A META-ANALYSIS OF THE PREVALENCE OF CLINICAL MANIFESTATIONS OF CHIKUNGUNYA VIRUS DISEASE IN BANGLADESH

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Abstract

Background: *Chikungunya is known as a mosquito-borne viral disease. It is transmitted to the human body by infected mosquitoes and caused different symptoms. The main aim of this study was to investigate the percentage of Chikungunya virus disease (CHIKV) patients who would had different clinical features at the acute or sub-acute stage of this disease in Bangladesh.*

Methodology: *In this meta-analysis, PubMed Central and BanglaJOL had been searched. Total 8 eligible studies had been selected for quantitative analysis. The pooled prevalence (PP) was used as effect measure to find the number of patients who would had different symptoms at acute or sub-acute stage of CHIKV disease. The pooled prevalence and 95% confidence interval (CI) had been calculated using random effects model. To measure the presence of heterogeneity Cochran chi-square test was used and I^2 was used to quantify the heterogeneity.*

Result: *This meta-analysis indicated significant association between CHIKV disease patients and fever was [PP: 0.99; p-value = 0.00], joint pain [PP: 0.95, p-value = 0.00], rash [PP: 0.55, p-value = 0.00], joint swelling [PP: 0.38, p-value = 0.001], headache [PP: 0.48, p-value = 0.007], pruritus [PP: 0.37, p-value = 0.001], myalgia [PP: 0.62, p-value = 0.00], co-morbidity [PP: 0.56, p-value = 0.001] at the acute stage of the disease and joint pain persists > 1 month [PP: 0.50, p-value = 0.001] at the sub-acute stage of this disease.*

Conclusion: *In this meta-analysis ever, joint pain were found as most frequently occurred symptoms at the acute stage of CHIKV disease.*

Keyword: *Chikungunya virus disease, clinical symptoms, meta-analysis, acute-stage, sub-acute stage.*

Introduction

Chikungunya is an infectious disease, caused by infected mosquitoes (alpha virus family). This virus was first identified in Africa in 1952 and in Asia in 1960.[1,2] Aedes aegypti mosquitoes is the main vectors of Chikungunya in Bangladesh.[3] It is basically a RNA virus. The name "Chikungunya" has been derived from kimakonde language, meaning that "to become controlled".[1] Chikungunya has been established its presence more than 60 countries of the world.[1] Chikungunya is self-remitting disease. More than 92-96% patients have developed symptoms after mosquito bite.[4,5] Most of the common symptoms are fever, joint pain, rash, headache, myalgia, oral ulcer, muscle pain etc.[3,6] and those symptoms are fully cure after few days onset of the disease, but symptoms such as joint pain or arthritis may be persist for several months or sometimes several years. The disease has a long-term effect on the patients. Female patients and individuals whose age more than 40 years have more risk to develop long-term effect after CHIKV disease.[7,8] Three stages have been classified according to the persisting time of symptoms; acute stage (< 3 weeks onset of the disease), sub-acute stage (3 to 12 weeks) and chronic stage (> 12 weeks).[9]

In 2008, the first recognized outbreak of chikungunya in Bangladesh was identified in Chapainwobabgong, Rajshahi, the northwest area of the country and 32 cases were identified.[10] The 2nd outbreak had been occurred in sathiya upozila Pabna in 2009.[11]. In late October 2011, an outbreak of fever and severe joint pain was reported by a local health office in Dohar sub-district in Dhaka and 196 cases were identified.[12] In 2012 an outbreak of chikungunya had been reported in the village of palpara in Tangail district and 364 individuals had been reported with this disease.[13]

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About 13176 clinically confirmed cases in 17 out of 64 districts were identified by Ministry of Health in April 1, 2017 to September 7, 2017.[14] More than a million of people in Dhaka city were at risk of infection with Chikungunya.[15]

Bangladesh have a high risk of developing this disease.[16] For 2017 epidemic of CHIKV disease, patients were monitored by Institute of Epidemiology, Disease Control and Research (IEDCR). Patients were confirmed for CHIKV disease on the basis of RT-PCR (Reverse transcription polymerase chain reaction) test in IEDCR.[14,16,17] Chikungunya virus disease has appeared as one of the major public health problem in Bangladesh, because a large proportion of population were affected by this disease. It has become a significant economic and medical burden for Bangladesh. This disease is also associated with the reduced quality of life of the affected people, because of clinical manifestation at the acute stage of the disease.[16] In this study it is interesting to find out the proportion of patients who would had symptoms at the acute or sub-acute stage of this disease.

Search strategy

Relevant articles were searched from PubMed Central and BanglaJOL up to July 2018 to identify different symptoms at acute or sub-acute stage of CHIK disease for Bangladeshi patients. The search strategy was "Chikungunya" and "Bangladesh" and there was no time limitation to include data in the study. The search strategy was limited to the articles which were written in English language, studies only for human and studies conducted in Bangladesh. All the studies were screened by title and abstract to identify the eligible studies for this meta-analysis. Cross-sectional studies, case-series studies, cohort studies, follow-up studies were considered for this meta-analysis. Complete search strategy of this meta-analysis was showed in figure 1.
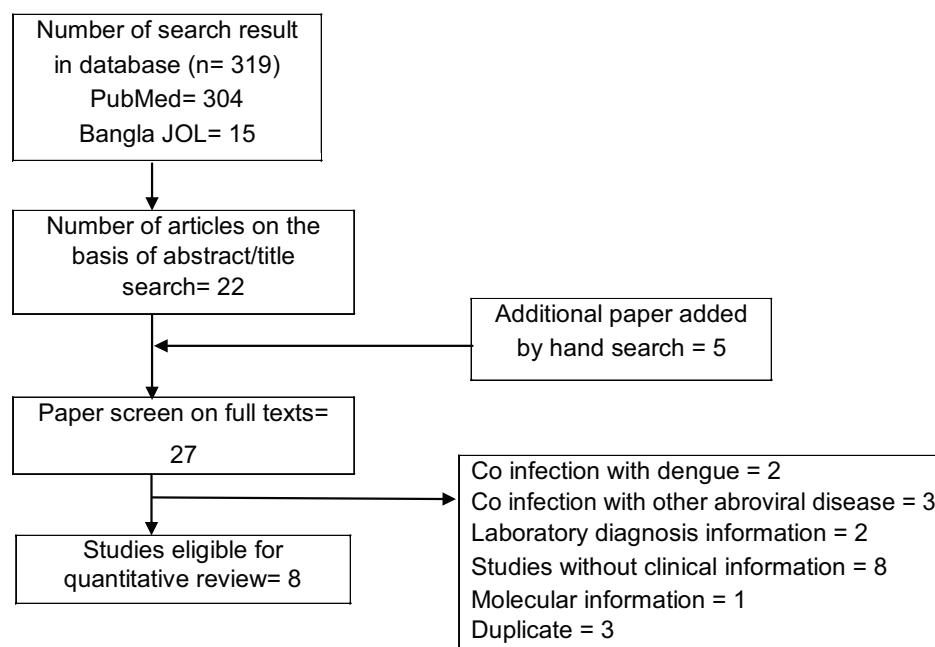
Study eligibility and selection

Original articles with proportion of serology positive patients confirmed by diagnosis procedures such as RT-PCR (Reverse transcription polymerase chain reaction), ELISA (enzyme-linked immunosorbent assay) or IgM (Immunoglobulin M) for CHIKV disease were included in this study. Studies were included in this analysis if the information of clinical manifestation of the patients at acute or sub-acute stage of CHIKV disease were available. Studies that included patients of CHIKV disease co-infection with other abroviral disease and duplicate articles were excluded.

Statistical Analysis

This meta-analysis was executed using statistical programming software R, 3.1.1 version with Meta package and Microsoft Excel spreadsheet. Pooled prevalence and 95% confidence interval were calculated by random effects model to summarize weighted effect size along with each individual study. Random effects model was used because the prevalence of different studies were not same[18]. In the meta-analysis, Q statistic was used to find the presence

Flowchart of search strategy:

Number of search result in database (n= 319)
PubMed= 304
Bangla JOL= 15

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Number of articles on the basis of abstract/title search= 22

Additional paper added by hand search = 5

↓

Paper screen on full texts= 27

Co infection with dengue = 2
Co infection with other abroviral disease = 3
Laboratory diagnosis information = 2
Studies without clinical information = 8
Molecular information = 1
Duplicate = 3

↓

Studies eligible for quantitative review= 8

Fig.-1: *Flowchart of search strategy to select eligible studies for this meta-analysis.*

of heterogeneity among the studies, was used to measure the percentage of variation across studies that arise due to heterogeneity and was used to measure between studies variance. Combining only the significant published studies had been lead to publication bias. That's why funnel plot was used in this meta-analysis to find publication bias among the included studies.[19,20]

Result

Total eight studies were eligible for our analysis of Bangladeshi patients in this article. Studies with CHIKV disease patients of different areas of Bangladesh were included in this analysis. Patients serologically confirmed for CHIKV disease were only included. Geological, demographical, clinical characteristics of the patients and total CHIKV disease patients (N) were described in Table 1 and summary of the meta-analysis

was described in Table 2. Graphical representation of the pooled prevalence of the variables were showed in figure 2. The pooled prevalence of CHIKV disease patients for fever was 0.99 [95% CI: (0.96 -1.0), Z-value= 46.29, p-value = 0.00], which indicates that 99 % CHIKV disease patients would had fever at the acute stage of the disease (Figure 2A), for joint pain [PP: 0.95, 95% CI: (0.92 - 0.98), Z-value= 8.98, p-value = 0.00], which indicates that 95% CHIKV disease patients would had joint pain at the acute stage of the disease (Figure 2B), for rash [PP: 0.55, 95% CI: (0.41 - 0.68), Z-value= 7.79, p-value = 0.00], for joint swelling [PP: 0.38, 95% CI: (0.16 - 0.59), Z-value= 3.48, p-value = 0.001], for headache [PP: 0.48, 95% CI: (0.13 -0.83), Z-value= 2.69, p-value = 0.007], for pruritus [PP: 0.37, 95% CI: (0.15 - 0.59), Z-value= 3.25, p-value = 0.001], for myalgia [PP: 0.62, 95% CI: (0.55 - 0.70), Z-value= 16.35, p-value = 0.00], for joint pain > 1 month [PP:

Table-I
Characteristics of included studies.

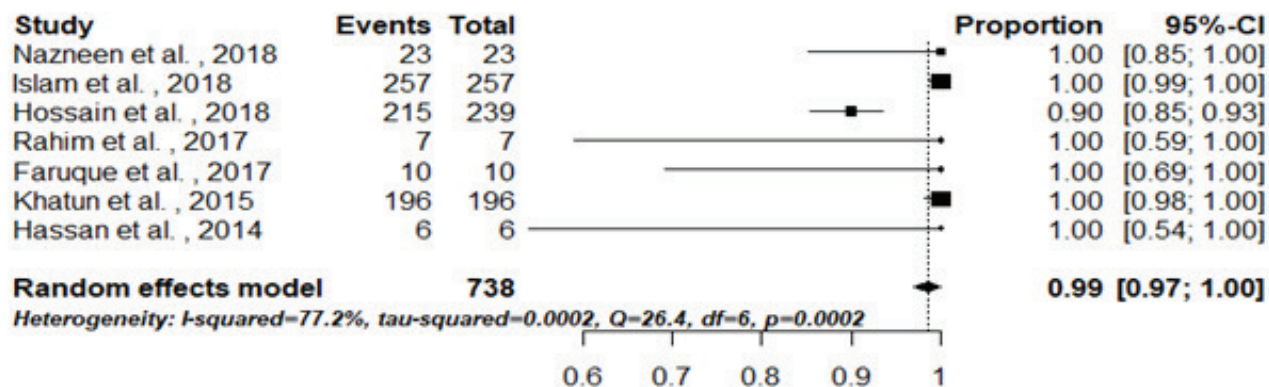| Author, Year	Study region	Study period	Study design	Sample size	Age, Gender	Main findings
Islam et al., 2017 [5]	Dhaka city	2017	Cohort	257	Mean age = 43, Male= 90 Female= 167	Fever 100%, joint pain 99%, rash 58%, pruritus 32%, oral ulcer 1.13%, diabetes 22%, hypertension 30%.
Nazneen et al., 2018 [17]	Dhaka city	2017	Cross-sectional	23	Male= 19 Female=4	Comorbidities were presented among 96% of the patients, fever 100%, joint pain 39%, rash 21%.
Hossain et al., 2018 [16]	Dhaka city	2017	Cross-sectional	239	Mean age = 34 Male= 126 Female= 113	Comorbidities was presented among 74% of the patients, arthralgia 100%, rash 78.2%, myalgia 64.9%, pruritus 61.9%, headache 69%, joint pain 198%.
Rahim et al., 2017 [21]	Dhaka city	2011	Case-series	7	Mean age= 39, Male=4 Female=3	Fever 100%, arthritis 71%, rash 29%.
Faruque et. al. 2017 [22]	Several area of country	2008-2009	Follow-up	10	Median age= 35, Male=4 Female=6	Fever 100%, joint pain 100%, headache 30%.
Khatun et al., 2015 [12]	Dohar Dhaka	2011	Case-series	196	Median age= 35	Fever 100%, joint pain 100%, rash 76%, itching 50%, joint swelling 29%, headache 12%.
Hassan et al., 2014 [23]	Dhaka	2012	Case-series	6	Mean age= 39.5, female= 6	Fever 100%, arthritis 100%, rash 67%. 33% patients suffered from joint pain < 2 months after acute infections.
HSB, 2009 [10]	Rajshahi and Chapaina wabganj	2008	Case-series	39	Mean age= 39 Male= 19 Female= 20	Fever 100%, joint pain 100%, myalgia 62%, rash 39%, oral ulcer 8%. 29 patients still suffered from joint pain for more than one months after the recovery of fever.

Table-II
Summary table for random effect meta-analysis.

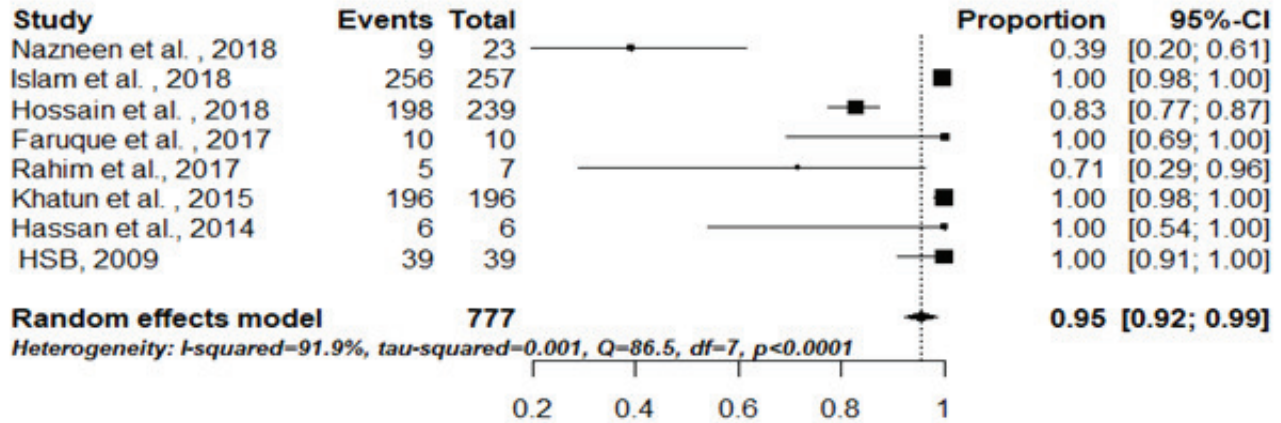| Factors	Pooled prevalence (95% CI)	Test for overall effect		Test for Heterogeneity		
		z-value	p-value	Q statistic	p-value	I
Fever	0.99 (0.97 – 1.00)	46.27	0.000	26.35	0.0002	77.2%
Joint pain	0.95 (0.92 – 0.98)	8.98	0.000	86.54	0.0001	91.9%
Rash	0.55 (0.41 – 0.68)	7.79	0.000	79.94	0.0001	92.5%
Joint swelling	0.38 (0.16 – 0.59)	3.48	0.001	76.54	0.0001	92.5%
Headache	0.48 (0.13 – 0.83)	2.69	0.007	507.2	0.0001	99.2%
Pruritus	0.37 (0.15 – 0.59)	3.25	0.001	133.83	0.0001	97.8%
Myalgia	0.62 (0.55 – 0.70)	16.35	0.000	2.51	0.285	20.3%
Oral- Ulcer	0.13 (0 – 0.33)	1.30	0.192	97.9	<0.0001	98.7%
Joint pain >1 month	0.50 (0.22- 0.79)	3.45	0.001	21.76	<0.0001	90.8%
Co-morbidity	0.56 (0.22 – 0.91)	3.20	0.001	161.25	<0.0001	98.8%

95% CI= 95% confidence interval, Cochran's Q statistic for heterogeneity, I Index for percentage of heterogeneity.

0.50, 95% CI: (0.22 - 0.79), Z-value= 3.45, p-value = 0.001], for co-morbidity [PP: 0.56, 95% CI: (0.22- 0.91), Z-value= 3.20, p-value < 0.00]. All the above results were statistically significant since p-value is very small for all of those variables. However the pooled prevalence of CHIKV disease patients for oral ulcer was [PP: 0.13, 95% CI: (0.00 - 0.33), Z-value= 1.30, p-value = 0.192], which indicates that 13% CHIKV disease patient would had oral ulcer at the acute stage of the disease but this result was not significant since p-value is large.

Publication bias was investigated with a funnel plot for standard error (SE) by proportion for all the variable separately. Funnel plot was showed in figure 3. An evidence of publication bias were founded using funnel plot for variable fever, joint pain, rash, joint swelling, headache, pruritus, oral ulcer, co-morbidity, joint pain persists more than one months because some of the variables for those studies residing outside of the funnel. But no evidence of publication bias was founded for variable myalgia since all of the studies residing inside of the funnel.


Figure 2A: *Forest plot for variable fever*

Study	Events	Total		Proportion	95%-CI
Nazneen et al. , 2018	9	23		0.39	[0.20; 0.61]
Islam et al. , 2018	256	257		1.00	[0.98; 1.00]
Hossain et al. , 2018	198	239		0.83	[0.77; 0.87]
Faruque et al. , 2017	10	10		1.00	[0.69; 1.00]
Rahim et al., 2017	5	7		0.71	[0.29; 0.96]
Khatun et al. , 2015	196	196		1.00	[0.98; 1.00]
Hassan et al., 2014	6	6		1.00	[0.54; 1.00]
HSB, 2009	39	39		1.00	[0.91; 1.00]
Random effects model		**777**		**0.95**	**[0.92; 0.99]**

Heterogeneity: I-squared=91.9%, tau-squared=0.001, Q=86.5, df=7, p<0.0001

Figure 2B: Forest plot for variable joint pain

Figure 2: Forest plot for the prevalence of the clinical symptoms of CHIKV disease at acute or sub-acute stage of the disease in Bangladesh. Pooled prevalence along with all individual studies were showed in the plot with 95% CI. Pooled prevalence estimates were presented with a diamond and individual studies were presented with a square. **2A**, selected studies for variable fever. **2B**, studies for joint pain. Forest plot had been also drawn for variable rash, joint swelling, headache, pruritus, myalgia, oral ulcer, Co-morbidities, joint pain> 1 month and shows a significant result for all variable except variable oral ulcer.
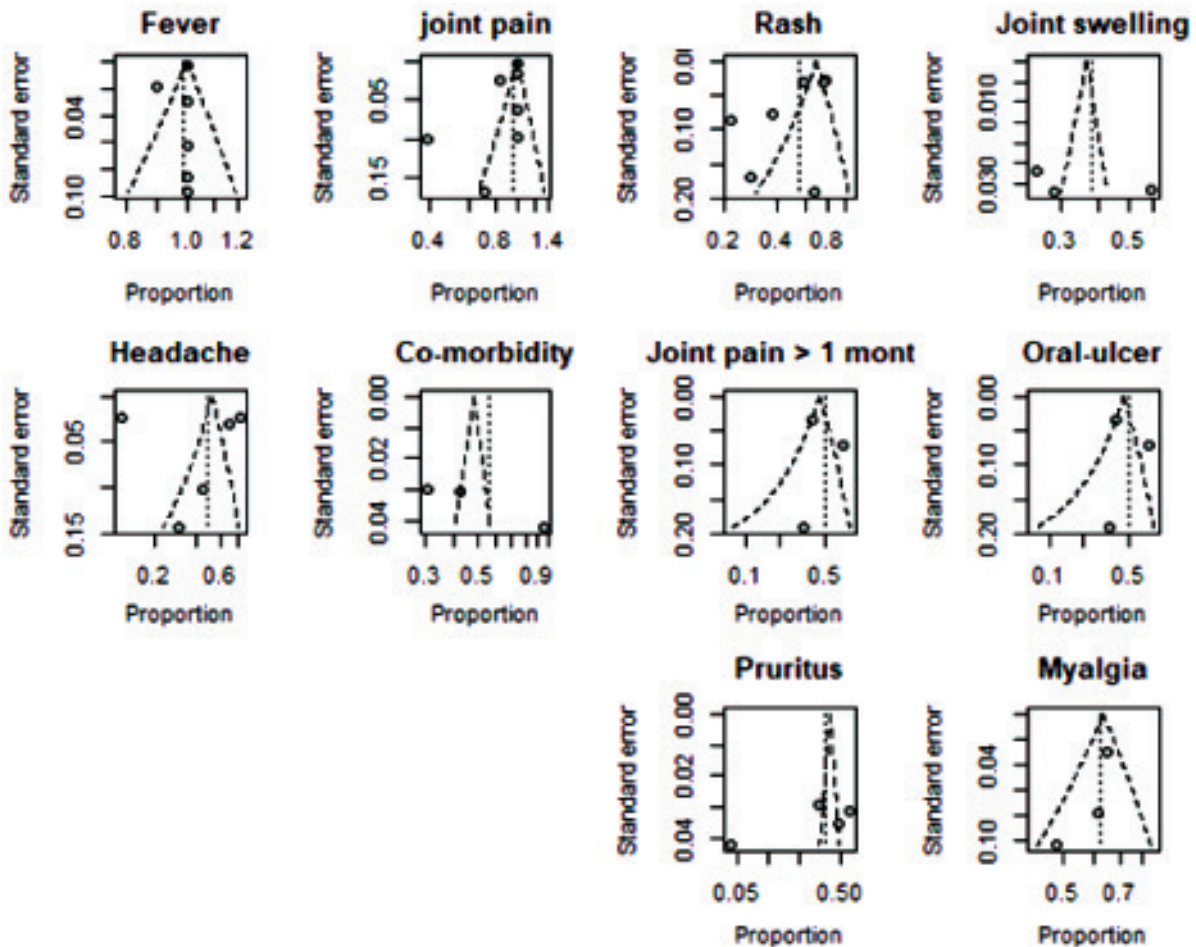
Figure 3: Funnel plot to detect publication bias in the data for all the considered variables.

Discussion and Conclusion

In the recent years chikungunya virus disease seems to be a worrisome coming epidemic in Bangladesh. Bangladesh has a high risk of developing mosquito-borne disease, such as Chikungunya but less than Dengue and Malaria. Every year many individuals have been affected by this disease in Bangladesh. Aedes aegypti and aedes albopictus are considered as the main vector for the transmission of this disease in this region.[3,12] Chikungunya virus disease has been usually emerged in Bangladesh after the rainy season. Different clinical symptoms such as fever, joint pain, rash, headache, joint swelling, pruritus, oral ulcer, vomiting, diahoria etc were found at the time of the outbreak of Chikungunya disease.[3,6] The first outbreak of CHIKV disease was identified in 2008 in Bangladesh.[12] But the outbreak of CHIKV disease in 2017 in Bangladesh breaks all the records of the past. On the report of Ministry of Health, more than 13 176 clinically confirmed cases in 17 out of 64 districts were identified for this disease in 2017.[14] According to the result of our meta-analysis, clinical symptoms such as fever, joint pain, joint swelling, rash, headache, pruritus were found as significant symptoms (p-value < 0.01) and oral ulcer was found as insignificant symptom (p-value > 0.01) at the acute stage and joint pain persists more than 1 month was found as significant (p- value < 0.01) symptom at sub-acute stage of CHIKV disease patients in Bangladesh. Among all those symptoms, fever, joint pain were found as most frequent symptoms at acute stage of CHIKV disease. Chikungunya is not a life-threatening disease. Older people whose age is greater than 40 years, female patients and the patients having different comorbidities such as diabetes, hypertension, and cardiovascular disease have a high risk of developing this disease.[7,8,17] More than 30% patients have joint pain more than one months in the outbreak of 2011.[13] This disease is diagnosed by RT-PCR test in first week onset of the disease and IgM test between 5 days to 1 month onset of the disease.[21] Those diagnosis procedures are highly expensive for most of the Bangladeshi people, so low cost diagnosis procedure should be invented for the affected patients.

Conclusion

As there is no appropriate vaccine to prevent this disease and medicine for the treatment of the disease, awareness of not being affected by this disease is the key word for it. Vector control is the most effective way to control this disease. Government and private agencies have already taken the challenge to control this disease in the city and rural areas of the country.

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