International Journal of Advances in Medicine
Arora BS et al. Int J Adv Med. 2017 Apr;4(2):568-572
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20171062

Original Research Article

Major aetiologies of acute undifferentiated fever in 2013 and 2014: an experience in retrospect

Balvinder Singh Arora[1]*, Monika Matlani[1], Karnika Saigal[2], Indu Biswal[1], Santhosh Rajan[1], Arun Padmanandan[3], Saudan Singh[3]

[1]Department of Microbiology, [3]Department of Community Medicine, Vardhman Mahavir Medical College (VMMC) and Safdarjung Hospital, New Delhi 110029, India
[2]Department of Microbiology, Chacha Nehru Bal Chikitsalya Hospital, Delhi, India

Received: 14 December 2016
Accepted: 16 January 2017

***Correspondence:**
Dr. Balvinder Singh Arora,
E-mail: dr_arorabalvinder007@yahoo.com

ABSTRACT

Background: Major aetiologies of acute undifferentiated fever (AUF) show wide variations, especially in developing countries including India. A better understanding of 'AUF causes' helps in better management of such cases with attendant reduction in morbidity and mortality. The present analytical study, retrospective in nature, estimates burden of the AUF in the years 2013 and 2014 with some useful information and conclusions.
Methods: Important pathogens 'investigated for' either as a 'direct or indirect evidence' included - Malaria parasite, Dengue virus, Salmonella typhi and paratyphi A and Chikungunya virus. Malaria testing included examination of peripheral blood smear with Giemsa stain and also immuno-chromatographic test to detect lactate dehydrogenase (LDH) for *Plasmodium falciparum* and *Plasmodium vivax* and also HRP2 for detection of *Plasmodium falciparum* infections. For dengue and chikungunya virus infections - specific IgM antibodies - were detected by ELISA test. Enteric fever was diagnosed by detecting IgM and IgG antibodies using enzyme immunoassay. For Widal test, agglutinating antibodies against the O and H antigens of S. typhi and "H" antigens of '*S. paratyphi A'* were undertaken. All the test procedures, including sample collections, were performed as per manufacturer's recommendations, and, as per 'standard operating procedures (SOPs)'.
Results: Of the 10,670 samples received for dengue investigations, 3646 i.e. 34.17% tested seropositive for dengue cases. Percentage seropositivity for chikungunya was 18.6 (8/48). For dengue, 1193 (43.92%) and 488/577 (84.57%) samples were positive in the year 2013 and 2014 respectively in Delhi alone. Annual peak in months of September to November was observed for dengue while a bi-annual pattern was observed for malaria with two peaks occurring in months of May-June and August-September respectively for the year (s) i.e. 2013 and 2014. Enteric fever was present throughout the year with no specific distribution pattern. Majority of patients were from Delhi and adjoining Haryana followed by Western Uttar Pradesh. Co-infection of dengue with enteric fever was observed in only four cases.
Conclusions: Dengue, chikungunya, malaria and enteric fever were the most important major causes of AUF in the year 2013 and 2014. Improved interactions with clinician counterparts generating awareness about major aetiologies of AUF would help in timely detection of such illnesses and hence better management reducing morbidity and mortality in the long run.

Keywords: AUF, Chikungunya, Dengue, Malaria

INTRODUCTION

Precise information about major aetiologies of acute undifferentiated fever (AUF) is important for effective management to reduce morbidity and mortality, especially in developing countries including India.[1,2] Given the observations that major infective aetiologies of AUF undergo variations in trends and occurrences, the present retrospective study is an attempt to understand the incidence of such infections in populations attending to a city hospital with an attached teaching institution over a period of two years i.e. 2013 and 2014.[3-6]

METHODS

A total of 38635 (thirty-eight thousand six hundred thirty-five) samples were received in the microbiology laboratory from clinically suspected cases of AUF who were either admitted in wards or attended the out-patient departments (OPD) from beginning January 2013 to end December 2013 and from beginning January 2014 to end December 2014 (02 years). Demographic data including age, sex and place of residence of the patient were categorized and analyzed. Important pathogens looked for, as per the physicians' tests requisitions, included Plasmodium parasite - *Pl. vivax* and *Pl. falciparum*, Dengue virus, *Salmonella typhi* and *S. paratyphi A* (for enteric fever) and Chikungunya virus infection. Malaria testing was done by examination of peripheral blood smear with Giemsa stain and also immuno-chromatographic test to detect lactate dehydrogenase (LDH) for *Plasmodium falciparum* and *Plasmodium vivax* and also HRP2 for detection of *Plasmodium falciparum* infections (DiaSys Diagnostics Pvt Ltd, India). For dengue and chikungunya virus infection, specific IgM antibodies were detected by dengue IgM antibody capture ELISA test supplied by National Institute of Virology (NIV), Pune. Enteric fever was diagnosed by detecting IgM and IgG antibodies using enzyme immunoassay (EIA) (Typhi- Point, supplied by AB Diagnopath Pvt Ltd, India). The results of the test were interpreted as per the kit literature. Widal test to detect agglutinating antibodies against the O and H antigens of S. typhi and "H" antigens of *S. paratyphi A* was undertaken as per manufacturer's instructions. Since, most physicians start antimicrobial therapy without waiting for the blood culture reports and also there being a lack of clear cut information about whether antibiotic had been administered before sample collection for blood culture; therefore, results of blood culture tests were not included in the present retrospective analysis. Separate laboratory division exists for Hepatitis A, B, C, E and as per the institutional policy data sharing is not allowed nor it is transmitted to our laboratory, therefore such data could not be incorporated. Although scrub typhus is currently emerging as an important cause of AUF, but due to lack of availability of kits, and, poor index of clinical suspicions reflected in no physician requests, its incidence could not be ascertained. All the test procedures, including sample collections, were performed as per manufacturer's recommendations and on site 'standard operating procedures (SOPs)'.

RESULTS

Of the 10,670 samples received for dengue investigations, 3646 i.e. 34.17% tested seropositive for dengue cases. For dengue, 1193 (43.92%) and 488/577 (84.57%) samples were positive in the year 2013 and 2014 respectively in Delhi alone (Table 2). Percentage seropositivity for chikungunya was 18.6 (8/48) (Table 1). For enteric fever -10.9% i.e. 1408 of total 12881 were positive over the duration of 24 months. In 2013 the sero-positivity was 10.9% while in 2014 it was 11% (Table 1).

Table 1: Distribution of acute undifferentiated fever (AUF) cases in years 2013 and 2014.

	2013		2014		Total duration - 24 months	
	Samples	**Positives (%)**	**Samples**	**Positives (%)**	**Samples**	**Positives (%)**
Dengue	6903	2916 (42.2)	3767	730 (19.3)	10670	3646 (34.17)
Chikungunya	25	4 (16)	18	4 (22)	48	8 (18.6)
Enteric Fever	7459	809 (10.9)	5422	599 (11)	12881	1408 (10.9)
Malaria	5493	224 (4)	9548	488 (5.1)	15041	712 (4.7)

Interestingly, in Delhi, in 2013, there were 463 seropositive cases amounting to 72% of the total 643 cases seen while in 2014 the seropositivity was 75.69% (299 positive out of 395 cases seen) (Table 2). A total of 15,041 samples were received for detection of malaria, of these only 712 (4.7%) were found positive (Table 1). Of these, records analyzed revealed 591 i.e. 83% were Pl. vivax while Pl. falciparum accounted for only 121 (17%). Male patients (58.4%) outnumbered females (41.6%). The age of the patients with AUF cases ranged from 3 months to 80 year with nearly 90 per cent in age group 12 - 60 years. Majority patients were young in their second, third or fourth decades of life. Annual peak in months of September to November was observed for Dengue while a bi-annual pattern was observed for malaria with two peaks occurring in months of May-June and August-September respectively for the years i.e. 2013 and 2014 (Figure 1 and 2).

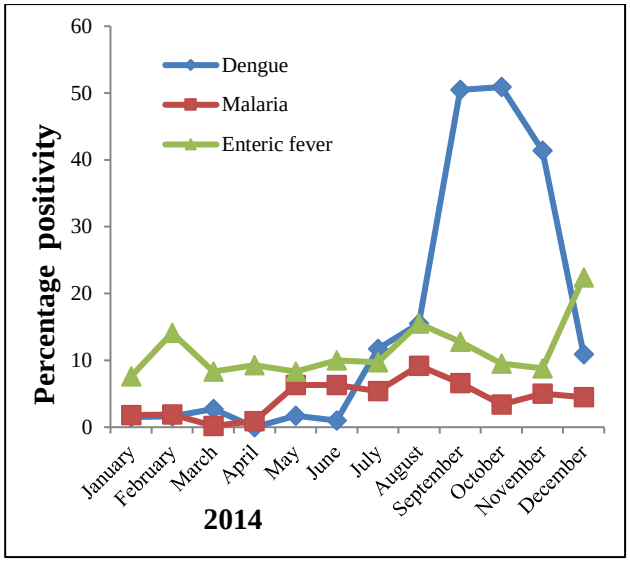

Figure 1: Month wise distribution of dengue, malaria and enteric fever cases for the years 2013 and 2014 in Delhi, India and adjoining areas.

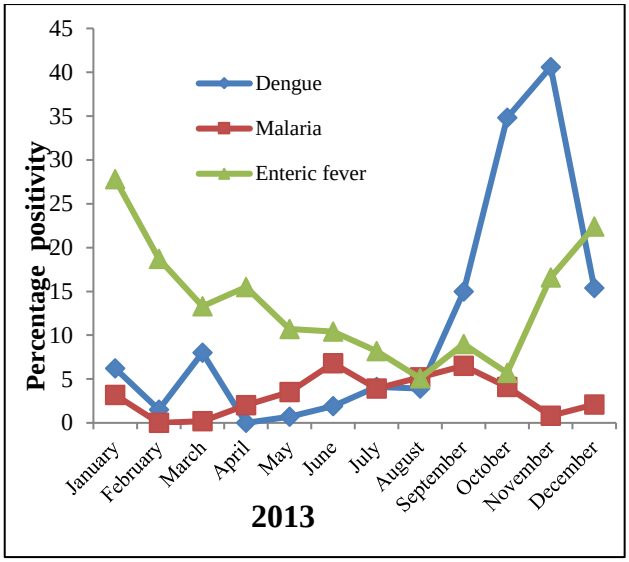

Figure 2: Month wise distribution of dengue, malaria and enteric fever cases for year 2014.

Table 2: Distribution of dengue and enteric fever cases in the years 2013 and 2014 in Delhi and adjoining places.

	Dengue		Typhoid	
	Year (2013)	**Year (2014)**	**Year (2013)**	**Year (2014)**
Delhi	1193 (43.92%)	488 (84.57%)	463 (72.0%)	299 (75.69%)
Haryana	993 (36.56%)	57 (9.87%)	93 (14.46%)	58 (14.68%)
Uttar Pradesh	483(17.78%)	12 (2.07%)	59 (9.17%)	27 (4.19%)
Rajasthan	26 (0.95%)	8 (1.38%)	12 (1.86%)	4 (1.01%)
Others	21 (0.77%)	12 (2.07%)	16 (2.48%)	7 (1.77%)
Total	**2716**	**577**	**643**	**395**

Enteric fever was present throughout the year with no specific distribution pattern. Majority of patients were from Delhi and adjoining Haryana followed by Western Uttar Pradesh. However, some of the patients as immigrants were from other far states of north and central India (Table 2). From the records, co-infection of Dengue with Enteric fever was observed in only four cases.

DISCUSSION

The study revealed a heavy burden with four major tropical infections viz. dengue, chikungunya, enteric fever and malaria for the years 2013 and 2014. Overall seropositivity of 34.17% for Dengue virus infection, 18.6% for Chikungunya infection, 10.9% for Enteric fever and 4.7% for Malaria parasite was observed. For dengue, an upsurge has been noticed since mid-1990s with epidemic waves in urban areas especially in the capital city of Delhi.[1] As per National Vector Borne Disease Control Program (NVBDCP) data, the number of dengue cases reported in India in 2013 alone was about 74,454 with 167 deaths.[2] It was endemic in 16 states across the country.[2] With extensive immigration from neighbouring states, Delhi continues to have substantial proportions of populations living in crowded and impoverished areas with poor sanitations.[3] With reported endemicity of all four serotypes, Delhi has witnessed several outbreaks of dengue since 1967 and of these outbreaks of 1996, 2003 and 2006 were the important ones.[4] In 2010, a study by Singh, Balvinder et al revealed IgM seropositivity for dengue cases to the extent of 38.3% in September, and, from September onwards till December, 2010 same author reported it as 37.36%.[5] The high number of dengue cases (34.17%) in present retrospective analysis corroborates the observation that Delhi has become hyper-endemic for dengue. For chikungunya, for the same years i.e. 2013 and 2014, only 43 clinical samples were received and 8 were positive (18.6 %). As per NVNDCP data, in 2013 alone 18,639 cases of chikungunya were recorded.[2] Chikungunya seropositivity with dengue co-infections in outbreaks has been recorded in the range 40-62%.[5]

For malaria, a total of 15,041 physicians recommended clinical samples were received for malaria detection for these two years i.e. 2013 and 2014. Of these only 712 (4.7%) were found positive by serology or by peripheral smear taken together. Malaria investigations, in Indian settings, is very enthusiastically advocated and over reported.[6] A total of 591/712 samples i.e. 82.17%, in the present retrospective analysis, were positive for P. vivax while P. falciparum accounted for only 121 i.e. 17.83% cases. Similar results are documented in Indian literature and are in accordance with the other reports from North and South India.[7] Malaria remains a leading cause of morbidity and mortality globally. Presently, official records for malaria in India, as per available data at NVBDCP resources, indicate 0.7-1.6 million confirmed cases and 400 -1,000 deaths annually.[8]

About seasonal variations, for dengue and chikungunya, in both the years, the maximum numbers of seropositive cases were recorded in the post monsoon period. Such seasonal variations have been reported in previous studies from Delhi.[5,9] Malaria showed two peaks, one in June and other in September, in both the year's i.e. 2013 and 2014. Ecological and climate factors influence the seasonal prevalence of both the mosquitos' *A. aegypti* and Anopheles, and *A. aegypti* larval indices are also high during the monsoon and post monsoon period.[10]

For enteric fever, in this retrospective analysis, a total of 1408 (10.9%) cases tested positive and peaks of enteric fever cases were observed in December during both the years. This peak incidence may be attributed to festival season in North India. Under the Integrated Disease Surveillance Program (IDSP), 31 outbreaks of enteric fever were reported from 2010 to 2013 with disease peaking from July to October with maximum cases reported from U.P (15.2%).[2] A study published from North India showed two peaks corresponding to the months of February- April and July - October over a period of ten years.[11] Enteric fever has now become virtually prevalent throughout the year with peaks observed as late as in November, probably due to increasing population and lack of proper civic amenities.

Among the effected patients, over all, male patients (58%) outnumbered female patients (41.6%). Most of the patients were young adults in their second, third and fourth decades of life. Similar male to female predominance has been demonstrated in other studies from North India.[12] Male preponderance may be due to the outdoor activities undertaken for earning the livelihood, with accompanying more exposure to mosquito bites, especially in the post monsoon season; unhygienic food and contaminated water. All these factors lead to increase in cases of AUF and such seasonal upsurge in fever cases is well recorded.[12] Not only in Delhi, studies conducted in Northern and Southern parts of the country have also shown similar results. Studies conducted by Joshi R et al on the non-malarial causes of AUF in Central India, and Thangasu S. and Natarajan P on the causes of AUF in South India, and on disease spectrum of AUF by Chrispal A et al, have put forth similar observations as found in the present retrospective study.[6.13.14] According to a study by Singh R et al - dengue, malaria, and enteric fever were the main illnesses confronting the physicians in the region of Uttarakhand.[15] Studies by Gopalakrishnan et al, and Kashinkunti et al have advocated similar findings. In countries like Thailand, Malaysia and Nepal - dengue, malaria, scrub typhus, leptospirosis and enteric fever have been identified as main causes of AUF.[16-22] Apart from these four major aetiologies, Abrahamsen et al from South India, in a cohort study, showed that bacterial infections (38%), TB (19%) were also significant common causes of AUF.[19] A study from East India reported that TB (53%), neoplasms ((17%) and Collagen vascular disorders (11%) were also very important causes of fevers.[12,19-21]

About co infections, four cases of co-infections with enteric fever and dengue were identified. A study from South India reported co-infection of dengue with enteric fever in only 6 cases (6/858: 0.7%) while a study from North India reported it as high as 7.8%.[14] Delhi and NCR region has virtually become endemic for both these infections and unless the index of clinical suspicion is high, the diagnosis of co infections is likely to be missed. From a clinician's viewpoint, overlapping clinical pictures and false positive laboratory results tend to mask the clinical assessment, and therefore, hitherto, such co-infections need be kept in list of causes of AUF for differential diagnosis. Such a thinking order is important for laboratory physicians and also physicians engaged in practice of community medicine.

Limitations of the study was viral studies are not done in routine. Scrub typhus serology is not done in routine and low index of clinical suspicion by treating physicians may be the other reason. True numbers of cases of co-infections may have been missed due to the variables like precisions and accuracies of the laboratory tests applied, qualitative differences in the laboratory skills of investigators involved, and relatively poor sharing of data across laboratories. The study is a retrospective analysis and not a prospective one. It is felt that community and hospital based well planned prospective studies are required to know the evidence based information about the true incidence, prevalence, and precise aetiologies of AUF. With limitations in considerations, it is concluded that dengue, chikungunya, malaria and enteric fever, in that order, were the most important major aetiologies of AUF in the year 2013 and 2014 over duration of 24 months. Surveillance, establishment, maintenance and analysis of the epidemiologic data need be done on regular basis to know the precise incidence and distribution of AUF aetiologies. Periodic studies on AUF causes will help update and modify the existing policies and ensure need based delivery of preventive services. Laboratory diagnostic services may also be upgraded by introduction of newer tests. A clinical, laboratory

confirmed diagnosis helps initiate right lines of treatment. It will help to reduce morbidity and mortality in the long run and hence improve the community health.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Neeraja M, Lakshmi V, Dash PK, Parida MM, Rao PVL. The clinical, serological and molecular diagnosis of emerging dengue infection at a tertiary care institute in Southern. India J Clin Diagn Res. 2013;7(3):457-61.
2. National Vector Borne Disease Control Programme. Dengue/ dengue haemorrhagic fever, 2013. Available at http://www.nhp.gov.in/nvbdcp Accessed on 16 March 2014.
3. Neeraja M, Lakshmi V, Teja VD, Umbala P, Subbalakshmi MV. Serodiagnosis of dengue virus infection in patients presenting to a tertiary care hospital. Indian J Med Microbiol. 2006;24(4):280-2.
4. Cecilia D. Current status of dengue and chikungunya in India. WHO South- East Asia. J Public Health. 2014;3(1):22-7.
5. Arora BS, Chugh S, Gupta B, Aggarwal KC. Dengue and chikungunya virus fever outbreaks in Delhi, Ig M serology status: a recent experience. Nat J Basic Med Sci. 2012;2(4):336-40.
6. Joshi R, Colford JM, Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. Am J Trop Med Hyg. 2008;78(3):393-9.
7. Chakravarti A, Kumar A, Matlani M. Displacement of dengue virus type 3 and type 2 by dengue virus type 1 in Delhi during 2008. Indian J Med Microbiol. 2010;28:412.
8. Malaria situation. National Vector Borne Disease control Programme. Available at http://nvbdcp.gov.in/Doc/mal_situation_Jan2015.pdf.
9. Kanungo S, Dutta S, Surrender D. Epidemiology of typhoid and paratyphoid fever in India. J Infect Dev Ctries. 2008;2(6):454-60.
10. Katyal R, Singh K, Kumar K. Seasonal variations in A. aegypti population in Delhi, India. Dengue Bull. 1996;20:78-81.
11. Banerjee T, Shukla BN, Filgona J, Anupurba S, Sen MR. Trends of typhoid fever seropositivity over ten years in North India. Indian J Med Res. 2014;140(2):310-3.
12. Susilawati TN, McBride WJ. Acute undifferentiated fever in Asia: a review of the literature. Southeast Asian J Trop Med Public Health. 2014;45(3):719-26.
13. Thangarasu S, Natarajan P. A protocol for emergency department management of acute undifferentiated febrile illness in India. Int J Emer Med. 2011;4:57.
14. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JA, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors: an experience from a tertiary care hospital in South India. Trop Doctor. 2010;40(4):230-4.
15. Singh R, Singh SP, Ahmad N. A study of aetiological pattern in an epidemic of acute febrile illness during monsoon in a tertiary health care institute of Uttarakhand, India. J Clin Diagn Res. 2014;8(6):MC01-03.
16. Gopalakrishnan S, Arumugam B, Kandasamy S, Rajendran S, Krishnan B. Acute undifferentiated febrile illness among adults - a hospital based observational study. J Evolut Med Dent Sci. 2013;2(14):2305-19.
17. Kashinkunti MD, Gundikeri SK, Dhananjaya M. Acute undifferentiated febrile illness- clinical spectrum and outcome from a tertiary care teaching hospital of north Karnataka. Int J Biol Med Res. 2013;4(2):3399-402.
18. Jena B, Prasad MNV, Murthy S. Demand pattern of medical emergency services for infectious diseases in Andhra Pradesh - A geo-spatial temporal analysis of fever cases. Indian Emerg J. 2010;1(5):821.
19. Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, et al. The aetiology of febrile illness in adults presenting to Patan Hospital in Kathmandu, Nepal. Am J Trop Med Hyg. 2004;70(6):670-5.
20. Sripanidkulchai R, Lumbiganon P. Aetiology of obscure fever in children at a university hospital in northeast Thailand. Southeast Asian J Trop Med Public Health. 2005;36:1243-6.
21. Leelarasamee A, Chupaprawan C, Chenchittikul M, Udompanthurat S. Aetiologies of acute undifferentiated febrile illness in Thailand. J Med Assoc Thai. 2004;87:464-72.
22. Ellis RD, Fukuda MM, McDaniel P, Welch K, Nisalak A, Murray CK, et al. Causes of fever in adults on the Thai-Myanmar border. Am J Trop Med Hyg. 2006;74:108-13.

Cite this article as: Arora BS, Matlani M, Saigal K, Biswal I, Rajan S, Padmanandan A, Singh S. Major aetiologies of acute undifferentiated fever in 2013 and 2014: an experience in retrospect. Int J Adv Med 2017;4:568-72.