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A review of concurrent infections of malaria and dengue in Asia

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ABSTRACT

Concurrent infections of malaria and dengue are when both of these mosquito-borne diseases occur simultaneously in an individual. In this review, reported cases with these co-infections in Asia are discussed. The focus is on the overlapping clinical presentations and the difficulties encountered in differential diagnosis. Also, cases reported in some special conditions, *viz.*, pregnancy, foetal infections, and co-infections with one or more other infectious agents are highlighted. Due to similar clinical presentations of malaria and dengue, these co-infections may give rise to an incorrect diagnosis. Moreover, the treatment regimens for these co-infections are not the same as those for mono-infections. Hence, a delay in implementing the appropriate treatment regimen for these concurrent infections due to poor diagnosis can be fatal. The present review is intended to increase awareness about the clinical significance and the importance of these co-infections among clinicians, public health workers and health authorities in the Asian region. Though malaria-dengue concurrent infections are seldom reported from the Asian region, it is probably increasing particularly in the countries known to be endemic for both of the above diseases. A compulsory reporting of the incidences of malaria-dengue concurrent infections is recommended.

1. Introduction

Both 'malaria' and 'dengue' are known to be rapidly spreading mosquito-borne diseases and of high importance in terms of both mortality and morbidity, posing a worldwide public health problem due to ease in globalised travel [1]. Malaria is a protozoan parasitic infection caused by *Plasmodium* spp. which is usually transmitted by *Anopheles* spp. The major *Plasmodium* spp. infecting humans are *Plasmodium falciparum* (*P. falciparum*), *Plasmodium vivax* (*P. vivax*), *Plasmodium ovale* and *Plasmodium malariae* [2]. Currently, human infections with the simian malaria parasite, *Plasmodium knowlesi*, have been reported from forested regions of South-East Asia, particularly, the Borneo Island [3]. In humans, the malaria parasites grow and multiply first in the liver cells and then in the red blood cells (RBCs) [2]. The stages of the parasite during the erythrocytic cycle are those that cause the clinical symptoms of malaria. When the gametocytes are picked up by a female *Anopheles* mosquito during a blood meal, the sexual reproduction of the parasite begins in its gut. The zygote develops from the fusion of the gametocytes leading to the formation of oocyst and sporocyst in sequence. After 10–18 days, the parasites are found as sporozoites in the mosquito's salivary glands. These sporozoites then infect another victim when the mosquito takes its next blood meal and the cycle starts again [2].

Dengue is also a mosquito-borne disease that is due to infection by single stranded RNA viruses of four distinct serotypes (DEN-1, 2, 3 and 4) under the family Flaviviridae. Each of these serotypes is usually transmitted by *Aedes aegpti* [2]. The typical transmission cycle of dengue follows the human-vector-human cycle, similar to malaria. However, there is also a great potentiality for the dengue virus (DENV) to shift from an animal transmission cycle to a human transmission cycle. The

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DENV circulating in the human blood is ingested by female mosquitoes while feeding. The virus then infects and replicates in the mosquito mid gut. Finally, it infects and replicates in the haemocoel and the salivary glands of the mosquito. From the salivary gland, the virus is then transmitted to other humans during the succeeding feeding time [4].

Concurrent infections of malaria and dengue are when both the diseases occur simultaneously in an individual. Since there are similarities in the clinical characteristics between these two infections, diagnosis of malaria and dengue co-infections might be either misdiagnosed or misinterpreted as mono-infections [5]. As of today, there are many cases of malaria-dengue co-infections reported from various regions in the world following the first case which was reported in July 2005 in France [6]. Although documented cases of malaria and dengue concurrent infections are rare in Asia, there is evidence of their clinical severity when compared to either of the infections alone [6]. Dengue and malaria are difficult to clinically differentiate, but the treatment of these co-infections is very different. A delay in instituting an appropriate management can be fatal, which is emphasized in the cases discussed elsewhere [7]. In fact, clinical and biological pictures of co-infection cases are different from single infections, and bivariate comparisons show more differences between malaria-dengue and dengue than between malaria-dengue and malaria [6].

This review highlights the emerging problem of concurrent infections of malaria and dengue in the Asian region. A discussion on the clinical features of these concurrent infections based on actual case reports from different countries in Asia might aid in creating increased awareness on the importance of these co-infections among communities, clinicians, and public health workers, as well as the regional health authorities. This will pave the way for relevant action plans to be initiated to address this health issue.

2. The incidence of dengue-malaria co-infections from various countries in Asia

Malaria and dengue are two major arthropod-borne infections in the tropics, but dual infections are only described rarely [7–12]. Published data over the last decade from Asian countries, especially India, show an apparent increase in the incidence of concurrent infections of malaria and dengue. Table 1 summarizes the number of cases reported from different countries in the Asian region. A fatal case with co-infections of *P. falciparum* malaria and dengue was reported from East Timor, where the malaria diagnosis was late due to false negative results with malaria rapid diagnostic test (RDT). Eventually, the diagnosis was made based on microscopic examinations that revealed falciparum parasitaemia of more than 30% [7]. Similarly, in North India, a six-month pregnant lady was diagnosed with *P. falciparum*, *P. vivax* and dengue co-infections [13]. In this case, it is important to note that the co-infection was diagnosed in a timely manner and treated, resulting in complete recovery with feto-maternal well-being. To have efficient management and control of these malaria-dengue co-infections, there is a need for a good database, which is currently not in place due to lack of published information from this region.

Table 1
Country-wise distribution of reported incidences of malaria-dengue co-infections in Asia.

Country name	Number of cases	Reference
India	26	[10,11,13–35]
Pakistan	4	[36–39]
Indonesia	1	[40]
Cambodia	1	[41]
Japan	1	[42]
Malaysia	1	[5]
Bangladesh	1	[43]
East Timor	1	[7]
Total	36	

3. Clinical presentations and pathogenesis

Clinical presentations of malaria and dengue are similar. However, there are minor differences, as the causative organisms and their pathogenic mechanisms are different and need to be addressed. Usually, similar clinical presentations lead to misdiagnosis of the co-infection status. Thrombocytopaenia is a strong predictor of dengue fever, and is associated with a probability of malaria [44,45]. Both dengue and malaria are reported to coexist in thrombocytopenic patients, especially those presenting with acute febrile illness, as reported from a study elsewhere [37]. Anaemia is a major symptom seen in malaria infections, which is a consequence of the blood stages causing intense intravascular haemolysis. This is not notable in dengue cases [46]. However, anaemia is frequent in concurrent infections. Besides, a significant decrease in platelets and haemoglobin content, reduced aspartate aminotransferase levels and elevated alanine aminotransferase levels are also seen in concurrent infections [46].

Other clinical manifestations in malaria are myositis, rhabdomyolysis and acute renal failure [22]. It is postulated that in malaria, tumour necrosis factor-α (TNF-α), increased blood viscosity, red cell sequestration in skeletal muscle, metabolic toxins released by the parasite, and lactic acidosis may cause myositis, skeletal muscle necrosis and myoglobinuria [47,48].

In a study done in French Guiana, the clinical presentations in the cases of malaria and dengue co-infections were more severe than those seen in mono-infections [6]. It was also concluded from the above study that concurrent infections tend to be notably more severe for cases with haematologic abnormalities, such as thrombocytopaenia and anaemia, which are known risk factors of severe dengue fever and/or malaria. However, whether this increased severity results from longer evolution duration or increased virulence or both remains to be identified [6].

In a case report from the Brazilian Amazon, only half of the co-infected patients with severe thrombocytopaenia responded well with treatment. Whereas in French Guiana, thrombocytopaenia was the major complication among co-infected patients. Hence, the degree of thrombocytopaenia was not concluded to be related to the clinically significant bleeding [49]. The clinical use of haemoglobin as a co-infection marker is tricky, as both infections impact the RBCs by individual mechanisms. So, the haemoconcentration may not comprise the same relevance to evaluate the severity of co-infection [49].

The clinical features of concurrent infections and mono-infections with dengue are reported to be similar. Significantly, less severe outcomes of the infections in the patients may be attributed to early diagnosis and treatment [23]. From a study conducted during the 2012 dengue outbreak in Pakistan, it was reported that the rate of co-infections was high in cases of dengue fever. There was no significant difference in severity of the disease, except that co-infected patients had a lower rate of jaundice [36]. Other clinical and laboratory parameters were comparable. Another study concluded that prolonged fever with normal to low haematocrit and marked thrombocytopaenia were concurrent infection manifestations [37]. However, such findings were solely based on serological diagnosis, which is not considered to be the gold standard to confirm an acute DENV infection, as the non-specific reactivity for DENV and positive immunoglobulin M (IgM) of past infection cannot be ruled out in those serological assays [49].

Other underlying conditions in malaria-dengue co-infections are rhabdomyolysis and sickle cell disease. While dengue can cause rhabdomyolysis, malaria can also cause acute infection. For example, TNF-α, RBC sequestration in skeletal muscle, increased blood viscosity, and toxins from the parasite together with lactic acidosis can lead to this problem [40]. In the case of sickle cell disease, there have been multiple DENV serotype infections, malaria and sickle cell disease co-infection. The presence of co-infection and disease could lead to severe complications [27].

There have been conflicts on the severity of dengue and malaria co-infection in terms of its clinical manifestations. The outcomes are distinct in each study, but they differ greatly in patient selection criteria and diagnostic methods. Hence, further well-designed prospective studies are warranted for a better understanding of the clinical differentiation of these two important mosquito-borne diseases.

4. Concurrent infection in pregnancy and foetal infection

The first case of malaria and dengue co-infection in pregnancy was reported from a northern province in India where a 6-month pregnant woman admitted for suspected malaria was later diagnosed with a *P. vivax* and *P. falciparum* infection. She was later diagnosed with dengue co-infection. Subsequently, she recovered with foetal well-being due to timely diagnosis as well as appropriate management [13]. This case demonstrates the importance of timely management, as early diagnosis has proven to be lifesaving for both mother and foetus. In another Indian study, a total of 300 blood samples from febrile pregnant women were tested to rule out dengue infection. Dengue infection was detected in 7.3% cases. Two women had co-infections with malaria and dengue. The outcome of a patient co-infected with dengue and *P. vivax* malaria in the later study was reportedly intrauterine death of the foetus at Week 37 [34].

Another cross-sectional study in the Brazilian Amazon presented four co-infected pregnant women with more severe complications in comparison to other co-infected patients [50]. This study revealed that the predominant dengue serotypes in the co-infected group were DENV-2 and DENV-4. Similarly, in a case series of 11 hospitalised co-infected patients from the Brazilian Amazon, two pregnant women presented with severe complications, as designated by the World Health Organization severe malaria criterion and warning signs for severe dengue [49].

Co-infections in pregnancy are a challenge for diagnosis and clinical management due to the additional stress of the physiological changes during pregnancy [34]. Therefore, urgent medical attention is required for a rapid and accurate diagnosis so that efficient medical management of the co-infections can reduce the high mortality rates in pregnancy-related cases.

5. Host immune responses in malaria and dengue co-infection

Heightened levels of TNF and interferon-γ (IFN-γ) have been systematically associated with increased clinical disease severity in both malaria and dengue fever in many case series [46]. The increased TNF levels with significantly high numbers of interactions in the chemokine or cytokine networks suggest that cytokines may be involved in the pathogenesis of malaria and dengue fever comorbidity. Interleukin-6 (IL-6) has been implicated in the pathogenesis of severe dengue, as this cytokine enhances the production of anti-platelet and the induction of tissue plasminogen activator, leading to an increased risk for bleeding. These findings on immune markers support that co-infected cases present with more severe inflammation and disease status compared to mono-infections [46].

Circulating cytokines and inflammatory mediators can be used as biomarkers in early diagnosis. As the immunopathogenesis of malaria and dengue produce common multiple cytokines and inflammatory responses, which regulate the spectrum of the infection, understanding that the key factors associated with increased morbidity can lead to a better clinical prognosis. A study of host immune response patterns in malaria and dengue co-infection revealed that co-infected individuals produced higher median concentrations of IFN-γ, IL-6, and chemokine (C–C motif) ligand 4 than the mono-infected groups. Network analyses of plasma chemokines revealed that co-infection exhibited a distinct immune profile with critical roles for TNF, IL-6 and IFN-γ [46].

6. Complications in co-infections with other pathogens

Multiple infections in a single case would drastically change the spectrum of clinical manifestations, which would complicate the diagnosis process. There are a number of reports from Asian countries describing co-infections of malaria and dengue with other agents [17–20,22,28,29,32,34,35] (Table 2). Multiple concurrent infections with overlapping clinical manifestations can pose a serious diagnostic challenge as well as a management dilemma. Fevers similar to those with malaria and typhoid are often exhibited with any of the arboviral infections that are endemic to the tropical regions of Asia [20]. The many overlapping features

Table 2
Case reports of co-infection with other pathogens.

Country in Asia	Other infections	References
India	Hepatitis A	[17,35]
	Hepatitis E	[35]
	Chikungunya	[20,28]
	Leptospirosis	[29]
	Filariasis	[18]
	Scrub typhus	[22]
	Typhoid	[32]
Malaysia	Leptospirosis	[5]

and similarity of symptoms seen in patients presenting with acute febrile illness, such as high fever, headache, nausea and myalgia may complicate the diagnosis of acute fever.

There have been cases of dengue and malaria infections with leptospirosis, hepatitis, typhoid and chikungunya infections, even up to the presence of 4 acute infections at the same time [35]. In such cases, laboratory investigations are important to arrive at a definite diagnosis, but in settings of mixed infections, the interpretation may be challenging [35]. It is important to acknowledge the presence of other infections in the dual infections of malaria and dengue by considering all of the symptoms presented by the patient to reach a rapid and correct laboratory diagnosis and effective treatment. All of the reported studies on multiple infections have shown that malaria and dengue co-infections with other agents can be more severe and fatal.

7. Diagnostic dilemma in malaria and dengue co-infections

Both malaria and dengue can cause acute febrile illness. However, malaria can be chronic in contrast to dengue. The triads of haematological findings *viz.*, atypical lymphocytosis, haemoconcentration and thrombocytopaenia, might be a clue for differential diagnosis of dengue infection rather than other tropical infections, including malaria [1]. However, a more specific diagnosis of either condition is advised.

In most cases, the diagnosis of dengue is made based on the detection of IgM antibody, whereas malaria is diagnosed by microscopic examination of a blood smear. Although the IgM antibody titre using ELISA appears strongly positive for dengue, it can also be associated with malaria [51]. In some patients, the IgM is detectable by the 2nd to the 4th day from symptom onset, while in other patients, there is no detectable IgM until the 8th day [38]. Anti-dengue IgM false negative reactions are observed in secondary infections and there is a small percentage of secondary infection patients without detectable IgM antibodies [38].

When the ELISA test is not available, rapid tests such as the strip assays are available for qualitative detection of dengue IgM and immunoglobulin G. However, the ELISA test generally performs better than rapid tests in terms of absence of cross-reactivity with other arboviruses and false negative results [2]. A dengue IgM capture ELISA test should be performed following the RDT to avoid presence of cross-reactivity among arboviruses, which has occurred with patients with leptospirosis, malaria and past dengue infection [2,52].

In all settings, the microscopic examination of both thick and thin film remains the gold standard for confirmation of malaria [53]. This is because the thick film is more sensitive in detecting malaria parasites due to higher concentrated blood, which allows a larger volume of blood to be examined, and the thin film allows parasite species identification [53]. It is important that once *Plasmodium* is detected, a blood film for malaria parasite test on *P. vivax* is performed daily while the patient is in the hospital, then weekly for 4 weeks during follow-ups, and finally, monthly for 11 months during follow-ups [53].

Malaria RDTs are based on the detection of circulating parasite antigens, and this should be used if microscopy is not available. If the blood film examination is negative within patients of malaria manifestations, a series of blood films should be examined at 6–12 h intervals or RDT can be used [4]. The RDT that utilises histidine rich protein 2 only detects *P. falciparum*, whereas the parasite lactate dehydrogenase and aldolase based tests can detect both gametocytes of malaria parasites. Hence, there is variability in performance of the tests for non-falciparum, which is recommended [53]. One of the concerns involving rapid tests is the failure to detect high parasite densities due to the absence of histidine rich protein 2 in certain malaria parasites, leading to negative results as presented in a case report [7].

In endemic areas, malaria and dengue infections can coexist in the same patient. Although malaria and dengue cause quite similar symptoms and signs, the treatment of these two illnesses is different. Any suspicion of malaria in disease-endemic areas must be excluded with microscopy and/or rapid antigen test. Failure to recognize malaria or dengue co-infections would delay the initiation of proper therapy and result in increased morbidity and mortality [26]. The fatal case of co-infections with *P. falciparum* malaria and dengue in East Timor due to delayed diagnosis of malaria with malaria $_{RDT}$ serves as a reminder of the fallibility of RDT and the importance of parasitological diagnosis through microscopy, as malaria infections can be fatal within a few hours of symptom onset [7].

There was a question raised sometime back as to why concurrent malaria and dengue infections are not common? One of the major reasons of a less common incidence of the concurrent infections may be due to different specific mosquito vectors and their habitats. The habitat of the vector for malaria is in forests, whereas the habitat for the vector for dengue is in urban locations [1]. The co-infection is also thought to be due to exposure to two different mosquito vectors at a given time. The immunity to each infection in the endemic area is also a possible factor [54]. However, the actual number of incidences is probably underestimated in areas known to be highly endemic for both malaria and dengue, as in the developing countries of the tropical belt in Asia. It is possible that the actual number of incidences is not diagnosed or not documented. The concurrent infection can be easily forgotten. When one underlying cause is diagnosed in acute febrile illness, the possibility of other infections is usually not taken into consideration.

8. Conclusions and recommendations

The current review of literature reveals that the concurrent infection of malaria and dengue, though seldom reported, is showing an increase in incidence in these diseases' endemic countries in Asia. Even with the scarce case reports in Asia, the co-infections of malaria and dengue have recently been recognised to be an important clinical problem. Considering the possibility of concurrent infection in cases of atypical clinical manifestations or acute febrile illness, an early diagnosis is essential. Thereby, the treatment regime can be lifesaving. There is a great need to increase awareness of this concurrent infection among physicians and other healthcare personnel, and there is also a need for them to report the incidences. Development of new diagnostic tests to detect both infections in a single test format, and the implementation of public engagement programs for prevention and control of these mosquito transmitted infections, are warranted.

Conflict of interest statement

We declare that we have no conflict of interest.

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