Original Article

Acute Febrile Illness: A Systematic Review Of Infectious Aetiologies Among Patients

Kaushalendra Kumar[1*], Ranjana Patnaik[2], Hema Kumari[3], Neha Sharma[4]

[1*,2,3,4]Clinical Research Division, Dept. of Bio-Sciences, School of Basic and Applied Sciences, Galgotias University, Noida,

***Corresponding author:-** Kaushalendra Kumar

[1*]Clinical Research Division, Dept. of Bio-Sciences, School of Basic and Applied Sciences, Galgotias University, Noida, IN Email id: kaushalendra.kumar@galgotiasuniversity.edu.in
DOI: 10.47750/pnr.2022.13.S08.667

Abstract

Acute febrile fever, a key rationale for hospitalization, and the infections that accompany it cause significant morbidity and death in children globally, as well as in athletes during training and competitive seasons. Infections of the central nervous system are a rare cause of AFE (Acute febrile encephalopathy) in the elderly. Scrub typhus meningoencephalitis is rare and frequently overlooked in the elderly. Human febrile disease agents can differ by region and nation, implying that diagnosis, treatment, and control programs must rely on a methodological review of area-specific aetiologies. Malaria transmission is declining in many parts of the world, and the use of rapid tests for malaria has made people more aware of arboviruses, rickettsioses, leptospirosis, and respiratory viruses as possible causes of fevers. Arboviruses are the world's most prevalent cause of human febrile sickness. In recent decades these are among the important pathogens discovered, causing significant outbreaks of human disease. Rickettsial infections, which are newly developing vector-borne re-emerging febrile illnesses in which humans are accidental dead hosts, are a prominent source of non-malarial febrile sickness. Over the last decade, there has been an increase in public awareness of non-malarial febrile diseases. The high temperature of the body is associated with an increase in metabolic demands, dehydration or dryness, and temperature dysregulation. We conducted a thorough literature analysis and summarised the current epidemiology, illuminating various variables that contribute to the development of this disease across the world.

Keywords:- Acute febrile illness, Epidemiology, Hospitalization, Febrile encephalopathy

INTRODUCTION

Acute undifferentiated fever (AUFI) or acute febrile illness (AFI) is a disorder characterized by a high fever that resolves on its own within three weeks or, in rare situations, lasts for a maximum of two weeks. It is a common reason for hospitalization and is treated as such (Alluisi et al., 1980). The various signs and symptoms of acute febrile illness which include fever, loss of consciousness, and many more are represented in figure 1.

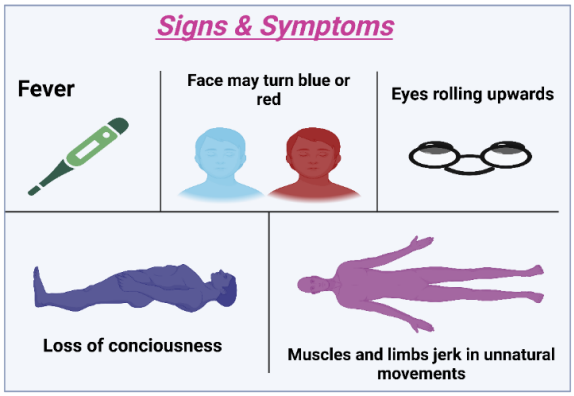

Figure 1. Representation of signs and symptoms for acute febrile illness

A fever is a natural physiologic response to an immunological stimulation or illness that aids in the host's survival and shortens the duration of the condition (Atkinson et al., 1993). Febrile reactions are linked to infectious organisms, blood products, tissue damage, and maybe other factors. The magnitude of the febrile reaction is determined by the concentration of antipyretic chemicals produced naturally by the body itself as well as circulating prostaglandins and cytokines. The definition of normal body temperature varies according to the source (Belda et al., 2007). Physiological changes like changes in body temperature depend on the measuring site and endogenous variables such as biological rhythms, age, fitness, and other related activities (Biddle, 2006). As shown in table 1, clinically acceptable temperatures for various body areas including forehead temperature (38.0°C), rectal temperature (38.0°C), axillary temperature (37.2°C), and

mouth temperature (37.8°C). Researchers found that biological rhythms in inactive and sedentary people had greater daily amplitude and frequency of oral temperatures than those in physically active people (Pinto et al., 2022).

Table 1. Ranges of normal body temperature

	Rectal	**Oral**	**Axillary**	**Tympanic**
°C				
Women	37.0 (36.8-37.1)	36.2 (33.2-38.1)	-	37.0 (36.8-37.1)
Men	37.0 (36.7-37.5)	36.7 (35.7-37.7)	36.3 (35.5-37.0)	36.5 (35.5-37.5)
°F				
Women	98.6 (98.2-98.8)	97.2 (91.7-100.6)	-	97.9 (96.3-99.5)
Men	98.6 (98.1-99.5)	98.0 (96.3-99.9)	97.3 (95.9-98.6)	97.7 (95.9-99.5)

Several infections, including scrub typhus, leptospirosis, malaria, and dengue, cause a sudden onset of chills and high fever with a mild to severe headache (Ogoina, 2011). Even though febrile illness as a disease condition is still under-recognized by health organizations, especially WHO. However, it can cause significant morbidity and death among children all over the world. According to studies conducted among those who were admitted, the case fatality rates for people with febrile illnesses who required hospitalization varied from 5 percent to 24 percent (Virhia, 2022).

Table 2 Description of variables

Variable	**Description of variable**
Study season	Summer/winter/Rainy
study country	country of origin of the patients.
Population Status	Inpatients, outpatients, or both
Sample tested	Sputum, CSF, urine, nasopharyngeal aspirates/swabs
Dimensions of the sample	The total number of samples: HIV-positive individuals are eliminated wherever feasible.
Diagnostic test	Detection of diagnostic tests (indirect, direct, combination)
Duration of fever	Depending upon the case

Dengue fever is the most common arboviral infection in humans that has been clinically recognized. Pathogenic spirochaetes are the most common causative agents belonging to the genus Leptospira. The transfer of causative spirochaetes to humans can be via both direct and indirect means i.e., the direct contact of humans with any animal infected or indirectly through exposure to freshwater with urine from an infected animal. Leptospirosis, A word-wide distributed zoonotic disease that affects both animals and humans (Grundy and Houpt, 2022; Wainaina et al., 2022; Zhang et al., 2014).

One of the main causes of acute fever in the western Pacific region is scrub typhus. This is caused by the parasite called Orientia tsutsugamushi and can be spread to humans by the bite of larval mites or chiggers (Brown et al., 1984).

It is possible to contract murine typhus, which has a widespread distribution across the world if flea faeces contaminated with Rickettsia typhi infects the disturbed skin or is breathed into by a human. Q fever is a zoonotic disease caused by the obligate intracellular bacteria Coxiella burnetii, which was formerly classified as a member of the genus Rickettsia (Faine, 1999; Fournier et al., 2004). If a person has been exposed to these things, how they look and how they act are usually used to make a diagnosis of these disorders. Most of the time, these disorders are found by looking at a person's medical history, which includes information about their symptoms, exposure to certain things, and the results of blood tests (Istúriz et al., 2000).

Rickettsial infection: A common cause of acute febrile illness

Rickettsial infections, triggered by obligatory intracellular gram (-) coccobacilli that proliferate within the cells (eukaryotic), are newly developing or re-emerging fever diseases in which humans are unwitting hosts (Kim et al., 2004). Rickettsiae are classified into three subgenera: Scrub typhus, typhus group, and spotted fever group (SFG). All rickettsioses are zoonoses, which means they are present in infected arthropods which act as natural carriers and can transfer the illness precipitously to its offspring (La Scola and Raoult, 1997). Arthropods (lice, ticks, fleas, mites, etc.) can spread these illnesses to wild or domesticated animals such as cattle, dogs, and many more. Even though rickettsial infections have the same symptoms, the pathogenic species and the severity of their illness can be different in different parts of the world (Leelarasamee et al., 2004; Parola et al., 2003; PicKard et al., 2004; Raoult and Marrie, 1995). SFG now possesses roughly 15 pathogenic rickettsioses, including rickettsia pox, Rocky Mountain spotted fever (RMSF), and Boutonneuse fever caused by strains such as Rickettsia akari, Rickettsia, and many more. Thus, it is critical to recognize both normal and atypical rickettsial infection presentations immediately to provide immediate diagnosis and treatment in each location, which can result in severe morbidity and death. Rickettsial infections are a big source of fever for people who have been to areas where they are common (Robinson et al., 1976).

Display, analysis, & Diagnosis

Rickettsial infection is frequently associated with an acute febrile sickness characterized by headaches, body aches, and joint pains like those associated with a variety of other tropical infections. At the end of the first period of SFG rickettsioses

infection, a distinct erythematous rash affecting mostly the palms, trunk, soles, and limbs but sparing the face is frequently seen. Scrub typhus and several SFG rickettsioses, such as African tick bite fever, may present with a distinctive entrance lesion or eschar (Sankasuwan et al., 1969; Silpapojakul et al., 1987, 1993; Sirisanthana et al., 1994). Acute sensorineural hearing impairments have been associated with Scrub typhus such as tinnitus or deafness, assisting in the identification of the condition. Additionally, they may have localized or widespread non-tender or slightly painful lymphadenopathy, as well as different degrees of hepatosplenomegaly (Suputtamongkol et al., 2003). Although most patients recover without therapy, it is well established that delayed diagnosis results in significant multi-organ involvement, septicaemia, and mortality. Pneumonitis, acute respiratory distress syndrome (ARDS), myocarditis, meningoencephalitis, and acute kidney damage are all characteristics of severe disease. Cranial nerve palsy and transverse myelitis are the vasculitis symptoms that may develop in patients with undetected chronic diseases (Walker, 1996).

Among the South Asian regions, Purpura fulminans caused by Rickettsiae conorii which remain undiagnosed can cause purpuric lesions that may develop peripheral gangrene, necrosis of the skin, and consumptive coagulopathy which is frequently fatal.

In endemic areas, every suspected patient should be evaluated for acute febrile illness, particularly if they present with a distinctive skin rash. Eschars, on the other hand, are typically seen in soggy parts of the body (such as behind the breast, or the groins), along the garment straplines, or in the skin folds (Parola et al., 2005). Due to the link with ticks and other vectors, rickettsia infections are more prevalent during the warmer months and among those who engage in outdoor activities.

A recent visit of the people and their activities during the visit such as intimate contact with wild or domestic animals, sleeping on scrubland, signs of tick bites, and ecotourism all assist in the identification of the suspected cases among the people residing in the non-endemic area as they visit an endemic area (Aung et al., 2014; Ericsson et al., 2004; Tsay and Chang, 1998; Walker, 2007). In temperate climates, warmer summer months have been associated with an increase in the prevalence of rickettsial sickness. It's been linked to tick migration from neighbouring endemic areas throughout the summer season, their aggressive behaviour, and frequent connection with humans while participating in various outdoor activities. Thus, even in temperate countries, particularly during the summer months, rickettsial infections should be included in the differential diagnosis of acute febrile sickness. Careful documentation of unusual clinical presentations and efforts to identify causative organisms and their treatment responsiveness aid should be recorded properly (Katoch et al., 2016; Luke et al., 2017; Paris et al., 2013; Premaratna et al., 2006).

Investigations & Treatment

Basic laboratory studies, which include peripheral white blood cell counts, usually fail to separate rickettsial infections from some of the other prevalent febrile illnesses. Thrombocytopenia is a common occurrence (Kim et al., 2007). The patient may experience hyponatremia, pleocytosis of the CSF fluid, a slight to moderate increase in markers of inflammation, and abnormalities in the liver (AST/ALT) or kidney (serum creatinine) biochemistry. Individuals with severe illness, on the other hand, should be expected to have large discrepancies from normal haematological or chemical indicators (Putli Bai, 2015). Most infections are confirmed serologically, with immunofluorescence or ELISA-based methods used to detect increasing IgG and IgM titters in conjunction with a high index of clinical suspicion to confirm the infection. However, early in the course of the illness, serological tests may come out negative. Based on the high rate of morbidity and mortality associated with rickettsial infections, the use of anti-rickettsial drugs such as doxycycline is recommended early in the course of the infection based only on clinical suspicion (Graves et al., 2006; Raoult and Drancourt, 1991; Tantibhedhyangkul et al., 2010; Watt et al., 1996). When confirmatory tests are not available, rapid clinical response to anti-rickettsial drugs such as doxycycline might be used to make a presumptive diagnosis if the patient is sick. In a biosafety level III facility, people who deal with rickettsia bacteria can grow the bacteria in cell culture to further their research. They can also look at buffy coat samples or skin samples from people who have had eschars or vasculitis lesions using molecular diagnostic techniques such as PCR, to see if they have the disease (Kim et al., 2004; Purvis, 2000; Watt et al., 2000).

The treatment regime includes antibiotics such as tetracycline, doxycycline, and azithromycin. These antibiotics are found effective against the majority of rickettsial illnesses (Olson et al., 1980). All SFG infections should be treated with doxycycline (100 mg twice a day for 5–7 days) to eliminate the infection. The majority of other rickettsial illnesses respond to a treatment regimen that is comparable to this one. In certain circles, it has been asserted that the O tsutsugamushi Kato strain possesses an inherent resistance to quinolones (Archibald et al., 1998; Bell et al., 2001; Liu et al., 2012; Twartz et al., 1982).

In northern Thailand, it has been noted that doxycycline and chloramphenicol sensitivity has decreased. Rifampicin (300–450 mg twice a day) is better than doxycycline in terms of time to defervescence and recurrence rates in scrub typhus in these individuals when administered for one week. In areas where tetracyclines are less effective than azithromycin (500 mg), a single dosage of azithromycin (500 mg) may be as effective as seven days of doxycycline treatment (Aregawi et al., 2011; Bouyou-Akotet et al., 2009; D'Acremont et al., 2010; Karema et al., 2012; Mharakurwa et al., 2013).
When treating rickettsial infections with a high mortality rate, such as Rocky Mountain spotted fever, or when confirmation facilities are not accessible, empiric therapy based only on clinical suspicion is recommended, according to

the World Health Organization (Otten et al., 2009). For a long time, chloramphenicol was prescribed to patients suffering from rickettsial infections. However, because of the severe negative consequences, its use is restricted (Chipwaza et al., 2014).

Fluoroquinolones have been linked to bad side effects, so they are not recommended for treating rickettsial sickness (Biggs et al., 2016; Walker, 1995; Wormser et al., 2006). Although doxycycline is not regularly used in children under the age of 8, recent studies have found no evidence of damage associated with short courses. Azithromycin is suggested during pregnancy for the treatment of rickettsial disease (Lee et al., 2017; McGready et al., 2014).

Preventative medicine and patient education

The education of the public on rickettsial sickness and its route of exposure helps to produce a reduction in the occurrence of the disease. Tick, lice, mite, and flea bites should be avoided at all costs, especially when living in or traveling to endemic areas, according to the Centres for Disease Control (Colvin et al., 2012; Hsiao et al., 2006; Punjabi et al., 2012; Rudinsky et al., 2009; Watt et al., 2010). It is possible to reduce the risk of rickettsial infection by applying insect repellent, wearing long-sleeve shirts, permethrin-impregnated clothes, inspecting for insects after outdoor activities, and using trousers, socks, and closed-toe shoes, all of which are beneficial. Due to the lack of an effective immunization, the majority of rickettsial infections, including Rocky Mountain spotted fever, are now untreatable. Doxycycline (200 mg) is effective at preventing scrub typhus, but no study has been done to see if this medication can also protect against other rickettsioses (Abba et al., 2014; Kurokawa et al., 2013; Mueller et al., 2014; O'Shea et al., 2015; Thriemer et al., 2013).
Delays in detecting and treating a disease can have a wide range of negative effects on various parts of the body, including the brain.

An analysis of a specific case

According to the findings of a study, acute undifferentiated febrile sickness was studied in three north-eastern hospitals, five Thai hospitals (including one in the south), and many other locations in the nation (Akachi and Atun, 2011; Leslie et al., 2014; Masanja et al., 2012; Odaga et al., 2014). Those patients who were hospitalized between 2001 and 2002 and who satisfied the WHO requirements for having a fever of fewer than 15 days duration were included in the research. According to the procedure, which was authorized by the Thai Ministry of Public Health's ethical review committee, written informed permission was acquired from each patient who was subjected to the investigation (Sievers et al., 2008). Five millilitres of blood were drawn from the patients, and a variety of tests were done, including platelet count, blood cell count, plasma concentrations of glucose and electrolytes, serum concentration of urine analysis, chest radiography, liver function test, and many others (Bouyou-Akotet et al., 2012; Joshi et al., 2008; Kibuuka et al., 2015; Mwanziva et al., 2008). It was estimated that around 68.3 percent of the 845 patients who were admitted to the hospital and who were between the ages of 35 and 40 years old seemed to have their acute fever reasons effectively recognized. In 31.7 percent of the population, the reason for the lack of a diagnosis was still unknown. Figure 2 depicts the study's main findings, which are summarised in the text (Amexo et al., 2004; Folster et al., 2012; Mengo et al., 2010; Wain et al., 1999).

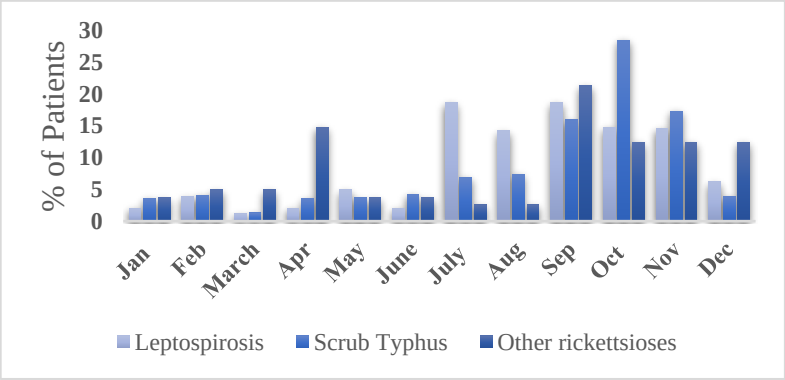

Figure 2. Seasonal changes in the percentage of study patients

The Prevalence of Febrile illness among different Age-Groups

Acute Febrile Illness in Children

In 2010, worldwide estimates of child deaths revealed that about two-thirds of fatalities in children under the age of five were caused by infectious diseases, with malaria being one of the top three causes (Miriagou et al., 2004).

In low-and middle-income countries (LMICs), when scarce resources limit diagnostic capability, clinical care is seldom aided by knowledge of the prevalent local and regional causative infections. As a result, acute febrile sickness is frequently misdiagnosed as malaria, particularly in Sub-Saharan Africa (Miriagou et al., 2004). However, with the development of quick malaria diagnoses and the adoption of malaria-control policies in various countries, the number of identified malaria cases has decreased significantly. As a result, overdiagnosis and overtreatment of malaria in febrile illnesses have become widely recognized, necessitating a better knowledge of nonmalarial causes of acute fever illness (Bate et al., 2008).

The effectiveness of malaria control efforts in LMICs in lowering malaria transmission has made acute febrile sickness in children a research priority, although it has yet to be recognized as a disease condition. Accurate diagnosis and treatment are hindered by the absence of distinguishing clinical features and problems in getting them. A lack of diagnostic capabilities in many low- and middle-income countries (LMICs) is hampering our ability to create efficient clinical algorithms and make educated therapeutic judgments since many of the new research causes remain a mystery (Bhengsri et al., 2011; Chen et al., 2010; Siddiqui et al., 2006). There are still many diagnostic challenges, such as the inability to get convalescent and acute serologies from the same patient, or the difficulty in interpreting results, such as when molecular diagnostics detect infections in asymptomatic controls. Viruses are a common cause of acute febrile illness, but even in low-and middle-income countries (LMICs), the prevalence of viral aetiology is still under-documented (Anderson et al., 2007). Malaria treatments are frequently misapplied because there is no evidence that they work, and empiric antibiotics are frequently overused because there is no evidence that they work (administered to up to 60% of patients without a malaria admission diagnosis). Acute febrile illness in children has come a long way in recent years, but more diagnostic tools are still needed for better surveillance in low-and middle-income countries (LMICs) and faster and more thorough aetiological investigations (Chong et al., 1997). Acute febrile diseases, like pneumonia and diarrhoea, need large, rigorous, multicentre aetiology investigations. Antimalarial and antibacterial treatment can be used more effectively if we know more about the causes of acute febrile disease. Antimicrobial resistance can also be tracked (Senn et al., 2011).

Fever-induced encephalopathy in the elderly

The prevalence data on morbidity and mortality of scrub typhus in India remains unknown. O. Tsutsugamushi is the bacteria that causes the illness, which is marked by fever, an open sore, swelling of lymph nodes, and multiple organ failure (Viswanathan et al., 2013). Doxycycline is often effective in treating it. In India, the first instances were documented in 1934 in Himachal Pradesh. The trombiculid mite's larvae transmit the sickness to humans. Although rodents are the natural hosts, people become infected accidentally because of chigger bites. The infection might spread via hematogenous or lymphatic channels (Jamil et al., 2015). By the third-fourth day following the bite, chills and fever have developed, and a rash and lymphadenopathy have developed by the end of the first week. The incubation period is between six and twenty days. Serious complications such as pneumonia, hepatitis, acute kidney damage (AKI), acute respiratory distress syndrome (ARDS), and meningitis developed during the second week of sickness. Acute febrile encephalopathy (AFE) is characterized by the presence of fever with a change in a mental state shown by confusion, behavioural abnormalities, disorientation, or other cognitive deficits. Sepsis-associated encephalopathy caused by noncentral nervous system (CNS) infections is the most prevalent cause of AFE in the elderly (age > 65 years). Streptococcus pneumonia, Mycobacterium tuberculosis, Brucella species, herpes virus, Staphylococcus aureus, Pseudomonas species, and Acinetobacter species are the most prevalent pathogens linked with CNS infection in AFE in the elderly. Scrub typhus is an uncommon cause of AFE in the elderly (Oaks et al., 1983).

Report on a Case

A 70-year-old man farmer with a prior medical history of ischemic posterior circulation stroke in 2013 and full recovery appeared with intermittent fever, chills, and rigors, as well as a five-day maculopapular rash across the trunk as represented in figure 3. Additionally, he experienced a three-day altered sensory state with no headache, vomiting, seizures, or localized neurological impairments (Oaks et al., 1983; Tsay, 2002). On physical examination, fever, tachycardia, disproportionate tachypnoea, maculopapular rash on the trunk and all four limbs, and an eschar on the right thigh were all observed. He lacked indications of meningitis. He presented with hypoactive delirium, fine bilateral crackles, and hypoxemic respiratory failure, all of which indicated atypical pneumonia. Anaemia, thrombocytopenia, and azotaemia were discovered during the initial laboratory assessment. The cerebrospinal fluid (CSF) indicated lymphocytic pleocytosis, increased protein levels with normal glucose, and adenosine deaminase activity (ADA). Additionally, he had cerebral magnetic resonance imaging due to AFE (Sheybani et al., 2016). He was tested for all probable tropical illnesses, but the Weil–Felix test resulted in a positive result. He was diagnosed with scrub typhus with meningoencephalitis, AKI, and perhaps atypical pneumonia and treated with intravenous doxycycline 100 mg twice daily and oral rifampicin 600 mg once a day for seven days, in addition to supportive treatment. After two days, the fever and altered sensorium subsided, and he was discharged in stable condition (Cagatay et al., 2010; Pai et al., 1997).

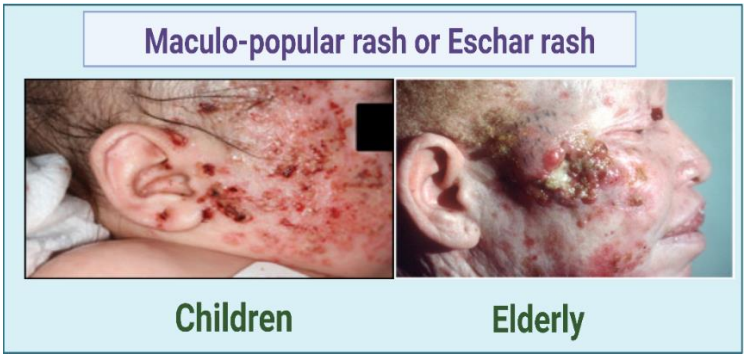

Figure 3. Maculo-popular rash or Eschar rash in children and elderly

DISCUSSION

The aging immune system's capacity declines with age, increasing the aged person's vulnerability to infection. Confusion, the primary symptom of encephalopathy, occurs in up to 50% of elderly hospitalized patients (Iqbal et al., 2015; Kim et al., 2006). When disorientation is accompanied by fever, the immediate thought is of CNS infection. However, only 7.4 percent of individuals with AFE have CNS infection. Scrub typhus meningoencephalitis is a rare cause of AFE in the elderly and is notoriously difficult to identify due to the poor sensitivity of clinical symptoms such as fever and neck stiffness (Varghese et al., 2013). Our patient appeared with a fever and altered mental status in the absence of neck rigidity; nonetheless, because of the presence of eschar and strong clinical suspicion, he received an early diagnostic lumbar puncture, which aided in establishing the diagnosis (Chappuis et al., 2013). Typhus is derived from the Greek term "Typos," which means "fever with stupor" or "smoke," and refers to people with severe rickettsioses who have a clouded sensorium. Peripheral neuropathy, Guillain–Barre syndrome, acute transverse myelitis, cerebral microbleeds, infarcts related to secondary CNS vasculitis, meningoencephalitis, and cerebellitis are all examples of CNS symptoms. Scrub meningoencephalitis presents clinically similarly to viral or tuberculous meningitis (Recht et al., 2017). Following a period of fever, encephalopathy develops over a varied length of time. Neck stiffness is not prevalent, and eschar, the pathognomonic characteristic of scrub typhus, was rarely observed in several scrub meningoencephalitis investigations. Patients might come as early as three days after developing a fever or as late as two weeks (Cifuentes et al., 2013; Brett M Forshey et al., 2010; Vitor-Silva et al., 2016). There is no predominance of one sexual orientation over another. Our patient was a 65-year-old man, a farmer who appeared with a 5-day fever and encephalopathy. He did not have neck stiffness, but he did have an eschar. CSF analysis is typically mostly lymphocytic, with normal protein, glucose, and ADA levels (Kumar et al., 2016; Limper et al., 2012; Reller, de Silva, et al., 2016; San Martín et al., 2010). The cerebrospinal fluid polymerase chain reaction is a confirmatory diagnostic for scrub meningoencephalitis. However, because serum scrub IgM (immunoglobulin Mu) ELISA is easily available, it can be used to confirm scrub typhus in the presence of clinical characteristics consistent with meningoencephalitis, particularly in resource-limited situations (Reller, Chikeka, et al., 2016). The CSF picture was consistent with earlier investigations, and the final diagnosis was determined based on clinical symptoms and serology, as recommended in resource-limited settings (Gubler, 1996; Mackenzie et al., 2004; WHO, 2015). Oral or injectable doxycycline 100 mg twice daily for 1–2 weeks is the preferred therapy. Azithromycin is the medication of choice for pregnant women. In the event of an insufficient response to doxycycline, chloramphenicol or rifampicin may be employed. To avoid the development of resistance, rifampicin should be administered in conjunction with azithromycin or doxycycline. Rifampicin is not generally advised in locations with a high prevalence of tuberculosis (Manock et al., 2009; Phuong et al., 2006; Weaver et al., 2004; Weaver and Barrett, 2004; Yuill, 1986).

FINDINGS

CNS infection is a rare cause of AFE in the elderly. A thorough clinical examination, on the other hand, can aid in establishing an accurate diagnosis. Doctors must be on the lookout for scrub typhus, even in places where it is common. This is especially true for the elderly who arrive with AFE (Bruce et al., 2005; Watts, Hayes, et al., 1997; Watts, Oberste, et al., 1997).

Instances of febrile sickness in various locations

Latin America

Malaria has historically been the most common cause of fever in tropical areas of the Amazon basin, but significant progress toward malaria control over the last decade has resulted in a decreased incidence and a higher proportion of patients with acute febrile illness (AFI) who don't even display malaria (Aguilar et al., 2004). This dramatic shift away from malarial to nonmalarial febrile disease has posed difficulty in determining the causes of nonmalarial febrile illness as well as identifying prevention strategies and appropriate diagnostic techniques. An arthropod-borne virus was identified as a major aetiological agent of human febrile sickness in the following scenario: Fever and inadequate sanitation lead to the expansion of transmitting mosquitoes, increasing dengue virus infections. Further research established the Zika virus and chikungunya as other causes of febrile sickness (Caceda and Kochel, 2007).

In Latin America, the causes of acute febrile illness (AFI) are varied, and their complexity grows as the proportion of fevers caused by malaria declines, malaria control strategies are implemented, and novel pathogens arise in the region (Aguilar et al., 2009). It is critical to shedding light on the gaps in the epidemiological characteristics and geographic spread of numerous AFI aetiologies in this setting (Ansari et al., 1993). In a study on the aetiology of community-acquired fevers other than malaria in Latin America, and to identify knowledge gaps and research needs, they identified 17 papers that met the inclusion criteria, describing 13539 patients (Innis et al., 1989). The median number of pathogens examined per participant ranged from one to sixteen. For 50% of people, a causal pathogen could be identified (Montoya et al., 2003; Powers et al., 2006; R Development Core Team, 2011). Dengue virus was the most frequently reported pathogen over the research periods, with roughly 15 investigations. The Chikungunya virus was followed by the Zika virus in 10 investigations. In studies reporting concurrent infections, 2.4 percent of participants were found to have co-infections. Hospital mortality was observed in 49% of trials, ranging from 0% to 20%. Dengue fever is the most frequently reported febrile disease, indicating its relevance, whereas Zika and chikungunya viruses have shown growing trends since their regional introduction (Cabezas S, 2005). Systematic and standardized techniques for the detection of various pathogens are required since they will almost certainly uncover an increased burden of neglected diseases such as Rickettsia spp. and arenaviruses. The absence of point-of-care testing and a standardized strategy constrains health professionals' ability to give care and the efficacy of surveillance for AFI in the region (Forshey et al., 2009).

Western South America

It is imperative that we better understand arbovirus transmission patterns to reduce the impact on human health in endemic regions as well as the potential for further spread. In terms of epidemiological features and geographic distribution of South America, several indigenous arboviruses are poorly characterized. As stated in the study report (Brett M Forshey et al., 2010), the researchers conducted a laboratory-supported, clinic-based investigation in Peru, Ecuador, Bolivia, and Paraguay to identify the causative agents linked with nonspecific febrile illness as a first step toward bridging this knowledge gap. These researchers described the geographic distribution of multiple arboviruses in these research locations and the relative contributions of these arboviruses to human febrile illness. The researchers in Peru also looked at the time and epidemiological patterns of arbovirus infections, as well as the variables that are linked to arbovirus infections.

Patients with acute (undifferentiated) febrile illness who were hospitalized in outpatient hospitals and were 5 years of age or older were included in this study. Other symptoms include headaches, joint discomfort, sore throats, coughing, vomiting, and stiff necks, among others. Children under the age of five were included if they showed haemorrhagic signs of dengue haemorrhagic fever (DHF), which included epistaxis, pleural effusion, platelets less than 100,000/ml, petechiae, bloody stool, and vomit. Children beyond the age of five were excluded. A seven-day fever or a cause of infection that could be recognized, such as sinusitis, pneumonia, acute otitis media, or an acute urinary tract infection, were also considered exclusion criteria. Each patient's demographic information, medical history, and clinical features were collected using a standard questionnaire that was sent to all participants. Patients with fever in malaria-endemic regions were screened for Plasmodium spp. by clinic or hospital staff using conventional diagnostic procedures at each location if they were suspected of having malaria. Filtering peripheral blood samples was accomplished by microscopic analysis of stained, thick blood samples. Slides should be smeared with a marker. Patients who tested positive for malaria were afterward invited to participate in the NMRCD experiment in some locations owing to the danger of arbovirus co-infection. Malaria results were recorded alongside symptoms and demographic information in the NMRCD trial. During the acute period of illness, blood samples were obtained from each patient, and convalescent samples were collected 10 days to 4 weeks later for serological tests if this was possible. A total of 15 mL of blood was obtained from participants over the age of 10, with a maximum of 7 mL of blood collected from children under the age of 10. During the arm venepuncture, the skilled phlebotomists used standard procedures and safety rules to get blood samples from the patient.

FINDINGS

In the study, which took place between May 2000 and December 2007, a total of 20,880 people were recruited from research locations in Bolivia, Ecuador, Paraguay, and Peru, for a total of 20 years. Peru had 18,201 participants (87.3 percent). Bolivia had 2,090 participants (10.1 percent), Ecuador had 351 people (1.8 percent), and Paraguay had 241 participants (0.8 percent). Participants were recruited from 14 health clinics or hospitals in and around Iquitos, Peru, accounting for more than half the total (10,740; 51.5 percent) of those who took part. There were 10,921 men (53%) and 9,920 women (48.1%) of the people who gave demographic information. The participants' median age was 24 years (range: 0–92 years), with 90% ranging in age from 6 to 49 years. In addition to fever, 97 percent of the people who took the survey said they had malaise, a headache 92.5 percent, chills 90.3 percent, muscle pain 81.5 percent, and achy joints. Thirteen thousand eight hundred eighty-one febrile illness patients were investigated, and 13,260 (63.6 percent) had matched acute and convalescent-phase samples retrieved, whereas 7,622 (36.6 percent) had just acute-phase samples (no convalescent samples). According to the data, most patients (15,913/19,634; 81.1 percent) presented to a healthcare facility within four days of the onset of their ailment. The first-thick smear test was performed on a sample of participants (n = 9,801; 47 percent) before participation to determine whether they had malaria. 585 (6.1 percent) of these were found to be positive. In this study, patient samples were tested for recent infection with members of the Flaviviridae, Togaviridae, and Bunyaviridae viral families using the IFA and IgM ELISA methods (Ansari et al., 1993). It was discovered that 32.5 percent of febrile patients had arbovirus infection, with the rate ranging from 9.4 percent in Cusco to 40 percent in other locations (p 0.001). (Iquitos). 2,863 of 4,424 febrile episodes (13.8 percent) were verified by IFA or RT-PCR, but 1,562 IgM seroconversions (7.6 percent) were not validated by these procedures. A total of 413 people were sick because of fevers that were confirmed. This means that only 21.3 percent of the 4,424 fevers were confirmed. There were no arbovirus co-infections found by IFA. In the study, presumed arboviral infections were allocated to an additional 2,371 individuals (11.5 percent). In this study, the most successful virus isolation and RT-PCR detection occurred when participant specimens were collected during the first four days after illness onset. When data were available, 2,457 (15.5 percent) of the 15,912 people who got sick within four days of the start of the illness (where data was available) had an arbovirus that had IFA. Only 3.9 percent (144 out of 3,722) of those who reported symptoms five days or more after the beginning of the symptoms were found to have IFA.

Sri Lanka

According to the World Health Organization (WHO), dengue fever affects about 100 countries. There is strong evidence that dengue fever happens in 128 countries (Lanciotti et al., 1992).

Asia accounts for roughly 70.1 percent of the disease burden. According to the World Health Organization's Global Strategy for Dengue Prevention and Control, greater surveillance is necessary to accurately assess the dengue illness burden. Increased monitoring would assist in dengue reporting, prevention, and control, while incidence rates and clinical data would also help define clinical objectives for future vaccine effectiveness trials (Brett M. Forshey et al., 2010).

A two-year prospective cohort study was conducted in Sri Lanka to investigate the dengue fever incidence in Angoda, Colombo district (NCT02570152) (Tissera et al., 2022). The primary purpose of this study was to ascertain the prevalence of acute febrile illness (AFI) caused by laboratory-confirmed dengue (LCD). Secondary objectives include finding the incidence of AFI caused by non-LCD, describing AFI symptoms, and estimating the incidence of AFI caused by LCD by dengue virus type (DENV) and age group. Participants were recruited from families with at least one minor and one adult (51 years of age) and were monitored weekly on a planned basis and, in the event of AFI, on an unscheduled basis. At AFI visits, blood was obtained for DENV testing, and symptoms were documented for 7 days following the AFI start as shown in figure 4. There was a total of 2,116 individuals enrolled (972 children and 1,034 adults). There was a total of 56 LCD incidents observed (an overall incidence of 14.3 per 1,000 person-years). Children aged 5 years (21.4 per 1,000 person-years) and children aged 5–11 years (22.8 per 1,000 person-years) had the highest incidence, compared to adults aged 18 years (9.3 per 1,000 person-years). LCD was caused by DENV-2 (83.7 percent) in most cases (n = 6/47), followed by DENV-1 (n = 7) and DENV-3 (n = 6/7). LCD symptoms included headache, fatigue, myalgia, loss of appetite, and arthralgia. AFI caused by non-LCD occurred at a rate of 47.3 per 1,000 person/year. Finally, the research study showed that the LCD incidence for a DENV-2-dominated epidemic is equal to the passively reported dengue incidence for 2017, which was one of the deadliest outbreaks in recent history.

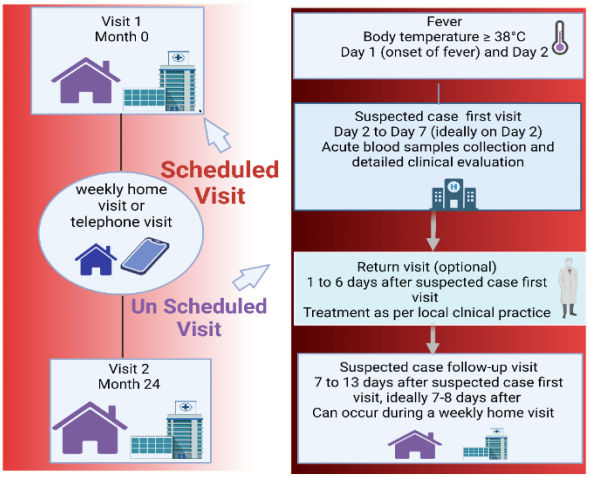

Figure 4. Scheduled and unscheduled visits to identify suspected case

Africa

The increasing prevalence of NMFIs necessitates a meta-analysis of the causal agents. To find aetiologic agents, the EMBASE, WOS, African Journals, and Scopus databases were examined.

Findings

A total of 134 trials involving 382,945 patients from 24 to 54 countries were conducted. A diverse array of causal agents as described, with a significant geographical variation. In total, dengue, salmonella, and klebsiella viruses were detected in the meta-analysis (Balmaseda et al., 2006; Chowell et al., 2008; Halstead, 2006, 2007; Kuno, 2003; PAHO, 2007). The amount of research included has expanded over time, particularly after 2010, to find the highest number of strains feasible. 88 percent of the research in data analysis is free of confounding variables. 52% of fever cases don't have a clear description of where the temperature was taken. This can make it hard to figure out the cause of the fever and how long it lasted (Makino et al., 1994).

The findings analysis report made a clear distinction between febrile and non-febrile instances to aid in diagnosis. This is the region-by-region representation of the African continent. Salmonella was the most frequently reported agent as the major cause of febrile illness in the eastern area. Other sections of the African continent, including the western, southern, and northern hemispheres, have seen a drop in the number of cases, showing Salmonella, orthopneumoviruses, and Rickettsia, respectively (Robertson, 1996). Alphaviruses and flaviviruses were the viral agents implicated. In conclusion, NMFIs is highly prevalent in African fever patients. Control of NMFIs has been hampered by the current COVID-19 pandemic because of the following reasons (I) the capacity of overburdened health systems (II) Restricted activity in healthcare systems (III) Frequent overlap between multiple clinical presentations (Bosch et al., 2007; Domingo and Niedrig, 2009; Turell et al., 2005).

Additionally, public health authorities' prioritization of COVID-19 may result in diagnostic and treatment delays for NMFIs, resulting in an increased illness burden. However, the integration of locally endemic NMFIs into the management of pandemic illnesses such as COVID-19 is a possibility (Morales et al., 2006). Harmonization of techniques is necessary to eliminate the enormous heterogeneity seen in existing fever research, particularly in case definition, study design (including sample size estimations to minimize selection bias), and diagnostic tool utilization. This could help improve summary estimates in future meta-analyses of NMFI aetiologic agents. It could also lead to more fever studies across the continent, which could reduce regional bias (Broom, 2007).

South-India

Scrub typhus (47.5 percent), spotted fever rickettsiosis (8.0 percent), leptospirosis (3.0 percent), dengue (7.0 percent), malaria (17.1 percent), and enteric fever (8.0 percent) were found in 47.5 percent of the 398 AFI patients (Zaidi et al., 2004).

Kidney failure, moderate to severe thrombocytopenia, Leukocyte counts, and splenomegaly with moderate to severe hyperbilirubinemia were all connected to malaria. Rashes, apparent blood loss, leukocyte counts that were normal or lower than normal, and thrombocytopenia that were moderate to severe were all indications of dengue fever (Joshi et al., 2008). Normal to low leukocyte levels and normal platelet levels were all linked to enteric fever. Accurate diagnosis and treatment guidelines for AFIs can only be developed if an extensive epidemiology database is in place (Kamarasu et al., 2007).

Treatment & Discussion

Per institutional review board permission, prospective observational research was conducted in a tertiary-care referral hospital (Vellore, South India) from January 2007 to January 2008 with institutional review board permission. A total of 160 patients aged 17 and above with a febrile illness lasting 6–22 days and needing hospitalization were included after informed consent was obtained after they had agreed to participate in the trial. Ineligible were those with weakened immune systems. Predetermined criteria were used to give diagnoses. Odds ratios were used to compare the clinical features of patients with a certain AFI to those in the control group (Lal et al., 2003).

We had 399 patients in all. There were 244 (60.3%) male participants in the study, with an average age of 40.7 (17.1). The most common states of residence for the patients (31.0 percent) were Tamil Nadu (66.4%) and Andhra Pradesh (66.5%). Almost three-quarters (74.5%) were unemployed, with the remainder working as laborers or farmers (39.8 percent). From July to October, AFI was most prevalent during the monsoon season and the subsequent months. 4.0 days before presentation, and 5.6 days after discharge from the hospital, were the average length of stay (Chandy et al., 2009; Kalayanarooj et al., 1997; Tsay, 2002). Mechanical ventilation, inotropes, and critical care were required by 19.3%, 16.0%, and 12.4% of patients, respectively. 47 people lost their lives (11.9 percent of the total).

The incidence of rickettsia fevers in the Indian subcontinent

As a result of an outbreak that occurred at the time of our study, limited awareness of the condition, and the therefore increased referral rate, we discovered a disproportionately large number of cases of scrub typhus (48.6%). Most malaria infections in South and Southeast Asia originate in India, particularly in the states of Orissa and Andhra Pradesh, which account for up to 80% of all cases (Anvikar et al., 2016). Dengue fever was found in 14.1% of AFIs in a rural population study in southern India (Bhaskaran et al., 2019; Chrispal et al., 2010) and 48% of AFIs in a hospital-based investigation in northern India's metropolitan areas (Shastri et al., 2020).

Interaction between the brain and spine

According to this study, aseptic meningitis affected 75.4 percent of patients, whereas convulsions affected 80 percent of patients. The most prevalent causes of altered sensorium, including coma, were scrub typhus (54.7 percent) and falciparum malaria (18.9 percent). Although cerebral malaria has been recorded in as many as 71% of complicated falciparum malaria cases, it was rather rare in that cohort.

Liver and kidney diseases

Most patients (71.2 percent) who were exposed to the liver sinusoidal epithelial cell-specific strain of Orentia tsutsugamushi experienced only minor increases in hepatic transaminase, alkaline phosphatase, or bilirubin levels (Horan et al., 2008). As a result of intravascular haemolysis, hepatocyte dysfunction, and bile stasis, malaria-induced hepatic injury causes moderate elevations in hepatic transaminases as well as severe mixed hyperbilirubinemia (CDC, 2001).

Febrile Illness in Athletes

Regular physical activity alters a wide range of physiological processes, including those that affect the immune system. Despite the paucity of research, it appears that excessive or severe exercise weakens the immune system, increasing the risk of infection. Mild-moderate exercise, on the other hand, can assist the body in fighting infection, relieving symptoms, and lowering the risk of developing chronic illness. The connection between physical activity and infection risk is sometimes portrayed as a J-shaped curve (Dick and Diehl, 2014). Moderate exercise boosts immunity above that of a sedentary person, but intense exercise depletes immunity over time (as shown by the curve). This reaction is influenced by factors such as duration and intensity of activity, type and intensity of activity, hormone and cytokine concentrations, changes in body temperature, water, or blood flow, and a variety of other variables (Nieman, 1997; Peake et al., 2017). Workouts that are conducted at 70 percent to 80 percent of one's maximal heart rate for 6–60 minutes, as well as those that are performed for more than 60 minutes, have been demonstrated to be detrimental to the immune system. T-cell proliferation is reduced as a result of intense exercise, weakening cell-mediated immunity and perhaps increasing the chance of contracting a virus (Turner and Brum, 2017). Athletes who switch from nose to mouth breathing because of higher oxygen demands are bypassing barriers that are part of the body's natural immune system, which allows for more foreign particles to become lodged in the airways. Secretory IgA is produced as a component of the acquired immune system and serves as the first line of defence against new infectious agents. After a lot of physical activity, secretory IgA flow rates may drop by as much as 50% to 70%, depending on the person. Most ultramarathoners had upper respiratory

infections (URI) for up to two weeks after the race. A 100 percent to 500 percent increased risk of infection has been observed for several weeks after participating in an endurance running race, though more recent studies have failed to corroborate these findings (Knechtle and Nikolaidis, 2018).

Anatomy and Physiology of Fever in Athletes

When a person has a fever, their body experiences several negative impacts, including increased dehydration, metabolic demands, and fluctuations in the body's temperature resulting in disturbed homeostasis of the body (Osilla et al., 2022). Fever is caused by pyrogens, which are either endogenous or exogenous substances that cause the hypothalamic set point to be reset, increasing body temperature. Hyperthermia, as opposed to fever, is defined as a rise in body temperature caused by increased heat production that surpasses the body's ability to effectively disperse the heat produced by the body (González-Alonso, 1998). While suffering from a fever, the body's typical cooling systems, such as vasodilation and sweating, are not activated, allowing the body to remain cool in times of heat stress. Febrile responses to a wide range of conditions, the most common of which is an infection, include a multistep adaptive response. Pyrogens, which can be either endogenous or external, are responsible for inducing this adaptive response. Toxins made by bacteria, viruses that infect humans, components of the bacterial cell wall, and Ag-Ab complexes are all examples of pyrogens that come from outside the body.

The binding of pyrogens to the macrophages acts as an activator for the release of Prostaglandin E2 which is stimulated by the release of cytokines, interferons, and interleukins acting as endogenous pyrogens. These substances connect to the hypothalamus preoptic region and cause the "set point" temperature of the body to be raised (Tan and Knight, 2018). Thermoregulatory regulation maintains the higher setpoint temperature until the danger or external stimulus that triggered it has subsided. During a feverish state, the body temperature seldom climbs over 40 degrees Celsius.

Corticotropin, alpha-melanocyte-stimulating hormone, ADH, and many other antipyretic hormones keep the fever under control by causing a negative feedback reaction in the body (Fuller et al., 2007). There may be an acute-phase reaction because of inflammation in some parts of the body, such as the endocrine system, autonomic systems, and changes in the body's behaviour and metabolism. Adrenaline hormone production causes an increase in heart rate, muscular tone, and metabolic rate (Haupt and Rackow, 1983). Every 1-degree Celsius increase in body temperature causes an increase in the metabolism of roughly 10%. By promoting glycolysis and producing vasoconstriction in the peripheral circulation, adrenaline continues to contribute to an increased body temperature. Additionally, the immune system reduces the amount of free glucose available in circulation and shifts to a more lipid and protein-based metabolism. The temperature rises due to reduced heat loss by conduction, radiation, and convection, as well as increased heat loss through conduction and radiation, caused by increased peripheral vascular resistance. When free glucose and peripheral blood flow are reduced, the immune system benefits, but muscle function suffers because there are fewer resources available to provide them. Antidiuretic hormone production is inhibited when a person has a fever, which can contribute to dehydration. Animals in a state of hyperthermia attempt to cool themselves using evaporative means. When someone is extremely dehydrated, their bodies are unable to cool themselves effectively, allowing them to save water at the risk of higher body temperatures (Fuller et al., 2007). Selective hypothalamic brain cooling is possible to maintain a healthy equilibrium between a person's thermoregulatory and osmoregulatory demands by selective hypothalamic brain cooling, which reduces evaporative heat loss and conserves body water. The daily body temperature of animals that were dehydrated was much higher than that of those that were well-hydrated. According to a study, heat and dehydration were shown to reduce cardiac output and blood pressure even more than each variable alone during exercise. It has been demonstrated that those who are dehydrated have a reduced ability to withstand heat stress. It might be hard to control one's core body temperature if one has a fever or isn't drinking enough water. This could cause dangerously high core body temperatures if one exercises while sick.

When people do a lot of exercises, they weaken their immune system, which makes them more likely to get sick quickly. As a result, mild-moderate exercise can keep infections at bay and symptoms and the risk of developing a long-term condition less likely. Fatigue, dehydration, and a temperature change are all possible side effects of a fever, as well as the increased metabolic needs. Even though fever has gotten less attention, it can have detrimental effects on the musculoskeletal system in people.

As a result, there is a decrease in strength and endurance, as well as an increase in muscle catabolism. Excessive activity during fever may worsen the sickness and increase death, according to animal studies. Humans are an exception to this rule. Most febrile illnesses do not have any evidence to back up any of the several return-to-play guidelines that have been produced over the years. The most important thing to remember is that you should avoid any physical activity until your temperature and dehydration are under control. Many different regions of the body are affected adversely by acute febrile diseases (Crump et al., 2017; Iroh Tam et al., 2016; Tun et al., 2016).

CONCLUSION

Acute febrile sickness is distinguished by a distinct, idiosyncratic, erythematous macules-popular rash or eschar (entry wound) depending on the organism and region and is related to high fatality rates which may vary from case to case. The severity of acute febrile illness is primarily influenced by the virulence of the rickettsial organism, and delays in diagnosis have been associated with the severe disease with multi-organ involvement and a high mortality rate. Scrub typhus is

predicted by the occurrence of deafness or tinnitus which are acute hearing impairments in a feverish patient. Morbidity and mortality in the patients suffering from acute febrile illness can be minimized through early diagnosis, and treatment, and by spreading awareness among individuals.

Given the relationship between arboviral infections and human disease, as well as the possibility of global demand, disease monitoring is an essential component of public healthcare provision, disease management, and the evaluation of the potential intervention. Unfortunately, the lack of pathogen-specific signs and symptoms, especially during the early phases of disease development, makes syndromic monitoring for the arbovirus quite difficult. Yet, substantial data for the other study locations are missing, but early results show that Rickettsia spp. and Leptospira spp. are prevalent human illnesses in the regions indicated in the review. DENV has been identified as the most frequent cause of febrile fever as per the various research done in Latin America. Furthermore, the expansion of diagnostic tools at low cost with ease in availability should be prioritized, predominantly to separate arbovirus infection from other illnesses for which effective and low-cost pharmaceutical treatment is now accessible. The absence of distinct clinical indications of many infections, as well as problems in getting an accurate diagnosis, restricts proper management. As a result, diagnostics are still not very good. For example, it's hard to get patients with both convalescent and acute serologies, and it's hard to figure out what the results mean when molecular diagnostics find infections in people who are not sick.

Funding status
Nil.

Declaration of conflicting interest
The authors declare no conflicting interest.

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