Original article

The first acute febrile illness investigation associated with dengue fever in Ethiopia, 2013: A descriptive analysis

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Abstract

Background: Dengue fever (DF) is a febrile illness caused by any one of four serotypes of the dengue flavivirus. Approximately 50 to 270 million DF infections occur every year globally. Dire-Dawa town of Ethiopia reported unidentified febrile cases in September 2013.

Methodology: We investigated the case to identify the etiology and source of the outbreak. Medical records were reviewed and descriptive data analysis was performed. Serum-samples were tested for arbovirus by Enzyme-linked Immunosorbent Assay (ELISA) and Real Time Polymerase Chain Reaction (RT-PCR) techniques. Vector surveillance was carried out in the affected area.

Results: A total of 11,409 suspected DF cases were identified from 12/9/2013 to 31/12/2013. The Attack Rate (AR) was 3.6%. Age groups consisted of 15-44 year-olds who were mostly affected (AR: 5.5%). Laboratory investigation showed that 50/88 (56.8%) samples were positive for DF infection, DEN-2 serotype. *Aedes aegypti* was identified both at indoor and outdoor levels. Breteau and container indices ranged from [19.3 - 36.4] and [8.1 – 25.2] respectively.

Conclusion: This is the first investigation that revealed DF in Ethiopia. We found artificial breeding sites were the primary source of the vector. Vector control should be in placed to interrupt the ongoing outbreak and ensure future prevention. DF needs to be included in the existing routine surveillance. [*Ethiop. J. Health Dev.* 2014;28(3):155-161]

Introduction

As the most imperative mosquito-borne viral disease distressing humans worldwide, DF continues to be a major public health problem in tropical and subtropical areas (1). It is a febrile illness caused by any one of four serotypes of dengue flavivirus (DEN-1, DEN-2, DEN-3, or DEN-4) (1-3). Dengue virus infection in humans is often in apparent and clinically indistinguishable (4), but can lead to a wide range of clinical manifestations, from mild fever to potentially fatal dengue shock syndrome (5). The lifelong immunity developed after infection with one of the four virus types is type-specific, and progression to more serious disease is frequently, but not exclusively, associated with secondary infection by heterologous types (6).

The transmission of DF occurs primarily through infected female *Aedes aegypti* mosquitoes which acquire the virus when feeding blood meals from infected humans (7, 8). *Aedes aegypti*, which has a multi-meal feeding behavior on several people, is most often found among humans in urban dwellings (9). An estimated 50 to 270 million DF infections occur every year globally, of which two million cases evolve to severe DHF, and 21,000 would result in death (10). No effective antiviral drugs yet exist to treat dengue infection and treatment therefore remains supportive (5-11). Furthermore, no licensed vaccine against DF infection is available (11, 13). Current efforts to curb DF transmission focus on the vector, using combinations of chemical and biological targeting of *Aedes aegypti* mosquitoes and management of breeding sites (5).

In Ethiopia, DF was diagnosed only among travelers that return to countries to which dengue was not endemic but never reported as occurring locally (1, 14, 15) and it is also not included among the lists of national reportable diseases (16). On September 12, 2013 Dire Dawa town administration health bureau reported non malaria febrile cases of unknown etiology. All the cases were examined for malaria parasites by microscopy by health centers in Dire Dawa, but only an average of 7% were positive for one of malaria parasites while the patients were sick. The number of cases had grown and even doubled over the weeks. The regional health bureau carried out an outbreak investigation, but they could not identify the source and the underlying agent by local capacity and therefore requested the national team for further investigation. Hence, the current investigation was carried out to identify and determine the etiology, source and magnitude of the outbreak that can be used to design control and prevention measures.

Methods

Study Area:

This investigation was conducted in Dire Dawa administrative council. Dire Dawa administrative council is found at a distance of 515 Kilometers from Addis Ababa to the Eastern part of the country and 333 Km from the international port of Djibouti. It is enclosed by the Somali and Oromia regional states. The council has nine operational districts (four rural and 5 urban districts). It is further classified into 10 urban and 37 rural kebeles (kebele is the smallest administrative unit in

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Ethiopia) (map 1). The administrative council is grouped in to arid and semiarid climatic zones. The north eastern part of Dire Dawa is relatively sparsely populated lowland populated by agro-pastoral and pastoral occupants, and the southeastern part of the administration comprises of the escarpment with mixed farming system. Dire Dawa lies between 1000 to 2000 meters above sea level. At a latitude and longitude of 9°36′N 41°52′E respectively. The average monthly temperature is 24.8 C^0 while the average annual rainfall amounts to 604 mm (17). During the investigation period there was a shortage of water in the town.

Data Collection:
Medical records were reviewed and daily line lists were collected from September 12/2013 to December 31/2013 from 16 health facilities (11 health centers, 2 hospital, 3 clinics). Discussion was held with few patinets to inform them of the method of investigation and enable them to understand thier clinical pictures. World Health Organization Suspected Dengue Fever case definition is used to identfy cases (18). Blood films were prepared for all patients visiting health facilities with febrile illnesses; tests were carried out by microscopy for malaria parasites at the health facilities (hospitals and health centers) by health facility laboratory experts and all malaria slide positive cases were excluded from the report thereby being ruled out as malaria.

Laboratory Investigation: Samples were collected to identfy the cause of the outbreak. Six 10 ml whole blood samples were collected from patients and transported to national bacteriology laboratory for culture at room temperature within 72 hours and incubated for at up to 7 days at $35C^o$–$37C^o$ aerobically. Growth of turbidity, hemolysis, gaseousness, or discrete colony was examined by microscopy daily. Laboratory investigations were performed on Yellow fever, DF, West Nile fevr, Rift Valley Fever, Crimean-Congo Hemorrhagic Fever and Chikungunya viruses on 88 serum samples collected from patiens using Enzyme-linked Immunosorbent Assay (ELISA) and Real Time Polymerase Chain Reaction (RT-PCR) techniques to identfiy underlying etiology. For further investigation and serotype characterization, serum samples were sent to WHO reference laboratory at the Inistitute of ?Pastuer Dakar in Senegal.

Entomological Investigation:
Considering the large number of cases recorded (11,409 cases), only kebeles that had recorded cases with lab confirmed tests (IgM or PCR) were selected for the entomological investigation. In total, 5 kebeles of Dire Dawa city were visited (Kebeles 2, 3, 5, 8, 9). In each selected kebele, a container survey was conducted in households where DF cases confirmed by laboratory tests (household index). In addition, households surrounding the index house were purposely selected and investigated. The artificial and natural mosquito breeding sites were inspected for the presence of larvae or pupae indoors and outdoors of the domestic environments. Samples were collected from infested containers and returned to laboratory for rearing and identification of the emerging adult. Mosquito adults collection was mainly focused on the resting stage using insecticide spray catch collection and aspiration by a backpack aspirator in selected dwellings.

Gravid Traps were occasionally set up in two kebeles using hay infusion as an attractant. Because of limited time of the investigations, these methods were only used in two Kebeles.

Data Analysis:
Descriptive data analysis was performed by time, person and place using microsoft office excel sheet. Attack rate was calculated by dividing the number of cases to the population (Population source: Dire Dawa Regional Health Bureau). Age and sex specific attak rates were also calculated by dividing the number of cases within specific age group or sex to respective age group and multiplying by 100. The Breteau Index (BI): total number of containers with larvae or pupae of *Aedes aegypti* per 100 Habitation Units (HU) and the Container Index (CI): percentage (%) of the number of positive containers divided by the number of containers inspected have been calculated (5,19). According to WHO an area is at an epidemic risk when these indexes are above the threshold of 5% for the BI, and 3% for the CI (20).

Ethical Considerations:
As a public health emergency response, this investigation was not categorized as research and informed consent was not required. Serum samples were collected only aiming to investigate the underlying causative agent and to guide appropriate outbreak control interventions. The direction was given from EPHI, the government organization which has a full mandate to conduct epidemiological investigation and respond to any public health emergencies.

Results
A total of 11,409 suspected Dengue Fever cases with one death were identified from September /2013 to December 31/2013. All these cases were negative for malaria by microscopy. Of these 5,729 (50.2%) were males and 5,680 (49.8%) females. The crude AR was 3.60% (3.61% in males and 3.60% in females). Almost all cases were outpatient consults; only 37 (0.32%) cases were admitted. The number of cases dropped over weekends and increased on Mondays. The trend increased to peak from the second week of October and started to fall from the second week of November (figure 2). The cases were unevenly distributed across the kebeles of the city administration. Accordingly, kebele 09 was mostly affected (AR: 6.16%, 5.78% in males and 6.55% in females) followed by kebele 01 (AR: 5.03 %, 6.10 % in

males and 3.95 % in females) (table 1). Median age was 21 years and the age range was 3 months to 95 years. The descriptive data analysis showed that the most affected age group is 15-44 years (AR: 5.43 %, 5.38% in males, 5.53% in females) followed by 45 years and above (AR: 3.16%, 2.96% in males, 3.36% in females). The least affected age group consisted of under-five-year-old children (1.1%) (Table2).

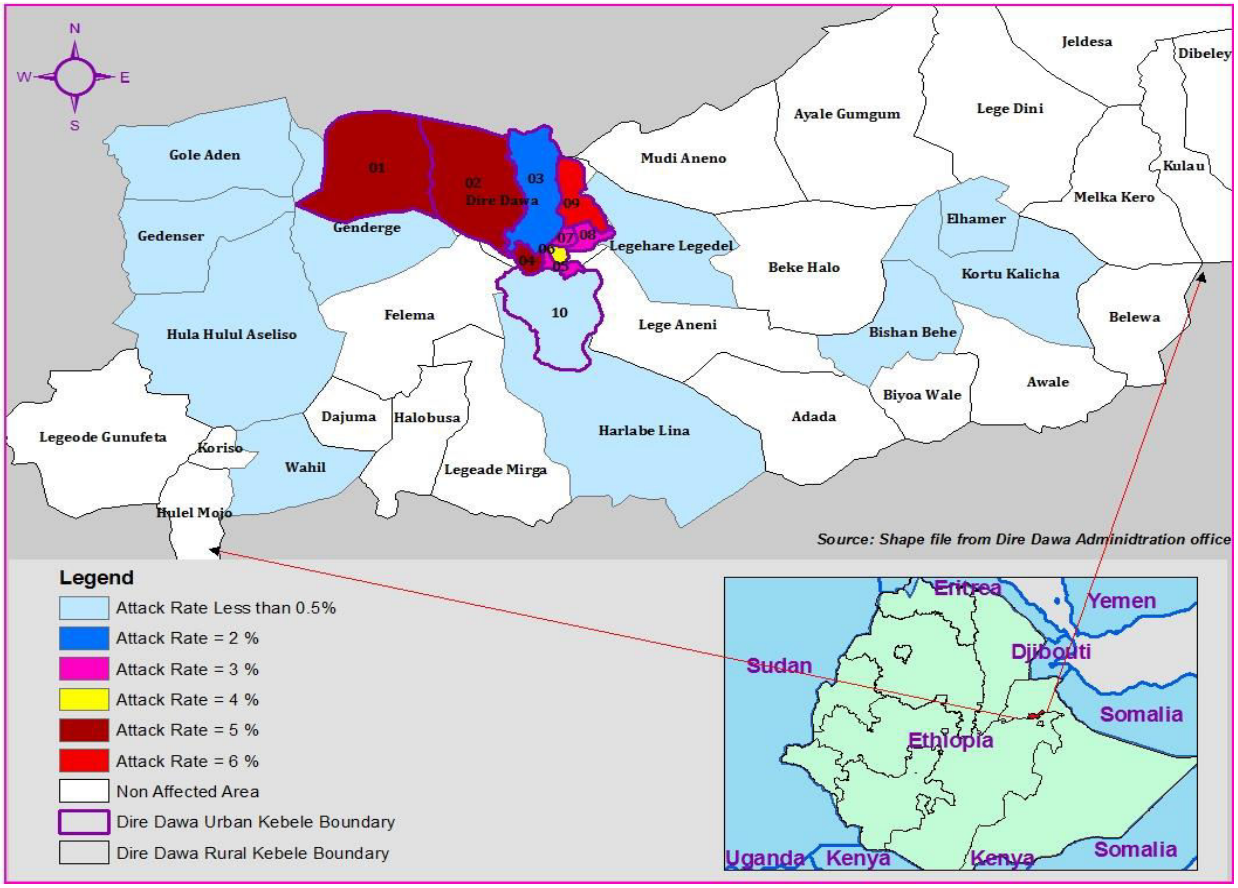

Figure 1: **Dengue fever affected area-Dire Dawa town, November 2013**

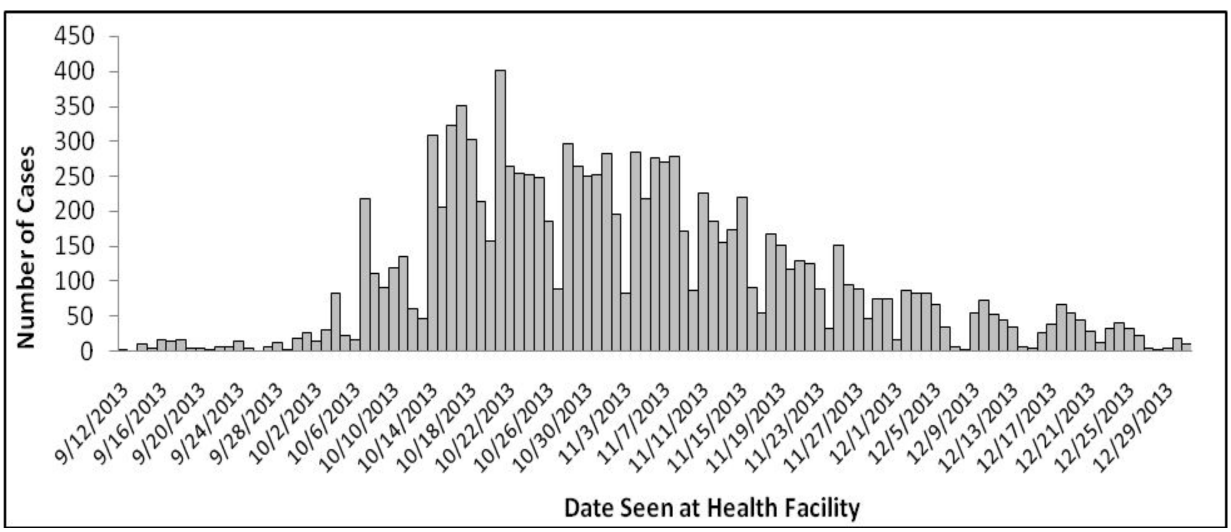

Figure 2: **Suspected dengue fever cases by date seen at health facility, Dire Dawa, September 12/2013 to December 31/2013**

The six whole blood samples cultured for bacterial infections showed no growth for *Salmonella* species, *Streptococcus pneumoniae*, E. coli, Klebsiella *Pneumonia*, and brucella species. Of the 88 serum samples tested for arboviruses, 50 (56.8%) were positive either by ELISA and/or PCR for dengue virus infection. All the serum samples tested negative for Rift valley Fever, Chikungunya, and Crimean-Congo virus. Serotyping of the Dengue virus showed a DEN-2 serotype.

Water-storage containers (Jerry cans, buckets and plastic/metallic drums) were the most common mosquito breeding sites encountered. A fair number of jerry cans were inadequate because they had holes and were mostly infested. Other breeding sites included traditional clay jars, flowerpots, bottles, tanks, and discarded containers. Of the total 563 (42 indoor and 521 outdoor) containers purposely investigated in five Kebeles, 96 (17%) were found to be positive for *Aedes aegypti*. Among 42 indoor containers examined, 5 (11.9%) containers and among 521 outdoor containers examined, 92 (17.5%) containers were found to be positive for *Aedes aegypti* breeding.

The risk indices show a high density of vector. The BI was 25.4:22.9 in Kebele 02, 23.4 in Kebele 03, 36.4 in Kebele 05, 19.3 in Kebele 8 and 27.0 in Kebele 09. Similarly, CI was 17.0: 10.7 in Kebele 02, 8.1 in Kebele 03, 23.2 in Kebele 05, 22.8 in Kebele 8 and 25.2 in Kebele 09 (Table 3).

Table 1: **The distribution of dengue fever cases by kebele and sex-Dire Dawa, September 12/2013 to December 31/2013**

Operational District	**Kebele**	**Population**			**Cases**			**Crude AR/100**	**Sex Specific AR/100**	
		Total	**Male**	**Female**	**Total**	**Male**	**Female**		**Male**	**Female**
Lega Harre	Kebele 09	51981	26094	25887	3204	1509	1695	6.16	5.78	6.55
Sabian	Kebele 02	51641	25924	25717	2556	1313	1243	4.95	5.06	4.83
Genda Kore	Kebele 04	25018	12559	12459	1221	623	598	4.88	4.96	4.80
Lega Harre	Kebele 08	35230	17685	17545	1048	480	568	2.97	2.71	3.24
Lega Harre	Kebele 07	27342	13726	13616	847	399	448	3.10	2.91	3.29
Genda Kore	Kebele 06	19817	9948	9869	760	388	372	3.84	3.90	3.77
Melka Jebdu	Kebele 01	14,129	7093	7036	711	433	278	5.03	6.10	3.95
Addis Ketema	Kebele 05	21323	10704	10619	555	317	238	2.60	2.96	2.24
Dire Dawa	Kebele 03	23636	11865	11771	479	252	227	2.03	2.12	1.93
Melka Jebdu	Genda Rige	2502	1256	1246	11	7	4	0.44	0.56	0.32
Melka Jebdu	Asseliso	6474	3250	3224	5	2	3	0.08	0.06	0.09
Melka Jebdu	Hula Hulul	1000	502	498	2	1	1	0.20	0.20	0.20
Biya Awale	Bishan Behe	4202	2109	2093	1	1	0	0.02	0.05	0.00
Biya Awale	Elhammer	1128	566	562	1	0	1	0.09	0.00	0.18
Melka Jebdu	Gedenser	837	420	417	1	1	0	0.12	0.24	0.00
Addis Ketema	Gelo Belina	11479	5763	5717	1	1	0	0.01	0.02	0.00
Melka Jebdu	Goladag	955	479	476	1	0	1	0.10	0.00	0.21
Addis Ketema	Harla	1000	502	498	1	1	0	0.10	0.20	0.00
Biya Awale	Kalicha	5283	2652	2631	1	0	1	0.02	0.00	0.04
Lega Harre	Legadol	4036	2026	2010	1	0	1	0.02	0.00	0.05
Dire Dawa	Legedin	1845	926	919	1	1	0	0.05	0.11	0.00
Wahili	Wahili	5693	2858	2835	1	0	1	0.02	0.00	0.04
Ground Total		316550	158908	157642	11409	5729	5680	3.60	3.61	3.60

Source of population: Dire Dawa Health Buearu

Table 2: **The distribution of dengue fever by age groups and sex-Dire Dawa, September 12/2013 to December 31/2013**

Age Group	Population			Suspected Cases			Percent	Crude AR/100	Sex Specific AR/100	
	Population	Male	Female	Total	Male	Female			Male	Female
Under 5	46216	23201	23016	581	303	278	5	1.26	1.31	1.21
5-14	96231	48308	47923	2200	1182	1018	19	2.29	2.45	2.12
15-44	136117	68330	67786	7429	3679	3750	65	5.46	5.38	5.53
45+	37986	19069	18917	1199	564	635	11	3.16	2.96	3.36
Total	316550	158908	157642	11409	5729	5680	100	3.60	3.61	3.60

Source of population: Dire Dawa Health Buearu

Table 3: **Aquatic stages prospecting and Dengue epidemic risk indices for each Kebele in Dire Dawa, Ethiopia December 6 – 12th 2013**

Community	HU	No of positive container/No of container inspected										Total	Indices	
		Jerry can		Bucket/ Jar		Barrel	Flower pots		Discarded	Tyres	Bottles			
		In	Out	In	Out	Out	In	Out	Out	Out	Out		BI	CI
Kebele 09	122	0/2	6/39	0/2	16/46	-	1/1	2/6	8/30	0/5	-	33/131	27.0	25.2
Kebele 08	93	0/2	6/34	0/1	7/33	2/6		-	2/2	1/1	-	18/79	19.3	22.8
Kebele 02	61	0/1	7/71		2/21	4/30		1/3	0/4	0/1	-	14/131	22.9	10.7
Kebele 03	47	0/16	1/62	1/6	6/36	-		-	0/1	0/4	3/11	11/136	23.4	8.1
Kebele 05	55	0/4	4/33	3/7	13/40	-		-	0/1	0/1		20/86	36.4	23.2
TOTAL	378	0/25	24/239	4/16	44/176	6/36	1/1	4/9	10/38	1/12	3/11	96/563	25.4	17

BI: Bretau index (>5% = risk); CI: Container index (>3% = risk)

Discussion

This investigation revealed that a large scale dengue fever serotype DEN-2 outbreak occurred in Dire Dawa town. A total of 11,409 suspected dengue fever cases, which mostly affected persons aged 15-44 years old were identified. Among the 88 (0.8%) serum samples collected to identify the cause of outbreak 50 (56.8%) were positive for dengue fever either by ELISA and/or PCR. The risk indices show a high density of vectors in all investigated containers. *Aedes aegypti*, is the unique dengue vectors that infested all containers.

This study had a number of limitations. Because of the urgency to timely respond to the outbreak, analytical study was not carried out. The association of possible risk factors with the cases was not evaluated. Because of the objective of the investigation and shortage of diagnostic reagents, only limited specimens were collected relative to the large number of cases. Although the epidemiologic investigation provided limited information on the association of risk factors for infection, detection of DEN-2 in multiple specimens by ELISA and or PCR underscores the existence of Dengue Fever.

The investigation shows that populations aged 15-44 years old were mostly affected. As the age increases, so does the probability of being affected by DF. In Brazil, DF is predominantly reported among adults and increased with age; in contrast, in the Americas and in Southeast Asia, children are the most affected subpopulation (21, 22). In this outbreak, both males and females were equally affected. Similarly household survey of dengue infection in central Brazil indicates that the prevalence of DF infection was similar between males and females and increased with age (22).

Samples were collected to identify underlying causative agents. Of the samples collected and tested, more than half were DF positive. One positive case is an action threshold for DF to declare as an outbreak (23). Hence, our findings indicate the emergency of DF particularly DEN-2 outbreak in Dire Dawa town. DEN-1 and DEN-2 are mostly the cause of DF epidemic in Africa (2, 23).

Despite the fact that Ethiopia is one of the DF endemic countries (1), this is the first detected and reported outbreak attributed to DF. However, DF epidemic caused by all four serotypes has been documented in Africa since 1980, with 22 countries reporting sporadic cases. High prevalence of antibody to DF virus in limited serologic surveys suggests endemic DF virus infection in many parts of Africa (1, 15).

The entomological investigation indicates that all containers such as jerry cans, buckets, clay jars, plastic/metalic drums, tires, barrels, flower pots, bottles and discarded containers were infested by *Aedes aegypti* mosquito. Studies conducted in Tanzania show that *Aedes aegypti* breeds in tree holes, leaf axels, gutters, tires, ground pools, discarded pots, tanks, plastic rubbers, buckets, pure water nylons and aluminium containers (24, 25), which concurs with our findings. During the investigation, we observed that all households stored water in different containers in and outside of the house because of shortage of water in the town. *Aedes aegypti* mosquito has successfully adapted itself to human dwellings where water is stored both inside and outside the premises (26). The abundance of breeding sites found in five investigated Kebeles contributed to the high density of Aedes aegypti infestation and the dengue fever cases. The risk indices, Entomologic indices, BI and CI, indicate that all investigated kebeles are at high risk for DF transmission. The risk indices calculated were over the threshold (20).

***Conclusion*:**

It is evident from the investigations that the acute febrile illness outbreak was caused by DF virus serotype DEN-2. People in the 15-44 years age bracket were mostly affected while children under five were the least affected age groups. Kebele 09 was the most affected area. The risk indices show a high density of vectors in all investigated containers. *Aedes aegypti*, a unique dengue vector, infested all containers.

In the absence of vaccination and effective drugs, the only intervention is vector control to contain the current outbreak and ensure prevent future prevention. Environmental management should be undertaken by emphasizing on artificial manmade mosquito breeding sites. To monitor the trend of the disease and point out public health significance, DF needs to be included in the existing disease surveillance system.

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