

An emerging threat of Dengue and Chikungunya co-infection: Need of developing a pre-diagnostic screening tool

ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Dengue and Chikungunya infections have caused large outbreaks globally and millions of people have been affected worldwide. They are transmitted by *Aedes aegypti* and *Aedes albopictus* respectively and can cause potentially severe acute illnesses and or debilitating chronic disease. Coinfection with both diseases is not new and has been reported on patients from Asian, African and Pacific countries. The need to differentiate between two infections is also very important because minute differences in treatment and, misdiagnosis can hamper epidemiological understanding of both diseases. Use of symptoms differentiation, scoring systems and simple laboratory parameters is discussed in this article which can be used to accurately identify cases of mono and co-infections. The paper emphasizes on development of a pre-screening diagnostic criteria to differentiate between these two diseases which will not only reduce unnecessary testing but will also prevent misdiagnosis.

Keywords: Dengue, Chikungunya, Aedes, Coinfection, Disease Outbreaks, Public Health

INTRODUCTION:

Limited resources and the great diversity of acute febrile illness (AFI) etiologies in tropical regions challenge diagnosis, treatment, and public health responses to endemic and epidemic diseases.^[1] Widely distributed in tropical and subtropical areas throughout the world, Chikungunya virus (CHIKV) and Dengue virus (DENV) cause acute illnesses mainly characterized by fever and arthralgia. CHIKV has recently caused large outbreaks, and DENV is a global plague, with tens of millions of cases each year.^[2,3] Dengue fever is caused by a class of pathogens called as *Flavivirus* that belongs to the family of Flaviviridae and Chikungunya, being caused by the *Alphavirus* of family *Togaviridae*.^[4] Both dengue and chikungunya diseases are transmitted by *Aedes aegypti* and *Aedes albopictus* respectively and can cause potentially severe and or debilitating chronic disease. While dengue has been recorded as the most rapidly spreading mosquito-borne viral disease in the world, chikungunya has recently re-emerged after an interval of several decades. It represents a risk for millions of people in the Indian Ocean areas, Africa, Southeast Asia and more recently has spread to the Caribbean, Pacific and Europe.^[5] Dengue is endemic in both urban and semi urban areas of India and was first isolated in India in 1945. Delhi situated in the northern part of India, had outbreaks of dengue due to different dengue virus types in 1967, 1970, 1982, 1988, 1996 and 2003.^[6] In India, the chikungunya virus was first isolated in 1963 in Kolkata followed by epidemics in Chennai, Pondicherry and Vellore in 1964; in Visakhapatnam, Rajahmundry and Kakinada in Andhra Pradesh in 1965 and in Nagpur, also in 1965. The last officially recorded outbreak in India was reported in Barsi in Maharashtra in 1973. The disease re-emerged in India in October 2005 after remaining silent for nearly 32 years. Andhra Pradesh was the first state to report this disease in December 2005. Kerala was the worst affected state in 2007 with approx. 3.6 million fever cases. Thereafter it has been repeatedly reported from 13 different states of India and has resulted in 1.4–6.5 million estimated cases across the country.^[7] The capital of India, New Delhi is still battling with increased number of Dengue and Chikungunya cases in post monsoon season of 2016.

COINFECTION – A REALITY:

Coinfection with dengue virus (DENV) and CHIKV has been reported on patients from Asian, African and Pacific countries.^[5] These two diseases now co-circulate in many countries and pose a challenge to clinicians because they may require different clinical management even though their manifestations can be similar.^[8] Both dengue and chikungunya viruses often co-circulate in the mosquito and are transmitted to human beings as co-infections following the mosquito bite.^[9] Many factors influence the geographical spread of both viruses, including vector distribution (both are spread by *Aedes* mosquitoes), human travel, urbanization, and climatic changes.^[8] Kushwah RBS et al in their study from India confirmed the fact of co-habitation of dengue and chikungunya viruses in field mosquitoes. It reported the concurrent infection of DENV serotypes and CHIKV from the same pool of *Ae. Aegypti* collected from field sites.^[10] Nimmannitya et al in 1962 reported the first case of coinfection in Thailand.^[11] Human coinfection with DENV and CHIKV have been reported in India since 1967.^[12] Subsequent serologic investigations in Southern India indicated that the 2 viruses can coexist in the same host.^[13] The rates of coinfection in various areas in India have been different. The prevalence of co-infection using serological methods have been reported as 2.7% by kalawat et al^[14], 2.8% by Omarjee et al^[15], 12.4% by Taraphdar et al^[16] and 6.7% in londhey et al^[9]. Several studies have been done to describe the severity of dengue-chikungunya coinfection. Two studies, Chahar et al^[13] and Gandhi et al^[17] have described increased severity with coinfection. The mortality rate in Gandhi et al was 12% in coinfecting patients as compared to 2% in monoinfected patients^[17]. Various other studies did not report any increase in mortality with coinfection.^[15,16] This makes the situation unclear and warrants further investigations.

IS DIFFERENTIATION NECESSARY?

The need to differentiate between two infections is also very important because of minute differences in treatment and, misdiagnosis can also hamper epidemiological understanding of both diseases. Misdiagnosis of dengue fever as chikungunya (or missing a dengue infection when coinciding with chikungunya) risks delaying or disrupting dengue-specific intensive supportive treatment which can have a ten-fold impact on likelihood of progression from dengue fever to severe disease. It also risks inappropriate prescription of arthralgia-alleviating nonsteroidal anti-inflammatory drugs (often employed in treating chikungunya patients) which could lead to severe bleeding in patients with thrombocytopenia or Dengue Hemorrhagic Fever (DHF). The opposite and potentially more likely scenario in which chikungunya infection is misdiagnosed as dengue (or missed in a co-infected individual) masks the true geographical extent of CHIKV and population at risk of infection.^[18] In some patients chikungunya can progress to cause chronic arthritis. Hence these patients have to be followed up on a long term basis.^[9] 5.6% of the patients developed chronic arthritis over a period of 2 years after an acute chikungunya infection.^[19]

Since DENV and CHIKV share a seasonal transmission cycle and have a number of similarities in clinical presentation, they are difficult to distinguish without specialized serologic or molecular diagnosis. We in this article are going to discuss various modalities which might be able to differentiate between the two diseases using clinical features, and simple laboratory measures which have been devised in various articles.

DISEASE DIFFERENTIATION:

The disease can be diagnosed simply by performing serological and molecular diagnostic methods but the application of both tests on every patient is not cost efficient especially in a low resource setting. We have studied various articles on differentiation of the diseases on basis of scoring system, symptom differentiation and simple laboratory variables and will combine them in this article.

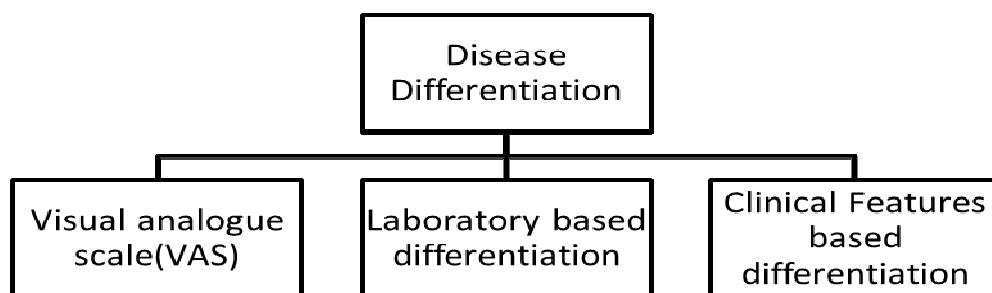


Figure 1: Various factors that can be used to differentiate between the Dengue and Chikungunya infection before using the molecular and serological diagnostic tests.

1. VAS SCORING:

In londhey et al, among the mono and dual infections, all mono CHIKV and 90% dual infections showed severe VAS score of 6-10, while in case of mono DENV, only 55% of patients showed severe VAS score. Some part of this finding was reproduced in Galate et al where all CHIKV infected patients had VAS score between 6-10 and only 15.78% of dual infected patients had VAS score less than 6.

This particular finding can be used to differentiate dengue mono infection from dual infection and chikungunya mono infection.

There was an important finding highlighted by Galate et al, which can further differentiate between CHIKV mono infection and dual infection as both have severe VAS score. The combination of Severe VAS and restriction of joint movement is more common in CHIKV mono infection than Dual infection. All the 6 patients with CHIK mono-infection had VAS score of 6–10 with restricted joint movement as compared to only 1 patient with dual infection which was statistically highly significant^[9,20]

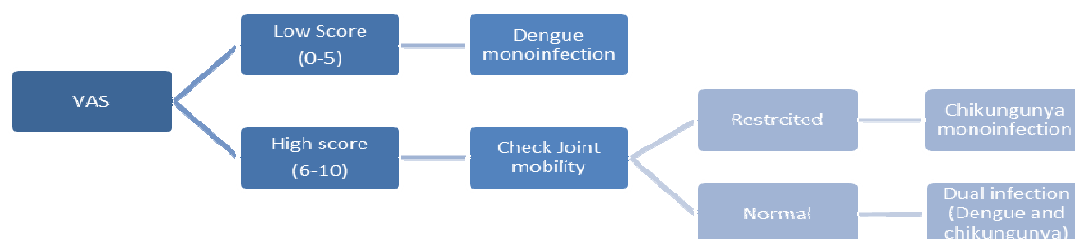


Figure 2: Flowchart to differentiate between Mono infection (Dengue/Chikungunya) and Dual Infection

2. Clinical features and laboratory values mediated differentiation:

1. Wonderful decision trees using clinical variable and laboratory variable are present. The decision trees use predictors of chikungunya and dengue to assist doctors in both well-resourced and resource-limited settings in diagnostic decision making. The decision trees are available in the article written by Lee et al.^[8]

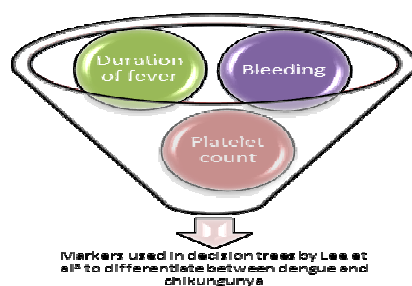


Figure 3: Various markers used by Lee et al⁸ in making decision trees to differentiate between dengue and chikungunya in a well-resourced setting and a resource-limited setting.

2. Various clinical features can be used to define the illness and differentiate between them. The following figure 4 demonstrates various features which can be used to differentiate:

Fever	• It is present in 100 % of all CHIKV, DENV and dual infection patients[16] but duration of fever and presence of fever at the time of presentation can be used to differentiate between the infection using one of the decision tree model by lee et al[8]
Arthralgia/joint restriction/joint swelling	• More in chikungunya infection than dengue infection[8,9,16]
WBC count	• Leucopenia was more commonly seen in patients with dengue infection as compared with chikungunya in which there was normal WBC count or an elevated WBC count [9,8] Also in one study Total leucocyte count has been shown to have higher levels in patients with co-infection than mono-infected patients[17]. So low levels of WBC can be used to include dengue into picture and exclude CHIKV and dual infection from the picture.
Platelet count	• Almost every study concludes the low levels of platelets to be related to dengue infection[8,9,13,16]
Diarrhea	• The most interesting observation made in the study of Taraphdar et al was diarrhoea which was reported only by the dual infected patients. but this finding is inconsistent as it was not reproduced in other studies[8, 9].

Figure 4: Demonstration of clinical features that can be used to differentiate between Dengue and Chikungunya Infection

To summarize, there are some features that can be combined and therefore can lead to formation of a clinical diagnostic criteria to decide the inclusion or exclusion of a disease.

CONCLUSION:

In this article evidence has been provided from various articles about the prevalence of dual infection in patients suffering from acute febrile illnesses. The reemergence of chikungunya has increased the dilemma in the diagnosis of acute febrile illness. We, thus suggest formation of protocols using clinical and low cost laboratory measures to correctly diagnose the illness so that proper laboratory and molecular diagnostic measures can be used in each patient in a cost effective manner. The Government of various states has capped the price of Dengue and Chikungunya tests at Rs. 600 each^[21]. Formulating the Pre-Screening criteria will reduce the cost of an additional test in every patient. We suggest the use of following measures to devise a Clinical screening tool:

1. VAS
2. Bone pain
3. Restriction of joint movement/swelling of joint
4. Fever
5. Increased/normal Platelet count
6. Increased/normal WBC count
7. Decision trees

Higher the score using the above variables higher are the chances of having Chikungunya as the cause of infection and may also suggest co-infection.

This is the appropriate time to formulate a study based on the factors described to make a screening tool and also study the entomological and epidemiological aspects of dengue and chikungunya causing mosquitoes.

REFERENCES:

1. Matthew R. Kasper, Patrick J. Blair, Sok Touch, Buth Sokhal, Chadwick Y. Yasuda et al. Infectious Etiologies of Acute Febrile Illness among Patients Seeking Health Care in South-Central Cambodia. *Am. J. Trop. Med. Hyg.* 2012; 86(2):246–53.
2. Pialoux G, Gauzere BA, Jaureguiberry S, Strobel M. Chikungunya, an epidemic arbovirosis. *Lancet Infect Dis* 2007; 7:319–27.
3. World Health Organization. Fact sheet no. 117: dengue and dengue haemorrhagic fever. Available at: <http://www.who.int/mediacentre/factsheets/fs117/en/>.
4. Seetha Dayakar, Iravathy K. Goud, Heera Pillai, Viji Remadevi, Sanjai Dharmaseelan, Radhakrishnan R. Nair, M. Radhakrishna Pillai. Molecular Diagnosis of Chikungunya virus (CHIKV) and Dengue virus (DENV) and its concomitant circulation in South Indian population. *Virology Reports* 2015; 5:56-62.
5. Kim Lien PT, et al., Surveillance of dengue and chikungunya infection in Dong Thap, Vietnam: A 13-month study. *Asian Pacific Journal of Tropical Medicine* (2015), j.apjtm.2015.12.008
6. Preeti Bharaj, Harendra S Chahar, Anubhav Pandey, Kavita Diddi, Lalit Dar, Randeep Guleria, Sushil K Kabra and Shobha Broor. Concurrent infections by all four dengue virus serotypes during an outbreak of dengue in 2006 in Delhi, India *Virology Journal* 2008, 5:1
7. Chattopadhyay S, Mukherjee R, Nandi A, Bhattacharya N. Chikungunya virus infection in West Bengal, India. *Indian J Med Microbiol* 2016;34:213-5
8. Lee VJ, Chow A, Zheng X, Carrasco LR, Cook AR, et al. (2012) Simple Clinical and Laboratory Predictors of Chikungunya versus Dengue Infections in Adults. *PLoS Negl Trop Dis* 6(9): e1786.
9. Vikram Iondhey, sachee agrawal nilima vaidya seema kini, JS Shastri et al. engue and chikungunya virus co-infections The inside Story. *Journal of the association of physicians of India* 2016; 64:36-40
10. Kushwah RBS, Jain J, Sharma A, Bhatnagar RK, Subbarao SK, et al. Co-Habitation and Concurrent Infection of Dengue and Chikungunya Viruses in *Aedes Aegypti* Field Populations from India. *2015 J Trop Dis* 4: 194.

11. Nimmannitya S, Halstead SB, Cohen SBN, Margiotta MR. Dengue and chikungunya virus infection in man in Thailand, 1962-1964. Observations on hospitalized patients with hemorrhagic fever. *Am J Trop Med Hyg.* 1969; 18: 954-71.
12. Myers RM, Carey DE. Concurrent isolation from patient of two arboviruses, chikungunya and dengue type 2. *Science.* 1967; 157:1307-8.
13. Chahar HS, Bharaj P, Dar L, Guleria R, Kabra SK, Broor S. Co-infections with Chikungunya Virus and Dengue Virus in Delhi, India. *Emerging Infectious Diseases.* 2009;15(7):1077-1080.
14. K alawat U, Sharma KK , Reddy SG. Prevalence of dengue and chikungunya fever and their co-infection. *Indian J Pathol Microbiol* 2011; 54:844-45.
15. Omarjee R, Prat CM, Flusin O et al. Importance of case definition to monitor ongoing outbreak of chikungunya virus on a background of actively circulating dengue virus, St Martin, December 2013 to January 2014. *Euro Surveill.* 2014; 19(13):pii=20753
16. Taraphdar D, Sarkar A, Mukhopadhyay BB, Chatterjee S. A comparative study of clinical features between monotypic and dual infection cases with Chikungunya virus and dengue virus in West Bengal, India. *Am J Trop Med Hyg* 2012; 86:720-3
17. Bhooshan S. Gandhi, Kaushal Kulkarni, Manasi Godbole, Shreya S. Dole, Shivani Kapur, Prajna Satpathy, Akshay M. Khatri et al. *International J. of Healthcare and Biomedical Research* 2015;3(3):117-23.
18. Luis Furuya-Kanamori, Shaohong Liang, Gabriel Milinovich, Ricardo J., Soares Magalhaes, Archie C. A. Clements et al. Co-distribution and co-infection of chikungunya and dengue viruses. *BMC Infectious Diseases* 2016;16:84
19. Ganu MA, Ganu AS. Post Chikungunya Chronic Arthritis. Our Experience with DMARDs over Two Year Follow Up. *J Assoc Physicians India* 2011; 59:83-86.
20. Galate LB, Agrawal SR, Shastri JS, Londhey V. Chikungunya Fever Among Patients with Acute Febrile Illness Attending a Tertiary Care Hospital in Mumbai. *Journal of Laboratory Physicians.* 2016;8(2):85-89.
21. The Times of India. Dengue fee capped at 600. Available at <http://timesofindia.indiatimes.com/city/gurgaon/Dengue-test-fee-capped-at-600/articleshow/52647115.cms>. Accessed on 11/9/2016