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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.

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

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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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