Novel interventions in treating dengue

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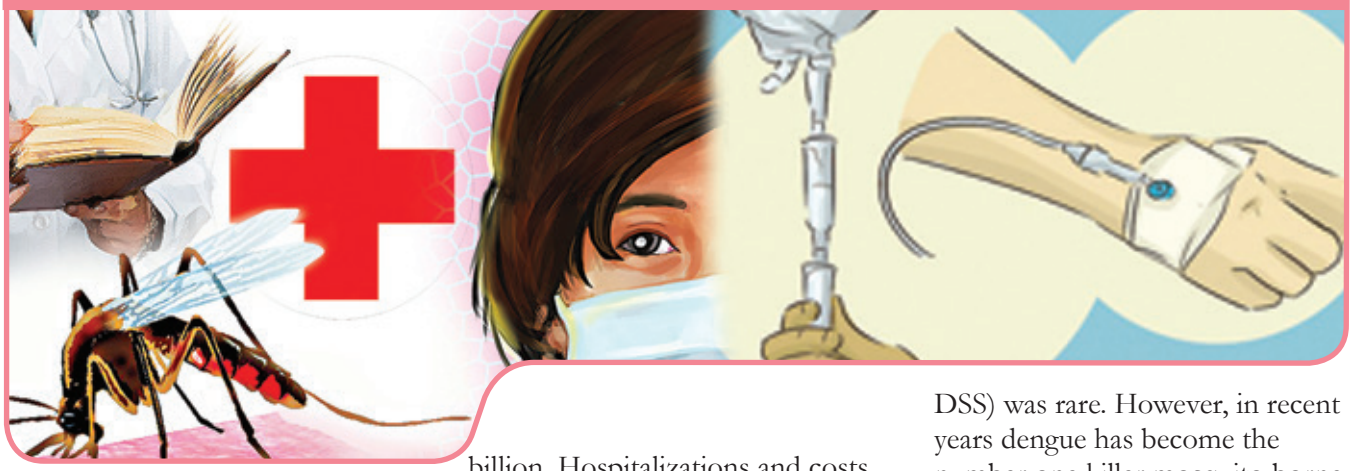


Dengue viral infections represent one of the most rapidly emerging mosquito borne infections in the world, spreading to many geographical regions. It is estimated that 390 million individuals are infected every year with the virus. As approximately 75% of those who are infected do not show any symptoms at all. 70% of those who are infected with the dengue virus live in Asia. The estimated annual global cost associated with dengue is $8.9 billion. Hospitalizations and costs due to dengue control activities was estimated to be US$ 3.45 million in year 2012, in Colombo, Sri Lanka, which highlights the economic burden due to these diseases in developing resource poor countries. Dengue viral infections have been endemic in Sri Lanka since the mid-1960s which was when the first cases of DF/DHF were reported. Although the Sri Lankan population had been exposed to the virus for decades, severe forms of dengue infection (DHF/DSS) was rare. However, in recent years dengue has become the number one killer mosquito borne infection in Sri Lanka. Not only is the incidence of dengue infections rising in Sri Lanka, but the infection is also spreading to all parts of Sri Lanka. The largest ever dengue epidemic occurred this year and more than 150,000 cases have been reported up to now (Diagram 1).

Dengue infection can occur following infection with any of the four dengue virus (DENV) serotypes (DENV1-4) which cause dengue disease and which are

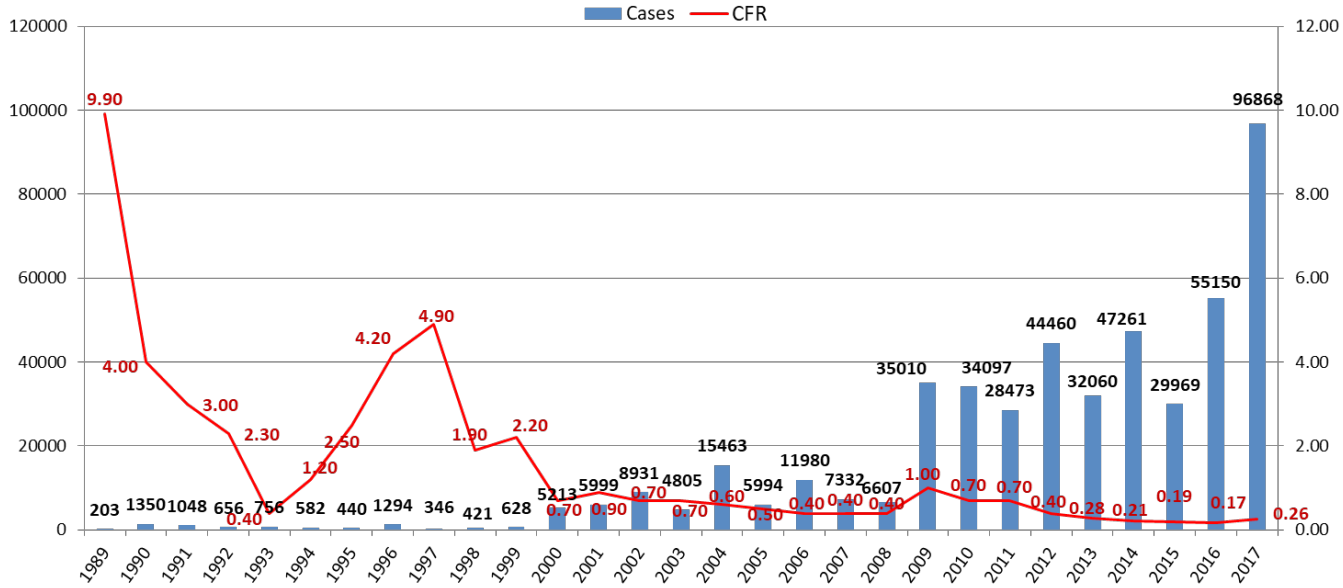


Diagram 1:The incidence and case fatality rates (CFR) due to dengue from 1989 up to June 2017 (kindly provided by Dr. Hasitha Tissera, Director, Dengue Control Unit, the Epidemiology Unit Sri Lanka)

closely related. The four viruses are 65% to 70% similar to each other (ie.the viruses are 65 to 70% homologous). Initial infection with a particular serotype is known as primary infection, which is usually asymptomatic or results in mild disease manifestations. Subsequent infection with other serotypes (secondary dengue infections) may lead to severe disease which manifests in the form of DHF/ DSS .Although infection is associated with a self-limiting illness in the majority of individuals, it can cause severe clinical disease manifestations such as dengue haemorrhagic fever (DHF) and organ involvement in a significant proportion of individuals. One of the research projects carried out by us showed that approximately 50% of children living in the suburban region in Colombo have had dengue by 10 years of age, and by 45 years approximately 95% of those living in the suburban areas in Colombo have had dengue.

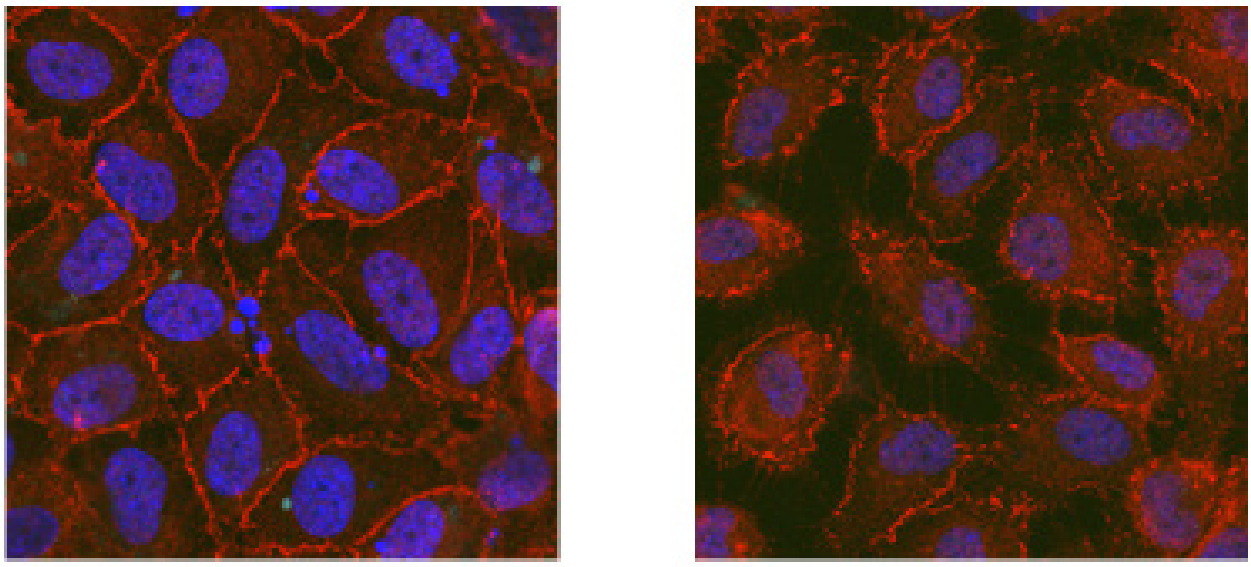
Clinical features and complications of dengue

Dengue infection typically manifests as a sudden onset febrile illness with muscle pain, joint pain and headache. The majority of individuals proceed to an uneventful recovery whereas some develop DHF, which is characterised by fluid leakage due to increased capillary permeability. Complications occur as a result of fluid leakage such as shock, pleural effusions, ascites along with other complications such as liver failure and encephalopathy. One of the most important issues to be monitored is the vascular leak from the blood vessels/ capillaries, which is the cause of severe dengue (DHF). In DHF fluid leaks from the capillaries accumulate in the lung and abdominal cavity. Therefore, once the patient is admitted, ultra sounds scans are done to see if the patient has developed leaks. Also the packed cell volume (PCV) or the haematocrit (HCT) is also monitored as an indicator of leaks. It is very important to know the moment when the patient is leaking and the extent of the leak. If leaking goes undetected, and if there is rapid leakage, the patient will go in to shock state. This in turn leads to liver and kidney failure, and if the shock persists for a few hours, it will lead to death. Therefore, the biggest challenge is to detect which patients show signs of a leak, as only 20-25% of those who develop symptomatic dengue do so.

During the leakage phase it is important to monitor the fluid that goes in, in the form of oral fluids or intravenous fluids and also the output in the form of urine. This is an abosolute requirment to calculate how much fluid that should be given to the patient. Giving too much as well as too little leads to complications, and the optimum amount should be given, which varies widely from

patient to patient. The rapid drop of the platelet count is an indicator that the patient may developing the severe disease (DHF). However, the lowering of platelet count is only an indicator of the possibility of a severe disease. Actually, low platelet counts are the result of severe illness and not the cause of it. Some individuals may have very low platelet counts but still may not have severe disease, whereas some with relatively high platelet counts develop severe disease. Therefore, although platelet counts are useful as an indicator to monitor and decide if the patient needs admission, the most important factor is the 'leakage'.

As shown in the above illustration (Fig.1), the fluid leaks through the gaps between the endothelial cells which line the capillaries. The image on the left shows what endothalial cells usually look like. As shown they are stuck together by a cement like substance. In the presence of serum from dengue patients (right image) gaps form between endothelial form leading to fluid leakage.



Endothelial cells in the presence of normal serum

Endothelial cells in the presence of serum from a dengue patient

Fig 1: Vascular leak in dengue patient

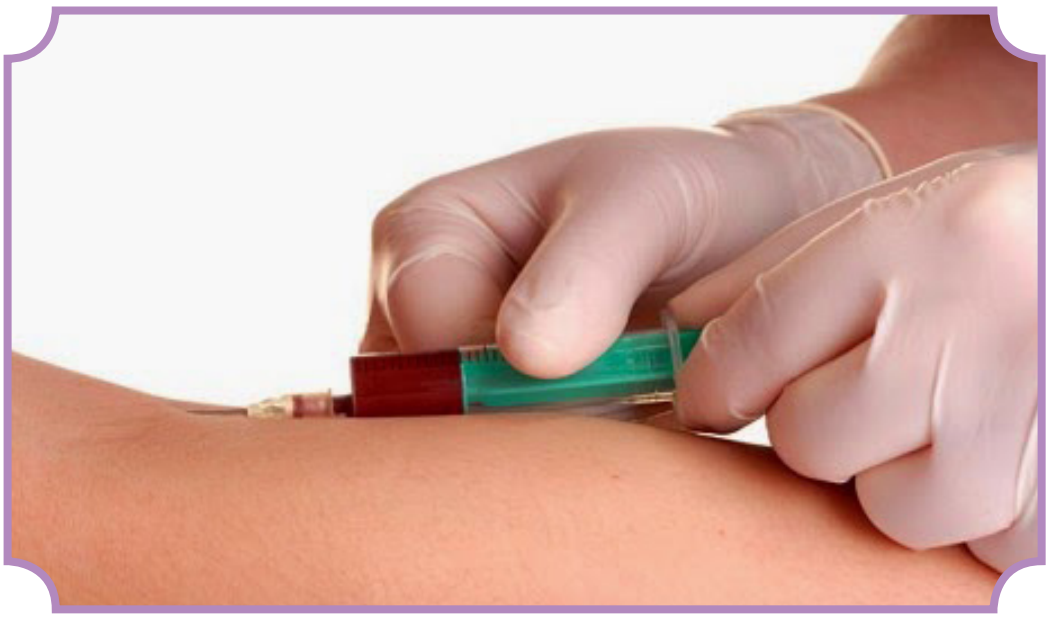
The cause of vascular leak and new treatment methods

We have found that the most important mediator that causes this leakage is what is known as the platelet activating factor (PAF). Once you detect that a patient is showing signs of leaking, it is important to replace the exact amount of fluid that is leaked. This leaking phase lasts only for 48 hours. Forty eight hours after the patient being in the leakage phase (critical phase), the fluid leakage stops, and the fluids that leaked is reabsorbed. This usually coincides with the rise in platelets. So it is natural for platelets to drop for 2 to 3 days and suddenly start picking up. No magical treatment is needed for this as this is what happens naturally.

Patients with DHF were shown to have very high levels of PAF during the critical phase (leakage phase). Fortunately there is already a drug known as rupatadine available that blocks this mediator. To find out if rupatadine is effective in dengue, we carried out a clinical trial to see if it works in dengue, and also whether it is safe to use.

Rupatadine has already been used for certain types of allergic diseases in many European countries, as well as in Australia, Japan, USA and India. So we know that the drug is safe and could also be given to children. We designed this trial so

that half of the patients will be given the drug and the other half a placebo (a drug which looks similar but with inactive ingredients). It is important to use a placebo in drug trials because, otherwise patients might feel that they are better when they are told that they are



been given a drug that might work. The treating doctors might also be biased when they are treating patients when they know certain patients are taking a drug. So in this trial, both doctors and patients were blinded (they did not know if they were taking the drug or placebo). This is very important to make sure that proper, unbiased scientific data are being collected. Also a proper statistically designed sample size should be taken to know if meaningful conclusions can be drawn instead of depending on 'unproven, non-scientific' claims.

We have completed the initial trial for a drug that reduces/ prevents this leakage and the results look promising. People given this drug (rupatadine) had fewer complications and a shorter duration of illness when compared to the placebo, especially when given early. Since the results look promising, we have just started the next phase of this trial, where we will give the drug in the outpatient department (before patients are admitted to hospital).

Precautions to take if you are diagnosed with dengue

It is very important to obtain medical attention if you have fever, at its very early stages. It would be dangerous to try unproven home remedies. Fortunately, most patients who develop dengue do not develop severe disease (DHF) and will be fine if given anything. However, there is no way to know who will develop severe disease, and it is too late when some people come to hospital. If patients come to hospital when they have developed shock the outcome is not good. Therefore, it is important to understand that if treatment is sought in a timely manner, deaths due to dengue would be extremely rare.

If you have fever it is important to do a full blood count and show the report to your doctor. You can also do the dengue NS1 antigen test at the same time. If your NS1 is positive, there is no need to panic because only around 20-25% of those who get dengue develop severe dengue (DHF). The likelihood of NS1 being positive is highest on day 1 of fever. Subsequently the rates of NS1 positivity gradually drops even if you have dengue. If NS1 is positive, it means that you do have dengue. However, even if you do the dengue NS1 test on day 1 of fever and it is negative, you can still have dengue. NS1 is negative in a significant proportion of patients, despite having dengue. Therefore, it is of utmost important to seek medical advice if you have fever, irrespective of whether your NS1 antigen test is positive or not.

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