STANDARD DEVIATIONS: Dengue! Dengue! Round II (…and it's worse the second time!)

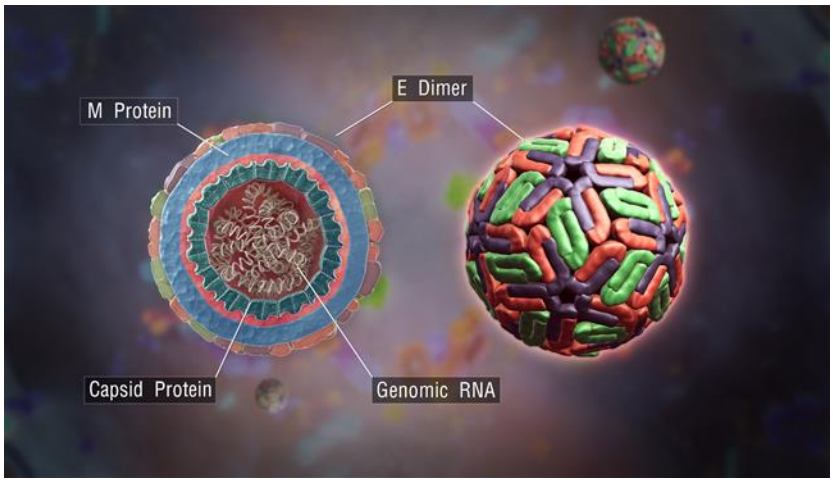
Greetings,

Put on some DEET and cover up, 'cuz we're headed into the weeds. And these weeds are full of dengue-carrying *Aedes* mosquitoes.

Here's the recap on why we're taking this field trip. Dengue is surging around the world. Although only about 25% of the hundreds of millions bitten will get symptoms, hundreds of thousands will be hospitalized and tens of thousands will die from disease. Urbanization and climate change mean billions (yes, billions) more people will become susceptible to infection. Laboratories around the world today are burdened with increased volume for diagnostic testing of virus and, more to the point, providing lab support for hospital patients with disease. Just because you are outside the range of this mosquito today is no reason to be unaware of the dynamics, consequences, and science. Understanding dengue will make laboratorians better prepared for the certain spread of this virus in particular, and better prepared for novel virus evolution overall. And, the smarter we are about what we do, the safer we become in how we do it.

Some virology stuff, some biology stuff, some lab stuff. I'm painting with very broad strokes to keep it easy to read.

Dengue belongs to the family *Flaviviridae*, a family of positive, single-stranded, enveloped RNA viruses. It's in the same genus (*flavivirus*) as Zika, West Nile, and Yellow Fever. *Flavus* is Latin for "yellow" and the nomenclature reflects the jaundice characteristic of Yellow Fever.



An educated guess at dengue virus structure.

Injected through mosquito saliva, dengue virus particles bind to dendritic cells. Its E envelope protein binds to a cellular receptor which mediates clathrin-mediated endocytosis. That binding

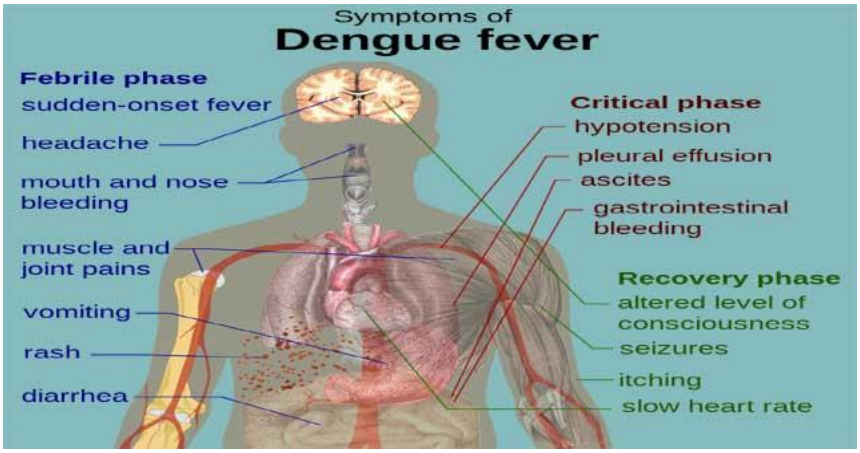
alters E (the pH changes) and allows for release of viral capsid and uncoating in the cytoplasm. There's an affinity for Endoplasmic Reticulum (ER) where host ribosomes translate (+)ssRNA into polypeptides that cleave into the viral proteins and stimulate RNA replication (synthesis is asymmetrical, making 10 times more of the positive-sense strand than the negative). Viral assembly occurs at the ER, budding from the ER through the Golgi into vesicles where pH and glycosylation permit maturation and exocytosis. Then it's on to another cell. That's it, in a nutshell (well, cell, really).

Cells respond to this invasion by producing a number of signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as fever, flu-like symptoms, and pain. Interferon jump starts the immune system to make antibodies (IgM initially, and IgG later). Antibodies bind to the pathogen marking it for destruction by macrophage or neutralizing its antigenicity. IgG persists as a remembered protein that B cells produce to provide lasting immunity. Easy, peasy, Immunology 101.

What makes dengue a different deal? There are 4 (really, 5) serotypes of dengue. When your immune system sees one serotype, it makes IgM and then IgG antibodies to that particular serotype. You itch and move on, immune to the dengue serotype you encountered. BUT, when you get bitten by *Aedes* carrying a different dengue serotype….things change.

The second time you see dengue, your immune system thinks IgG is already deployed. The new serotype fools your immune system, because the IgG binds but doesn't quite neutralize the virus. Now when it's phagocytized it is able to attack that macrophage. It's a Trojan Horse invasion. This sneaky way into the cells is known as antibody-dependent enhancement (ADE).

The ensuing sudden, huge, secondary viral load results in the changes that cause dengue fever and hemorrhagic sequelae, or dengue shock syndrome. All this viral activity causes an osmotic shift that floods the bloodstream. Capillary permeability moves that fluid into the body cavities, blood pressure drops and organs fail because they can't get nourishment. The bone marrow gets thrown out of whack and can't make platelets; coagulation and fibrinolysis go haywire and you go into shock and/or hemorrhage. There is no treatment for dengue.



So……the problem with dengue is not being bitten by a mosquito, but being bitten twice. Hundreds of millions of sero-positive individuals are at risk because of a secondary infection and the ADE trickery.

And, here's the kicker…….the vaccine for dengue works for people who are already sero-positive but endangers those who are dengue naïve. If you get the vaccine but have never had dengue, well, now you are at risk for a severe reaction when you do get bitten!

People who suffer from dengue require our laboratory help. There is the initial diagnostic assays to define the virus and serotype. Then those ill patients need monitoring for platelets, hematocrit, coagulation, electrolytes, enzymes, blood gases and the plethora of lab work necessary for the care required for hemorrhagic disease.

Next week I'll break down the epidemiology of dengue in 2019, the crushing surge we're seeing around the globe, trouble with vaccine, and the implications for hospitals and laboratories.

Have a great week and be safe,

Bryan

p.s. Some historical perspective about *Flaviviridae*. The US owes a debt to the *Aedes* mosquito. Mosquito-borne **Yellow Fever is the reason Thomas Jefferson made the Louisiana Purchase!** If Napoleon hadn't spent all his army and money in Haiti fighting the Spanish but (both) losing to YF he wouldn't have needed the cash infusion that selling land to America raised. Spain made a similar decision years later in deals with Mexico that led to our acquisition of the rest of the West.