

A Study on Travel-associated Febrile Illness among Patients Attending a Tertiary Care Hospital in Eastern India

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ABSTRACT

Background: Diagnosing the etiology of travel-associated febrile illness can be challenging due to the wide range of potential causes and the diverse geographic locations travelers may visit. Several factors contribute to this complexity including diverse pathogens, incubation period, multiple exposures, vector-borne diseases, immunization status, local outbreaks, and uncommon pathogens. The present study aimed to explore the characteristics and etiology of fever in returned travelers.

Methods: A prospective observational study was carried out over one year which included patients presenting with fever, who had a recent travel history of not less than 1 week. Each patient was enquired regarding their basic demographics, comorbidities, etiology, symptoms on presentation, days of fever, and travel-related details. Patient-reported risk factors were noted. Results were statistically analyzed.

Results: The study included 63 returned travelers who reported fever. The majority of the presentation was from the age group of 19–35 years, with the most common etiology being malaria (14.29%), followed by scrub typhus (9.52%) and typhoid (7.94%). While there were 6.34% cases of intercountry travel, 34.92% were cases of interstate travel and the rest were within the state. Average days of fever and symptom presentation widely varied with etiologies. Symptoms included rash, headache, hepatomegaly, anemia, chest abnormalities, leukocytosis, leucopenia, thrombocytopenia, hyperbilirubinemia, and transaminitis.

Conclusion: It is important on the part of clinicians, especially, tropical medicine specialists to formulate pretravel consultation guidance and immunization strategies. Prompt evaluation and management of febrile illness among returned travelers is warranted.

Keywords: Fever, Pretravel advice, Returned travelers.

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INTRODUCTION

With the increase in tourism, the frequency of diseases among persons returning from other countries and other states of the same country is also increasing. According to the United Nations World Tourism Organization (UNWTO), an estimated 2 billion persons are estimated to travel each year by 2030.¹ Fever is defined as a body temperature $\geq 38.3^\circ\text{C}$. It is an important symptom in the returning traveler seeking medical care, which can lead to hospitalization in up to 30% of cases and may be indicative of a severe disease.^{2,3} Climate change and environmental changes have led to shifts in vector distribution areas, so the formerly “classic” tropical diseases, such as arboviral infections, are also being reported to occur even during travel to European countries.⁴

Diarrhea, fever, and skin changes constitute the most common manifestations of disease after travel to tropical and subtropical regions. The diagnostic evaluation should always progress in a series of steps, which must begin with a precise travel history and the identification of specific risk factors. Among travelers returning from sub-Saharan Africa, *Plasmodium falciparum* malaria remains the most common cause of fever, reported to affect around 50 per 1,000 travelers. Most commonly observed among individuals returning from trips to Southeast Asia, dengue fever has a reported incidence ranging from 50 to 160 cases per 1,000 travelers. Other diseases with potential complications include chikungunya, Zika fever, typhoid and paratyphoid fever, amoebic liver abscess, visceral leishmaniasis (kala-azar), leptospirosis, and, very rarely, imported cases of viral hemorrhagic fever. Coronavirus disease-2019

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(COVID-19) and influenza are also important differential diagnoses, especially in this post-COVID era.⁵

Fever often accompanies serious illness in returned travelers. The commonest life-threatening tropical disease associated with fever in returned travelers is malaria. As an increased temperature can signal the presence of an underlying rapidly progressive infection, early evaluation is warranted, especially in people who have visited areas with malaria recently. The initial focus while evaluating a febrile returned traveler should be to identify infections that are potentially life-threatening, treatable, or transmissible. In some cases, public health officials have to be alerted if the traveler is possibly contagious while traveling or infected with a pathogen of public health concern (such as Ebola virus or yellow fever virus). During an outbreak, special screening protocols are demanded. Even after complete diagnostic evaluation, a definite cause for fever might not be identified in some cases. The majority of the diseases in returned travelers are caused by common infections that must be considered in priority besides the more uncommon ones. Knowing the geographic area of travel is a major determining factor to make an idea about the causes. Engaging in activities during travel, such as exploring caves, receiving dental or medical care, participating in sexual activity, or obtaining new tattoos, along with potential exposures such as animal bites or contact with freshwater in schistosomiasis-endemic areas, as well as factors related to living arrangements (such as dwelling type, the use of mosquito nets, air conditioning, and window screens) can provide valuable insights. Pretravel vaccinations, malaria prophylaxis, etc. will also markedly reduce the likelihood of some infections, which also hold a relevant part of the history.⁶ The present study aimed to explore the characteristics and etiology of fever in returned travelers.

METHODS

A prospective observational study was carried out over 1 year in an eastern India tertiary care setup. The study conduct was permitted by the institutional ethics committee and written informed consent was obtained from all participants. The study included patients presenting with fever, who had a recent travel history of not less than 1 week. The study excluded those with a recent history of COVID-19 infection, pregnant females, and lactating mothers. Each patient was enquired regarding their basic demographics, comorbidities, etiology, symptoms on presentation, days of fever, and travel-related details. Patient-reported risk factors were noted.

Data were statistically analyzed. Descriptive variables were represented as frequency, percentage, mean, and standard deviation as applicable. All statistical analysis was carried out using GraphPad Prism (GraphPad Prism 8.0.2, San Diego, CA, USA) and Microsoft Excel.

RESULTS

The study included 63 returned travelers who reported fever. The mean age of the population was 35.79 years, ranging from 16 years to 88 years; 69.84% ($n = 44$) were males, while the rest were females. The majority of the presentation was from the age group of 19–35 years, followed by the age range of 36–50 years.

The most common etiology was malaria (14.29%), followed by scrub typhus (9.52%) and typhoid (7.94%). Human immunodeficiency virus (HIV), traveler diarrhea, and urinary tract infection were other etiologies present in 6.35% of individuals each. Other etiologies observed were influenza, giardiasis, dengue, hepatitis (A and

Table 1: Patient characteristics

Variables	Observations [frequency (%)]
Age (years)	
≤18	4 (6.34%)
19–35	32 (50.79%)
36–50	16 (25.39%)
51–65	7 (11.11%)
>66	4 (6.34%)
Type of travel	
Tourism	37 (58.73%)
Business/work	18 (28.57%)
Studies	5 (7.94%)
Visiting friends/family	3 (4.76%)
Comorbidities	
Diabetes mellitus	11 (17.46%)
Hypertension	10 (15.87%)
Hypothyroidism	1 (1.59%)
Chronic obstructive pulmonary disease	5 (7.94%)
Asthma	1 (1.59%)

E), insect bite dermatitis, pneumonia, meningitis, tuberculosis (pulmonary and extrapulmonary), visceral leishmaniasis, hydatid cyst, neurocysticercosis, amebic liver abscess, amebic dysentery, strongyloides, brucellosis, measles, chikungunya, Japanese encephalitis, and leptospirosis. High-grade fever was noted in 43 (68.25%) returned travelers. Among the cases of malaria, there was a single case of *P. falciparum*, while the rest were *Plasmodium vivax*. While there were 6.34% cases of intercountry travel, 34.92% were cases of interstate travel and the rest were within the state. 23.8% of cases reported having comorbidities. Comorbidities such as diabetes mellitus, hypertension, hypothyroidism, chronic obstructive pulmonary disease, and asthma were noted, with 11 cases having diabetes mellitus, followed by 10 cases having hypertension (Table 1). Patient-reported risk factors were noted in 41.26% of cases, which included consumption of street food and water (for traveler's diarrhea, giardiasis, amoebic dysentery, and hepatitis), insect bite (for insect bite dermatitis and scrub typhus), unprotected sex (for HIV), contact history (for tuberculosis, measles, and influenza).

Average days of fever and symptom presentation are widely varied with etiologies. Symptoms included rash, headache, hepatomegaly, anemia, chest abnormalities, leukocytosis, leucopenia, thrombocytopenia, hyperbilirubinemia, and transaminitis (Table 2).

DISCUSSION

Diagnosing the etiology of travel-associated febrile illness can be challenging due to the wide range of potential causes and the diverse geographic locations travelers may visit. Several factors contribute to this complexity including diverse pathogens, incubation period, multiple exposures, vector-borne diseases, immunization status, local outbreaks, and uncommon pathogens.⁷ Various infectious agents can cause febrile illnesses, including bacteria, viruses, parasites, and fungi. Different regions have distinct

Table 2: Etiologies and varied presentation

<i>Etiology</i>	<i>Presenting frequency (%)</i>	<i>Average fever days</i>	<i>Presenting symptoms and clinical findings</i>	<i>Laboratory abnormalities</i>
Malaria	9 (14.29%)	2.44	Headache (5), chills and rigor (8), nausea/vomiting (6), muscle pain (4), and hepatomegaly (6)	Anemia (3), thrombocytopenia (4), leukocytosis (9), hyperbilirubinemia (4), and transaminitis (5)
Scrub typhus	6 (9.52%)	9.33	Muscle pain (2), nausea/vomiting (1), lymphadenopathy (3), hepatomegaly (2), and chest abnormalities (2)	Anemia (3), leukocytosis (6), transaminitis (6), hyperbilirubinemia (6), and thrombocytopenia (6)
Typhoid	5 (7.94%)	9	Nausea/vomiting (3), pain abdomen (1), and hepatomegaly (5)	Leukopenia (5), hyperbilirubinemia (1), and transaminitis (5)
HIV	4 (6.35%)	142.5	Fatigue (1), lymphadenopathy (4), hepatomegaly (1), and chest abnormalities (2)	Anemia (4), leukopenia (4), and transaminitis (2)
Traveler's diarrhea	4 (6.35%)	2	Diarrhea (4), pain abdomen (4), nausea/vomiting (3)	Anemia (1), leukocytosis (4), transaminitis (1)
Urinary tract infection	4 (6.35%)	6.25	Increased frequency of micturition (3), and pain abdomen (1)	Anemia (3), and leukocytosis (4)
Influenza	3 (4.76%)	2.3	Chest abnormalities (3)	Leukocytosis (3), hyperbilirubinemia (1), and transaminitis (1)
Giardiasis	2 (3.17%)	11	Diarrhea (2), pain abdomen (1), and nausea/vomiting (2)	Leukocytosis (2)
Dengue	2 (3.17%)	3.5	Rash (2) and hepatomegaly (2)	Thrombocytopenia (2), leukopenia (2), hyperbilirubinemia (1), and transaminitis (2)
Hepatitis A	2 (3.17%)	14	Jaundice (2), nausea/vomiting (2), and hepatomegaly (2)	Leukocytosis (2), transaminitis (2), hyperbilirubinemia (2)
Insect bite dermatitis	2 (3.17%)	3	Rash (2) and pruritus (2)	Anemia (1), leukocytosis (2), and transaminitis (2)
Pneumonia	2 (3.17%)	4	Chest abnormalities (2)	Leukocytosis (2), hyperbilirubinemia (2), and transaminitis (2)
Meningitis	2 (3.17%)	4	Headache (2), nausea/vomiting (2), and lymphadenopathy (1)	Anemia (2), thrombocytopenia (1), leukocytosis (1), leucopenia (1), and transaminitis (2)
Tuberculosis (pulmonary)	2 (3.17%)	120	Chest abnormalities (2) and fatigue (1)	Anemia (2) and leukocytosis (2)
Tuberculosis (extrapulmonary)	2 (3.17%)	105	Fatigue (1), lymphadenopathy (2), and hepatomegaly (1)	Anemia (2) and leukocytosis (2)
Visceral leishmaniasis	1 (1.59%)	30	Fatigue (1), nausea/vomiting (1), and hepatomegaly (1)	Anemia (1), thrombocytopenia (1), and leucopenia (1)
Hydatid cyst	1 (1.59%)	7	Nausea/vomiting (1), Hepatomegaly (1)	Anemia (1), Leukocytosis (1), Hyperbilirubinemia (1), Transaminitis (1)
Neurocysticercosis	1 (1.59%)	28	Headache (1), and hepatomegaly (1)	Leukocytosis (1)
Amebic liver abscess	1 (1.59%)	4	Pain abdomen (1), nausea/vomiting (1), and chills (1)	Leukocytosis (1) and transaminitis (1)
Amebic dysentery	1 (1.59%)	6	Pain abdomen (1), diarrhea (1), hepatomegaly (1), and chest abnormalities (1)	Leukocytosis (1), transaminitis (1), and hyperbilirubinemia (1)
Strongyloides	1 (1.59%)	10	Pain abdomen (1) and diarrhea (1)	Anemia (1) and leukocytosis (1)
Brucellosis	1 (1.59%)	21	Malaise (1), muscle pain (1), hepatomegaly (1), and lymphadenopathy (1)	Leukocytosis (1), anemia (1), transaminitis (1), and hyperbilirubinemia (1)

(Contd....)

Table 2: (Contd...)

<i>Etiology</i>	<i>Presenting frequency (%)</i>	<i>Average fever days</i>	<i>Presenting symptoms and clinical findings</i>	<i>Laboratory abnormalities</i>
Measles	1 (1.59%)	4	Rash (1) chest abnormalities (1)	Thrombocytopenia (1), leukocytosis (1)
Chikungunya	1 (1.59%)	6	Rash (1) and joint pain (1)	Leukocytosis (1) and transaminitis (1)
Japanese encephalitis	1 (1.59%)	5	Headache (1), nausea/vomiting (1), and hepatomegaly (1)	Leukocytosis (1) and transaminitis (1)
Hepatitis E	1 (1.59%)	10	Jaundice (1), nausea/vomiting (1), and hepatomegaly (1)	Leukocytosis (1), transaminitis (1), and hyperbilirubinemia (1)
Leptospirosis	1 (1.59%)	3	Jaundice (1), nausea/vomiting (1), muscle pain (1), and hepatomegaly (1)	Leukocytosis (1), thrombocytopenia (1), anemia (1), transaminitis (1), and hyperbilirubinemia (1)

endemic diseases, and travelers may be exposed to pathogens not commonly encountered in their home country.⁸ The incubation periods for different infectious diseases vary. Some may manifest shortly after exposure, while others have a longer incubation period, complicating the identification of the source. Travelers often visit multiple locations during a single trip, increasing the potential for exposure to different pathogens. Additionally, they may engage in various activities, such as hiking, swimming, or consuming local foods, each carrying its own set of risks. Diseases transmitted by vectors (e.g., mosquitoes and ticks) can be prevalent in certain regions. Identifying these diseases requires knowledge of local vector populations and their associated pathogens.⁹ The traveler's vaccination history plays a role in narrowing down potential causes. Some illnesses can be prevented with vaccines, and the absence of immunization against specific diseases may increase the likelihood of infection. Travelers may encounter outbreaks of infectious diseases in the regions they visit. Staying informed about current health alerts and outbreaks is crucial for accurate diagnosis. Some infections are rare or emerging, and healthcare providers may not initially consider them, leading to delayed diagnosis. To overcome these challenges, healthcare professionals should consider a thorough travel history, including the specific locations visited, activities undertaken, and potential exposures. Laboratory tests, imaging studies, and consultation with infectious disease specialists may be necessary for a comprehensive evaluation. Rapid diagnostic tests and molecular diagnostics have also improved the ability to quickly identify the causative agents of febrile illnesses. Preventive measures, such as pretravel vaccinations, adherence to food and water safety practices, and proper use of insect repellents, can reduce the risk of travel-associated febrile illnesses. Travelers need to seek medical attention promptly if they experience fever or other concerning symptoms during or after their trip.

The present study probed into the characteristics and etiology of fever in returned travelers. Similar to our study, malaria has consistently been identified as a common cause of febrile illness in returned travelers, especially in individuals visiting tropical and subtropical regions.^{10,11} Studies often highlight the diversity of pathogens causing febrile illnesses in returned travelers. Apart from malaria, etiologies such as dengue, typhoid, rickettsial diseases, and gastrointestinal infections are commonly reported.

A European multicentric study with 765 cases, reported traveler's diarrhea and respiratory tract infections to be the etiology in 40.5% of the cases.¹² The rest of the cases, where a clear-cut diagnosis was not possible from history, are called acute undifferentiated febrile

illness (AUI). On evaluation of AUI cases, they reported malaria and arboviral infections to be the commonest cause of fever, with malaria constituting 21.1% of cases. among the arboviruses, dengue was the most common virus detected. Together, malaria and dengue contributed to the etiology of fever in 40% of cases. they reported falciparum malaria to be the most common type of malaria accounting for fever (85 out of 96 cases of malaria were falciparum). Bacterial infections ranked third regarding the etiology of AUI in their study, following malaria and viral infections. Rickettsial infections, leptospirosis, and enteric fever were the predominant bacterial etiologies. Helminthic infections, fungal infections, and mycobacterial infections were also found as etiology in a few cases in their study. Their study also noted noninfectious causes of fever in 15 cases. regarding the noninfectious causes, autoimmune and rheumatological diseases constituted 10 cases, and drug-induced fever was noted in 2 cases. The study also reported a heterogenous temporal distribution of cases along the year, with peaks in August and September. The country or region of visit was an important clue regarding etiology. They also found some clinical features and laboratory parameters to have a predictive role in determining the likely etiology of cases. A study by Imogen Buss et al.² analyzed data from 30 studies that reported malaria to be the commonest cause of febrile illness in returning travelers—accounting for 22% of cases. Dengue and enteric fever accounted for 5 and 2% of cases, respectively. Nontropical infections contributed to 36% of cases, with acute gastroenteritis and respiratory tract infections contributing to 14 and 13% of cases, respectively.

The age distribution and demographics of returned travelers with febrile illnesses can vary, but younger adults and males often comprise a significant portion. The age group most affected may depend on the study and the destinations included.¹³ This has been consistent with our findings too, where we have observed the presentation being in majority for the age cohort of 19–50 years. Comorbidities, particularly chronic diseases such as diabetes mellitus and hypertension, are frequently reported in returned travelers. These conditions can influence the severity and nature of the febrile illness, and the same has been reported in our study. The duration of symptoms and fever can vary widely based on the causative agent. Some infections may present with acute, short-term symptoms, while others may result in prolonged or relapsing febrile episodes.

Another study on travel-associated febrile illnesses based on a literature search of articles from 2001 to 2022, reported diarrhea, fever, and skin changes to be the commonest clinical manifestations

in returning travelers.⁵ Falciparum malaria was reported to be the most common cause of fever, accounting for 50 cases per 1,000 travelers. Dengue fever was noted to be the most common infective etiology for fever in travelers returning from Southeast Asia. Among respiratory viruses, influenza and COVID-19 were the most important on the list. The authors opined that the incubation period is an important hint towards etiology if it can be elicited properly. Symptom-based categorization of the diseases into syndromes helps in better evaluation and also helps in guiding empirical therapy before definite etiology can be ascertained. These syndromes include fever with rash, fever with jaundice, fever with headache/neurological signs, fever with respiratory symptoms, etc. Exposure history is also very important. Insect bite history, unprotected sexual intercourse, visits to caves, and details about food consumption are also important diagnostic clues.

Patterns of travel, such as intercountry and interstate travel, can differ based on the region and transportation infrastructure.¹⁴ Studies often emphasize the importance of obtaining a detailed travel history for accurate diagnosis. Studies consistently emphasize the importance of pretravel advice, including vaccinations, malaria prophylaxis, and awareness of local health risks. Adherence to preventive measures can significantly reduce the risk of febrile illnesses in returned travelers. Advice for travelers at a travel clinic outpatient setting or any primary care setting must include a few key elements in a pretravel consultation. These include a trip risk assessment based on a detailed review of the itinerary and the traveler's medical profile; immunizations; prevention of arthropod-borne infections, including malaria chemoprophylaxis (when indicated); food and water precautions and travelers' diarrhea management; and prevention of injuries and other conditions associated with travel. A detailed itinerary which should include cities and areas in a country to be visited, activities, and types of accommodations, is critical for the assessment of the risks of the trip and determination of the indications for specific vaccinations, malaria prophylaxis, and other preventive measures. Duration of the trip, list of countries visited, and transit stops are essential considerations, especially to assess immunization requirements there are various groups of travelers, each group with its specific risks and challenges. These groups include travelers visiting friends and relatives (VFR), budget travelers, last-minute travelers, long-term travelers, healthcare workers on medical missions, and medical tourists.¹⁵

Our study has its limitations in being a small sample study. The duration of the study being short, could not delve more into the seasonal variation and further comment on the same. Future studies should try to overcome these limitations.

CONCLUSION

It is important on the part of clinicians, especially, tropical medicine specialists to formulate pretravel consultation guidance and

immunization strategies. Prompt evaluation and management of febrile illness among returned travelers is warranted.

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