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Research Article

Study of adverse events following 2018 sub-national yellow fever vaccination in Ghana

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Abstract

Background: According to the Centers for Disease Control and Prevention (CDC), globally there is an estimated 200,000 cases of Yellow Fever Virus yearly, causing 30,000 deaths annually, with 90% of cases occurring in Africa. Where about 20% to 50% of people who get infected and develop severe symptoms from the yellow fever virus die.

WHO report showed that Ghana was among 27 African countries with a high risk of yellow fever outbreak at any time. In response, there was a need to amplify the immunization campaign against yellow fever. Ghana in collaboration with WHO, GAVI, the Vaccine Alliance, and UNICEF began a sub-national campaign to vaccinate approximately 5.3 million people against yellow fever targeting people between ages 10 and 60 years from November 28 to December 4, 2018. 459 Adverse Events Following the Immunization (AEFI) in Ghana were reported from 28th November 2018 to 1st January 2019. The yellow fever vaccine is regarded as one of the safest, but with few adverse events. Therefore, there is a need to assess the severity of the reported adverse events following immunization in the 2018 sub-national yellow fever immunization program in Ghana.

Objective: To study the Seriousness of adverse events following yellow fever vaccination in Ghana.

Methodology: A retrospective review of AEFI data through a surveillance system during a Yellow Fever vaccination campaign in Ghana. The data comprised suspected 459 adverse events following the immunization (AEFI). The reported AEFI from 28th November 2018 to 1st January 2019 was used for this study as secondary data. A total of 5.3 million people were vaccinated. All vaccine recipients were between the ages of 10 years to 60 years. Data were analyzed using frequencies and descriptive statistics in STATA version 15.

Findings and discussions: The study showed 459 (0.00086%) per 5.3 million recipients reported adverse events. The AEFI occurred mostly among females and persons aged 30-39 years. Out of the 459 recipients with adverse events, 432 (99.3%) recovered, and 3 (0.7%) died. The most common adverse event per region, sex, and age group is fever. The study also revealed AEFIs may have contributed to the death of 3 (0.000056%) per 5.3 million recipients. However, a causality assessment done by the Vaccine Safety Review Committee of independent experts showed no causality between the reported AEFI (deaths) and the YF vaccination. This indicates that the benefits of the vaccination outweigh the risk of adverse events or fatalities.

Conclusion: In conclusion, it was found that the benefits of the Yellow Fever Vaccination (YFV 17D) outweigh the risk of adverse events or fatalities. Reported Adverse Events following the 2018 sub-national yellow fever vaccination per 5.3 million recipients were 459 representing 0.0086%. There was no causality between reported deaths 3 (0.000056%) and the YF immunization. The adverse events that follow yellow fever immunization are not strong and suggest that most of the respondents do not have serious repercussions after the vaccination. Therefore, YF vaccination has saved millions of people from potential vaccine-preventable deaths in Ghana and beyond its borders and did not cause more harm than health benefits.

Introduction

The World Health Organization considers Yellow Fever, an acute viral hemorrhagic disease endemic in tropical areas of Africa and Latin America, as a threat to global health. The disease is caused by the yellow fever virus. The transmission of yellow fever virus to humans is through the bite of infected mosquitoes of the genus Aedes and Haemogogus. The signs and symptoms of the disease include fever with a headache, myalgia, vomiting, hepatitis with jaundice, and can also lead to renal failure and hemorrhagic syndrome. Currently, 32 African countries are considered at risk of yellow fever, with a population of 610 million and more than 219 million living in urban communities. The disease is endemic in ten South and

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Central American countries and in several Caribbean islands [1]. According to the Centers for Disease Control and Prevention (CDC), there is an estimated 200,000 cases of Yellow Fever Virus yearly in the globe, causing 30,000 deaths annually, with 90% of cases occurring in Africa. Where about 20% to 50% of people who get infected and develop severe symptoms from the yellow fever virus die [2]. To prevent the importation of the disease, many countries require proof of vaccination against yellow fever before they issue a visa. In Ghana, a yellow fever vaccine certificate is required on departure and arrival from all travelers 9 months of age and older. Yellow Fever Vaccine (YFV 17D) is a landmark in vaccine history. Without it, life in the tropics would be extremely difficult [3]. The YFV 17D is the major type of vaccine used in Ghana against YFV as per recommendation by WHO.

Public health policies to control and eradicate infectious diseases depend on the immunization success of specific vaccines. In many parts of the world where medical resources and health infrastructure are lacking, vaccines are a cost-effective public-health intervention. They are even more cost-effective in monetary terms in rich countries where the expensive treatment of infectious diseases is prevented, freeing up healthcare resources for purposes other than treating preventable diseases. Furthermore, immunization policies have enabled important achievements in public health, such as the eradication and/or control of yellow fever, smallpox, and poliomyelitis [4]. The last yellow fever outbreak in Ghana was reported in December 2011 in three (3) districts: Builsa and Kassena-Nankana-West in the Upper East Region and Kitampo-South in the Brong-Ahafo Region located in the mid-Western part of the country. A reactive yellow fever vaccination campaign started in February 2012, supported by the International Coordinating Group on Yellow Fever Vaccine Provision (YF-ICG) and the European Community Humanitarian Office (ECHO). Over 235,000 people in affected districts were targeted for vaccination, with the exclusion of pregnant women and children aged under one year. The vaccination exercise complemented a two-phased yellow fever preventive mass campaign targeting 7.5 million people in 43 districts in 8 regions [5].

Assured quality vaccines and safe immunization practices are pre-requisite to successful immunization programs. All vaccines go through safety checks before WHO Pre-Qualification (PQ) approval. The AEFI surveillance program is an integral part of the immunization program in Ghana to monitor vaccine safety. All AEFI reports undergoing a systematic causality assessment as per the WHO algorithm by trained committees [6]. like all vaccines, the YF vaccine causes AEFI [7]. Vaccines are effective in controlling and eradicating infectious diseases. However, AEFI can occur in susceptible individuals. "There have been rare reports of serious AEFI following the yellow fever vaccine. The rates for these severe AEFI, when the vaccine provokes an attack on the liver, the kidneys, or the nervous system are between 0 and 0.21 cases per 10 000 doses in regions where yellow fever is endemic, and from 0.09 to 0.4 cases per 10 000 doses in populations not exposed to the virus" [8]. Vaccine surveillance and follow-up systems are crucial to monitor issues related to AEFI. These AEFI systems, as summarized by Zhou et al are important to "(1) detect new, unusual, or rare vaccine adverse events; (2) monitor increases in known adverse events; (3) determine patient risk factors for particular types of adverse events; (4) identify vaccine lots with increased numbers or types of reported adverse events; and (5) assess the safety of newly licensed vaccines" [4].

Ghana has a successful immunization program and is the second country in Africa to join the WHO Vaccine Safety Network (VSN) after South Africa. The Vaccine Safety Network is a global network of websites, evaluated by the WHO that provides reliable information on vaccine safety. The Food and Drug Authority (FDA) in collaboration with the Expanded Program of Immunization (EPI) of Ghana Health Service (GHS) has created an effective surveillance system for immunization programs. In Ghana, AEFIs are collected by the FDA Safety Monitoring Department. Healthcare providers are trained on how to report suspected AEFI and the vaccine recipients also report suspected AEFI through a mobile number, hotline, WhatsApp, email, online (FDA website), and the Med Safety App. The information collected is in line with the WHO algorithm.

A WHO report shows that Ghana is among 27 African countries with a high risk of yellow fever outbreak at any time [5]. In response, there was a need to amplify the immunization campaign against yellow fever. Ghana in collaboration with WHO, Gavi, the Vaccine Alliance, and UNICEF began a sub-national campaign to vaccinate over 5.3 million people against yellow fever targeting people between ages 10 and 60 years (pregnant women excluded) in November 2018 [9]. Even though vaccines are very potent preventers of infection, they are associated with AEFI, most of which are minor, yet of global health concern [10]. Major vaccine safety controversies have arisen in several countries including Ghana. Such periodic vaccine safety is unlikely to do away with the AEFI both major and minor including severe local reactions, seizures, abscess, sepsis, febrile, fever, toxic shock syndrome, encephalopathy, congenital anomaly, disability, and death. These contribute to a high rate of vaccine hesitancy, a threat to public health in Ghana and global health. The yellow fever vaccine is regarded as one of the safest, but with few adverse events. This study will describe the distribution and seriousness of adverse events following sub-national yellow fever vaccination in Ghana from 28th November 2018 to 1st January 2019.

Methodology

Study design and data source

Secondary data on reported AEFI following Yellow Fever immunization in Ghana from 28th November 2018 to 1st January 2019, gathered by the FDA Safety Monitoring Department was used for this study. A total of 5.3 million people were vaccinated. The data were collected, AEFI were categorized into Serious and Non-serious using WHO Algorithm, data were analyzed using excel and STATA, and reported in tables. Age- and sex-specific reporting rates of all Yellow Fever vaccine-associated minor adverse effects (Non-serious adverse events) and Yellow Fever vaccine-associated major adverse effects (Serious adverse

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events) were calculated. Yellow Fever Vaccine (YFV 17D) was used for the immunization program. A causality assessment was done by the Vaccine Safety Review Committee of independent experts to determine whether there is a causality between the reported AEFI and the vaccination. Causality assessment reports are submitted to the FDA. AEFIs were collected by the FDA Safety Monitoring Department. Healthcare providers were trained on how to report AEFI and the vaccine recipients also reported AEFI through a mobile number, hotline, WhatsApp, email, online (FDA website), and the Med Safety App. The information collected was in line with the WHO algorithm. The data collected include patient demographics, vaccination, and type of AEFI. AEFI reports are routinely classified as serious or non-serious, with serious AEFI defined by the WHO and FDA regulatory definition as life-threatening or resulting in death, inpatient hospitalization, or prolongation of existing hospitalization or persistent or significant disability. AEFI is a routine surveillance program conducted as a public health function, therefore, it is not subject to Institutional Review Board review and informed consent requirements. 459 reported AEFI following the 2018 Yellow Fever sub-national vaccination from 28th November 2018 to 1st January 2019, were used for this study.

Exclusion criteria

Reports that do not have a date of vaccination and date of reported AEFI were set to be excluded. However, the requirement of Individual Case Safety and Report (ICSR) is complete if it has 4 items, including, reporter, event, vaccine, and patient. Therefore, no reported AEFI was excluded from this study.

Inclusion criteria

Secondary data that met the requirements of ICSR were included in this study. All 459 reports met the inclusion criteria for this study.

Outcome variable: AEFI, adverse events following YF vaccination.

Explanatory variable: Variables were found to be influencing outcome variables. In this study, they included sex, age, and region.

Sample size: 459 AEFI reports following the 2018 YF vaccination and reported as of 28th November 2018 to 1st January 2019 were used for this study.

Data management and analysis

Secondary data collected through the surveillance system included the reported AEFI, vaccine, patient name, age, sex, region, concurrent vaccine administration (if any), event: date and time of vaccination, date and time of symptom onset, symptom descriptions and outcomes.

The secondary data was obtained from the Food and Drug Authority in a Microsoft Excel spreadsheet. Data obtained were analyzed using STATA windows (version 15) by simple descriptive statistics. Variables were summarized into frequencies and continuous variables such as age were re-categorized into age groups. Frequency counts of all responses were presented in frequency tables. STATA version 15 was used to analyze the data. Cross-tabulation was used to compare the variables for possible correlation. WHO Algorithm case definitions were used to classify adverse events. Adverse events were classified as Serious Adverse Events and Non-Serious Adverse Events.

Data storage, security and usage

The secondary data was only accessible to the researcher and the supervisor. It was saved on a password-protected laptop and kept in the custody of the researcher.

Results and findings

Characteristics of persons with adverse events following yellow fever immunization

Table 1 presents characteristics of persons with adverse events following immunization of yellow fever sub-national vaccination in Ghana in 2018.

Table 1: Characteristics of persons with adverse events following YF vaccination.

Variables	Reported cases following YF Vaccination in 2018
Sex n (%)	
Male	186 (40.6%)
Female	272 (59.4%)
Age n (%)	
Under 17 years	61 (21.2%)
18-29 years	61 (21.2%)
30-39 years	107 (37.2%)
40-49 years	41 (14.2%)
50-59 years	18 (6.3%)
Regions n (%)	
Ashanti	53 (11.6%)
Brong-Ahafo	40 (8.7%)
Central	153 (33.3%)
Eastern	54 (11.8%)
Greater Accra	50 (10.9%)
Northern	14 (3.1%)
Upper East	51 (11.1%)
Volta	23 (5%)
Western	21 (4.6%)
Onset of AEFI n (%)	
Within 12 hours (same day)	237 (55.6%)
Within 24 hours (2nd day)	131 (30.8%)
Within 36 hours (3rd day)	32 (7.5%)
Within 48 hours (4th day)	15 (3.5%)
Within 60 hours (5th day)	5 (1.2%)
Within 72 hours (6th day)	4 (0.9%)
Within 84 hours (7th day)	2 (0.5%)
Outcome of AEFI n (%)	
Recovered	432 (99.3%)
Death	3 (0.7%)
Median Age	30
Median Date to the onset	1 (1-7)
Serious adverse events	15 (3.3%)
Non Serious adverse events	443 (96.7%)
Adverse Events per 5.3 million	459 (0.0086%)
Deaths per 5.3 million	3 (0.000056%)

[a]Sex unknown for 1 case; [b]Age unknown for 171 cases; [c]Date of onset unknown for 33 cases; [d]Classification of AEFI unknown for 1 case; [e]Outcome of AEFI unknown for 24 cases

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Overall, 459 (0.0086%) adverse events following Yellow Fever vaccination occurred among the recipients and 3 (0.000058%) death occurred from recipients that developed serious adverse events following the intake of the vaccine (Table 1). The onset of the adverse events mostly occurred within 12 hours (55.6%) and the majority of the persons were aged 30-39 years (37.2%) with a median age of 30 years. The females formed the greater portion (n = 272, 59.4%) of the cases with adverse events (Table 1). The adverse events occurred with a median of 1 (same day) after vaccination (range 1-7) and 30.8% occurred within 2 days of vaccination (Table 1). The region that recorded the highest number of persons that reported AEFI was the Central region (n = 153, 33.3%) and the Northern region (n = 14, 3.1%) had the lowest number of persons that reported AEFI.

Most commonly reported adverse events following yellow fever vaccination by sex

Table 2 presents the breadth of sex, age and region differences in response to the 2018 sub-national yellow fever vaccination. The most commonly reported adverse events after the sub-national Yellow Fever vaccination in 2018 were fever (23.4%), general body weakness (14.9%), rashes (13.4%), pain (12.7%), headache (11.8%), itching (10.3%), dizziness (6.4%), vomiting (4.6%) and malaise (2.5%) (Table 4.2.1). Fever accounted for the majority of the adverse events reported by both males (36.6%) and females (32.7%). For males, headache (26.9%), rashes (18.8%), and pain (18.8%) were other significant adverse events that occurred among them whiles females recorded general body weakness (23.2%), rashes (20.2%) and pain (18.4%) respectively (Table 2). The adverse events identified were generally dermatological, pyrexia/fever and pain.

Most common adverse events following yellow fever vaccination by age group

The most commonly reported adverse events after the sub-national Yellow Fever vaccination in 2018 among under 17-year-old persons were fever (28.6%), rashes (14.3%) and headache (14.3%). For those aged 18-29 years, the predominant adverse events were fever (15.6%), headache (15.6%) and vomiting (15.6%). For persons aged 30-39 years, the common form of adverse events were rashes (18.9%), fever (16.5%) and pain (11.9%). Those aged 40-49 years had pain (22.6%), fever (17.7%) and general body weakness (14.5%) as the most common adverse events. Finally, with regards to those aged 50-59 years, pain (24.1%), fever (20.7%), itching (13.8%) and general body weakness (13.8%) accounted for the most common adverse events (Table 3). Overall, fever stood as the leading adverse event for persons who had been vaccinated.

Most common adverse events following yellow fever vaccination by region

For the Ashanti region, fever (31%), rashes (16.9%) and itching (11.3%) were the leading adverse events. In the Brong Ahafo, dizziness (20.4%), fever (16.3%), headache (12.2%) and general body weakness (12.2%) were most common adverse events. In the Central region, fever (26.4%), general body weakness (26.4%), and headache (11.2%) were the most common adverse events following the 2018 sub-national Yellow Fever vaccination exercise. In the Eastern region, rashes (26.7%), fever (20%), and itching (17.8%) were the leading adverse events, and Greater Accra had a fever (24.3%), general body weakness (14.3%) and pain (14.3%) as the driving adverse events in the region. The northern region recorded pain (35.3%) and dizziness (29.4%) as the leading adverse events in the region. Upper East had a fever (34.3%), headache (27.1%), and pain (8.6%) as the driving adverse events in the region, and Volta region witnessed fever (20.8%), itching (16.7%) and pain (16.7%) as the common adverse events in the region. Finally, the Western region had rashes (40%) and itching (20%) as the driving adverse events in the region (Table 4). These results demonstrate that fever is the most common adverse event for persons who have been vaccinated within the period. Currently, there are no previous studies on regional or geographical differences in response to adverse events following yellow fever vaccination in Ghana.

Classification of adverse events according to age, sex, and region

Serious adverse events following the sub-national Yellow Fever vaccination were mostly present among those aged 18-29 years (33.3%) and persons below 17 years (33.3%) and females (53.3%). Serious AEFIs were common among persons living in the Greater Accra region of Ghana (66.7%). This result demonstrates that persons under 17 years, young adults (18-29 years), females, and persons living in the Greater Accra region are more likely to have serious adverse events following Yellow Fever vaccination (Table 5).

Benefits of YF vaccines outweigh the risks

Reported Adverse Events following the 2018 sub-national

Table 2: Most Commonly reported adverse events following Yellow Fever vaccination by sex.

All adverse events	*n* (%)	Male (*n* =186)	*n* (%)	Female (*n* =273)	*n* (%)
Fever	157 (23.4%)	Fever	68 (36.6%)	Fever	89 (32.7%)
General Body Weakness	100 (14.9%)	General Body Weakness	17 (9.1%)	General Body Weakness	63 (23.2%)
Rashes	90 (13.4%)	Rashes	35 (18.8%)	Rashes	55 (20.2%)
Pain	85 (12.7%)	Pain	35 (18.8%)	Pain	50 (18.4%)
Headache	79 (11.8%)	Headache	50 (26.9%)	Headache	29 (10.7%)
Itching	69 (10.3%)	Itching	24 (12.9%)	Itching	45 (16.5%)
Dizziness	43 (6.4%)	Dizziness	22 (11.8%)	Dizziness	21 (11.8%)
Vomiting	31 (4.6%)	Vomiting	15 (8.1%)	Vomiting	16 (5.9%)
Malaise	17 (2.5%)	Malaise	6 (3.2%)	Malaise	11 (4%)

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Table 3: **Most Common Adverse Events following Yellow Fever Vaccination by Age group.**

All adverse events	N (%)	< 17 (n = 91)	N (%)	18-29 (n = 96)	N (%)	30-39 (n = 109)	N (%)	40-49 (n =62)	N (%)	50-59 (n = 29)	N (%)
Fever	76 (19.6%)	Fever	26 (28.6%)	Fever	15 (15.6%)	Fever	18 (16.5%)	Fever	11 (17.7%)	Fever	6 (20.7%)
Itching	30 (7.8%)	Itching	5 (5.5%)	Itching	12 (12.5%)	Itching	9 (8.3%)	Itching	-	Itching	4 (13.8%)
Headache	43 (11.1%)	Headache	13 (14.3%)	Headache	15 (15.6%)	Headache	6 (5.5%)	Headache	7 (11.3%)	Headache	2 (6.9%)
Pain	55 (14.2%)	Pain	10 (11%)	Pain	11 (11.5%)	Pain	13 (11.9%)	Pain	14 (22.6%)	Pain	7 (24.1%)
General Body Weakness	37 (9.6%)	General Body Weakness	9 (9.9%)	General Body Weakness	4 (4.2%)	General Body Weakness	11 (10.1%)	General Body Weakness	9 (14.5%)	General Body Weakness	4 (13.8%)
Dizziness	30 (7.8%)	Dizziness	3 (3.3%)	Dizziness	8 (8.3%)	Dizziness	10 (9.2%)	Dizziness	8 (12.9%)	Dizziness	1 (3.4%)
Rashes	56 (14.5%)	Rashes	13 (14.3%)	Rashes	13 (13.5%)	Rashes	20 (18.3%)	Rashes	7 (11.3%)	Rashes	3 (10.3%)
Vomiting	41 (10.6%)	Vomiting	11 (12.1%)	Vomiting	15 (15.6%)	Vomiting	11 (10.1%)	Vomiting	3 (4.8%)	Vomiting	1 (3.4%)
Malaise	19 (4.9%)	Malaise	1 (1.1%)	Malaise	3 (3.1%)	Malaise	11 (10.1%)	Malaise	3 (4.8%)	Malaise	1 (3.4%)

Table 4: Most Common Adverse Events following Yellow Fever Vaccination by Region.

All adverse events	N (%)	Ashanti (*n* = 71)	N (%)	Brong (*n* = 49)	N (%)	Central (*n* = 250)	N (%)	Eastern (*n* =45)	N (%)
Fever	153 (25%)	Fever	22 (31%)	Fever	8 (16.3%)	Fever	66 (26.4%)	Fever	9 (20%)
Itching	53 (8.7%)	Itching	8 (11.3%)	Itching	5 (10.2%)	Itching	14 (5.6%)	Itching	8 (17.8%)
Headache	76 (12.4%)	Headache	7 (9.9%)	Headache	6 (12.2%)	Headache	28 (11.2%)	Headache	5 (11.1%)
Pain	62 (10.1%)	Pain	4 (5.6%)	Pain	5 (10.2%)	Pain	20 (8%)	Pain	5 (11.1%)
General Body Weakness	94 (15.4%)	General Body Weakness	1 (1.4%)	General Body Weakness	6 (12.2%)	General Body Weakness	66 (26.4%)	General Body Weakness	1 (2.2%)
Dizziness	41 (6.7%)	Dizziness	3 (4.2%)	Dizziness	10 (20.4%)	Dizziness	15 (6%)	Dizziness	-
Rashes	86 (14.1%)	Rashes	12 (16.9%)	Rashes	4 (8.2%)	Rashes	34 (13.6%)	Rashes	12 (26.7%)
Vomiting	29 (4.7%)	Vomiting	7 (9.9%)	Vomiting	2 (4.1%)	Vomiting	5 (2%)	Vomiting	1 (2.2%)
Malaise	17 (2.8%)	Malaise	7 (9.9%)	Malaise	3 (6.1%)	Malaise	2 (0.8%)	Malaise	4 (8.9%)
Greater Accra (*n* = 70)	**N (%)**	**Northern (n = 14)**	**N (%)**	**Upp. East (*n* = 70)**	**N (%)**	**Volta (*n* = 24)**	**N (%)**	**Western (*n* = 15)**	**N (%)**
Fever	17 (24.3%)	Fever	1 (7.1%)	Fever	24 (34.3%)	Fever	5 (20.8%)	Fever	1 (6.7%)
Itching	6 (8.6%)	Itching	-	Itching	5 (7.1%)	Itching	4 (16.7%)	Itching	3 (20%)
Headache	9 (12.9%)	Headache	2 (14.3%)	Headache	19 (27.1%)	Headache	-	Headache	-
Pain	10 (14.3%)	Pain	6 (42.9%)	Pain	6 (8.6%)	Pain	4 (16.7%)	Pain	2 (13.3%)
General Body Weakness	10 (14.3%)	General Body Weakness	1 (7.1%)	General Body Weakness	5 (7.1%)	General Body Weakness	2 (8.3%)	General Body Weakness	2 (13.3%)
Dizziness	3 (4.3%)	Dizziness	5 (35.7%)	Dizziness	3 (4.3%)	Dizziness	1 (4.2%)	Dizziness	1 (6.7%)
Rashes	6 (8.6%)	Rashes	1 (7.1%)	Rashes	4 (5.7%)	Rashes	7 (29.2%)	Rashes	6 (40%)
Vomiting	8 (11.4%)	Vomiting	1 (7.1%)	Vomiting	4 (5.7%)	Vomiting	1 (4.2%)	Vomiting	-
Malaise	1 (1.4%)	Malaise	-	Malaise	-	Malaise	-	Malaise	-

Table 5: Classification of adverse events according to age, sex, and region

Variables	Non-serious Age (*n* = 241) Sex (*n* = 442) Regions (*n* = 443)	Serious Age (*n* = 6) Sex (*n* = 15) Regions (*n* = 15)
Age group n (%)		
Under 17	59 (24.5%)	2 (33.3%)
18-29	59 (24.5%)	2 (33.3%)
30-39	65 (27%)	1 (16.7%)
40-49	41 (17%)	-
50-59	17 (7.1%)	1 (16.7%)
Sex n (%)		
Female	264 (59.7%)	8 (53.3%)
Male	178 (40.3%)	7 (46.7%)
Regions n (%)		
Ashanti	52 (11.7%)	1 (6.7%)
Brong-Ahafo	38 (8.6%)	1 (6.7%)
Central	152 (34.3%)	1 (6.7%)
Eastern	52 (11.7%)	2 (13.3%)
Greater Accra	40 (9%)	10 (66.7%)
Northern	14 (3.2%)	-
Upper East	51 (11.5%)	-
Volta	23 (5.2%)	-
Western	21 (4.7%)	-

[a]Classification of AEFI according to age unknown for 212 cases
[b]Classification of AEFI according to sex unknown for 2 cases
[c]Classification of AEFI according to region unknown for 1 case.

yellow fever vaccination per 5.3 million recipients were 459 representing 0.0086% (Table 6). The adverse events following the immunization did not contribute to the reported deaths of 3 (0.000056%) of the 5.3 million vaccinated (Table 6). Out of 459 vaccine recipients who reported adverse events, 432 (99.3%) of them recovered and 3 (0.7%) reported deaths had no causality between the YF vaccination and the AEF (Table 6). The reported adverse events following the YFV vaccination were not significant to outweigh its benefits. Therefore, the benefits of vaccination outweigh the risk of adverse events or fatalities. However, 24 (5.23%) of reported cases had outcome status of "unknown" and as such were removed from the analysis in Table 6.

Discussion

The study described the distribution of adverse events following the 2018 sub-national yellow fever immunization from 28th November 2019 to 1st January 2019, across regions, sex, and age. It also determined if the benefits of yellow fever vaccination outweighed the reported adverse events following immunization. This chapter presents detailed discussions of the findings of the study, with limitations and recommendations.

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Table 6: Reported classified AEFIs and outcome

Variables	Reported AEFIs
The outcome of AEFI n%	
Recovered	432 (99.3%)
Death	3 (0.7%)
Serious AEFIs	15 (3.3%)
Non Serious AEFIs	443 (96.7%)
AEFIs per 5.3 million	459 (0.0086%)
Death per 5.3 million	3 (0.000056%)

[a]Classification of AEFI unknown for 1 case
[b]Outcome of AEFI unknown for 24 cases.

- The chapter is organized into the following four major headCharacteristics of persons with adverse events following YF vaccination
- The breadth of Sex, Age and Region Differences in Response to YF Vaccination
- Distribution of Classified Adverse Events (Serious and Non-serious AEFIs) according to Age, Sex, and Region
- Benefits of YF Vaccines Outweigh the Risks.

Characteristics of persons with adverse events following YF vaccination

From the results, it is observed that the majority of female recipients reported AEFIs 272 (59.4%). The adverse events occurred mostly among females and persons aged 30-39 years. Possible reasons accounting for this finding include females being more concerned with their health and reporting their AEFI to the authorities without hesitation, genetic factors, hormones, immunization-anxiety related reaction, presence of comorbidity, and individuals having acute infection in a few months. High immunity levels could account for the high AEFI in the age group 30-39 years.

The median age of the recipients who reported AEFIs is 30 years old. It is confirmed in the findings of Lindsey, et al. [11], who reported similar results. Additionally, all these empirical investigations [12-15] affirmed that the majority of yellow fever adverse outcomes occur among females and persons either below or exactly 40 years.

The onset of the AEFIs was mostly reported within 12 hours (same-day vaccination started) 237 (55.6%). The adverse events occurred with a median of 1 (same day) after vaccination (range 1-7) and 131 (30.8%) reported within 2 days of vaccination (Table 1). Only 4 (0.9) AEFIs were reported on the 6th day of vaccination. This result corroborates Lindsey et al findings [11] that established that adverse events occurred within day one.

The central region reported the highest number of AEFIs and the Northern region reported the lowest AEFIs. From Table 1, most of the respondents 153 (33.3%) that reported AEFI were located in the Central region. This was followed by Eastern region 54 (11.8%), Ashanti region 53 (11.6%), Upper East region 51 (11.1%), Greater Accra region 50 (10.9%), Brong-Ahafo region 40 (8.7%), Volta region 23 (5%), Western region 21 (4.6%) and lastly Northern region 14 (3.1%). This result demonstrates that generally AEFI cases are found in the Central region and calls for further investigation as to why this region recorded such high cases compared with the other regions in the country. Currently, there are no previous studies on the distribution of adverse events following yellow fever vaccination in Ghana.

Furthermore, all these AEFIs are classified as non-serious adverse effects, per the World Health Organization algorithm. Further laboratory and collection of other information need to be done to establish a possible association between the YF vaccination and reported AEFIs. YF vaccine recipients 443 (96.7%) reported non-serious Adverse Events Following Yellow Fever Immunization (AEFI) while 15 (3.3%) of the recipients recounted serious Adverse Events Following Immunization (AEFI). This finding suggests that the adverse effects that follow yellow fever immunization are not strong and suggests that most of the respondents do not have serious repercussions after the vaccination. This result fails to reject findings in a similar research study which concluded that more than 90% of the adverse events following YF vaccination reported to VAERS from 2007 through 2013 were non-serious [16].

Per 5.3 million YF vaccine recipients, 459 (0.0086%) suffered adverse events following Yellow Fever vaccination and 3 (0.000056%) reported death (Table 1) had no causality with the YF vaccination according to the causality assessment report by the Vaccine Safety Review Committee of independent experts.

From the findings, the variable, sex was unknown in one case. 171 cases had their age unknown, 33 cases had an unknown date of onset, classification of AEFIs was also unknown for 1 case. Lastly, 24 cases had unknown AEFI outcomes.

The breadth of sex, age and region differences in response to YF vaccination

Adverse Events Following Immunization as indicated by the analysis included mainly fever, general body weakness, rashes, pain, headache, itching, dizziness, vomiting, and malaise. This finding affirms the results of an existing experimental study design conducted in Ghana where the most common adverse reactions following Yellow Fever vaccination included fever and mild reaction at the inoculation site [17]. In the same vein [11] also found similarly adverse events which comprised fever, headache, rash, urticaria, etc.

Regarding sex differences in response to YF vaccination, the majority of males reported fever as most leading AEFI 68 (36.6%) and females also recorded fever as the most alarming AEFI 89 (32.7%). Among the males, headache 50 (26.9%), rashes 35 (18.8%) and pain 35 (18.8%) were other major AEFIs that occurred among them. However, among the females the other leading AEFIs included general body weakness 63 (23.2%), rashes 55 (20.2%), and pain 50 (18.4%) respectively (Table 2). From the analysis, adverse events occurred mostly among females than males. This affirms the findings that female to male AEFI reporting rate ratio is 52.2:1.1, in an assessment of sex-specific differences in adverse events following immunization in Ontario [18].

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When it comes to age differences in response to YF vaccination, persons aged 30-39 years recorded most AEFIs 107 (43.3%), followed by recipients within the age group 18-29 years. Vaccine recipients between 40-49 years recorded the lowest adverse events following yellow fever vaccination, 18 (7.3%). This confirms the findings of [11]. That reported similar results. Additionally, all these empirical investigations [12-15]. Affirmed that the majority of yellow fever adverse outcomes occur among females and persons either below or exactly 40 years. Among the AEFIs reported after the sub-national Yellow Fever vaccination from 28th November 2018 to 4th December 2018, fever 26 (28.6%) was the most reported among recipients at 17 years old or lesser. Following: rashes (14.3%) and headache (14.3%). For recipients aged 18-29 years, the commonly reported AEFI included; fever 15 (15.6%), headache 15 (15.6%), and vomiting 15 (15.6%). The group with the most reported AEFIs; 30-39 years recorded rashes 20 (18.3%) as the leading AEFI among the age group. Second was fever 18 (16.5%) and third was pain 13 (11.9%). Those aged 40-49 years experienced pain 14 (22.6%), fever 11 (17.7%) and general body weakness 9 (14.5%) as the most common adverse events. Recipients aged 50-59 years recorded pain 7 (24.1%), fever 6 (20.7%), itching 4 (13.8%), and general body weakness 4 (13.8%) accounted for the most common adverse events (Table 2). Overall, fever 76 (19.6%) was the alarming adverse event for persons who had been vaccinated. From the findings, in response to age, there was a reduction in the sample from 459 to 247 due to the omission of some variables for 212 vaccine recipients by the healthcare providers.

With regards to regional differences in response to YF vaccination, in the Ashanti region, a fever of 22 (31%) was the most reported AEFI, following rashes of 12 (16.9%) and itching of 8 (11.3%). Dizziness 10 (20.4%), fever 8 (16.3%), headache 6 (12.2%) and general body weakness 6 (12.2%) were most common AEFIs reported in Brong Ahafo. The central region which recorded the highest AEFIs reported the following: fever 66 (26.4%), general body weakness 66 (26.4%), and headache 28 (11.2%) as the most common adverse events following the 2018 sub-national Yellow Fever vaccination exercise. In the Eastern region, rashes 12 (26.7%), fever 9 (20%) and itching 8 (17.8%) were the leading AEFIs, and Greater Accra had fever 17 (24.3%), general body weakness 10 (14.3%) and pain 10 (14.3%) as the common AEFIs in the region. The northern region presented pain 6 (35.3%) and dizziness 5 (29.4%) as the highly recorded AEFIs in the region. Whilst, Upper East recorded fever 24 (34.3%), headache 19 (27.1%) and pain 6 (8.6%) as the most reported AEFIs in the region. Fever 5 (20.8%), itching 4 (16.7%), and pain 4 (16.7%) were recorded as the common adverse events in the Volta region. However, a Western region that reported the lowest rate of AEFIs had rashes 6 (40%) and itching 3 (20%) as the alarming adverse events in the region (Table 2). Based on these results, fever is the most common AEFI for persons who have been vaccinated within the period in all the regions, apart from the Northern and West regions. Currently, there are no previous studies on regional or geographical differences in response to adverse events following yellow fever vaccination in Ghana.

Distribution of classified adverse events (Serious and Non-serious AEFIs) according to age, sex and region

Serious AEFIs following the sub-national Yellow Fever vaccination in Ghana from 28th November 2019 to 4th December 2019, were found common among persons below 17 years 2 (33.3%) and those aged 18-29 years 2 (33.3%). Recipients between ages 30-39 years and 50-59 years recorded 1 (16.7%) serious AEFI for each year group. Persons aged 40-49 years reported no serious AEFI. This finding is not consistent with an existing research study that reported rates for Serious Adverse Events following 17D YF vaccination as highest among persons aged 60–69 [19].

Serious AEFIs were mostly presented among females 8 (53.3%). Among males, it was 7 (46.7%). However, in a research study of 84 AEFIs, 50% of reported Serious Adverse Events occurred in males [19].

The findings of the study on the regional basis of the respondents showed that out of the fifteen serious cases reported, the majority 10 (66.7%) were located in the Greater Accra region, followed by the Eastern region 2 (13.3%), Ashanti region 1 (6%), Brong-Ahafo region 1 (6%) and Central region1 (6%) respectively. In terms of the non-serious AEFI cases reported most of the 152 (34.3%) were found in the Central region 152 (34.3%), followed by the Ashanti region 52 (11.7%), Eastern region 52 (11.7%), Upper East region 51 (11.5%), Greater Accra Region 40 (9%), Brong Ahafo region 38 (8.6%) amongst others. There should be a further study to investigate why the Greater Accra Region recorded most of the serious adverse effects following immunization in Ghana. The regional distribution is a novel step in this research given that existing studies have not looked at this in-country distribution [11,19].

Benefits of YF vaccines outweigh the risks

From the results, the death of 3 persons representing 0.000056% per 5.3 million persons vaccinated, may be a result of the yellow fever vaccination. The number of vaccine recipients that developed adverse events following the immunization was 459 persons representing 0.0086% per 5.3 million. Out of the respondents with adverse events, 432 (99.3%) had recovered and 3 (0.7%) deaths were reported. This result is consistent with [20] that found lower death rates following Yellow Fever vaccination. However, the causality assessment by the Vaccine Safety Review Committee of independent experts showed no causality between the reported deaths and the YF immunization.

This indicates that the benefits of the vaccination outweigh the risk of adverse events or fatalities. The deaths have no causal relationship with the yellow fever vaccine until further investigations are done in compliance with the WHO algorithm for AEFI as recommended by WHO. Adverse Event Following Immunization (AEFI) is described as any untoward medical occurrence which follows immunization, but that does not necessarily have a causal relationship with the usage of the vaccine [21]. This finding affirms the need for laboratory investigations to establish a possible relationship between the deaths and the yellow fever vaccination. 24 (5.23%) of reported

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cases had outcome status "not stated" and as such removed from the analysis. This finding fails to reject the existing literature that, Severe AEFIs are rare, and all the evaluations of the safety of immunization schedules recommended for both children and adults have found that the advantages of vaccines are always significantly higher than the problems they can cause and that there are no true problems that justify the modification of recommendations [22].

Conclusion

In conclusion, it was found that the benefits of the yellow fever vaccination outweigh the risk of adverse events or fatality. The adverse events that follow yellow fever immunization are not strong and suggest that most of the respondents do not have serious repercussions after the vaccination.

The most common Adverse Events Following Yellow Fever Immunization as indicated by the analysis was mainly fever. Deaths (0.4%) accounted for serious adverse events following immunization has to be established further by the Food and Drug Authority with the adherence to the reviewed WHO AEFI Algorithm which was published in 2018. Further laboratory and collection of other information need to be done to establish a possible association between the yellow fever vaccination and the reported death cases to rule out any confounding factors.

The findings also showed that gender has no significant relationship with adverse events following yellow fever vaccination. The research study revealed that AEFI cases reported, most of them 152 (34.3%) were found in the Central region. This finding calls for further investigation to identify contributing factors to such high reported cases in the Central region of Ghana. There were serious gaps in the data collection and reporting, which do not comply with the WHO Algorithm. Some important variables like age were not captured in the AEFI data.

Recommendations

The following are activities that can be ensured to improve the quality of adverse events following immunization reports, as part of measures to enhance the surveillance systems.

1. **Improvement of the quality of information reported:** The system of reporting adverse events by reporters: healthcare providers, parents or guardians, and vaccine recipients should be digitized through an online real-time application. With such a digitized surveillance system, incomplete reports on adverse events following immunization cannot be submitted. This will ensure zero missing information.

2. **Improving awareness creation:** Outreaches and educational activities through online print, traditional forums, the mass media, dailies, infographics, brochures, and social media should be used to create awareness of adverse events following yellow fever vaccines, and the means to report such adverse events should be communicated to them.

3. **Post-Licensure clinical studies:** The recorded serious and unknown complications of yellow fever vaccination are negligible or rare, but the safety of the yellow fever vaccine needs review. Clinical studies with vaccinated and unvaccinated groups should be conducted and all necessary unique laboratory investigations conducted to determine causality between reported adverse events and vaccination should be published to strengthen public confidence in vaccine safety.

4. **Further scientific research studies:** Further studies should be conducted to investigate why Central Region and Greater Accra region recorded more adverse events and serious adverse events respectively, following the sun-national yellow fever vaccination from 28th November 2018 to 1st January 2019. Further studies on immune response and AEFI after YF vaccination may be carried out among females and the age group 30-39 years.

Ethical approval: Ethical approval for this study was not needed. The study only used anonymized data from secondary sources.

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Author contributions

DAF conceived the idea and is the main author. DAF conducted the literature review, designed the methods, and conducted the data analysis.

FC supervised the study, advised the team, and reviewed the manuscript.

EG did the proofreading and critically revised the manuscript for intellectual content. All authors read and approved.

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