Prevalence of Yellow fever virus infection and associated factors among acute febrile patients in Arbaminch districts, Southern Ethiopia

Daniel Eshetu (Danieshetu@gmail.com)
Hawassa University College of Medicine and Health Sciences https://orcid.org/0000-0002-0094-0727
Tsegaye Alemayehu
Hawassa University College of Medicine and Health Sciences
Temesgen bizuayehu Wube
Hawassa University College of Medicine and Health Sciences

Research article

Keywords: Febrile illness, yellow fever virus, seroprevalence, Immunofluorescence

Posted Date: February 14th, 2020

DOI: https://doi.org/10.21203/rs.2.23497/v1

Abstract

Yellow fever is a rapidly emerging arthropod-borne viral infection, which causes considerable illness and death worldwide. However, little is known regarding the epidemiology of yellow fever virus infection in Ethiopia where mosquito-borne diseases like malaria are common. This study aimed to determine the seroprevalence of yellow fever virus infection and its associated factors among febrile illness in Arbaminch districts in Southern Ethiopia. An institution-based cross-sectional study was conducted in a consecutive group of 529 acute febrile patients between May to August 2016. Data on socio-demographic, environmental and clinical signs and symptoms were collected using structured questionnaires. Serum was used to detect anti-yellow fever virus IgG and/or IgM using indirect Immunofluorescent assay (Euro immune Biochip mosaics, Lübeck, Germany). A logistic regression analysis was done using SPSS V-20 (IBM Corp, 2012). P-value < 0.05 was taken as statistically significant. Of the tested 529 serum samples 14.9% and 7.2% were positive for anti-yellow fever IgG and IgM respectively. Among IgG positive patients, males accounted for 15.04% and female 14.85%. Yellow fever exposure was more in the younger age group; participants age less than 20 years (26.80%), followed by those in the age group above 60 years (26.47%). Further, the prevalence of yellow fever exposure among urban residents was 37.14%. Of the assessed risk factors, only constitutional symptoms were significantly associated with the Yellow fever virus (AOR = 0.28, 95% CI 0.30- 0.72.P < 0.011). The laboratory finding of this study shows, the level of exposure to yellow fever among febrile cases is relatively high; however, clinical diagnosis of febrile patients is a common practice in the study area. Therefore, Domestication and routine performance of yellow fever virus differential diagnosis will help to address the phenomenon of the virus.

Introduction

Yellow fever (YF) is a common health problem worldwide, which is caused by the yellow fever virus which is a member of the Flavivirus group in the family Flaviviridae, genus Flavivirus[1]. The genus Flavivirus contains approximately 70 viruses including YFV, dengue viruses (DENVs), Japanese encephalitis virus (JEV), and West Nile virus (WNV) that are of major human public health concern[2]. The virus transmitted primarily to humans and non-human primates through the bite of an infected female mosquito; *Aedes* species. Witches are responsible for transmission in Africa and the Americas[3].

The virus causes clinical symptoms ranging from mild illness with flu-like symptoms to severe disease including, fever, jaundice or hemorrhage and death[4]. YF continues to occur in epidemic situations and it is estimated to result in 130,000 human cases and 78,000 deaths annually in Africa alone[5]. In 2015–2016, urban outbreaks of YFV were declared in Angola and the Democratic Republic of Congo, and a sylvatic outbreak has been ongoing in Brazil since late 2016[6]. Ethiopia has experienced numerous YFV outbreaks since the 1940s. Between 1960 and 1962, the largest YFV outbreak ever recorded in Africa occurred along the River Omo, in South-West Ethiopia (Gamo Gofa, Jinka, and Kaffa regions) and resulted in approximately 200,000 human cases and 30,000 deaths[7].

In urban outbreaks, population density, crowding, low levels of population immunity, daily population movements in and out of, and around, the city, as well as conditions conducive to high vector density such as plentiful breeding sites in and around houses, all contribute to increasing transmissibility, raising the risk of large-scale outbreaks YF cases are difficult to diagnose from the clinical symptoms in the early stages of the illness because of"non-specific influenza-like symptoms" that are similar to those of other febrile illnesses. Differential diagnoses may include malaria, viral hepatitis, dengue, leptospirosis, or other hemorrhagic fevers[8]. WHO recommends a case definition for suspected YF as "any case presenting with acute onset of fever, with jaundice appearing within 14 days after the onset of the first symptoms" [9]. A little emphasis has been given for YF infection in Ethiopia. Because of the significant burden and clinical impact of YFV in YF patients, understanding the epidemiologic trends, route of transmission and associated risk factors have importance to undertake effective prevention measures. Therefore this study aimed to determine the prevalence of YFV infection and associated risk factors in acutely febrile patients in Arbaminch districts in southern Ethiopia.

Methods And Materials

This is a cross-sectional study conducted in Gamu gofa zone Arbaminch districts at selected health centers from May 2016 to August 2016. Arbaminch is located at 5.57–6.72^0 North latitude, 36.38–37.99^0 East longitude. The altitude ranges from 501m–3500m above sea level. The climatic condition of this site is Kola with an average annual rainfall of 1300.5mm and annual temperature ranging between 15.1^{0}C–27.5^{0}C.

Sample size and sampling techniques

Six hundred eighty-one consecutive acute febrile patients' with 37.5°C axillary temperature at initial evaluation and less than 7 days of onset of symptoms, at the outpatient departments of Lante health center, Shele health center, and Birbir health center are recruited. The study subjects were consecutive acute febrile patients with less than 7 days of onset of symptoms at health centers, this helps to confirm the infectious agent using RT-PCR as the virus can only be detected within the first few days of infection.

Blood specimen collection and sample analysis

All specimens were collected by a trained phlebotomist using a standard sterile technique. The blood samples were collected in serum separator tubes. The serum was separated and transferred to an appropriately labeled cryovial while the clotted blood component was appropriately disposed of as biohazard waste. liquid nitrogen was used to transport sera of the collected blood sample and it was stored in –80 deep freezers at Armauer Hansen Research Institute, Addis Ababa, Ethiopia until screened for anti-YF IgG and IgM. The screening was done using indirect immunofluorescence test (IIFT)

(EUROIMMUN, Lübeck, Germany) as per the manufacture's protocol. The presence of specific IgM or IgG antibody is proof of infection with the YFV.[7]

Data processing and statistical analysis

Data were entered in REDCap data software (8.0.3.@2018, Vanderbilt University), and analyzed using SPSS version–20 (Armonk, NY: IBM Corp). Logistic regression was used to detect the presence of an association between seropositivity and the independent variable. A variable with a P-value of < 0.25 at bivariate analysis was entered into a multivariable logistic regression model. In any case, a P-value of less than 0.05 was considered to be statistically significant.

Result

About 681 acute febrile patients were approached during the study period. 152 patients were excluded because 149 patients were positive for malaria, 2 patients were refused to give a blood sample and 1 patient was not mentally fit thus, data from 529 patients were considered for analysis. The proportions of female and male respondents were 57.3% and 42.7% respectively, with male to female ratio 0.75:1.Participants within the age group of 20 - 39 years accounted for 48.4% followed by the age group of under 20 years, 28.9%. Of the study participants, 39.9% had only primary school level education, 7.8% higher grade completed and 31.1% had no formal education. Most study participants (86.8%) were rural residents. Concerning their occupation, farmers, students, and housewives accounted for 38.8%, 22.7% and 19.7%, respectively (Table 1).

Out of 529 participants, 79 (14.9%) were found to be positive for IgG and 38 (7.2%) were positive for IgM of yellow fever virus by indirect immunofluorescent assay (IIFA). Male participants (15.0%) had a slightly higher rate of exposure to yellow fever virus infection compared to female participants (14.85%) although the difference was not found to be statistically significant (P > 0.05). The distribution of positive cases by age showed participants' age group under 20 years had more exposure to yellow fever virus (26.8%), followed by those in the age group above 60 years (26.5%). Further, the prevalence of yellow fever virus among urban residents and those who had primary school level education was 37.1% and 11.9% respectively. None of the socio-demographic factors such as age, sex, occupation, educational status, and resident site were found to be associated with yellow fever infection (Table 1).

30.18% and 11.83% of the study participants who do not use bed-net were positive for IgG and IgM respectively. 21.51% of those study participants who lived around the stagnant water was positive for IgG. 6.3% and 7.8% of those who had heard about the Yellow fever virus and had a recent mosquito bite are positive for IgG. However, there was no statistically significant association between those variables and the Yellow fever virus infection (Table 2).

Table 3 summarizes the exposure of Yellow fever virus infection and its association with different clinical factors. Majority, 11.02% of study participants manifested constitutionals symptoms, followed by cough,

7.5%, and headache, 6.7%. Other clinical features that the study participants experienced include neck stiffness 2.0%, eye blurred vision 2.01%, hearing loss 0.13%, sore throat 1.02%, crepitation 1.7%, abnormal heart sound 0.2%, enlarged liver 2.7%, flank pain 1.9%, tenderness 0.54% and rash 0.5%.(Table 3)

In bivariate analysis, candidate variables like blurred vision, rash, Headache, Diarrhea, high body temperature, and constitutional symptoms, occupation like an employee, student and age group of 20–39 are selected. In multivariate logistic regression, however, Yellow fever virus was only associated with constitutional symptoms (AOR = 0.28; 95% CI 0.30—0.72; p = 0.032). Out of 66 study participants who had Constitutional symptoms and positive for Yellow fever virus: 8.0% had only acute fever, 5.5% had acute fever and fatigue, 9.4% had fever and loss of appetite, 14.3% had fever, fatigue, and loss of appetite, 3.2% had acute fever, fatigue, loss of appetite and night sweet and 1.6% had acute fever, loss of appetite and night sweet

Overall there were no significant associations between factors such as sex, age residence, resent mosquito bite, use of bed net, use of mosquito repellant, stagnant water in the village and clinical sign and symptoms like headache, vomit, urination, abdominal pain, cough, shortness of breath

Discussion

Mosquito-borne diseases are common in Ethiopia, However little is known about the epidemiology of arboviruses including YFV. The outbreak of the infection in the 1960s caused many morbidity and mortalities[7, 10], and the irregular reports by the Ethiopian Federal Ministry of Health[11] call for systematic investigations to better describe the epidemiology of YFV in various localities.

In this regard, accurate epidemiological information from various localities of the country helps decision-makers, health providers and other concerned bodies plan an intervention and respond effectively. This study aimed to assess the burden of Yellow fever infection and its associated factors among febrile patients in southern Ethiopia where other mosquito-borne diseases are prevalent. Towards that end, an attempt was made to assess the exposure to Yellow fever virus infection by determining IgG and IgM in the study population.

The overall prevalence of Yellow fever virus infection in this study was 14.9% for IgG and 7.2% for IgM. This finding is comparable to the rate reported in the Central African Republic (13.3%)[12]. However, the observed rate of YFV exposure was lower than results in rural villages in Cameroon (26.9%)[13], and in lowlands of the Kenyan ocean coast (42%)[14]. In contrast, the prevalence of YFV exposure in this study was higher compared to the rates of 5.1%, 2.5%, 1.6% and 6% in Bolivia, Paraguay, Djibouti, and Kenya respectively[14–16]. Direct comparison between different findings may be difficult due to methodological differences, diagnostic tools employed and study population investigated. The difference may also be explained by the fact that the current study focused on the detection of IgG/IgM antibodies from febrile participants; however, some of the previous studies focused mainly on the detection of IgG antibodies from healthy participants (survey on healthy individuals) or detection of IgG antibodies in Yellow fever

outbreak situations. Diagnostic tools also make a difference as there is a considerable discrepancy between the performance of indirect ELISA and PRNT [17].

This study shows there is a significant difference in the rate of Yellow fever virus exposure with age this is in line with the study done elsewhere[18]. This study also showed no association between Yellow fever virus exposure and utilization of bed net, use of mosquito repellent, stagnant water and tree in the compound, staying outside at night, or knowledge about the virus.

As a cause of febrile illness, dengue virus infection is characterized by clinical features including high fever, headache, severe myalgia, nausea and vomiting, and frequent rash. However, the predominant clinical signs and symptoms of the infection may vary with populations in different geographical regions

Limitation of the study

To our knowledge, no data exists to rule-out cross-reactivity with other Flaviviruses in an endemic setting. Moreover, we have no febrile community controls or convalescent sera, and consecutive volunteering cases were used, because of this, there may be a probability of introducing bias. Thus, the findings of this study may not be generalized.

Conclusion

The laboratory finding of this study shows, the level of exposure to yellow fever among febrile cases is relatively high; however, clinical diagnosis of febrile patients is a common practice in the study area. Therefore, Domestication and routine performance of yellow fever virus differential diagnosis will help to address the phenomenon of the virus.

Abbreviations

YFV, yellow Fever virus; IIFA, immunofluorescent assay; ELISA, enzyme-labeled immune Sorbent assay; PRNT, plaque reduction neutralization test; AHRI- Armauer Hansen Research Institute

Declarations

Competing Interest

The authors declare there are no competing interests.

Authors’ contributions

DE has contributed to the conception, design, and acquisition of data. TB and TA contributed to data analysis, drafting or revising the article, all author gave final approval of the version to be published, and

agree to be accountable for all aspects of the work.

Acknowledgment

The authors would like to acknowledge the health professionals in the health settings who assisted with data collection and the study participants who kindly took part in the study. Our appreciation also goes to Mr. Temesgen Ewunetu and Fanuel Belayneh for their support.

We would also like to thank the Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Hawassa University for providing the transport service and the laboratory facility to store samples. We gratefully acknowledge the Armauer Hansen Research Institute (AHRI) that covered the cost of this project, providing the laboratory facility and the necessary materials. Our special thanks also go to the South Nation Nationalities Peoples Regional Health Bureau, Arbaminch Zone Health Bureau, Kola Shele Health Center, Lante Health Center and Mirab Abaya Health Center, that made us access to all requested information, use of possible resources

Consent for publication

Not applicable.

Fund

This study was sponsored by the Armauer Hansen Research Institute. The authors had access to the data in the study and the final responsibility to submit the paper.

Availability of data and materials

All data on which this article is based are included in the article.

Ethics and consent to participant

Ethical clearance was gained from the Institutional Review Board at the College of Medicine and Health Sciences of Hawassa University. Written consent was obtained from the study participants before data collection started. An anonymous questionnaire was used to assure the confidentiality of study participants.

References

1. Sanders EJ, Marfin AA, Tukei PM, Kuria G, Ademba G, Agata NN, Ouma JO, Cropp CB, Karabatsos N, Reiter P: **First recorded outbreak of yellow fever in Kenya, 1992-1993. I. Epidemiologic investigations**. *The American journal of tropical medicine and hygiene* 1998, **59**(4):644-649.
2. Ellis BR, Barrett AD: **The enigma of yellow fever in East Africa**. *Reviews in medical virology* 2008, **18**(5):331-346.
3. Monath TP, Vasconcelos PFC: **Yellow fevers.** *Journal of Clinical Virology* 2015, **64**:160-173.
4. Monath TP: **Yellow fever: an update**. *Lancet Infectious Diseases* 2001, **1**(1):11-20.
5. Garske T, Van Kerkhove MD, Yactayo S, Ronveaux O, Lewis RF, Staples JE, Perea W, Ferguson NM, Committee YFE: **Yellow fever in Africa: estimating the burden of disease and impact of mass vaccination from the outbreak and serological data**. *PLoS medicine* 2014, **11**(5):e1001638.
6. Kraemer MU, Faria NR, Reiner Jr RC, Golding N, Nikolay B, Stasse S, Johansson MA, Salje H, Faye O, Wint GW: **Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015–16: a modeling study**. *The Lancet infectious diseases* 2017, **17**(3):330-338.
7. Sérié C, Andral L, Poirier A, Lindrec A, Neri P: **Etudes sur la fièvre jaune en Ethiopie. 6. Etude épidémiologique**. *Bulletin of the World Health Organization* 1968, **38**(6):879.
8. Vainio J, Cutts F: **Yellow Fever. Global Programme for Vaccines and Immunization Expanded Programme on Immunization. Geneva: WHO** 1998:10.
9. Organization WH: **The yellow fever situation in Africa and South America in 2004**. *Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire* 2005, **80**(29):250-256.
10. Ardoin P, Rodhain F, Hannoun C: **Epidemiologic study of arboviruses in the Arba-Minch district of Ethiopia**. *Tropical and geographical medicine* 1976 **28**(4):309-315.
11. **Ethiopian Federal Ministry of Health (EFMOH). 2013/14. Annual Performance Report**. 2013/14.
12. Staples JE, Diallo M, Janusz KB, Manengu C, Lewis RF, Perea W, Yactayo S, Sall AA, Balekouzou A, Gamba EP *et al*: **Yellow fever risk assessment in the Central African Republic.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2014, **108**(10):608.
13. Kuniholm MH, Wolfe ND, Huang CY, Mpoudi-Ngole E, Tamoufe U, Burke DS, Gubler DJ: **Seroprevalence and distribution of Flaviviridae, Togaviridae, and Bunyaviridaearboviral infections in rural Cameroonian adults**. *The American journal of tropical medicine and hygiene* 2006, **74**(6):1078-1083.
14. Sutherland LJ, Cash AA, Huang YJ, Sang RC, Malhotra I, Moormann AM, et a: **Serologic evidence of arboviral infections among humans in Kenya**. *The American journal of tropical medicine and hygiene* 2011, **85**(1):158-161.
15. Forshey BM, Guevara C, Laguna-Torres VA, Cespedes M, Vargas J, Gianella A, et a: **Arboviral etiologies of acute febrile illnesses in Western South America, 2000-2007**. *PLoS neglected tropical diseases* 2010, **4**(8).
16. Andayi F, Charrel RN, Kieffer A, Richet H, Pastorino B, Leparc-Goffart I, et a: **A seroepidemiological study of arboviral fevers in Djibouti, the horn of Africa**. *PLoS neglected tropical diseases* 2014, **8**(12).

17. EUROIMMUN AG: **Biochips mosaics and profile for detection of Flavivirus infections instructions for indirect immunofluorescence test**. 2013.
18. Awando JA: **Seroprevalence of Anti-Dengue Virus 2 Sero complex Antibodies in out-patients with fever visiting selected hospitals in rural parts of Western Kenya in 2010-2011: a cross-sectional study** *The Pan African Medical Journal* 2013, **16**(73).

Tables

Table 1: Socio-demographic characteristics and its association with yellow fever among study participants

Characteristics	Total (%)	IgG +ve N (%)	IgM +ve N (%)	P-value COR	P-value AOR
Sex					
Male	226(42.7)	34(15.04)	16(7.08)	1	
Female	303(57.3)	45(14.85)	22(7.26)	0.47	
Age group					
< 20 yrs	153(28.9)	41(26.80)	20(13.07)	0.86	0.98
20 - 39	256(48.4)	21(8.20)	10(3.91)	0.10*	0.46
40 - 59	86(16.3)	8(9.30)	4(4.65)	0.67	0.77
> 60	34(6.4)	9(26.47)	4(11.76)	1	1
Educational status					
Primary school	211(39.9)	25(11.85)	12(5.69)	0.56	
Secondary school	112(21.2)	19(16.96)	9(8.04)	0.30	
College and above	41(7.8)	6(14.63)	3(7.32)	1	
NFE	165(31.2)	29(17.58)	14(8.48)	0.71	
Occupations					
Farmer	205(38.8)	26(12.68)	13(6.34)	0.87	0.95
Employee	57(10.8)	20(35.09)	9(15.79)	0.21*	0.26
Student	120(22.7)	14(11.67)	7(5.83)	0.25	0.34
Housewife	104(19.7)	13(12.50)	6(5.77)	0.76	0.88
Others	23(4.3)	6(26.09)	3(13.04)	1	1
Residence					
Rural	459(86.8)	53(11.55)	25(5.45)	0.47	
Urban	70(13.2)	26(37.14)	13(18.57)	1	

IgG, Immunoglobulin G; IgM, Immunoglobulin M; COR, Crude odds ratio; AOR, Adjusted odds ratio; NFE, No formal education

Table 2: Knowledge, practice and other characteristics of study participants and its association with yellow fever among study participants

Characteristics	Total, N (%)	IgG +Ve N(%)	IgM+Ve, N (%)	P-Value for COR	P-Value for COR
Heard about YF					
Yes	192(37.6)	31(16.15)	13(6.77)	1	
No	337(62.4)	48(14.24)	25(7.42)	0.84	
Use of Bed-Net					
Yes	360(68.1)	28(7.78)	18(5.00)	0.25	
No	169(31.9)	51(30.18)	20(11.83)	1	
Use of Mosquito Repellant					
Yes	7(1.3)	2(2.57)	1(14.29)	1	
No	522(98.7)	77(14.75)	19(3.64)	0.52	
Stagnant water in the village					
Yes	172(32.5)	37(21.51)	23(13.37)	1	
No	357(67.5)	42(11.76)	15(4.20)	0.61	
Trees around the compound					
Yes	453(85.6)	33(7.28)	31(6.84)	0.52	
No	76(14.4)	46(60.53)	7(9.21)	1	
Stay outside at night					
Yes	414(78.3)	41(9.90)	24(5.80)	1	24(5.80)
No	115(21.7)	38(33.04)	14(12.17)	0.33	14(12.17)
mosquito bite					
Yes	246(46.5)	44(17.89)	26(10.57)	0.74	26(10.57)
No	283(53.5)	35(12.37)	12(4.24)	1	12(4.24)

IgG, Immunoglobulin G; IgM, Immunoglobulin M; COR, Crude odds ratio; AOR, Adjusted odds ratio

Table 3: Clinical factors associated with yellow fever among study participants

Characteristics	Total, N(%)	IgG+Ve, N(%)	IgM+Ve, N(%)	P-Value for COR	P-Value for COR
Sore throat					
Yes	59(11.2)	9(15.25)	3(5.08)	1	
No	470(88.8)	70(14.89)	25(5.32)	0.36	
Crepitation					
Yes	29(5.5)	6(20.69)	2(6.90)	1	
No	500(94.5)	73(14.6)	36(7.20)	0.51	
Abnormal heart sound					
Yes	5(0.9)	1(20.0)	0(0.0)	1	
No	524(99.1)	78(14.89)	38(7.25)	0.91	
Enlarged liver					
Yes	30(5.7)	11(36.67)	6(20.0)	1	
No	499(94.3)	68(13.63)	32(6.41)	0.43	
Flank pain					
Yes	43(8.1)	13(30.23)	7(16.28)	1	
No	486(91.9)	66(13.58)	31(6.38)	0.63	
Blurred vision					
Yes	61(11.5)	10(16.39)	1(1.64)	1	1
No	468(88.5)	69(14.74)	37(7.91)	0.08*	0.26
High body Temperature					
37.5 - 38	284(53.7)	61(21.48)	23(8.10)	0.24*	0.31
>38	245(46.3)	18(7.35)	15(6.12)	1	1
Headache					
Yes	441(83.4)	49(11.11)	28(6.35)	0.23*	0.29
No	88(16.6)	20(22.72)	10(11.36)	1	1
Cough					
Yes	132(25.0)	25(18.94)	16(12.12)	1	1
No	397(75.0)	54(13.60)	22(5.54)	0.30	0.42

Shortness of breath					
Yes	13(2.5)	3(23.08)	1(7.70)	1	
No	516(97.5)	76(14.73)	37(7.17)	0.93	
Vomit					
Yes	85(16.1)	19(22.35)	11(12.94)	1	
No	444(83.9)	60(13.51)	27(6.08)	0.72	
Constitutional symptoms					
Yes	412(77.9)	42(10.20)	21(5.10)	0.014	0.032**
No	117(22.1)	37(31.62)	17(14.53)	1	1

lgG, Immunoglobulin G; lgM, Immunoglobulin M; COR, Crude odds ratio; AOR, Adjusted odds ratio; NFE, No formal education