



Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010

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ABSTRACT

Background: Serious, but rare adverse events following immunization (AEFI) have been reported with yellow fever (YF) 17D vaccine, including severe allergic reactions, YF vaccine-associated neurologic disease (YEL-AND) and YF vaccine-associated viscerotropic disease (YEL-AVD). The frequency with which YEL-AND and YEL-AVD occur in YF endemic countries is mostly unknown.

Methods: From 2007 to 2010, eight African countries – Benin, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo – implemented large-scale YF preventive vaccination campaigns. Each country established vaccine pharmacovigilance systems that included standard case definitions, procedures to collect and transport biological specimens, and National Expert Committees to review data and classify cases. Staff in all countries received training and laboratory capacity expanded.

Results: In total, just over 38 million people were vaccinated against YF and 3116 AEFIs were reported of which 164 (5%) were classified as serious. Of these, 22 (13%) were classified as YF vaccine reactions, including 11 (50%) hypersensitivity reactions, six (27%) suspected YEL-AND, and five (23%) suspected YEL-AVD. The incidence per 100,000 vaccine doses administered was 8.2 for all reported AEFIs, 0.43 for any serious AEFI, 0.058 for YF vaccine related AEFIs, 0.029 for hypersensitivity reactions, 0.016 for YEL-AND, and 0.013 for YEL-AVD. Our findings were limited by operational challenges, including difficulties in obtaining recommended biological specimens leading to incomplete laboratory evaluation, unknown case ascertainment, and variable levels of staff training and experience.

Conclusions: Despite limitations, active case-finding in the eight different countries did not find an incidence of YF vaccine associated AEFIs that was higher than previous reports. These data reinforce the safety profile of YF vaccine and support the continued use of attenuated YF vaccine during preventive mass vaccination campaigns in YF endemic areas.

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Abbreviations: ADEM, acute disseminated encephalomyelitis; AEFI, adverse event following immunization; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescent antibody; NEC, national expert committee; PV, pharmacovigilance; RKI, Robert Koch Institut; RT-PCR, reverse transcription polymerase chain reaction; YF, yellow fever; YFV, yellow fever vaccine; YFI, Yellow Fever Initiative; YFIC, Yellow Fever Investment Case; YEL-AND, yellow fever vaccine-associated neurologic disease; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; WHO, World Health Organization.

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1. Introduction

In 2006, the Yellow Fever Initiative (YFI) was launched to control a resurgence of yellow fever (YF) and reduce epidemic risk in sub-Saharan Africa through preventive vaccination campaigns [1]. The YF 17D vaccine has long been considered safe; however, serious adverse events following immunization (AEFIs) have been documented [2–7]. YF vaccine-associated neurologic disease (YEL-AND) is caused by neuro-invasion by the 17D virus resulting in post-vaccination encephalitis, acute disseminated encephalomyelitis (ADEM) or other neurologic manifestations; has a median onset of 13–15 days; and rarely results in death [8–10]. YF vaccine-associated viscerotropic disease (YEL-AVD) is an acute multi-organ

system dysfunction resembling wild-type YF infection, has an incubation period of 2–7 days, and has a case fatality ratio of >60% [8,10]. Severe allergic reactions include hypersensitivity, anaphylactic and anaphylactoid reactions [8,10].

YEL-AND and YEL-AVD have been described only in primary vaccinees and mainly in travelers [11,12] with estimated incidences of, respectively, 0.8 and 0.4 reported cases per 100,000 17D YF vaccine (YFV) doses [11,12]. In addition to travelers, YFV is used in infant immunization programmes in endemic areas and for mass vaccination during outbreaks. These latter uses rarely have included case-finding for AEFIs and consequently the incidence of YEL-AND and YEL-AVD in YF endemic countries is largely unknown. Recent reports from the Americas have reported incidence rates of 1.1 per 100,000 doses for YEL-AND and between 0.019 and 0.31 per 100,000 doses for YEL-AVD [13].

Since 2007, the World Health Organization (WHO) and partners have worked with countries in sub-Saharan Africa to enhance their capacity to detect, assess, and conduct clinical and laboratory investigation of suspected vaccine-associated events during YF vaccination campaigns. The main objective of this paper was to conduct a systematic analysis of all AEFIs reported during these campaigns and to estimate the incidence of YF vaccine-associated AEFIs.

2. Methods

2.1. Study design and setting

From 2007 to 2010, active surveillance of serious AEFIs was undertaken during preventive YF vaccination campaigns in Benin, Burkina Faso, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone, and Togo. All countries were included in the analysis except Burkina Faso due to unavailability of the national database. Both the 17D-204 and 17DD YF substrain vaccines were used.

2.2. Surveillance for adverse events

As part of the YF mass preventive vaccination campaign, all eight countries established enhanced case-finding for AEFI in addition to the existing routine AEFI reporting system integrated into the Expanded Programme on Immunization. Each country developed notification and investigation forms, standard operating procedures (SOPs) for collection of biological specimens, and a customized data entry tool for data management and analysis [14]. A national expert committee (NEC) was created and convened by each Ministry of Health (MoH); membership included clinical, pharmacology, epidemiology, and public health experts from the MoH, WHO country office and academic institutions. The role of the NEC was to approve AEFI surveillance plans, and to assess, monitor, and guide the investigation of suspected serious AEFIs, classify them, recommend additional testing of biological specimens if warranted, and determine causality using standard definitions where possible.

Health workers were trained to identify any adverse events during the vaccination campaign, to complete case report forms, and to send forms weekly to the national level. AEFI focal persons at district and regional levels supervised active case finding. Dedicated and trained staff identified potential cases in regional and national referral hospitals using standard case definitions through daily review of hospital registries, medical charts and interviews with emergency room staff. Neurological events (e.g., new onset of seizures, encephalitis, altered mental status), viscerotropic events (e.g., impaired hepatic or renal function, respiratory distress,) and severe allergic reactions were investigated. Active case finding continued for 30 days after the end of the immunization campaign.

2.3. Case definitions and classification

An AEFI was defined as any untoward medical occurrence in a person who had received YF vaccination in the last 30 days and which was thought to be caused by immunization. At the peripheral level, reported AEFIs were categorized as serious/non-serious. A serious adverse event included “any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life-threatening” [15]. After initial clinical and laboratory investigation, the NEC further categorized serious AEFIs according to suspected causality [16,17] (Fig. 1):

- Program Error—event caused by an error in vaccine preparation, handling or administration.
- Injection reaction—event from anxiety about, or pain from, the injection itself rather than the vaccine.
- Coincidental—event that happens after immunization but not caused by the vaccine.
- Vaccine reaction—event caused or precipitated by the vaccine when given correctly, caused by an inherent property of the vaccine.
- Unknown—cause of event cannot be determined.

2.4. Evaluating suspected serious AEFI

Serious AEFIs were assessed by clinical evaluation with a brief case history, presumptive diagnosis, observed or reported outcome, an epidemiological investigation, and collection of biological specimens with testing by both national and international laboratories depending on local capacity.

Following this extensive clinical and laboratory testing, vaccine reactions consistent with viscerotropic disease, neurological disease, or severe hypersensitivity reaction according to the United States Vaccine Adverse Events Reporting System (VAERS) case definitions [18] remained classified as suspected vaccine reactions (Fig. 1); those not consistent with the case definitions were allocated to one of the other categories according to available information. Each case with a clinical complex consistent with YEL-AND, YEL-AVD or severe hypersensitivity reaction due to YFV was further classified as suspect, probable, or confirmed, using WHO criteria [18]. Lastly, using available clinical and laboratory data for the YF vaccine-associated AEFIs we applied the Brighton criteria for anaphylaxis [19], a-septic meningitis [20], myelitis, encephalitis, ADEM [21], and viscerotropic disease (VTD) [22].

2.5. Laboratory analyses

Clinical laboratory testing, diagnostic procedures and biological specimen collection were increasingly standardized as experience was gained with each campaign [17], and varied with operational challenges. Additionally, cultural issues affected evaluations (e.g., autopsies). Thus, information available for each serious AEFI case varied. Where possible, blood, CSF, urine and tissue samples were tested by the YF International Reference Laboratory at the Robert Koch Institute (RKI), Berlin, Germany. YF quantitative reverse transcription polymerase chain reaction (RT-PCR) [23,24] was performed on specimens sent to the RKI, as was serology including IgM and IgG indirect immunofluorescence assay (IFA) (Euroimmun, Lübeck, Germany), neutralizing antibodies assay (in-house plaque reduction neutralization test, 90%) [25] and for anaphylaxis cases total IgE ELISA (Euroimmun, Lübeck, Germany) [26–28]. Viral culture for YF 17D virus isolation was performed only for those with a positive PCR result. Lastly, upon the NEC's request, additional testing was performed on blood or CSF samples, including a panflavivirus RT-hemi-nested PCR assay [29], generic herpesvirus

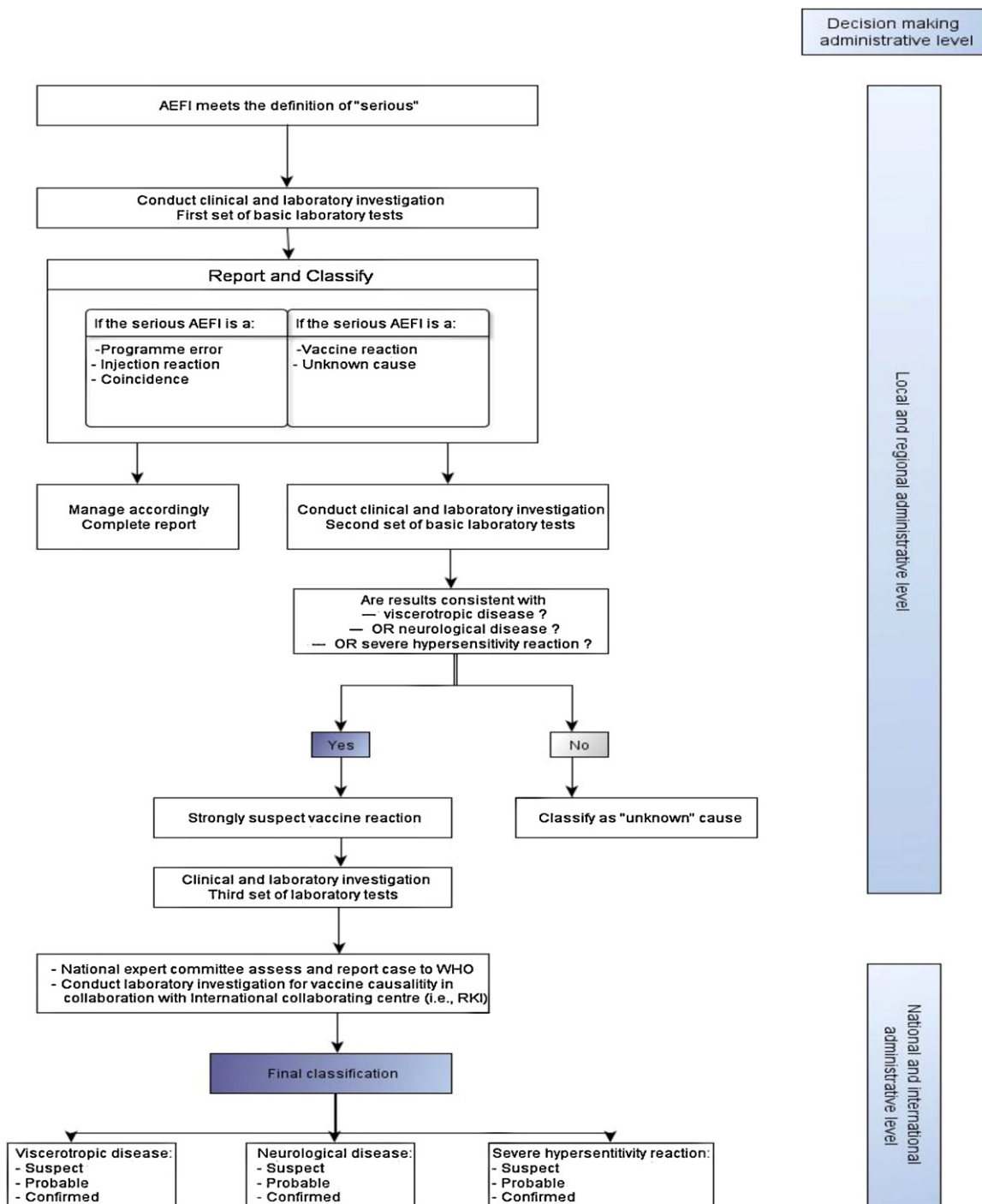


Fig. 1. Decision tree to classify by administrative level reported serious adverse events following immunization against yellow fever. Adapted from Ref. [17].

nested PCR [30], generic enterovirus RT-nested PCR [30], generic alphavirus RT-nested PCR [31], Lassa virus RT-nested PCR [32], dengue NS1 antigen detection, capture IgM and indirect IgG ELISAs (Panbio, Brisbane, Australia), and an in-house West Nile virus plaque reduction neutralization assay.

2.6. Database development and analysis

AEFI surveillance data collected for the YF vaccination campaigns were entered into country-specific databases, developed locally. To create a unified database to allow for comparative analyses the country-specific databases were reviewed and merged

using FileMakerPro 11, V3 (FileMaker Inc. Santa Clara, CA, USA). Variables in each dataset were matched to standard variables created in an iterative process to reflect the data available for each country. For example, as data were added country by country, new variables were created to accommodate information provided as experience with the campaigns developed and more data were collected over time. Standard data capture screens were created for demographic, clinical, laboratory, treatment and outcome variables, and information collected in French was entered in the database in English by bilingual team members. Patient-level clinical and laboratory information was not available for Togo and Senegal and therefore for these countries only summary data from

technical reports were included in the unified database. Observed discrepancies between the unified database and technical reports were reviewed and resolved with WHO YF control programme personnel. Where necessary country source data were requested and re-examined. Descriptive analyses were performed using the statistical package STATA® version 10 (College Station, TX, USA).

3. Results

During the eight campaigns, approximately 38 million vaccine doses were administered (Table 1). A total of 3116 AEFIs were reported (48% in males), 164 (5%) were considered serious by the NECs (Table 1) and 22 (13%) were classified as possible YFV reactions (Table 1). The incidence of YFV reactions was 0.058 per 100,000 doses with a variation by country from 0.017 to 0.252 per 100,000 doses.

Of the 22 YFV reactions, 6 (27%) were classified as suspected YEL-AND, 5 (23%) as suspected YEL-AVD and 11 (50%) as a hypersensitivity reaction (Table 2); among the hypersensitivity reactions, seven were classified as confirmed, none as probable, three as suspect and one as unclassified. YEL-AND, YEL-AVD and hypersensitivity reaction incidence rates were 0.016, 0.013, and 0.029 per 100,000 doses. YEL-AND and YEL-AVD cases were not clustered within or between countries. A history of receiving YF vaccination before the YF vaccination campaign was not available.

Of the 164 serious reported AEFIs, 142 were considered to be unrelated to YFV; these included program errors ($n=2$), injection reaction ($n=1$), coincidental causes ($n=121$), unspecified causes ($n=5$), and 13 cases for which the final NEC classification was unknown due to the absence of an in-depth investigation. The primary final diagnoses included malaria ($n=34$ [28%]), infectious meningoencephalitis ($n=15$ [12%]), dengue ($n=10$ [8%]), hepatitis A, B, or C ($n=10$ [8%]), and chronic or unspecified hepatitis ($n=8$ [7%]).

The mean age of the 22 YFV reactions was 26.6 years (median 24 years; SD: 21.4; range 3–78); 55% were males. The mean age of all 164 serious AEFIs was 22.7 years (median 18 yrs; SD: 19.6; range 1–83); 62% were male.

Among the 22 YFV reactions, the mean duration between date of vaccination and first appearance of symptoms was 1.8 days (median 1.0, range 0–14 days) for the hypersensitivity cases; for YEL-AND, 8 days (median 7.5, range 0–21 days) and for YEL-AVD, 4 days (median 4.0, range 0–9 days). For all 164 serious reported AEFIs, the mean delay in symptom onset was 6.3 days (median, 2; range 0–30 days).

Thirty-three deaths were reported. Health authorities classified 27 (82%) as serious AEFIs. Six were excluded from consideration: two due to complete absence of information, one because YFV had not been received, and three whose deaths had been classified as non-serious AEFIs, for which the country technical reports did not provide a rationale and for which we could not obtain additional information. The mean age of the remaining 27 patients was 31.5 years (median 34 years; SD 19.2; range 4–65 years) and 59% were males. Most deaths were classified as coincidental ($n=18$; 67%) and for three of these, diagnosis was facilitated by autopsy (Table 3). One death was due to a hypersensitivity reaction (anaphylactic shock) (4%), one was a suspected YEL-AND (4%) and four were suspected to have YEL-AVD (15%) (Table 3). For three (11%), the cause of death was unknown.

The 22 patients classified as having YF vaccine-associated AEFIs had symptoms and outcomes consistent with their final clinical categorization (Table 4a). Among these, 14 (64%) did not meet the applicable Brighton case definition for anaphylaxis, aseptic meningitis, myelitis, encephalitis, ADEM and VTD (Table 4a). Laboratory evaluations to rule out other diagnoses were based on

Table 1
Summary of adverse events following immunization (AEFI) surveillance following mass preventive yellow fever vaccination campaigns in Central and West Africa, 2007–2010.

Country	Year vaccination campaign	No of vaccine doses administered	Administrative vaccination coverage (%) ^a	Survey vaccination coverage (%) ^b	Total reported AEFIs	Total AEFI reporting rate per 100,000 doses	Reported serious AEFIs (% of total due to serious)	Serious AEFI reporting rate per 100,000 doses	YF vaccine associated AEFI (% of all serious)	YF vaccine associated AEFI reporting rate per 100,000 doses
Togo	2007	2 379 858	101.3	89.9	320	13.45	14 (4%)	0.59	6 (43%)	0.252
Senegal	2007	3 106 256	99.4	94.2	143	4.60	2 (1%)	0.06	2 (100%)	0.064
Mali	2008	5 865 651	98.7	83.3	116	1.98	7 (6%)	0.12	1 (14%)	0.017
Cameroon	2009	7 509 502	100.5	88.2	362	4.82	44 (12%)	0.59	2 (5%)	0.027
Sierra Leone	2009	3 977 674	96.7	NA ^c	653	16.42	8 (1%)	0.20	2 (25%)	0.050
Liberia	2009	2 894 623	99.4	NA ^c	234	8.08	23 (10%)	0.79	0 (0)	—
Benin	2009	6 316 808	99.8	90.6	535	8.47	52 (10%)	0.82	6 (11%)	0.095
Guinea	2010	5 959 039	98.3	89.1	753	12.63	14 (2%)	0.23	3 (21%)	0.050
Overall		38 009 411	99.4	—	3116	8.20	164 (5%)	0.43	22 (13%)	0.058

^a Administrative coverage is the number of doses administered to individuals/target population for each country.

^b The estimate includes data obtained from the vaccination card and by history. All coverage surveys were two-stage cluster surveys.

^c NA: Data not available.

Table 2

Case counts and incidence rates of 22 YF vaccine-associated AEFIs reported during mass preventive yellow fever vaccine campaigns in Central and West Africa, 2007–2010, by clinical syndrome.[‡] Of the eight included countries, Liberia did not report any cases and thus is not included.

Outcome	Countries	Case counts (N)	Reports per 100,000 doses administered
Acute neurotropic disease (YEL-AND)*	Benin	1	0.016
	Mali	1	0.017
	Senegal	1	0.032
	Sierra Leone	1	0.025
	Togo	2	0.084
	TOTAL	6	0.016
Acute viscerotropic disease (YEL-AVD)*	Guinea	2	0.034
	Senegal	1	0.032
	Togo	2	0.084
	TOTAL	5	0.013
Hypersensitivity reaction**	Benin	5	0.076
	Cameroon	2	0.027
	Guinea	1	0.017
	Sierra Leone	1	0.025
	Togo	2	0.084
	TOTAL	11	0.029
TOTAL		22	0.058

*All YEL-AND and YEL-AVD cases were classified as suspected cases due to lack of supporting data to further classify them as probable or confirmed YF vaccine-associated AEFIs.

**Note: Of the 11 hypersensitivity reactions, 3 were classified as suspected, 7 as confirmed, and one as unclassified.

clinical presentation and the biological specimens available. The 22 patients had different YF-specific tests, including five with no testing (Table 4b). Of 17 patients with an acute serum sample available for YF serology, five were IgM positive and 11 were IgG positive, of which four were strongly positive (IgG titres >1:500).

4. Discussion

This first report on the safety of YFV in preventive mass vaccination campaigns in Africa conducted under the YFI has revealed a lower risk of serious adverse events than that observed in studies of travellers. Studies of U.S. and European travellers have found YEL-AVD rates of 0.25 to 0.4 per 100,000 YFV [11,12,33]; YEL-AND rates of 0.25 to 0.8 [11,12,33] and up to 9.9 cases per 100,000 YFV doses using a sensitive case definition [34]; and rates of anaphylactic reactions of 0.9 [13] to 1.8 per 100,000 YFV doses [12]. These rates are over 15-fold higher than those we found. Our results are

comparable with results of a previous YF AEFI study conducted as part of an emergency vaccination campaign in 2001 in Abidjan, Ivory Coast [35]. This study reported an incidence of any serious YF AEFI of 0.31 per 100,000 doses (but no YEL-AVD or YEL-AND) versus 0.43 per 100,000 doses found in our analysis. Data from Brazil, another YF endemic country, were also similar to ours [13].

The lower rates in our study may be due to differences in the populations under surveillance. Most reports on YEL-AVD and YEL-AND have occurred among first-time YF vaccinees without pre-existing YF immunity [36]. Our analysis included populations living in endemic YF areas who may have naturally acquired immunity against wild-type YF and cross-protection from exposure to other circulating flaviviruses such as dengue or West Nile. This immunity might provide protection against YEL-AVD or YEL-AND. Previous YF immunization also could have lowered the risk of YEL-AVD and YEL-AND in our study, as the participating countries had successfully introduced or extended their routine infant YF immunization programmes in the last decade and most had previously conducted emergency campaigns in response to YF outbreaks [37].

Other explanations for the lower AEFI incidence in our study must be considered, especially underreporting. For example, based on the number of vaccinated persons and local crude annual mortality rates [38], more than 38,000 deaths within one month of vaccination would be expected in the eight countries. However, only 33 deaths were reported. Furthermore, in hospitals, potential cases were not systematically investigated as health care providers assumed that specific symptoms were due to known diseases (e.g., malaria or bacterial meningitis) or considered that the AEFI was not associated with the YFV (e.g. road traffic injuries, malnutrition). In these instances, vaccination status was not obtained, which hindered active case finding and obtaining clinical information.

To increase sensitivity, vaccine safety monitoring has low specificity by design. Our own findings illustrate the co-morbidity that can make diagnosis challenging in this context: of the 164 cases classified as serious AEFI, 121 (74%) were found to have coincidental causes of illness, mainly complications due to malaria, meningo-encephalitis, or hepatitis infections.

None of the YF vaccine-associated cases had YF genome testing on human tissue, including that obtained from organ biopsy or autopsy (the latter was conducted for just one of six YF vaccine-associated deaths). For serology, convalescent serum samples were missing for 96% of patients, since patients usually did not return to the hospital for follow-up. Where samples were available, we found improper labeling, faulty containers, improper storage, and delays between collection, shipment, and receipt at (inter)national levels.

Table 3

Overview of biological samples for serious AEFI (*n* = 164) reported during preventive yellow fever vaccination campaigns in Central and West Africa, 2007–2010, and analyzed at the international YF reference laboratory (Robert Koch Institute (RKI)).

Country	Serious AEFI cases reported	Serious AEFI cases analyzed by RKI	Acute Serum/Plasma specimens ^a	Convalescent Serum specimens ^b	Blood	CSF	Urine Acute/Convalescent	Stool	Autopsy
	(<i>n</i>)	(<i>n</i>)	(<i>n/n</i>)	(<i>n/n</i>)	(<i>n</i>)	(<i>n</i>)	(<i>n</i>)	(<i>n</i>)	(<i>n</i>)
Benin	52	29	17/5	0	25	6	19/3	2	3
Cameroon	44	7	5/0	4	3	3	6/34	0	0
Guinea ^c	14	0	NA ^e	NA	NA	NA	NA	NA	NA
Liberia	23	23	12/1	0	10	3	10/1	1	0
Mali	7	7	7/0	1	0	2	0/0	0	0
Senegal ^d	2	0	NA	NA	NA	NA	NA	NA	NA
Sierra Leone	8	7	5/0	3	4	5	2/2	0	0
Togo	14	10	10/0	0	0	0	0/0	0	0
Total	164	83	56/6	8	42	19	37/10	3	3

^a Acute serum or plasma is a sample taken at onset of symptoms.

^b Convalescent serum is a sample taken at 21–35 days after onset of symptoms.

^c Samples from the YF Guinea campaign were not received at the RKI due to problems with the international shipment.

^d Samples for the YF campaign in Senegal were sent to the Institut Pasteur in Dakar, Senegal and no information is available on the number and type of samples used for the analyses. Only serological results for YF IgM and IgG listed in the technical report were available.

^e NA: not available.

Table 4a

Stratified by country, case characteristics for serious adverse events following immunization related to yellow fever vaccine ($n = 22$) reported during mass preventive yellow fever vaccination campaigns in Central and West Africa, 2007–2010.

ID	Age years	Sex	Country	Final classification and attribution	Primary symptoms	Outcome	Days from vaccination to symptom onset	Days from vaccination to first clinical evaluation	Malaria	Human immuno- deficiency virus (HIV)	Other evaluated etiologies
4	20	F	Benin	Neurologic reaction, transverse myelitis. Brighton myelitis case definition level 3	Fever, paraparesis	Recovered	4	17	NA ^a	negative	Syphilis negative, dengue negative, West Nile virus negative, alphavirus negative, flavivirus negative, herpes (blood) negative
12	4	M	Mali	Neurologic reaction Brighton case definition not applicable	Facial paralysis	Recovered	12	13	NA	negative	Hepatitis B negative, rapid test against <i>Neisseria</i> <i>meningitidis</i> , A, B/E coli K1, C, Y/W 135; <i>Haemophilus</i> <i>influenzae</i> Type b; <i>Streptococcus</i> <i>pneumoniae</i> ; and group B <i>streptococci</i> , negative
13	4	M	Senegal	Neurologic reaction Brighton encephalitis case definition NF ^b	Lower extremity muscle spasm and incoordination	Recovered	11	11	NA	NA	Viral ^c encephalitis negative; bacterial meningitis negative; viral meningitis (herpes simplex virus, varicella-zoster virus, Epstein-Barr virus) negative
16	42	F	Sierra Leone	Neurologic reaction Brighton encephalitis case definition NF	Fever, headache, generalized convulsions, altered mental status	Death (no autopsy done)	2	6	negative	positive	Syphilis: VDRL positive, TPHA ^d negative, hepatitis B negative
20	54	M	Togo	Neurologic reaction, meningitis Brighton aseptic meningitis case definition NF	Pain and cervical stiffness	Recovered	<1	3	negative	negative	None
21	25	F	Togo	Neurologic reaction Brighton case definition not applicable	Facial paralysis	Recovered	<1	8	NA	negative	None

9	15	M	Guinea	Viscerotropic reaction Brighton VTD ^e case definition NF	Abdominal pain, fever, muscle weakness, anorexia	Death (no autopsy done)	4	6	positive	negative	Hepatitis B/C negative
10	34	M	Guinea	Viscerotropic reaction Brighton VTD case definition NF	Coma, jaundice and bleeding	Death (autopsy done) ^f	4	6	positive	NA	None
14	28	M	Senegal	Viscerotropic reaction Brighton VTD case definition NF	Febrile jaundice	Recovered	6	6	negative	NA	Viral ^e encephalitis negative, hepatitis B negative
17	5	F	Togo	Viscerotropic reaction, nephritic syndrome, allergy Brighton VTD case definition NF	Fever, facial and lower extremity edema	Death (no autopsy done)	9	15	negative	negative	None
19	40	F	Togo	Viscerotropic reaction, hemorrhagic syndrome, death (no autopsy) Brighton VTD case definition NF	Black stools, nausea (black vomit), fever	Death (no autopsy done)	<1	<1	NA	NA	None
1	3	F	Benin	Hypersensitivity, severe pulmonary infection Brighton anaphylaxis NF	Respiratory distress	Recovered	<1	<1	negative	NA ^b	Dengue negative
2	12	F	Benin	Hypersensitivity severe allergic reaction Brighton anaphylaxis NF	Edema, generalized urticaria	Recovered	14	15	positive	NA	Dengue negative, hepatitis A/B/C negative, flavivirus negative
3	4	M	Benin	Hypersensitivity, anaphylactoid reaction, bacterial infection post vaccination Brighton anaphylaxis level 2	Edema	Recovered	<1	<1	NA	NA	Dengue negative
5	25	M	Benin	Hypersensitivity, severe allergic reaction Brighton anaphylaxis NF	Fever, muscle weakness, dizziness	Recovered	2	2	negative	NA	None

Table 4a (Continued)

ID	Age years	Sex	Country	Final classification and attribution	Primary symptoms	Outcome	Days from vaccination to symptom onset	Days from vaccination to first clinical evaluation	Malaria	Human immuno- deficiency virus (HIV)	Other evaluated etiologies
6	19	F	Benin	Hypersensitivity, severe allergic reaction Brighton anaphylaxis NF	Fever, muscle weakness, dizziness	Recovered	1	1	negative	NA	Dengue negative
7	4	F	Cameroon	Hypersensitivity Brighton anaphylaxis NF	Fever, facial edema, general pruritus	Recovered	1	3	positive	NA	Hepatitis B/C negative, alphavirus negative, Lassa virus negative, dengue negative
8	28	M	Cameroon	Hypersensitivity Brighton anaphylaxis level 2	General edema, urticaria, airway obstruction	Recovered	<1	<1	NA	NA	Dengue IgG positive
11	78	M	Guinea	Hypersensitivity, anaphylactic shock Brighton anaphylaxis level 2	Dyspnea, nausea, vomiting	Recovered	<1	1	NA	NA	None
15	62	M	Sierra Leone	Hypersensitivity Brighton anaphylaxis case definition NF	Fever, generalized body pains, weakness, facial edema	Recovered	<1	24	negative	NA	Hepatitis B positive, hepatitis C negative, flavivirus negative, alphavirus negative, Lassa virus negative, dengue IgG positive
18	57	F	Togo	Hypersensitivity, anaphylactic shock Brighton anaphylaxis case definition NF	Loss of consciousness	Death (no autopsy done)	<1	<1	NA	NA	None
22	23	M	Togo	Hypersensitivity, Stevens-Johnson syndrome Brighton case definition not applicable	Ulceration of lips, general vesicular eruption	Recovered	1	9	negative	negative	None

^a NA: not available.^b NF: not fulfilled (meaning the applicable Brighton case definition was not met).^c Rift Valley fever, Crimean-Congo hemorrhagic fever, dengue, chikungunya virus, West Nile virus.^d Treponema Pallidum Hemagglutination Assay.^e VTD: Viscerotropic disease.^f The autopsy samples obtained could not be analysed at the Robert Koch Institute due to problems with the international shipment.

Table 4b

Stratified by disease category yellow fever specific test results for serious adverse events following immunization ($n = 22$) related to yellow fever vaccine and reported during mass preventive yellow fever vaccination campaigns in Central and West Africa, 2007–2010.

ID	Final Classification	Acute Serum/Plasma ^a		Convalescent Serum ^b		Cerebro-spinal fluid		YF real-time reverse transcription-quantitative Polymerase chain reaction (YF RT-qPCR)				Reciprocal Neutraliza-tion titer (1:x)	Total IgE (IE/ml)	Days between vaccination and sample collection ^d
		IgM (1:10)	IgG (1:100)	IgM (1:10)	IgG (1:100)	IgM (1:10)	IgG (1:100)	Serum	Blood or plasma	CSF ^c	Urine			
4	YEL-AND	+	+	NA		NA		–	–	NA	–	–	NA	17
12	YEL-AND	+	+	NA		–	–	–	NA	–	NA	11	NA	15
13	YEL-AND	–	+	NA		NA		–	NA	NA	NA	NA	NA	11
16	YEL-AND	–	++	NA		–	+	–	–	–	NA	NA	NA	6
20	YEL-AND	+	+	NA		NA		NA	NA	NA	NA	NA	NA	4
21	YEL-AND	+	++	NA		NA		NA	NA	NA	NA	22	NA	8
9	YEL-AVD	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
10	YEL-AVD	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
14	YEL-AVD	–	+	NA		NA		–	NA	NA	NA	NA	NA	6
17	YEL-AVD	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
19	YEL-AVD	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
1	Hypersensitivity	–	+	NA		NA		–	–	NA	–	12	>500	4
2	Hypersensitivity	–	++	NA		NA		–	–	NA	NA	16	>500	15
3	Hypersensitivity	–	+	NA		–	–	NA	–	NA	–	25	>500	2
5	Hypersensitivity	–	–	NA		NA		–	–	NA	NA	NA	>500	3
6	Hypersensitivity	–	–	NA		NA		–	–	NA	–	NA	>500	5
7	Hypersensitivity	–	–	NA		–	–	–	++	+	–	NA	>500	6
8	Hypersensitivity	–	–	+	++	NA		–	–	NA	–	–	>500	1
11	Hypersensitivity	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
15	Hypersensitivity	+	++	NA		NA		–	–	NA	–	<10	>150	25
18	Hypersensitivity	NA	NA	NA		NA		NA	NA	NA	NA	NA	NA	NA
22	Hypersensitivity	–	–	NA		NA		NA	NA	NA	NA	44	NA	9

N/A: not available.

–: negative; no detectable anti-YFV antibodies or genome.

+: positive detection of anti-YFV antibodies or genome.

++: strongly positive detection of anti-YFV antibodies (>1:500).

^a Acute serum or plasma is a sample taken at onset of symptoms.

^b Convalescent serum is a sample taken at 21–35 days after onset of symptoms.

^c CSF: Cerebro-spinal fluid.

^d This is the time between vaccination and sample collection for the analyses to be conducted at the Robert Koch Institute, Berlin, Germany.

These issues could have compromised sample integrity causing the low observed to expected number of IgM positive samples based on the timing of post vaccination sample collection. Since anti-17D IgM antibodies appear on approximately day eight and rise until day 14 after vaccination [39] one would have expected to see IgM titers at least in the seven cases with samples taken later than one week. However, only four cases were positive. Other explanations for the observed low IgM rate could be the presence of other flaviviruses in the area causing a cross-reactive memory immune response to the YF vaccination, thereby resulting in lower or absent IgM levels. Lastly some idiopathic factors among vaccinees could have led to no or delayed seroconversion.

Occasionally, NECs could not follow standard criteria for assigning causality due to the unavailability of certain investigations or tests (e.g., neuroimaging, electroencephalogram). Consequently, we cannot be certain that the serious AEFI cases that were classified as YF vaccine-associated actually resulted from receipt of YFV. For example, one of the YF vaccine-associated hypersensitivity cases had onset of symptoms 14 days following YF vaccination; in combination with widespread hypersensitivity to helminth infections in the region [40], this makes vaccine induced hypersensitivity unlikely. In addition, due to a lack of information, some cases considered coincidental may have been misclassified as not related to YF vaccination. Lastly, among the 22 YF vaccine-associated AEFIs, the majority did not meet the applicable Brighton case definition due to a lack of required supporting laboratory testing and results.

The recommended AEFI surveillance tools and active case finding methods were progressively introduced and standardized as a result of experience gained in each country. Thus, data collection differed by countries and more recent campaigns had more detailed information available for analysis. Furthermore, the actual implementation of surveillance and criteria used for referral likely varied based on country specific issues (e.g., motivation and training of team, previous experience with YF among clinicians) and improvements in surveillance; hence, increased reporting did not necessarily mean improved surveillance, as cases may have been referred inappropriately. For example, these issues may have resulted in the much higher YF AEFI incidence observed in Togo.

Despite the limitations of conducting AEFI surveillance in Africa and difficulties encountered in case classification, several strengths can be reported. First, numerous teams in eight different countries initiated extensive efforts to find YF AEFIs and yet did not find rates greater than those reported previously from the literature. Second, our intervention supported development of NECs and raised awareness of AEFIs in countries with limited pharmacovigilance experience. As a result, some NECs have now become permanent functional committees and have conducted AEFI assessments for other vaccines such as the meningococcal A conjugate vaccine. This experience will support further capacity building in vaccine pharmacovigilance, as will new initiatives such as the WHO Programme for International Drug Monitoring [41].

Further strengthening of surveillance and special studies can help answer additional questions, such as further defining the incidence of YEL-AND and YEL-AVD, defining demographic risk groups for AEFI, and assessing the role of co-morbidities (e.g., HIV infection) in altering YF AEFI risk. Despite these remaining questions, the findings of this systematic analysis reinforce understanding of the safety profile of YFV and support continued use of attenuated YFV during mass preventive campaigns in YF endemic areas.

Competing interests

The competing interest of the authors, including financial interests and relationships and affiliations relevant to the subject of the manuscript are as follows: JGB, and BDG work for Agence de

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Authors' contributions

JGB was responsible for study design, data management, analysis and interpretation, and she drafted the manuscript. RFL initiated the study, developed the study design and contributed to the data analysis and interpretation, and project coordination. EA contributed to data management and interpretation. OV contributed to study design, data analysis and interpretation, and was responsible for project management. DJ was responsible for creating the unified database and data management. CD, MB, and MN conducted the laboratory analyses and contributed to data interpretation. WP contributed to study design, data analysis and interpretation. BDG contributed to study design, data analysis and interpretation and supervised AMP's scientific contribution to the study over the entire study duration. SY was responsible for oversight of data collection during the eight YF preventive vaccine campaigns and contributed to data interpretation. All authors critically reviewed the manuscript and validated the final version.

Ethics considerations

This multi-country analysis was made possible by public health surveillance activities in the context of national preventive immunization programmes. In all participating countries, surveillance was implemented under the authority and supervision of national ministries of health, and with the technical guidance of WHO. Members of the National Expert Committees were appointed by Ministers of Health. All health workers involved in the surveillance received training. Clinical care was provided according to the national standard of care, including patient consent. Additional costs related to clinical investigation and care resulting from the identification of adverse events were budgeted for and covered by national authorities with support from the Yellow Fever Initiative.

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