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Research Article

The Extent of Co-Infection with Dengue and Scrub Typhus Among Patients Experiencing Acute Febrile Illness: A Retrospective Study of Patients Visiting a Tertiary Care Hospital in Southern Rajasthan, India

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ABSTRACT

Background: In tropical countries including India Dengue, Scrub typhus, Malaria, Typhoid & Leptospirosis are common causes of acute febrile illness. Although co-infections of dengue, malaria, leptospirosis and typhoid in various combinations have been described, data on Dengue and Scrub typhus co-infection are distinctly limited. As both the diseases are individually present in our area, but co-infection is not yet explored this study was done to understand the burden and pattern of co-infection.
Methods: A retrospective hospital-based, cross-sectional study was done in the Department of Microbiology of a tertiary care referral hospital of Kota district in Rajasthan, India, from January 2021 to December 2023. Dengue IgM ELISA tests were performed using the ULTRA Dengue IgM Capture ELISA (SD BIOSENSOR) kit and Scrub typhus the IgM ELISA tests were performed using the SCRUB TYPHUS IgM MICROELISA (J. Mitra & Co. Pvt. Ltd.) kit.
Results: In the current study we analyzed a total of 35335 patients that were admitted with fever and were tested for Dengue. Of these, 1851/35335 (5.23%) patients were diagnosed to have dengue fever. These patients were subsequently tested for co-infection with Scrub typhus infection. Of 1851 dengue - positive patients 37 (1.99%) were diagnosed with co-infection of Scrub typhus.
Conclusion: Co-infections are being reported from various parts across the globe. Clinicians ought to maintain a strong awareness of the possibility of co-infections in areas where these infections are common to ensure early diagnosis and treatment.

Keywords: *Dengue-Scrub co-infection, Dengue, Scrub typhus, Kota, Southern Rajasthan.*

INTRODUCTION

In tropical countries including India Dengue, Scrub typhus, Malaria, Typhoid & Leptospirosis are common causes of acute febrile illness.
Dengue fever is caused by single-stranded RNA viruses of the genus Flavivirus, transmitted by the bite of the infected Aedes mosquito, and is considered an endemic disease in the Indian subcontinent. [1]

Scrub typhus is caused by Orientia tsutsugamushi and has recently re-emerged as a major public health problem in the Asian countries. [2] This acute febrile illness was classically known to be endemic in the so-called 'tsutsugamushi triangle,' which extends from Pakistan in the west to Japan in the east and Australia in the south. However, new reports have also emerged from various parts of Africa, Chile, and Kenya. [3–5] In the Middle East, a new related species, Orientia chuto, has been described. [6]

Concurrent infection with multiple pathogens is common in tropics, posing diagnostic and treatment challenges. Although co-infections of dengue, malaria, leptospirosis and typhoid in various combinations have been described, data on Dengue and Scrub typhus co-infection are distinctly limited. The Indian climate provides an environment conducive to the propagation and transmission of both Dengue and Scrub typhus. Both diseases have several similar clinical and laboratory features, including rash, thrombocytopenia, and hepatic dysfunction. However, concurrent infection with both pathogens is exceedingly rare, primarily due to the different vectors involved. [7] Scrub typhus can lead to severe complications, and it matters further; the symptoms of both diseases often overlap, making accurate diagnosis and treatment challenging.

In Rajasthan, both diseases emerged as important causes of febrile illness in the monsoon and post-monsoon seasons. Recently scrub infection has brutally gripped various districts of Rajasthan, including Kota, with Udaipur, Rajsamand, Chittorgarh, and Baran with the high positive rate. [8] Amongst them, the maximum cases were reported from Udaipur with 776, followed by Jaipur, Kota, Alwar, Chittorgarh, Bharatpur, Rajsamand, Dausa, and Sikar, and fatalities were also observed from Bundi, Alwar, and Jhalawar. [9] Our hospital caters to the medical needs of the population residing in the physiogeographic region of Kota, Bundi, Baran, and Jhalawar, and the region experiences subtropical monsoons, mild and dry winters, and sizzling summers. Within this zone, altitude varies from 350 to 1500 m. As both the diseases are individually present in our area, but co-infection is not yet explored this study was done to understand the burden and pattern of co-infection. The objective of this study is to estimate the prevalence of co-infection with Scrub typhus in patients diagnosed with dengue fever by the ELISA IgM test and to compare the Dengue-Scrub co-prevalence between Male vs. Female, OPD vs. IPD, and Rural vs. Urban so as to ascertain if there is any difference or trend variation between the above-mentioned groups. We will also analyze to find out the weather and month of maximum prevalence for Dengue and Scrub typhus infections.

MATERIAL & METHODS

A retrospective hospital-based, cross-sectional study was done in the Department of Microbiology of a tertiary care referral hospital of Kota district in Rajasthan, India, from January 2021 to December 2023. A total of 35335 patients were attended for complaint of acute undifferentiated fever (AUF) during the study period that were tested for Dengue by the ELISA IgM method, and of these, 1851/35335 were diagnosed to have dengue fever with positive dengue serology. These patients were subsequently tested for Scrub typhus infection by the ELISA IgM method. Dengue IgM ELISA tests were performed using the ULTRA Dengue IgM Capture ELISA (SD BIOSENSOR) kit and Scrub typhus the IgM ELISA tests were performed using the SCRUB TYPHUS IgM MICROELISA (J. Mitra & Co. Pvt. Ltd.) kit.

Inclusion criteria: All patients who had ELISA reported Scrub typhus among those diagnosed with dengue fever by IgM ELISA during January 2021 to December 2023. Medical records with incomplete data were excluded from the study.

RESULTS

In the current study we analyzed a total of 35335 patients that were admitted with fever and were tested for Dengue by the ELISA IgM method. Of these, 1851/35335 (5.23%) patients were diagnosed to have dengue fever with the positive dengue ELISA IgM method. These patients were subsequently tested for co-infection with Scrub typhus infection by the ELISA IgM method. Of 1851 dengue - positive patients 37 (1.99%) were diagnosed with co-infection of Scrub typhus.

In 2021 we reported 997 out of 9289 patients (10.73%) were positive for the Dengue by ELISA IgM method; among those 997 Dengue Positive patients, 12 (1.20%) were also found positive for Scrub typhus by the ELISA IgM method.
In 2022, we reported that 157 out of 7928 patients (1.98%) were positive for the Dengue ELISA IgM method; among those 157 Dengue-positive patients, 4 (2.54%) were also found positive for the Scrub typhus ELISA IgM method.
In 2023 we reported 697 out of 18118 patients (3.84%) were positive for the Dengue ELISA IgM method; among those 697 Dengue- positive patients, 21 (3.01%) were also found positive for the Scrub typhus ELISA IgM method.

TABLE 1: DENGUE PREVALENCE YEAR WISE

YEAR	TESTED	DENGUE POSITIVE	DENGUE PREVALENCE (%)
2021	9289	997	10.73%
2022	7928	157	1.98%
2023	18118	697	3.84%
TOTAL	35335	1851	5.23%.

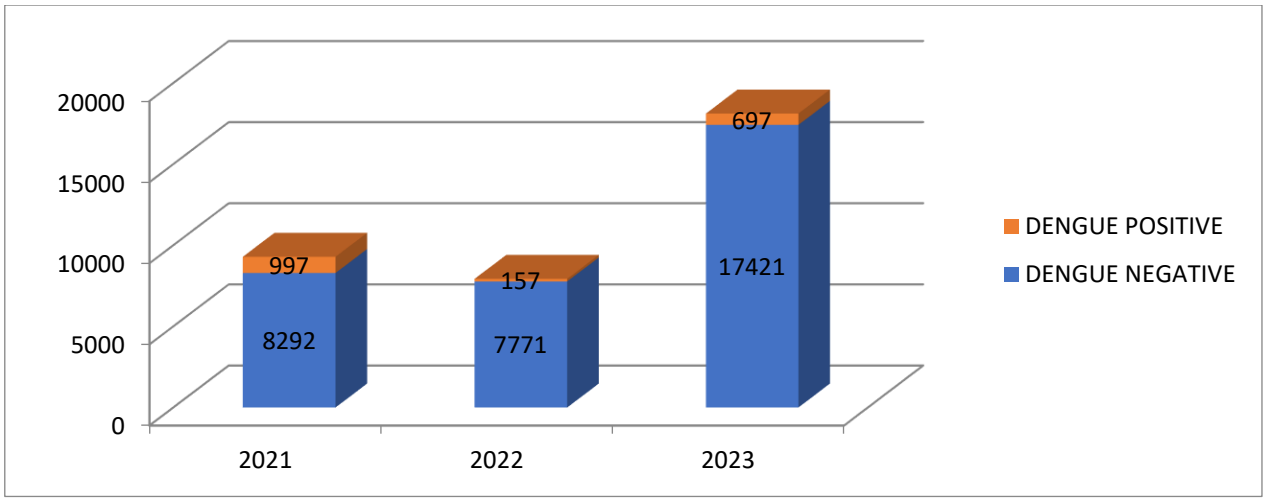

FIGURE 1: DENGUE PREVALENCE YEAR WISE

TABLE 2: DENGUE POSITIVE AND SCRUB TYPHUS CO-INFECTION YEAR WISE

YEAR	DENGUE POSITIVE	CO-PREVALENCE OF DENGUE AND SCRUB	CO-INFECTION (%)
2021	997	12	1.20%(12/997)
2022	157	4	2.54%(4/157)
2023	697	21	3.02%(21/697)
TOTAL	1851	37	1.99%(35/1851)

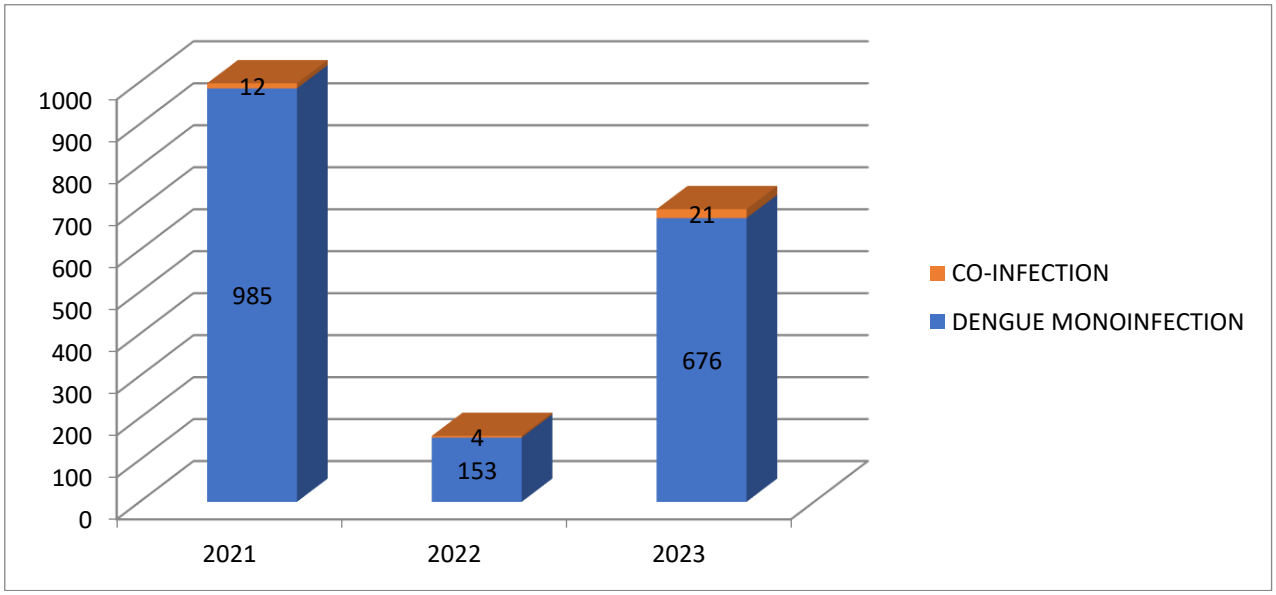

FIGURE 2: DENGUE PREVALENCE AND SCRUB TYPHUS CO-INFECTION YEAR WISE

In the year 2021, co-prevalence among males was 50% (6 co-infected out of 12), and among females, it was 50% (6 co-infected out of 12).
In the year 2022, co-prevalence among males was 25% (1 co-infected out of 4), and among females, it was 75% (3 co-infected out of 4).
In the year 2023, co-prevalence among males was 78.95% (15 co-infected out of 19), and among females, it was 21.05% (4 co-infected out of 19).
Total co-prevalence among males was 59.45% (22 co-infected out of 37), and among females it was 40.54% (15 co-infected out of 37).

TABLE 3: COMPARISON OF CO-INFECTION IN MALES AND FEMALES (YEAR WISE)

YEAR	CO-PREVALENCE (MALE)	CO-PREVALENCE (FEMALE)
2021	6	6
2022	1	3
2023	15	4
Total	22 (59.45%)	15 (40.54%)

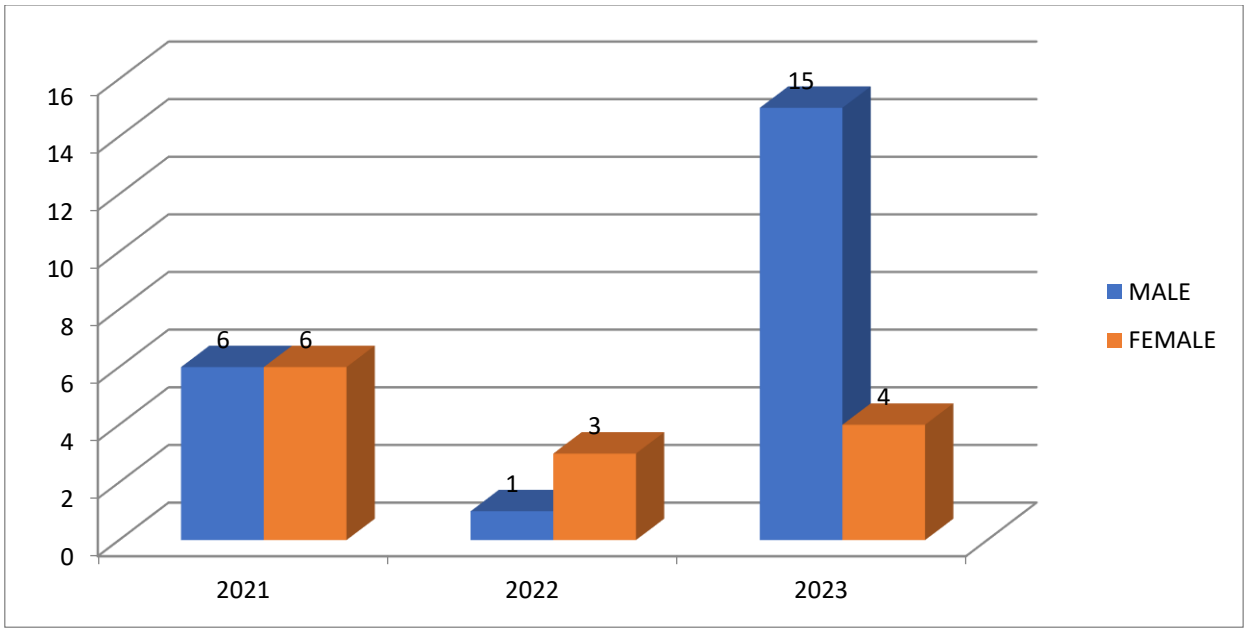

FIGURE 3: COMPARISON OF CO-INFECTION IN MALE AND FEMALE (YEAR WISE)

In the year 2021, co-prevalence among OPD patients was 16.66% (2 co-infected out of 12 patients), and among IPD patients, it was 83.33% (10 co-infected out of 12 patients).
In the year 2022, co-prevalence among OPD patients was 25% (1 co-infected out of 4 patients), and among IPD patients, it was 75% (3 co-infected out of 4 patients).

In the year 2023, co-prevalence among OPD patients was 71.74% (15 co-infected out of 21 patients), and among IPD patients, it was 28.57% (6 co-infected out of 21 patients).
Total co-prevalence among OPD patients was 48.64% (18 co-infected out of 37 patients), and an IPD patient was 51.36% (19 co-infected out of 37 patients).

TABLE 4: COMPARISON OF CO-INFECTION IN OPD AND IPD PATIENTS (YEARWISE)

YEAR	OPD CO PREVALENCE	IPD CO PREVALENCE
2021	2	10
2023	1	3
2024	15	6
TOTAL	18(48.64)	19(51.36%)

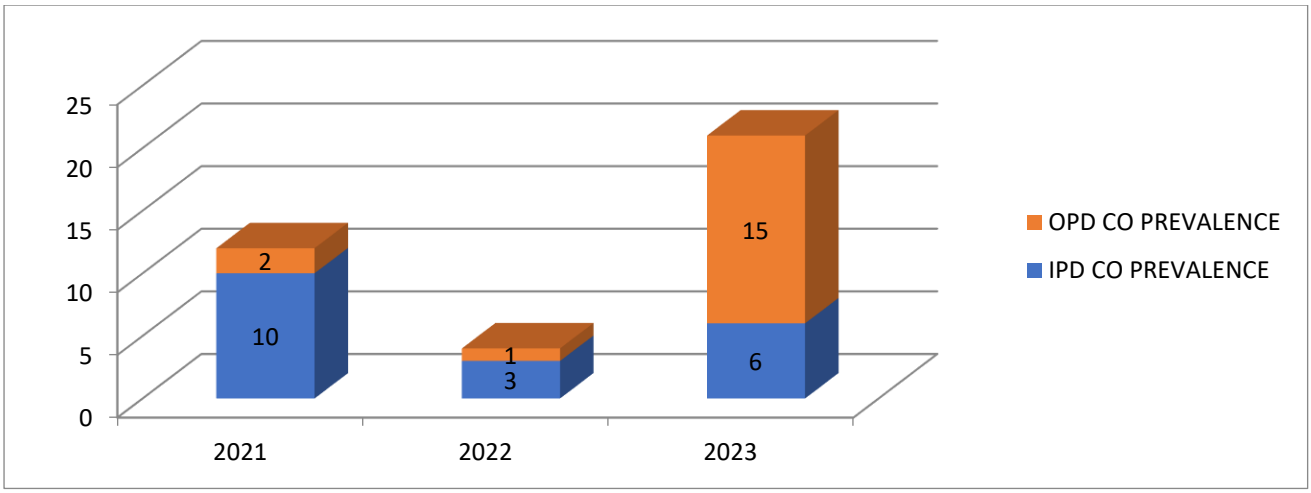

FIGURE 4: COMPARISON OF CO-INFECTION IN OPD AND IPD PATIENTS (YEARWISE)

Out of 12 co-infected patients reported in the year 2021, 2 (16.67%) were Urban patients and 10 (83.33%) were Rural patients.
Out of 4 co-infected patients reported in the year 2022, 1 (25%) was Urban patients and 3 (75%) were Rural patients.
Out of 21 co-infected patients reported in the year 2023, 6 (28.57%) were Urban patients and 15 (71.42%) were Rural patients.
Total co-prevalence among Urban patients was 24.33% (9 co-infected out of 37 patients), and Rural patients were 75.67% (28 co-infected out of 37 patients).

TABLE 5: COMPARISON OF CO-INFECTION IN URBAN AND RURAL PATIENTS (YEARWISE)

YEAR	URBAN PREVALENCE (%)	RURAL PREVALENCE (%)
2021	(2/12) 16.67%	(10/12) 83.33%
2022	(1/4) 25%	(3/4) 75%
2023	(6/21) 28.58%	(15/21) 71.42%
Total	9 (24.33%)	28 (75.67%)

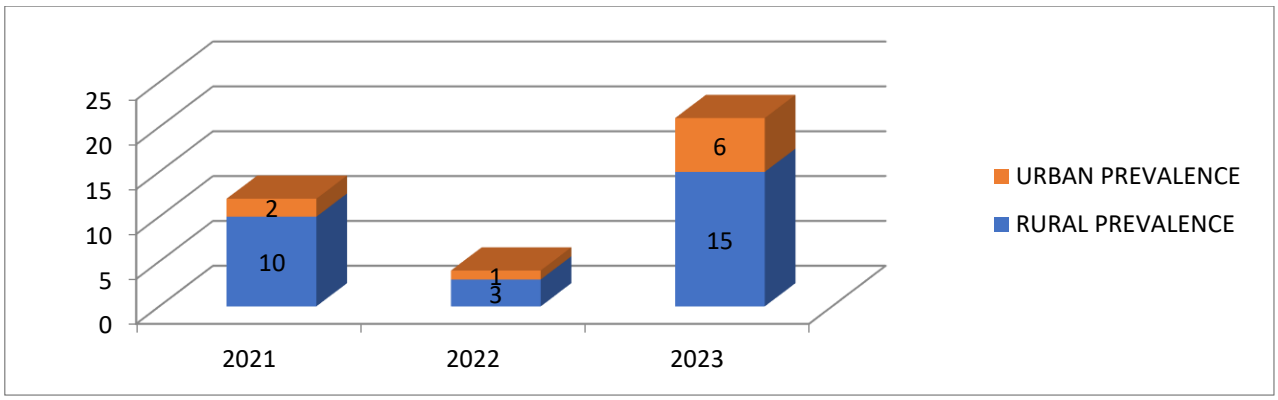

FIGURE 5: COMPARISON OF CO-INFECTION IN URBAN AND RURAL PATIENTS (YEARWISE)

TABLE: 6 MONTH-WISE DISTRIBUTIONS OF CO-INFECTION CASES

Month	2021	2022	2023
January	0	1	0
February	0	0	0
March	0	0	0
April	0	0	0
May	0	0	0
June	0	0	1
July	0	1	0
August	0	0	1

September	3	1	5
October	5	0	8
November	2	1	3
December	2	0	3
Total	**12**	**4**	**21**

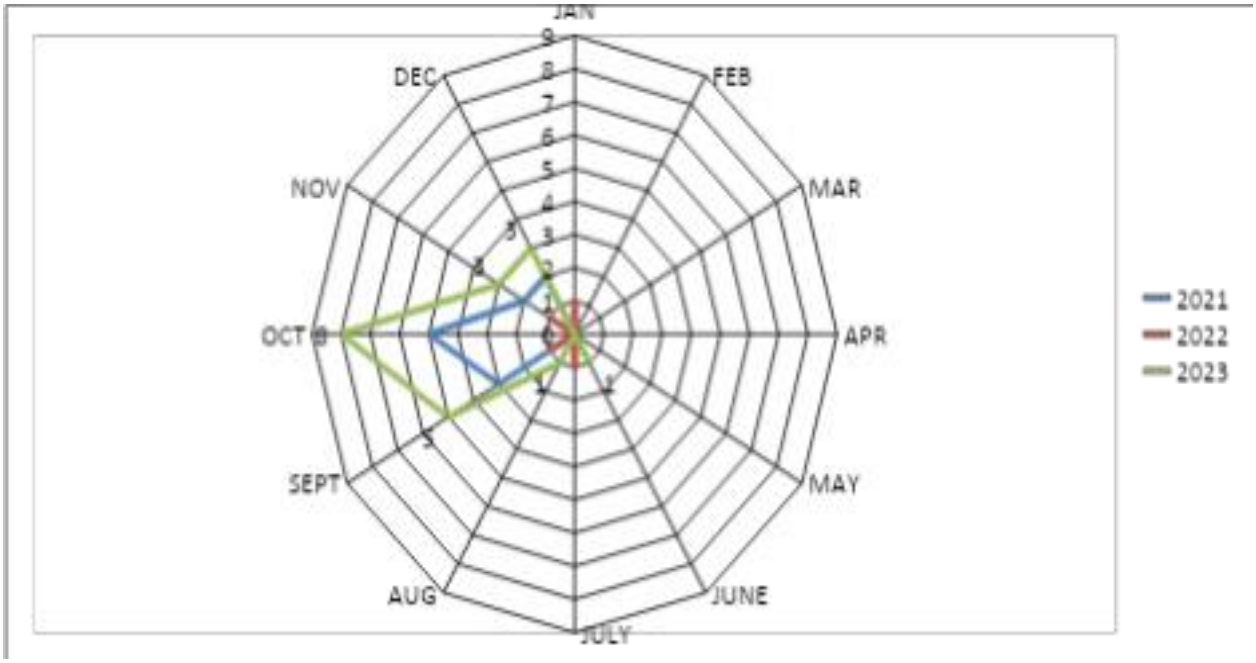

FIGURE 6: MONTH-WISE DISTRIBUTIONS OF CO-INFECTION CASES IS SHOWN IN.

DISCUSSION

Scrub typhus and dengue remain the main vector-borne diseases causing acute undifferentiated febrile illness in the "tsutsugamushi triangle." In many parts of India, these two infections together comprise more than half of all acute undifferentiated febrile illnesses. Despite the difference in pathogenesis, both share the same seasonal distribution, demographic, and clinical features, and if not recognized early, they are associated with significant mortality. [10]

As both the infections are common in our region and there is a favorable environment for both the vectors of the disease, the probability of co-infection is always there. There is only a limited awareness about the possibility of co-infections, especially when a firm primary diagnosis like dengue has been made, resulting in a high chance of missing the co-infection, resulting in severe morbidity and mortality. [11]

In the current study we found an overall prevalence (years 2021-2023) of 5.23% for Dengue fever. We found the highest prevalence (10.73%) in 2021 and the lowest (1.98%) in 2022. Deepashri Pratyeke et al. [12] reported 9.75% Dengue prevalence in 2022, and Sujeet Raina et al. [13] reported 7.8% in 2016, while Priya et al. [14] reported 37.1% prevalence in 2012-2016. The high prevalence reported by Priya et al. might be due to the selection of the pediatric population and coastal area for study.

In the current study, we observed a co-prevalence of 1.99% of Scrub typhus in Dengue positive patients, which was 1.20% in 2021, 2.54% in 2022, and 3.02% in 2023. Similarly, Prasan Kumar Panda et al. [15] reported 1.02% (1 out of 98) in 2014-15, and Rakhecha et al. [16] also reported 2.72% (46 out of 1687) in 2021 in Maharashtra. Sujeet et al. [13] also reported 1.3% in 2016 in Himachal Pradesh. Priya et al. [14] reported 16.03% in the pediatric population from 2012 to 2016 in Pondicherry.

In the current study, we observed a higher co-prevalence in male patients 59.45% in comparison to females (40.54%). Deepashri et al. [12] also reported similar prevalence: 60% in males and 40% in females.
In the current study, total co-prevalence among OPD patients was 48.64% (18 co-infected out of 37 patients), and IPD patients were 51.35% (19 co-infected out of 37 patients). We observed a higher co-prevalence in admitted patients in comparison to outdoor patients. The higher percentage of IPD patients requiring admission indicates the more serious nature of co-infections. It reveals that masking of one infection hampers the progression of recovery. The masked infection was not considered and remains untreated, leading to detrimental health effects and often requiring admission.

In the current study, we observed the highest prevalence and co-prevalence during August-December. Sayan Malakar et al. [17] also reported August-November as the highest prevalence months for acute febrile illness (AFI). The monsoon and post-monsoon seasons are a favorable situation for the flourishing of vectors for both the diseases.

In the current study we observed a significant difference of co-prevalence between rural and urban populations. Total co-prevalence among rural patients was 75.67% (28 co-infected out of 37 patients), and urban patients were 24.33% (9 co-infected out of 37 patients). Significantly higher prevalence in rural populations is due to the favorable ecosystem for the vectors of both the diseases (clean stagnant water for the Aedes aegypti mosquito and scrub vegetation for Trombiculid Mites). The practice of barefoot walking, wearing open sandals, improper clothing in paddy fields, cutting of fodder and grass for animal husbandry and carrying it on their thighs and back and open defecation in the farm were also some reasons for the higher prevalence in rural areas.

CONCLUSION

Co-infections are being reported from various parts across the globe. Although studies are limited for dengue and scrub co-infection, both the vector-borne diseases have overlapping clinical features and the same peak season of positivity, so thorough workup and studies are required to evaluate the actual rates of co-infections. Also, early screening of suspected patients and their prompt treatment for co-infections is the need of the hour, which can lead to significant reduction in mortality and morbidity. There are also economic benefits in terms of the requirement of decreased hospital stays. Clinicians ought to maintain a strong awareness of the possibility of co-infections in areas where these infections are common to ensure early diagnosis and treatment.

Strengths of the study:

Over the course of three years, data was gathered from a single hospital with a sizable sample size. Additionally, across the course of the study, the same company's ELISA kits were utilized, ruling out any change in results reported from kit to kit.

Limitations of study:

The study could not incorporate all clinical details about the patients (signs, symptoms, and laboratory reports) as we did a retrospective analysis. The ELISA IgM kit may have cross-reactivity with other antibodies, which may result in false positivity or false negativity. Real-time PCR and other molecular methods are necessary for confirmation, but they were not carried out in our study.

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Conflicts of interest: There are no conflicts of interest.

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