary temperature $> 37.5^{\circ}\text{C}$ or oral temperature $> 38.0^{\circ}\text{C}$) on the day of inclusion were not enrolled. Other non-inclusion criteria were an acute infectious disease, chronic deteriorating illness, malignant disease, a coagulopathy, or a known allergy to eggs, polymyxin, or neomycin. Any subject who was receiving immunosuppressive therapy or who had received human immunoglobulin during the previous six months was not included. The use of immunoglobulin, immunosuppressive agents, or known inhibitors or inducers of liver enzymes was also prohibited during the study period. Women were only included if they were not pregnant or breast-feeding, and had been using a reliable means of contraception for at least three months before the study.

Vaccine. All viral vaccines were obtained from usual commercial sources, under the same conditions. The freeze-dried, stabilized, mono-dose PM-YF (Stamaril[®]; Pasteur

Mérieux Connaught) is a live, attenuated virus prepared from the 17D–204 strain, and is free from avian leukosis virus. The lyophilized vaccine is reconstituted with a supplied diluent (buffered saline solution) to a total volume of 0.5 ml. Each 0.5-ml dose of reconstituted vaccine contains live, attenuated yellow fever virus ($\geq 1,000$ mouse 50% lethal doses [LD_{50}s]), lactose, sorbitol, L-histidine hydrochloride, L-alanine, and 0.4% (w/v) sodium chloride diluent solution up to a volume of 0.5 ml. Two usual commercial lots of vaccine (no. M5140 and L6076) were randomized in this study to verify the batch consistency.

The comparator yellow fever vaccine was a commercially available vaccine (Arilvax[®]; Evans Medical, licensed to Wellcome). It is also a lyophilized preparation of live, attenuated virus prepared from the 17D–204 strain that is reconstituted before use with a supplied diluent. Each 0.5-ml dose of this vaccine contained live, attenuated yellow fever virus ($\geq 1,000$ mouse LD_{50}s), neomycin (< 2 IU/ml), polymyxin B sulfate (< 5 IU/ml), sorbitol, hydrolyzed gelatin, sodium chloride, potassium chloride, disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate, and water for injection up to a volume of 0.5 ml. All vaccine used in this study was from a usual commercial batch (BYF/1/344).

Each lyophilized vaccine was reconstituted with diluent less than 1 hr before injection and administered subcutaneously into the deltoid region.

Immunogenicity evaluation. Venous blood samples (5 ml) for serologic analysis were taken before vaccination (D0), and then at D10–14 and D28. Yellow fever virus neutralizing antibodies were assayed by measuring the reduction in viral plaques on cultured porcine kidney (PS) cells using the 17D virus as the antigen,¹⁵ which is the standard technique used for assessing the response to yellow fever vaccine today.¹⁶ Plaque reduction neutralization was performed in PS cell 24-well microplate cultures (8.105 cells/ml and 0.2 ml/well) mixing 100 plaque-forming units (pfu) of 17D yellow fever virus with various serum dilutions and guinea pig pooled sera as a source of complement in equal volumes. A viral back-titration was also performed (in duplicate) by mixing an equal volume of normal human serum and the test viral dilution and a 1:5 viral dilution. This mixture provided 100 and 20 pfu in the respective dilutions. The first international reference preparation of monkey yellow fever serum (National Institute for Biological Standards and Control, Pottery Bar, United Kingdom) was used as a positive quality control, and a nonimmune serum (Serum Stateninstitut, Copenhagen, Denmark) was used as a negative control. The neutralizing antibody titer was the reciprocal of the highest serum dilution that reduced the number of viral inoculum plaques by at least 80%. A yellow fever virus neutralizing antibody titer $\geq 1/10$ is accepted as a serologic surrogate of clinical protection,⁷ and subjects were considered to have seroconverted if they had a neutralizing antibody titer above this threshold. Results were also expressed in international units per milliliter (IU/ml) using the reference preparation of monkey yellow fever serum containing 143 IU/ml. In our bands, a 1/10 dilution corresponds to a titer of approximately 1.0 IU/ml. Although these units are not usually used in the literature to express yellow fever neutralizing antibody titers, we provide these additional data to enable our results to be compared with those from other laboratories using a stan-

TABLE 1

Yellow fever neutralizing antibody responses in healthy adults at 10–14 and 28 days after vaccination with one of two licensed yellow fever vaccines*

Time after vaccination (days)	PM-YF (n = 93)	W-YF (n = 92)
D10–D14 GMT (1/dilution)[95% CI]	26.0 [20.0–33.6]	18.4 [14.8–22.8]†
GMT (IU/ml)[95% CI]	2.26 [1.75–2.90]	1.04 [1.32–2.03]
Seroconversion ($\geq 1/10$)(%)	86%	88%
D28 GMT (1/dilution)[95% CI]	124.0 [99.4–155.0]	90.9 [71.9–115.0]‡
GMT (IU/ml)[95% CI]	10.92 [8.85–13.47]	8.03 [6.32–10.20]
Seroconversion ($\geq 1/10$)(%)	100%	99%§

* PM-YF = Stamaril®; Pasteur Mérieux Connaught (Lyon, France). W-YF = Arilvax®; Evans Medical–Wellcome (Liverpool, United Kingdom). GMT = geometric mean titer; 95% CI = 95% confidence interval. Results are given in reciprocal dilutions (1/dilution) and international units per milliliter (IU/ml). Seroconversion was defined as a yellow fever virus neutralizing antibody titer $\geq 1/10$ in an initially seronegative subject.

† Statistically significant between-group difference: Wilcoxon's test, $P = 0.04$.

‡ Statistically significant between-group difference: Wilcoxon's test, $P = 0.02$.

§ Equivalent according to one-sided equivalence test, $P = 0.001$.

dardized unit system. Serologic analyses were performed by the Pasteur Mérieux Connaught Clinical Sero-Immunology Laboratory (Val de Reuil, France).

Safety evaluation. Subjects were observed for 15 min after vaccination for immediate reactions. The subject was asked to record local events occurring within 10–14 days of immunization, and systemic events within 28 days, on a self-monitoring form. Solicited local reactions (listed on the form) were pain at the injection site, redness ≥ 3 cm in diameter, induration/swelling, and hematoma ≥ 3 cm in diameter. Solicited systemic reactions were fever (axillary temperature $> 37.5^{\circ}\text{C}$, oral temperature $> 38.0^{\circ}\text{C}$), asthenia, headache, myalgia/arthritis, and gastrointestinal symptoms (including nausea, vomiting, abdominal pain and diarrhea).

A 5-ml blood sample was taken before vaccination and a second sample was taken at D28 for the following hepatic function tests: serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), γ -glutamyl transpeptidase (GGT), and alkaline phosphatase. Any subject who had an abnormal laboratory value > 3 times the upper limit of the normal range was monitored with weekly tests until the value returned to within the normal range.

The percentage of subjects who presented with at least one local or systemic reaction or an abnormal hepatic function test result, between D0 and D10–14 (local reactions) and D0 and D28 (systemic reactions and hepatic function abnormalities) was calculated.

Statistical analysis. Two batches of PM-YF vaccine were used in this study. It was considered that if the 95% confidence interval of the ratio of geometric mean titer (GMT) values for the two batches (no. M5140/no. L6076) contained 1.0 at both sampling times, then there was no significant difference between the batches, permitting their results to be pooled for a global comparison of PM-YF with W-YF.

The primary objective of the study was to demonstrate that the seroconversion rate obtained with PM-YF derived from the PV26 working seed was within 10% of that achieved by the W-YF reference vaccine. The equivalence of the two vaccines could be accepted if the superior limit of the 95% confidence interval for the arithmetic difference between the two seroconversion rates was less than 10%. The number of evaluable subjects required, using a one-sided equivalence test with an α -risk of 5% and a β -risk of 10%, was estimated to be 101 per group, requiring a total study population of 202 subjects. The statistical analysis was

performed by the Biometry Department of Mapi S.A. (Lyon, France) using SAS software (SAS Inc., Cary, NC).

RESULTS

Subjects. Two hundred eleven healthy adult subjects were recruited for this study, 106 in the PM-YF group and 105 in the W-YF group. Subject characteristics were comparable in the two groups: the mean age was 32 years in the PM-YF group (range = 18–65 years) and 31 years in the W-YF group (range = 18–69 years); women represented 62% of the subjects vaccinated with PM-YF and 65% of those who received W-YF.

Only three subjects, two in the PM-YF group and one in the W-YF group, failed to complete the study (lost to follow-up). One subject in the W-YF group did not attend the D10–14 visit, but returned for the D28 evaluation.

Upon sera analysis, five subjects in the PM-YF group and nine subjects in the W-YF group were found to be seropositive at the start of the study for yellow fever virus neutralizing antibodies (titer $\geq 1/10$). These subjects were not included in the immunogenicity analysis. Eight subjects with missing blood samples at D0 or D28, and three subjects with a major protocol deviation (receiving prohibited therapy during the study [beclomethasone]) were also excluded from this analysis. Evaluable immunogenicity data were thus available for 185 subjects, 93 in the PM-YF group and 92 in the W-YF group.

Immunogenicity analysis. After pooling of PM-YF batches, the ratio of GMT values for the two PM-YF batches (no. M5140/no. L6076) showed no significant difference (at the 95% level) between batches: D0–14, 0.85 (0.5, 1.44); D28, 1.45 (0.93, 2.26); This permitted the results to be pooled and a global comparison of PM-YF with W-YF was performed.

Immunogenicity at D10–14. Ten to fourteen days after vaccination, the proportions of subjects who had seroconverted for yellow fever neutralizing antibodies ($\geq 1/10$) (Table 1) were similar in the two groups (86% in the PM-YF group and 88% in the W-YF group). The GMT value at this time was significantly higher in the PM-YF group (26.0 1/dilution) than in the W-YF group (18.4 1/dilution) ($P = 0.04$, by Wilcoxon test; Table 1). Groups appeared comparable for the distribution of visit times between D10 and D14.

The good consistency of the two batches of PM-YF vac-

TABLE 2

Local and systemic reactions reported by healthy adults after vaccination with one of two licensed yellow fever vaccines*

	PM-YF (n = 106)	W-YF (n = 105)
Percentage of subjects with ≥ 1 reaction		
Local reactions†	16%	15%
Number of events		
Pain	10	10
Redness	5	4
Hematoma	3	4
Induration/swelling	0	3
Systemic reactions‡	16%	18%
Number of events		
Fever§	0	0
Asthenia	8	11
Headache	13	12
Myalgia	9	6
Arthralgia	1	1
Gastrointestinal events	5	2

* PM-YF = Stamaryl®; Pasteur Mérieux Connaught (Lyon, France); W-YF = Arilvax®; Evans Medical-Wellcome (Liverpool, United Kingdom).

† Reported within 10–14 days of vaccination.

‡ Reported within 28 days of vaccination.

§ Axillary temperature $> 37.5^{\circ}\text{C}$, oral temperature $> 38.0^{\circ}\text{C}$.

cine was confirmed at this early time point for both seroconversion rate (no. M5140, 83%; no. L6076, 89%) and GMT value (no. M5140, 24.2 [95% confidence interval = 16.3–36.0] 1/dilution; no. L6076, 27.9 [19.9–39.0] 1/dilution).

Immunogenicity at D28. One month after vaccination, all 93 evaluable subjects in the PM-YF group and 99% (91 of 92) in the W-YF group had seroconverted for yellow fever neutralizing antibodies (Table 1). A one-sided equivalence test confirmed that the seroprotection rates achieved by the two vaccines were equivalent ($P = 0.001$). The GMT value at this time was statistically significantly higher after vaccination with PM-YF (124.0 1/dilution) than after vaccination with W-YF (90.9 1/dilution) ($P = 0.02$, by Wilcoxon test; Table 1).

The immunogenicity of the two batches of PM-YF was comparable at D28. All subjects in each batch group had seroconverted for yellow fever virus neutralizing antibodies, and GMT values [with 95% confidence intervals] revealed no significant difference between batches (no. M5140, 148.6 [108.1–206.3] 1/dilution; no. L6076, 103.4 [76.1–140.3] 1/dilution).

Safety analysis. Immediate reactogenicity. All randomized subjects were included in the safety analysis. No subject who received PM-YF vaccine experienced an immediate reaction; four subjects (4%) in the W-YF group presented with redness of the injection site in the 15 min following vaccination. These reactions were not considered serious and all subsided spontaneously.

Local reactogenicity. During the course of the trial, 17 subjects (16%) in the PM-YF group and 16 subjects (15%) in the W-YF group reported the occurrence of one or more local reactions within 10–14 days of vaccination (Table 2). Pain was the most frequently reported reaction, but in no case was this severe, and all episodes subsided spontaneously within five days.

Systemic reactogenicity. Systemic reactions within 28 days of vaccination were reported by 17 subjects (16%) in

the PM-YF group and 19 subjects (18%) in the W-YF group (Table 2). No episodes of fever occurred. Headache, asthenia, and myalgia were the most commonly reported events, but were mostly of mild intensity and subsided in an average of approximately 24 hr.

Liver function tests. One month after vaccination, three subjects, two in the PM-YF group and one in the W-YF group, had AST levels elevated more than three times above the upper limit of normal (40 IU/ml). In no case, according to the investigators, was the elevated transaminase level attributed to the vaccine. For one subject in the PM-YF group (AST = 497 IU/ml), following extensive investigations for known viral infections, including yellow fever, the cause was assigned by the investigator to a nonspecific intercurrent viral illness, with no relation to vaccine; for the other subject in this group (AST = 151 IU/ml), the elevation of the AST level was attributed to a concomitant medication (mefloquine) for which an increased transaminase level is a noted possible adverse reaction. Both subjects were followed up until their enzyme levels returned to within three times the upper limit of normal. The subject in the W-YF group who presented with elevated AST levels at D0 (182 IU/ml) and D28 (152 IU/ml) was found upon questioning to consume alcohol regularly. No other potentially clinically relevant change in any of the other hepatic function test results was observed for any of these three subjects.

DISCUSSION

Yellow fever 17D vaccine is extremely efficacious and safe, and has been a major success story in the control of this disease in the Americas and Africa. Nevertheless, a recent report of the re-emergence of yellow fever in Africa and South America³ serves as a timely warning that immunization of travelers to and inhabitants of at-risk countries must be maintained, if not increased. The WHO, the United Nations Children's Fund (UNICEF), and the World Bank have recommended that 33 African countries at risk for yellow fever add the vaccine to the established Expanded Program on Immunization.^{17,18}

The WHO is responsible for approving manufacturers of yellow fever vaccine^{19,20} and has put in place a seed-lot system.⁷ Approximately 20–25 million doses of vaccine are produced annually by a combination of 12 producers,¹¹ each using one of three primary seeds (17-204, 17DD, or 17-204-WHO). However, immunologic and safety data concerning these 17D yellow fever vaccines obtained in well-controlled, randomized studies adhering to GCP guidelines are rarely reported in the peer-reviewed literature. This is of particular concern in view of some reports of reduced immunogenicity of certain yellow fever vaccines.¹² A meeting on yellow fever held by WHO in May 1998 emphasized that seroconversion rates to yellow fever vaccine reported in recent mass campaigns in Nigeria and Brazil ranged from 60% to 75%. These rates are considerably lower than the formerly reported 95%, and could be as low as 65% in healthy travelers who received other heat-stabilized 17D.^{13,21} vaccines. The WHO stated that should these poor seroconversion rates be confirmed, then serosurveys will be commissioned in Africa and Latin America to assess the serologic response to yellow fever vaccines.¹³ In this context, it would also seem advis-

able for all established approved yellow fever vaccine manufacturers to verify on a regular basis the immunogenicity and safety of their yellow fever virus working seeds to ensure that the vaccines provide adequate protection.

As part of the process necessary for the clinical validation of a new working seed of a licensed yellow fever vaccine, the immunogenicity and safety of two batches of PM-YF, derived from primary seed 17D-204, were compared with those of a commercially available reference vaccine, derived from the same primary seed, in a large-scale, randomized study. We report the immunogenicity results both in reciprocal dilutions, as is commonplace in the literature, and also in IU/ml, so as to be able to compare our results with those from other trials that use a standardized unit system in their serologic analyses.

A single dose of PM-YF was highly immunogenic, resulting in a 100% seroconversion rate for yellow fever virus neutralizing antibodies one month after vaccination. These results were in agreement with those recently reported in young adults when this vaccine was reconstituted by a typhoid Vi subunit vaccine and given intramuscularly in association with an inactivated hepatitis A vaccine.²²

At both two weeks and also one month after vaccination, GMT values were statistically significantly greater in subjects who received PM-YF compared with those who received the reference vaccine. Nevertheless, in our study centers, according to the primary statistical hypothesis used in this study, a one-sided equivalence test revealed that in terms of seroconversion rate at D28, the two vaccines were equivalent.

Most assessments of the immunogenicity of yellow fever vaccines are performed one month after vaccination, when neutralizing antibody titers reach their peak.⁷ This relatively long time required to check the seroprotective response to vaccination may pose a problem if travel to a yellow fever endemic region is required on short notice, or if protection must be ascertained rapidly in epidemic conditions. Our results show that while antibody titers are clearly lower at D10-14 than at D28, in terms of seroprotection, 80 (86%) of 93 subjects in the PM-YF group and 81 (89%) of 91 subjects in the W-YF group who eventually seroconverted at D28 had seroconverted at the early time point. Therefore, assessments made 10-14 days after vaccination could be useful in the majority of cases if an early confirmation of a seroprotective response is needed.

The two batches of PM-YF prepared from the new working seed PV26 were consistent in terms of immunogenicity (seroconversion and GMT value) at D10-14 and D28, confirming the reliability of the manufacturing process of this viral vaccine.

Both yellow fever vaccines were safe. No immediate hypersensitivity reaction with rash or urticaria was reported, and based on a panel of standard hepatic function tests, there were no clinically significant abnormalities that were associated with use of yellow fever vaccine. No case of fever occurred. Reactions to the vaccines were generally mild and transient, and consisted mainly of pain at the injection site, with headache, myalgia, or asthenia.

Although differences in yellow fever neutralizing antibody GMT values were found, the 17D yellow fever vaccines from two different European manufacturers were high-

ly immunogenic and safe, and were equivalent in terms of seroconversion rates obtained one month after vaccination. It would seem worthwhile to compare the immunogenicity and safety of the different licensed or WHO-approved vaccines at regular intervals using such rigorous, GCP-compliant, clinical trial methods to ensure maximum seroprotective levels of antibodies are maintained in the face of an increasing risk of exposure to yellow fever virus in endemic areas.

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