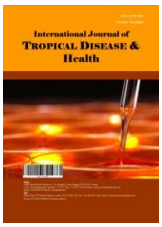

International Journal of TROPICAL DISEASE & Health

40(3): 1-10, 2019; Article no.IJTDH.54064
ISSN: 2278–1005, NLM ID: 101632866

Epidemiological Characteristic of Malaria Coinfected with Dengue Fever in Hodeidah, Yemen

Asma'a Al-Areeqi[1*], Saeed Alghalibi[1], Qais Yusuf[1], Isra'a Al-Masrafi[1] and Mohammed Amood Al-Kamarany[2]

[1]Microbiology Branch, Department of Biology, Faculty of Science, Sana'a University, Sana'a, Yemen.
[2]Department of Pharmacy Practice, Faculty of Clinical Pharmacy, Hodeidah University, Center for Tropical Medicine and Infectious Diseases (CTMID), Authority of Public Al-Thawra Hospital, Hodeidah, Yemen.

Authors' contributions

This work was carried out in collaboration among all authors. Authors AAA and IAM designed the study, performed the statistical analysis and wrote the protocol and wrote the first draft of the manuscript. Author MAAK managed the analyses of the study and revised the manuscript. Authors SA and QY managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2019/v40i330230
Editor(s):
(1) Dr. Nasser Mousa, Professor, Department of Tropical Medicine, Mansoura University, Egypt.
Reviewers:
(1) Nkengazong Lucia, Cameroon.
(2) Joseph Baruch Baluku, Mulago National Referral Hospital, Uganda.
(3) Naresh Kumar, Mewar University, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/54064

Original Research Article

Received 08 January 2020
Accepted 31 January 2020
Published 18 February 2020

ABSTRACT

Introduction: Malaria and dengue fever are the most prevalent vector-borne diseases in tropical areas and represent major public health problems. They are transmitted by mosquito namely *Anopheles* and *Aedes aegypti*, respectively. Hodeidah is a high density with these vectors. Also, co-infection of these diseases has (malaria and dengue) become undetected due to lack of suspicious clinical suspicion and overlapping symptoms.
Aim of the Study: The study aimed to detect the prevalence of co-infection with malaria and dengue fever, determine the clinical presentation within febrile patients in Hodeidah city and determine some potential risk factors associated with co-infection.
Methods: A cross-sectional study was conducted (from January to December 2017) in febrile patients. All patients were designed into three groups: Group A (co-infected with malaria and dengue); Group B (malaria as mono-infection) and Group C (dengue as mono-infection). The diagnosis of malaria was by microscopic and rapid diagnostic test (RDT) and the dengue virus was

**Corresponding author: Email: asmaa.areeqi@gmail.com;*

detected using enzyme-linked immunosorbent assay (ELISA). The diagnosis was performed in Center of Tropical Medicine and Infectious Diseases (CTMID), Authority of AL-Thawra Public Hospital-Hodeidah, in collaboration with the Tihama Foundation for Medical-Pharmaceutical Studies and Research (TFMPSR), Hodeidah, Yemen.

Results: Out of 270 febrile patients, 82 cases (30.4%) patients were malaria – dengue coinfection, 100 cases (37.0%) of malaria, 21 cases (7.7%) of dengue and 67 cases (24.8%) were non-malaria and non-dengue. The most common symptoms were fever, headache, arthralgia, myalgia and retro-orbital pain, where the clinical symptoms of co-infected patients were more like dengue than malaria. One death was reported in malaria – dengue coinfection, with a case fatality rate (CFR%) of 1.2% (1/82).

Conclusion: Our results show a high prevalence of malaria – dengue coinfecion in Hodeidah, Yemen as the first time. These due to a high density of vectors in this region and endemic areas for malaria and dengue. Furthermore, surveillance strategies, preventive measures and healthcare worker's education are critical for curtailing this problem and lifesaving.

Keywords: Co-infection; malaria; dengue; Hodeidah city; Yemen.

1. INTRODUCTION

Malaria and dengue fever are among the major public health problems grouped into mosquito-borne diseases. Annually, approximately 429,000 and 12,000 people die and another 212 million and 96 million are estimated to fall ill from malaria and dengue [1,2]. Malaria parasites are transmitted by female Anopheles mosquitoes, whereas dengue is transmitted by female Aedes mosquitoes [3]. Co-infection of these two diseases (malaria and dengue fever) is possible in geographical locations where the respective vectors co-exist [4]. One such location includes Yemen where various studies have described the acute presentation of malaria and dengue mono-infection in the country.

Malaria, dengue, and chikungunya fever infections were reported in Yemen. An epidemic of dengue fever infection in Yemen was reported to have occurred in 1954, which affected 98% of the population of Hodeidah [5]. In 1984, travellers returning from Yemen to the USA that were serologically confirmed to have the dengue [6]. The United Nations International Children's Emergency Fund (UNICEF) reported that the dengue hemorrhagic fever was a notable disease in Yemen since 1994 [7,8]. The first dengue outbreak was confirmed in 2003, in Shabwah governorate. Later, WHO reported epidemics of dengue fever in some parts of Yemen that spread in the coastal planes of Tehama and Abyan that the dengue fever became epidemic in some parts of Yemen that spread in the coastal planes of Tehama and Abyan [9]. Also, malaria is an endemic in Hodeidah, Yemen [10].

On the other hand, Malaria and dengue share common symptoms which overlap when patients present acute febrile illness such as high fever, headache and myalgia. Recent studies have shown that malaria and dengue co-infection may be more severe than those seen in mono-infection case [11,12]. Due to this similarity and lack of specificity of symptoms, misdiagnosis is often common among clinicians and is more probable when these infections occur simultaneously [12,13].

The consequences of misdiagnosis of malaria as dengue or vice versa and under-reporting of co-infection could reflect a limitation of epidemiological update of these diseases [13]. Co-infection may also be associated with increased morbidity, mortality, and increased health care cost. Description of co-infections may help in primary and secondary preventive care of patients with infections [14].

Data on co-infection of malaria and dengue are scarce or almost unavailable in our region. Therefore, this study was performed to: 1: determine the prevalence of malaria and dengue virus co-infection among febrile patients in Hodeidah city, Yemen; 2: determine some potential risk factors associated with the diseases and; 3: demonstrate the clinical presentation of patients with co-infection and compare it with mono-infected patients.

2. MATERIALS AND METHODS

2.1 Study Area

This study is conducted in the Hodeidah city, Yemen. The Hodeidah city is the local coastal capital of the fourth largest governorate in Yemen, "Hodeidah governorate". It is located on

a flat and narrow coastal plain, between the foothills of the highlands and the Red Sea known as Tehama; the area is 181 km^2, involves three districts (Hali, Hawak and Meena) with an estimated population of 415,283 [15]. It has a tropical zone, and the climate can be described as being hot, windy, and humid. The highest temperature can reach 38 to 40°C, during the summer while the rest of the year temperature ranges between 27-35°C [15]. This region is endemic for malaria and dengue due to the high-density vectors, risk of transmission and outbreaks that are linked to poor infrastructure, rainfall and warmer temperatures [16]. The main hospitals in Hodeidah city were selected as sample collection sites.

2.2 Study Population and Design

This study is designed as cross-sectional study. It included all patients admitted at both the in-patient and out-patient departments in selected hospitals in Hodeidah city between the period of January 2017 and December 2017. To be considered into the study, patients are selected based on several symptoms. Hence, patients with an acute febrile illness and exhibit two or more of the following symptoms; headache, arthralgia, myalgia, retro-ocular pain, rash or hemorrhagic manifestation were included in the study. On the other hand, patients who are already diagnosed to have other diseases such as enteric fever or non-febrile were excluded.

2.3 Data Collection

Data were collected using a standard questionnaire that was divided into several sections. Section 1 concerns the patients' demographic profiles. Specifically, information on socio-demographic data such as age, gender, educational level, income status and house structure were obtained. Section 2 requires information on patients' clinical symptoms such as fever, headache, nausea, vomiting, myalgia, arthralgia and rash. Finally, section 3 intends to identify some risk factors such as presence of bogs, trash and sewages. This filling of questionnaire was performed by researcher.

2.4 Sample Collection Procedure

To obtain the intended sample, about 5ml of blood was collected by venipuncture from febrile patients transferred into two separated sterile bottles; the first bottle (anti-coagulant) represented one third of the whole blood and was (3—5 drops) used for the RDT malaria parasite detection, approximately 20 µl of which was used to prepare thin and thick blood films for malaria investigation. The second bottle (anticoagulant-free) represented two third of the whole blood that was allowed to clot at room temperature which later centrifuged (3000 rpm 5 minutes). The serum was transferred into two separate Eppendorf tubes (one was the original sample and the second was the backup sample) and stored in refrigerator at -20°C. Twenty-four hours prior to performing the serological assay, samples were thawed in a refrigerator overnight at 4°C.

2.5 Laboratory Testing

Malaria was detected in the samples using a rapid test kit (Combo CareStart, Access Bio, Inc. USA) according to the manufacturer's instructions. The species identification and quantitation of parasites determined on thin and thick blood films with 20% Giemsa stain, all steps were taken according for WHO [17]. A slide was considered negative when there were no parasites in the 100 high power fields [18]. For the diagnosis of dengue, Sera samples were analyzed for anti-dengue virus IgM and IgG by enzyme linked immunosorbent assay (ELISA) using commercial diagnostic kits (Calbiotech Inc., USA) according to the manufacturers' instructions. The optical density was measured at 450 nm. A positive result was calculated based on the ratio of the optical density obtained with the test sample divided by the calculated cut-off value. Samples having an index value >1.1 were considered positive. After diagnosis, a subject was declared to be co-infected if both malaria microscopy and a dengue IgM were positive. Then, patients were grouped into three groups representing different infections; malaria and dengue co-infection (Group A), malaria mono-infection (Group B) and dengue mono-infection (Group C).

2.6 Statistical Analysis

The data obtained were entered and analyzed using Statistical Package Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, USA). The chi-squared (X^2) test was used to compare the proportion of quantitative variables between the two groups. Descriptive analysis for numerical data consists of mean with standard deviation (SD) was using T-test to compare of mean between two groups. The p-value less than 0.05 ($p < 0.05$) was considered as statistically significant.

3. RESULTS

3.1 General Characteristics of Patients

This study has recorded a total of 270 febrile patients attending selected hospitals in Hodeidah City, which are Authority of General Al-Thawra Hospital, Military General Hospital, Al-Rasheed Hospital, Al-Aqsa Hospital, Al-Salakhana Hospital and Al-Amal Hospital. The majority of study participants were from the out-patients department (60.4%). In term of gender, this study has seen a large number of male patients than the female patients. The male represents 64.4% of total participants while female patient represents 35.6%. The age range was from 2-88 years old, with a median age of 21.5 years, the highest infected age group was between 16-30 years (49.2%). Almost half of participants in this study (47.8%) received education up to secondary level. Consequently, 231 patients belong to low income status (85.6%). Finally, most of the participants (57.0%) were living in rural areas and 53.7% were living in random houses (Table 1).

3.2 Prevalence of Malaria and Dengue Co-infection according to the Socio-demographic Characteristics

Out of 270 acute febrile patients, co-infection of malaria-dengue (Group A) was found in 82 cases (30.4%), malaria mono-infection (Group B) in 100 cases (37.0%) and dengue mono-infection (Group C) in 21 cases (7.8%), while 67 cases (24.8%) were determined as negative for malaria and dengue. In addition, this study also notes on one death case that belongs to co-infection group (Group A) with a case fatality rate (CFR %) of 1.2% (1/82). The prevalence of the whole results in this study was summarized in Table 2.

Regarding for the species of malaria. *P. falciparum*, *P. vivax* and mixed infections were found in 78 (95.1%), 3 (3.6%) and 1 (2.4%), respectively, among co-infection cases. While among the cases of malaria mono-infection *P. falciparum* and *P. vivax* was found in 96 (96%) and 4 (4%), respectively.

Table 1. General characteristics of patients in Hodeidah city, Yemen (n = 270)

Variables	Number(n)	Ratio (%)
Hospitalization		
In-patient	107	39.6
Out-patient	163	60.4
Gender		
Male	174	64.4
Female	96	35.6
Age		
1-15	89	33.0
16-30	133	49.2
31-45	35	13.0
46-60	8	3.0
≥61	5	1.8
Educational level		
Illiterate	24	8.9
Primary	98	36.3
Secondary	129	47.8
University	19	7.0
Income status		
Low status	231	85.6
Moderate status	39	14.4
High status	0	0.0
Residency		
Rural	154	57.0
Urban	116	43.0
House structure		
Random	145	53.7
Apartment	125	46.3

Table 2. Overall prevalence of malaria and dengue co-infection

Characteristics	Dengue Positive		Dengue Negative		Total	
	n	%	n	%	n	%
Malaria Positive	82	30.4	100	37.0	182	67.4
Malaria Negative	21	7.8	67	24.8	88	32.6
Total	103	38.2	167	61.8	270	100

Table 3. Prevalence of malaria and dengue co-infection according to the socio-demographic characteristics, Hodeidah, Yemen (N = 270)

Patients characteristics	Participants		Co-infection (A)		Malaria (B)		Dengue (C)		p- value	
	n	%	n	%	n	%	n	%	A×B	A×C
Hospitalized										
In-patient	107	39.6	55	51.4	29	27.1	9	8.4	0.01	0.04
Out-patient	163	60.4	27	16.5	71	43.5	12	7.3		
Gender										
Male	174	64.4	56	32.1	69	39.6	17	9.7	0.9	0.2
Female	96	35.6	26	27.0	31	32.2	4	4.1		
Age (years)										
1-15	89	33.0	18	20.2	41	46.0	4	4.4	0.04	0.4
16-30	133	49.2	51	38.3	46	34.5	14	10.5		
31-45	35	13.0	12	34.2	11	31.4	3	8.5		
46-60	8	3.0	1	12.5	2	25.0	0	0.0		
≥61	5	1.8	0	0.0	0	0.0	0	0.0		
Educational level										
Illiterate	24	8.9	3	12.5	8	33.3	2	8.3	0.2	0.3
Primary	98	36.3	25	25.5	41	41.8	5	5.1		
Secondary	129	47.8	49	37.9	47	36.4	11	8.5		
University	19	7.0	5	26.3	4	21.0	3	15.7		
Income status										
Low status	231	85.5	73	31.6	89	38.5	18	7.7	0.9	0.7
Med status	39	14.4	9	23.0	11	28.2	3	7.6		
High status	0	0.0	0	0.0	0	0.0	0	0.0		
Residency										
Rural	154	57.0	54	35.0	61	39.6	8	5.1	0.5	0.02
Urban	116	43.0	28	24.1	39	33.6	13	11.2		
House structure										
Random	145	53.7	54	37.2	55	37.9	9	6.2	0.1	0.07
Apartment	125	46.3	28	22.4	45	36	12	9.6		

Table 3 shows a comparison of the three groups (A, B and C) according to patients' socio-demographic characteristics. First, type of hospitalization shows that patients with co-infection of malaria-dengue are to be more frequent in in-patient department with a total of 55 patients (51.4%) than the out-patient department (16.5%). On the other hand, more out-patients are identified when malaria is registered as mono-infection 71 patients (43.5%). The p value < 0.05 indicates the statistically significant association between hospitalization and a prevalence of group A with group B and group C.

Males were more distribution in all the three groups A, B and C than the females which were 32.1%, 39.6% and 9.7% respectively, while this difference was not statistically significant (p value > 0.05). Next, patients aged 16-30 years old were more susceptible to acquire co-infection (Group A) with total number of patients was 51 (38.3%) and 14 (10.5%) patients with dengue mono-infection (Group C); whereas malaria mono-infection (Group B) sees patients were in the age group of 1-15 years old (46.0%). This produces a p value of < 0.05 thus indicating significant association with co-infection.

In the aspect of income status, positive cases were mostly observed among patients with low income status across all type of group infection; 73 patients in Group A (31.6%), 89 patients in Group B (38.5%) and 18 patients in Group C (7.7%). Next, the frequencies of cases in rural areas were almost similar between the co-infection 54 (35.0%) and malaria mono-infection 61 (39.6%). The frequencies in the urban areas however show more cases of dengue mono-infection 13 (11.2%) which indicates significant association with co-infection of malaria-dengue when the *p* value is < 0.05.

3.3 Distribution of Studied Cases According to the Clinical Features

According to Table 4, it is clear that fever was present in all patients (100%). In fact, fever was the common symptom reported in all groups (A, B and C) with percentage 30.4%, 37.0%, and 7.8% respectively. Other common symptoms to be reported by most patients are headache (61.4%), abdominal pain (53.3%) and arthralgia (44.8%). Retro-orbital pain symptom was reported in Group C (27.5%) and this is followed by 24.6% in Group A and 21.7% in patients from Group B. It was significantly more in Group A as compared to Group C (p = 0.01) but was not different significantly with group B (p = 0.33), hence, it is comparable with malaria. Regarding bleeding manifestation like purpuric rashes over skin, epistaxis, and sub-conjuctival haemorrhage, these symptoms were present in 9 patients (37.5%) of co-infection in Group A, 7 patients (29.2%) of Group C and 2 patients in Group B (8.3%) which was statistically significant as compared between groups A and B (p = 0.02) and between groups A and C (p = 0.01).

3.4 Risk Factors Associated with Co-infection

Finally, this study wants to identify the potential risk factors associated to co-infection of malaria-dengue. Table 5 shows the prevalence of mono and co-infection according to vector breeding sites that have been identified as the risk factors. From the result, it can be seen that the highest percentage of mosquitoes breeding site was the bogs 40.4% (Group A), 29.3% (Group B) and 15.6% (Group C) hence producing a significant association between co-infection as compared to malaria mono-infection (p = 0.01) and dengue mono-infection (p = 0.02). On the other hand, water tank, sewage, trash and tires were shown to associate the presence of co-infections mostly trash (33.1%) and sewage (32.6%) although they have not shown a significant association with co-infection. Another risk factor identified was water storage tools as evident in the three groups A (32.8%), B (26.7%) and C (10.3%). This indicates a significant association between co-infection as compared to Group B (P = 0.04), but this difference was found to be not significant with Group C (p = 0.3).

4. DISCUSSION

This study is deemed to be the first study conducted to investigate the co-infection with malaria and dengue among febrile patients in Hodeidah city and in Yemen generally. Even though Hodeidah has been reported to be among the endemic regions with malaria and dengue, there have not been any attempts of epidemiological studies on such.

From the results, it has been revealed that the overall prevalence of co-infection (malaria with dengue) among all the cases with fever was 82 (30.4%), 100 (37.0%) of cases were found positive for malaria mono-infection, 21 (7.8%) of cases had dengue mono-infection, while 67 (24.8%) of febrile patients were negative for both malaria and dengue.

This study has highlighted a high prevalence of co-infection (30.4%) in Hodeidah city, Yemen. Such result is within the similar range of percentage to what was found in Pakistan that has 32.6% and 23.2% respectively [12,19]. The high prevalence of co-infection with malaria and dengue in febrile patients in our study could be associated to the similarity of clinical features of malaria and dengue fever. In this case, symptoms for dengue fever may easily be confused with malaria if the patient does not receive careful evaluation by clinical practitioners and vice versa. This observation agreed with Ali et al and Hisam et al [20,21].

In addition, we also found that *P. falciparum* was present in majority of the cases 78 (95.1%) among co-infection cases. However, *P. vivax* and mixed infection was found in 3 (3.6%) and 1 (2.4%), respectively. This result similar to Mohapatra et al. from India (88.8%) [4].

Next, the malaria – dengue co-infection was mostly observed in in-patients (51.4%), when it is compared to mono-infection (27.1%) and (8.4%), respectively. Such result is not surprising

Table 4. Comparison of the clinical features of cases mono and co-infection, Hodeidah, Yemen

Clinical features	Participants N = 270		Co-infection (A) n=82		Malaria (B) n = 100		Dengue (C) n = 21		P- value	
	n	%	n	%	n	%	n	%	A×B	A×C
Fever	270	100.0	82	30.4	100	37.0	21	7.8	*	*
Abdominal Pain	144	53.3	45	31.2	50	34.7	15	10.4	0.553	0.218
Myalgia	93	34.4	44	47.3	7	7.5	19	20.4	0.01	0.02
Headache	166	61.4	76	40.3	41	24.6	17	10.2	0.01	1.00
Retro- orbital Pain	69	25.5	17	24.6	15	21.7	19	27.5	0.33	0.01
Arthralgia	121	44.8	34	28.1	31	25.6	17	14.0	0.16	0.01
Chills	108	40.0	37	34.2	48	44.4	15	13.8	0.76	0.04
Nausea	101	37.4	38	37.6	29	28.7	9	8.9	0.75	0.61
Diarrhea	21	7.7	7	33.3	5	23.8	2	9.5	0.38	0.88
Vomiting	92	34.5	39	42.3	20	21.7	13	14.1	0.04	0.03
Bleeding	24	8.8	9	37.5	2	8.3	7	29.2	0.02	0.01

**Same percentage, no comparison necessary; p-value < 0.05 (significant)*

Table 5. Prevalence of malaria and dengue co-infection according to vector breeding sites (as risk factors), Hodeidah, Yemen

Risk factors	Patients N = 270		Co-infection (A) n = 82		Malaria (B) n = 100		Dengue (C) n = 21		X^2		*p*- value	
	n	%	n	%	n	%	n	%	A×B	A×C	A×B	A×C
Water storage tools	116	42.9	38	32.8	31	26.7	12	10.3	4.5	0.7	0.04	0.34
Water tank	90	33.3	27	30	22	24.4	9	10	2.7	0.7	0.09	0.43
Bogs	109	40.4	44	40.4	32	29.3	17	15.6	8.6	5.1	0.01	0.02
Sewages	89	32.9	29	32.6	23	25.9	10	11.2	3.3	1.0	0.07	0.38
Trash	118	43.7	39	33.1	32	27.1	10	8.5	3.5	0.0	0.05	1.00
Tires	58	21.5	15	25.9	11	18.9	5	8.6	1.9	0.3	0.22	0.57

p-value < 0.05 (significant); Chi square (X^2) ≥ 3.9 (significant)

because it is expected that patients with co-infection will prolong the disease duration if they do not receive early diagnosis and hence, will result in hospitalization. Nevertheless, there was a significant association between co-infection group and both mono-infection groups with hospitalized patients ($p < 0.05$). Almost Similar findings were seen in studies by Epelboin et al [11] and Magalhães et al. [22], who found that the duration of fever was longer in co-infection patients and they were hospitalized more frequently than malaria and dengue mono-infection.

In terms of gender, males were found to be more susceptible to have co- infection and both mono-infection of malaria and dengue. However, the differences between male and female were not statistically significant. Similar result of co-infection was found in French Guiana [11], Pakistan [12] and India [23]. For this particular finding, it is believed that the habits of males when they are in hot areas such as wearing cut clothes that leave their arms and legs exposed may cause them to be infected more than females who go out quietly covered. Males are also perceived to be more active in outdoor activities which make them more vulnerable to the bites of mosquitoes. This observation is consistent with other studies conducted in Yemen [10,8].

The next variable that this study has looked into is age. People in between 16-30 years old were likely to have co-infection 51 (38.3%) and dengue mono-infection 14 (10.5%). This particular finding was almost found with outcomes from studies conducted in Brazil [22] and in Pakistan [12]. On the other hand, people aged from 1-15 years old were more likely to have malaria mono-infection 41 (46.0%) which is consistent to studies carried out in Hajjah [24] and Hadrmout, Yemen [25]. The possible reason for the high number of co-infection and malaria

mono-infection in these age groups (16-30 years and 1-15 years, respectively) was again due to the high activities that individuals from these age groups participated that often require them to be in outdoor during day. As a result, it increases the exposure to vector bites.

Another finding that the current study can report is the high prevalence of co-infection and malaria mono-infection in rural areas which is also the same observation that was found in random houses. Our finding concurred with a study in India [26] whose found maximum cases from rural areas in co-infection and malaria mono-infection.

On the other hand, dengue mono-infection was found to be common in urban areas and apartment houses with a significant association between the prevalence rate of co-infection with dengue mono-infection and place of residency (rural or urban areas) is P. v < 0.05. This finding agreed to what has been found in Al-Hodiedah [8].

One important yet interesting observation in our study is that the occurrence of co-infection (malaria-dengue) were prevalence in rural areas. The traditional belief that malaria occurs in rural areas while dengue is more prevalent in urban areas may not be applicable. If such belief is practiced, it can pose risk of misdiagnosing dengue as malaria and vice versa due to common similar symptoms. Hence, our study has shown evidence that it might not be such a case. This an explanation is in agreement with a study in French Guiana [27].

Even though dengue was earlier known as an urban disease, the trend is now changing due to environmental and societal changes and improper water storage practices which have resulted in the invasion of the vector into the rural areas. Frequent movement of the population has also helped the virus to be spread into the rural areas [28].

Patients with co-infected are found to exhibit clinical features more like dengue mono-infection than the malaria mono-infection. Therefore, the similarity in symptoms between these infections may complicate the diagnosis of co-infection. Our finding was similar with previous studies in Brazil and in India [22,4]. Analysis on the symptoms of all patients has shown fever to be the commonest symptom (100%) in all the three groups. This result was similar to what has been found in Pakistan and in India [12,26].

Moreover, bleeding manifestation which is similar to dengue was common in patients with co-infection (malaria and dengue). Therefore, screening for malaria in patients with dengue is necessary for diagnosis of such cases. Studies in India and French Guiana [4,11] also have reported similar findings. This suggests a possible synergistic pathogenic mechanism, which could be linked to both capillary fragility and coagulation disorders, but not the low platelets count [22]. According to WHO, bleeding is uncommon in malaria [29] but can be possible in malaria with common platelets low [30]. Consequently, malaria with bleeding manifestation is considered as severe malaria [4].

Furthermore, breeding sites of mosquitoes were found to be linked to the existence of co-infection, and both malaria and dengue mono-infection, where bogs were the highest percentage in all three the groups. The rest of breeding sites such as trash, water storage tools, sewages, water tank and tires further help in spreading of the infection despite these places are common habitat of mosquitoes to live in. Where many people do not cover the bogs, leave dumpsites in the street and uncovered water storage tools and tank, all these factors contribute to modify the environment and directly influence in increase breeding for mosquitoes in urban and rural areas. This practice consequently supports the transmission of malaria and dengue to human [31].

Finally, mortality was seen in one case only (1/82) which was registered with co-infection (1.2%). In this case, the patient was a pregnant woman who had been delayed in the diagnosis and treatment. It should be noted that co-infections in pregnancy presented more complications and challenges for diagnosis and clinical management due to the additional stress of the physiological changes during pregnancy [32]. Therefore, accurate diagnosis of the co-infections can reduce the high mortality rates in pregnancy-related cases.

5. CONCLUSION

Our study for the first time has contributed to showing a high prevalence of malaria – dengue co-infection in Hodeidah city, Yemen. The high prevalence is due to a high density of vectors in this region. Following this outcome, the co-infection should be suspected in endemic areas for malaria and dengue, especially the two

infections are clinically difficult to differentiate which caused the overlapping symptoms and failure or delay in diagnosis and treatment. Furthermore, surveillance strategies, preventive measures and healthcare worker's education should be critical for curtailing this problem and lifesaving in the future.

CONSENT AND ETHICAL APPROVAL

Ethics statement of the study acknowledged distinctive consent from committee of Biology Department, Faculty of Sciences, attained approval from the Ethics Committee of Sana'a University and Center of Tropical Medicine and Infectious Diseases, Authority of Public Al-Thawrah Hospital, Hodeidah, Yemen.

ACKNOWLEDGEMENTS

Authors are grateful to Sana'a University, Faculty of Science, Biology Department, for their dedicated work to successfully complete the study. The study could not have been successful without the cooperation of Center of Tropical Medicine and Infectious Diseases Center (CTMID), Al-Thawra Authority of Public Hospital, Also, Tihama Foundation for Medical – Pharmaceutical Research and Studies (Dr. Tariq Abdulkarim, Dr. Nahla Saeed, Dr. Fatimah Al-Ahdal) for helping in lab work in testing of samples, many thanks to Prof. Abdulwahed Al-Serouri and Dr. Mohammed AL-Kamarany for their corporation with data analysis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. World Health Organization (WHO). World malaria report. Geneva, Switzerland: World Health Organization; 2017.
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, Drake JM, Brownstein JS, Hoen AG, Sankoh O, Myers MF. The global distribution and burden of dengue. Nature. 2013;496 (7446):504-507.
3. World Health Organization (WHO), Increased risk of urban yellow fever outbreaks in Africa. Global Alert and Response (GAR); 2010.
4. Mohaptra M, Patra P, Agrawda R. Manifestation and outcome of concurrent malaria and dengue infection. Journal of Vector Borne Diseases. 2012;49(4):62-265.
5. Van Kleef E, Bambrick H. and Hales S. The geographic distribution of dengue fever and the potential influence of global climate change. TropIKA, Net, (AHEAD). 2010;1-18.
6. Jimenez-Lucho VE, Fisher EJ, Saravolatz LD. Dengue with hemorrhagic manifestations: An imported case from the Middle East. American Journal of Tropical Medicine and Hygiene. 1984;33(4):650-653.
7. Yemen situation report reporting period. United Nations International Children's Emergency Fund (UNICEF); 2012.
8. Abdullah QY, Ogaili M, Alahdal M, AL-Kamarany MA. Dengue Fever Infection in Hodeidah, Yemen: Risk Factors and Socioeconomic Indicators. British Biomedical Bullieten. 2015;3(1):58–65.
9. World Health Organization (WHO). Global strategy for dengue prevention and control 2012-2020. Geneva. (WHO); 2012.
10. Al-Mekhlafi AM, Al-Mekhlafi HM, Mahdy MA, Azazy AA, Fong MY. Human malaria in the highlands of Yemen. Annals of Tropical Medicine & Parasitology. 2011; 105(3):187-95.
11. Epelboin L, Hanf M, Dussart P, Ouar-Epelboin S, Djossou F, Nacher M, Carme B. Is dengue and malaria co-infection more severe than single infections? A retrospective matched-pair study in French Guiana. Malaria Journal. 2012;11(1):142.
12. Assir MZK, Masood MA, Ahmad HI. Concurrent dengue and malaria infection in Lahore, Pakistan during the 2012 dengue outbreak. International Journal of Infectious Diseases. 2014;18:41-46.
13. Baba M, Logue CH, Oderinde B, Abdulmaleek H, Williams J, Lewis J, Laws TR, Hewson R, Marcello A, D'Agaro P. Evidence of arbovirus co-infection in suspected febrile malaria and typhoid patients in Nigeria. The Journal of Infection in Developing Countries. 2013;7(01):051-059.
14. Raja JM, Mary A. and Usha, S. A Study on dual infections in pyrexia cases. Health Sciences. 2016;5(8):150-155.
15. CSO. Central Statistical Office. Statistical yearbook. Ministry of Planning and Development, Sana'a, Yemen; 2010.
16. International Organization for Migration (IOM). Malaria in Yemen: Needs

assessment. Regional MER project management unit P.O. Box 930285. 11193 Amman. International Organization for Migration. Jordan; 2017.
17. World Health Organization (WHO). Basic malaria microscopy. Part 1. Learner's guide. Geneva, Switzerland: WHO, 1991.
18. Cheesbrough M. District laboratory practice in tropical countries. Part 1. 2nd Edition. Edinburgh: Cambridge University Press, UK. 2006;185-186.
19. Abbasi A, Butt N, Sheikh QH, Bhutto AR, Munir SM, Ahmed SM. Clinical features, diagnostic techniques and management of dual dengue and malaria infection. Journal of the College of Physicians and Surgeons Pakistan. 2009;19(1):25-29.
20. Ali N, Nadeem A, Anwar M, Tariq WU, Chotani RA. Dengue fever in malaria endemic areas. Journal of the College of Physicians and Surgeons-Pakistan: (JCPSP). 2006;16(5):340-342.
21. Hisam A, Khan MB, Kadir E, Azam N. Frequency of co-existence of dengue and malaria in patients presenting with acute febrile illness. JPMA. The Journal of the Pakistan Medical Association. 2014;64(3): 247-251.
22. Magalhães BM, Siqueira AM, Alexandre MA, Souza MS, Gimaque JB, Bastos MS, Figueiredo RM, Melo GC, Lacerda MV, Mourão MP. *P. vivax* malaria and dengue fever co-infection: A cross-sectional study in the Brazilian Amazon. PLoS Neglected Tropical Diseases. 2014;8(10):3239.
23. Rao MRK, Padhy RN, Das MK. Prevalence of dengue viral and malaria parasitic co-infections in an epidemic district, Angul of Odisha, India: An eco-epidemiological and cross-sectional study for the prospective aspects of public health. Journal of Infection and Public Health. 2016;9(4):421 428.
24. Shnawa BH, Al-Ezzi AA, Abed GH, Al-Salahy MB, Mandour AM, Mohamed M. Prevalence of *Plasmodium falciparum* in Abs, Hajjah Governorate Northwest Yemen. International Journal of Biosciences. 2016;9(1):59-71.
25. Bamaga OA, Mahdy MA, Mahmud R, Lim YA. Malaria in Hadhramout, a southeast province of Yemen: Prevalence, risk factors, knowledge, attitude and practices (KAPs). Parasites & Vectors. 2014;7(1): 351.
26. Verma RK, Giri R, Singh N, Gupta C, Jain A. A Study on clinical presentation and outcome of concurrent malaria and dengue infection from a malaria endemic zone of north India. Journal of Medical Science and Clinical Research (JMSCR). 2016;4: 15116-15127.
27. Meynard JB, Ardillon V, Venturin C, Ravachol F, Basurko C, Matheus S, Gaborit P, Grenier C, Dussart P, Quénel P. First description of a dengue fever outbreak in the interior of French Guiana, February 2006. European Journal of Public Health. 2009;19(2)183-188.
28. Prasad J. National Guidelines for Clinical Management of Dengue Fever. World Health Organization. 2014;21.
29. World Health Organization (WHO). Guidelines for the treatment of malaria. Geneva, Switzerland. WHO; 2006.
30. Lacerda MVG, Mourão MPG, Coelho HCC. and Santos JB. Thrombocytopenia in malaria: who cares? Memorias do Instituto Oswaldo Cruz. 2011;106 (1):52-63.
31. Mulati OK. Prevalence of dengue viral infections among febrile patients in Mombasa County, Kenya. M.Sc. thesis, University of Kenyatta; 2014.
32. Singla N, Arora S, Goel P, Chander J, Huria A. Dengue in pregnancy: An under–reported illness, with special reference to other existing co–infections. Asian Pacific Journal of Tropical Medicine. 2015;8(3): 206-208.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/54064