EDITORIAL

REPURPOSED DRUGS FOR RE EMERGING DISEASES: IVERMECTIN IN ARBOVIRUSES

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ABSTRACT

The disease currently known as Dengue has been described more than 2000 years ago. It is an arbovirosis, being the Aedes family mosquitoes its vectors. The incidence of dengue is increasing in almost the entire world. No effective treatments have been described. Vaccines are still experimental and high risk. Neither a satisfactory form of prophylaxis nor an effective treatment have been developed to date. In the present work, we update the knowledge about this virus, while presenting an effective, simple, safe and accessible alternative for its eradication.

ABSTRACT

Dengue is the common name of a disease that was first described over 2,000 years ago. It is an arthropode-borne disease, where mosquitoes of the Aedes family are involved as vectors. The incidence is growing almost everywhere. There are no effective treatments. Vaccines are still experimental and risky. There is not a proper prophylaxis method. In this publication, we update the knowledge of this disease, and also present an effective, simple, safe and affordable alternative tending to dengue eradication.

KEY WORDS : dengue ivermectin re-emerging diseases

CONCEPTS ABOUT EMERGING AND RE-EMERGING DISEASES

An emerging infectious disease is one caused by a newly identified and previously unknown infectious agent capable of causing public health problems at a local, regional or global level.

Re-emerging diseases are defined by the reappearance and increase in the number of infections of an already known pathology that, due to the few cases registered, had already ceased to be considered a public health problem, but which -now- causes an alarming return .

In the specific case of Dengue, in our environment -Argentina- it is a re-emerging disease, and it is already entering the endemic category.

HISTORICAL AND EPIDEMIOLOGICAL ASPECTS OF DENGUE

A disease that can fit into what we know today as dengue was described in China in the 3rd century during the Chin dynasty (approximately 265-420 AD).

In the 6th and 10th centuries, corresponding to the Tang dynasty (610 AD) and during the Sung dynasty (992 AD), reports of similar cases were made.

In China, the disease was called “poisonous water” due to the association of river sources and insects.

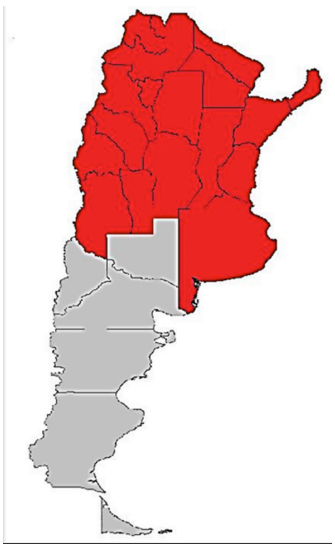
The clinical description included fever, rash, arthralgia, myalgia, and hemorrhage.

After almost seven centuries, similar cases appeared in French Guianas (1635) and Panama (1699).

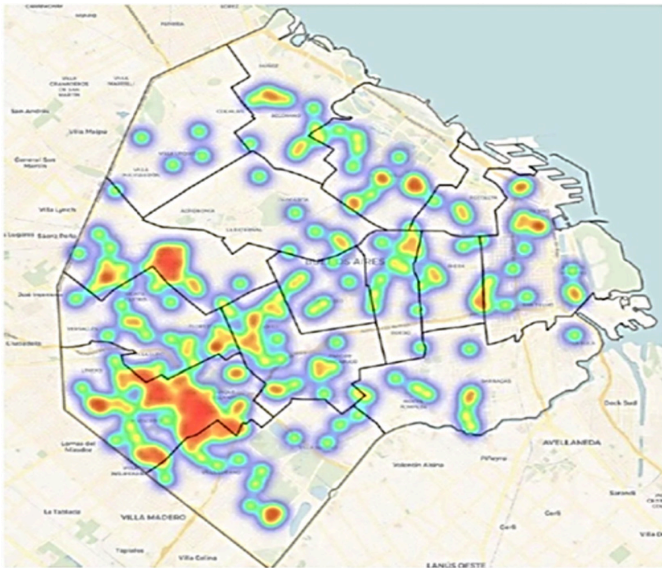
A century later several cases arose in Cairo, Philadelphia,

Seville ("benign fevers of Seville"), etc.
The possibility of a pandemic was suggested, in 1788.
This coincided with the rise of commercial shipping.
A second pandemic spread from Africa to India and from Oceania to the Americas, from 1823 to 1916.
In 1916 the first known dengue outbreak occurred in Argentina, which was introduced through a case imported from Paraguay.
The control campaigns carried out by the Pan American Health Organization in the Americas around the middle of the 20th century led to a decline in the area colonized by A. aegypti.
In the 1970s, cases were only detected in the insular sector of Central America and in the extreme north of South America.
However, a decade later there was a reinvasion of the vector to the south and the disease once again reached the territory of Argentina.
In 1997, 20 imported dengue cases were registered and in 1998 there was a new outbreak in the Chaco region of Salta: the most affected city was Tartagal.
During that same year, there were more than 300 autochthonous cases, which confirmed the presence of the A. aegypti vector in Argentine territory.
In the following years, cases of dengue were registered without interruption; the most important dengue outbreak occurred in 2004, with 98% of the cases of autochthonous origin.
The Aedes aegypti was detected again in Argentina from the year 1984, and it is distributed
currently from the north of the country to the provinces of Buenos Aires, La Pampa and Mendoza.
The Aedes albopictus was found in the provinces of Misiones and Corrientes.

DISTRIBUTION OF DENGUE IN ARGENTINA, PRIOR TO THE SARS-COV2 PANDEMIC

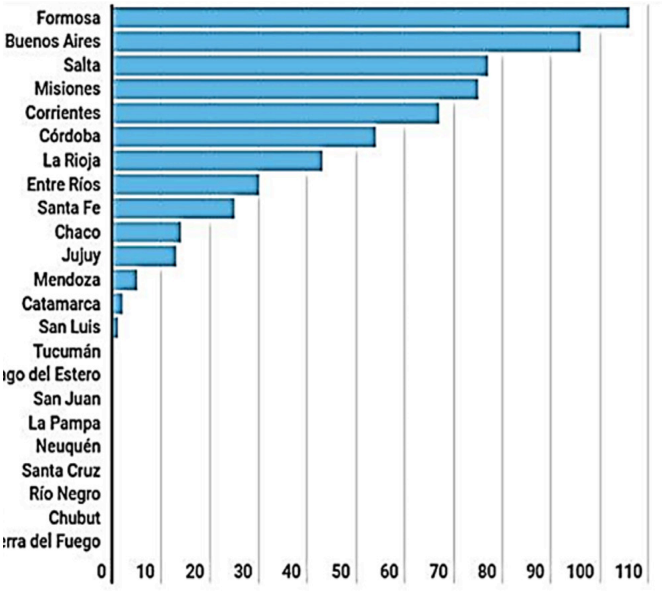


METROPOLITAN AREAS MOST AFFECTED BY AUTOCHTHONOUS CASES



So far in 2023 -including March- more than 28,000 cases of dengue and more than 900 of chikungunya have been confirmed throughout the country, with 13 deaths from the first cause.
According to the report, 28,235 cases of dengue were reported, of which 25,419 acquired the infection in the country; and it was also detailed that during epidemiological week 12 there was a 27.7% increase in cases compared to the previous week.
It was also reported that at the moment, the circulation of this virus was identified in 14 jurisdictions corresponding to three regions:
Central Region (Buenos Aires; Autonomous City of Buenos Aires; Córdoba; Entre Ríos; Santa Fe); NEA Region (Corrientes; Formosa; Chaco) and NOA Region (Catamarca; Jujuy; La Rioja; Salta; Santiago del Estero and Tucumán).

TERRITORIAL DISTRIBUTION OF DENGUE CASES



CONCEPTS ABOUT DENGUE VIRUSES

Dengue is one of the major public health problems caused by communicable diseases in the Americas.

Dengue fever and, moreover, dengue hemorrhagic fever constitute an economic burden for the affected regions.

The direct and indirect costs of each epidemic include medical care, sometimes with intensive care; the loss in production due to the absence from work of sick adults and relatives of affected children and, in some cases, other important losses, such as the decrease in tourism.

The risk conditions are given by:

(a) high levels of Aedes infestation;

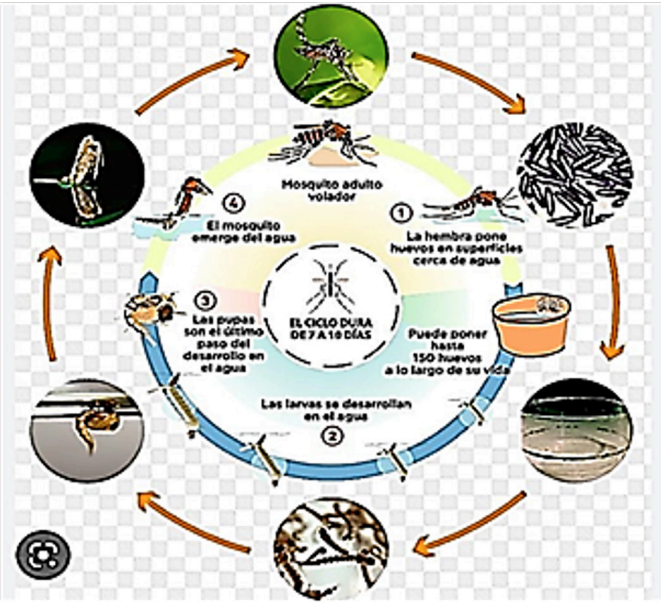
(b) epidemic activity of dengue and DHF in bordering countries (Brazil: serotypes DEN1, DEN2 and DEN3, including cities with DHF and Paraguay: DEN1 and DEN2);

(c) high population movement towards countries with active transmission;

(d) absence of sustained vector control activities.

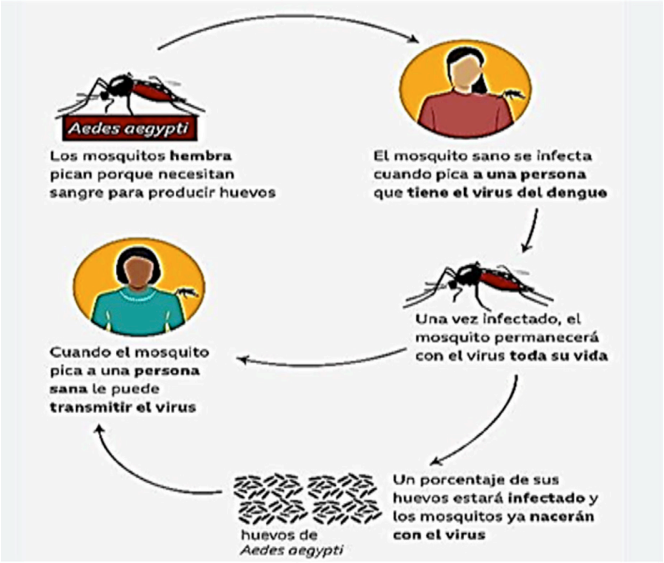
The life cycle of the virus involves the mosquito (A. aegypti, A. Spegazzini and A. Albopictus) as an intermediate host and vector.

DENGUE VIRUS LIFE CYCLE



Among the MERCOSUR countries, the most serious case is that of Brazil, where approximately 63% of the 375,000 cases reported in America during 2000 were registered, with a worrying speed of growth of the epidemic.

MODE OF DENGUE TRANSMISSION



The role of the asymptomatic patient as an indicator of risk and generation of outbreaks

A recent study suggests that the number of “hidden” infections in an area (infected people showing no symptoms) is the key indicator of dengue risk in the area.

The number of mosquitoes in a location alone does not predict the risk of infection.

In general, about 50-70% of dengue cases are asymptomatic, making detection by public health officials impractical, and the current study reveals that asymptomatic cases are linked to one-third of the broadcast.

In Iquitos, Peru, data was collected over six years.

The study involved 4,600 people in two different neighborhoods. It was seen that the cases of symptomatic patients would represent only the tip of the iceberg of the disease in the context of an outbreak.

Infected people who do not develop symptoms go about their daily routines, unknowingly infecting any mosquito that bites them, which can then spread the virus to more people.

The participating subjects were surveyed three times a week about their mobility.

This data was used to map “activity spaces”, such as residences, churches and schools.

Study participants were also followed to determine if they experienced any dengue symptoms.

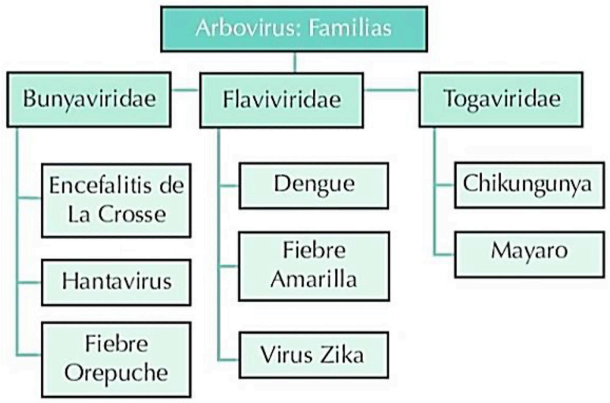
Blood tests confirmed a total of 257 symptomatic cases during the six-year study period.

That led to investigations of other participants whose activity spaces overlapped with the symptomatic cases.

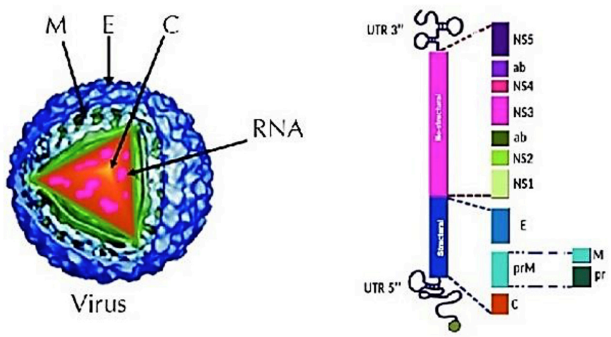
Blood tests confirmed that more than 2,000 of these location-based contacts had dengue infections, and more than half of them reported not having any noticeable symptoms.

The results also identify the role of asymptomatic "superspreaders" in a dengue outbreak.
A small number of activity venues (8%) were associated with more than half of the infections, and the majority of cases associated with those venues were asymptomatic patients. The study also broke down infections by virus serotype. In addition, he measured the number of mosquitoes in the activity spaces. From this study, it was possible to conclude that the prediction of risk for a place requires a cascade of circumstances:
A large number of asymptomatic cases frequenting the site combined with high levels of mosquitoes and
A large number of people are not immune to the particular serotype of dengue virus that is circulating.
Taxonomy. The dengue virus belongs to the Flaviviridae family.

FAMILIES OF VIRUSES CLASSIFIED WITHIN THE ARBOVIRUSES



There are four variants, serotypes 1, 2, 3 and 4.
Immunity is serotype-specific, so infection with a certain serotype confers permanent immunity against it (homologous immunity), and only for a few months against the rest of the serotypes (heterologous immunity).
Dengue virus (DENV) is classically subdivided into 4 well-described serotypes (DENV 1, 2, 3 and 4).



STRUCTURE OF THE DENGUE VIRUS

However, since October 2013, serotype 5 (DENV 5) has been mentioned in the literature, without epidemiological relevance for the moment.
It has an 11 kb RNA genome that encodes ten proteins that will make up the virus: three
structural and seven non-structural.

The structural ones are the Capsid protein (C), Membrane protein (M), and
Wrap (E).
Nonstructural (NS) proteins are NS1, NS2A, NS2B, NS2B, NS3, NS4A, NS4B, and NS5.

structural proteins

The virus presents a nucleocapsid formed by Protein C, which covers the genome.
This structure is surrounded by a lipid bilayer where the M and E proteins are found.
The M protein is formed from a precursor (prM), which participates in the regulation of viral fusion and folding of the E protein.
Membrane glycoprotein E is involved in membrane fusion, virion morphogenesis, and receptor binding.
Protein E is the one that establishes the serotype, with a similarity of 60-70% in the amino acid sequence between the four DENVs.

nonstructural proteins

The NS1 glycoprotein has 3 categories:
Residents of the endoplasmic reticulum, membrane-anchored, and the secreted form (which may be in the extracellular space, thereby stimulating the immune system).
In the serum of patients with DENV, the presence of immunoglobulins against this protein has been demonstrated.
Immunoglobulins against NS1 (in vitro) can cause antibody-dependent and complement-mediated lysis in infected and uninfected cells, which partly explains the damage to the endothelium, and its pathophysiological consequences.
NS2A is an integral membrane protein that participates in RNA replication, through of a mechanism not yet well defined establishes whether the RNA will serve as a template for the production of viral components or if it is to be enveloped and become part of a new virion.
NS2B is a cofactor of the NS3 protease.
NS3 is associated with nucleoside triphosphatase and helicase functions during viral RNA synthesis.
NS4A is an integral protein critical for vesicle formation.
NS4B is a suppressor of gamma and beta interferon.
NS5 plays an important role in RNA synthesis and interferon blocking, acts as a polymerase in viral transcription and replication.

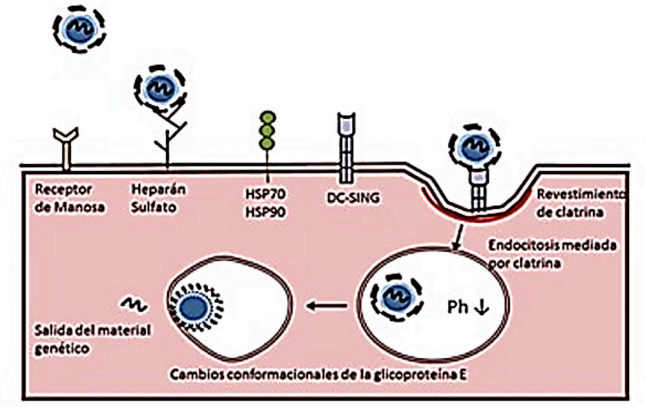
In both mammalian cells and mosquito vector cells, the cycle begins with the approach of the DENV to the cell surface.
Protein E interacts with proteins and proteoglycans (such as heparan sulfate) of the cell membrane, thereby mediating attachment and endocytosis.
Due to their high negative charge, proteoglycans favor the approach of the viral particle.
There is evidence to suggest that the laminin receptor LAMR1 interacts specifically with the E protein, and that this is the one that probably promotes endocytosis.
Other proteins that possibly act as receptors such as ICAM-3 and DC-SIGN (Dendritic Cell Specific Intercellular Adhesion Molecule-3-Grabbing Non integrin,CD209) are mentioned in the literature.
The endocytic vesicle becomes an early and late endosome and subsequently fuses with a lysosome, which lowers the pH, inducing a conformational change in the E protein that favors the release of the nucleocapsid into the cytoplasm.
The mechanism by which viral RNA replication occurs is still not fully clarified; however, it is known that said nucleotide translates a complete polypeptide, which is processed at the endoplasmic reticulum level by cell-specific proteases and by the NS3.
With the activity of the latter, structural and non-structural proteins are released, which are assembled in the same reticulum.
Subsequently, a maturation process occurs that involves the Golgi apparatus.
When the virus is released through exocytosis, the E protein acquires its final conformation favored by the neutral extracellular pH, with which it can be recognized by new cells and thus start the viral cycle again.

PATHOGENESIS

Cell Tropism

The cells that have classically been postulated to be infected by the virus are: monocytes, macrophages, dendritic cells, keratinocytes and CD4+ and CD8+ lymphocytes, however it has been demonstrated that it can also do so in: hepatocytes, endothelium, fibroblasts, neurons and platelets, in the latter it has even been shown that they can complete their viral cycle.
Dendritic cells and keratinocytes are the primary sites of infection, as they have direct contact with the viral inoculation by the arthropod.
From here the virus migrates to the lymph nodes, where it amplifies and spreads the infection, with the eventual compromise of all the aforementioned cells, once it reaches the circulatory system.

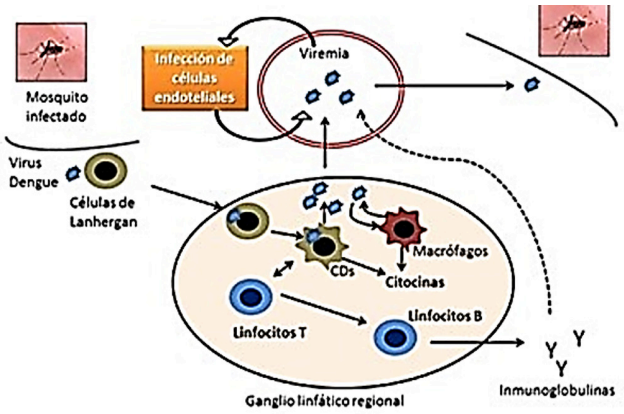
RECIPIENTS INVOLVED IN THE ENTRY OF THE VIRUS



Immune response in primary infection

The E glycoprotein is the one with the highest exposure in the virus; it has been observed that the immunity against DENV is mainly mediated by neutralizing antibodies against said protein, although also to a lesser extent against prM, C and non-structural ones. The NS1 protein has gained relevance in recent investigations as a highly immunogenic.
Initially, when the infection is established, there is a response with secretion of interferons (IFN) of type I, in addition to activation of the complement system.
In parallel, by recognition of the antigen-presenting cells and the infected cells, a stimulus is produced to the Natural Killer lymphocytes, and the formation of of a complex defensive cascade.

EVENTS IN THE FIRST STAGE



The activation of these immune cells, and especially CD8+ T lymphocytes, generates a state
antiviral and proinflammatory, there is an increased production and release of interleukins,
where they stand out: IL-1”, IL-2, IL-4, IL-6, IL-7, IL-8, IL13, IL-18, TGF-1”, TNF-! and type II IFN (#).
The adaptive immune response to a primary infection corresponds to the production by B cells of IgM against viral

antigens, and then IgG, especially IgG1 and IgG3.
IgM are detected by the fifth or sixth day by ELISA, and can remain positive for 2 to 3 months, which is an important consideration when making a serological diagnosis.

Immune response in second infection

In a second DENV infection an accelerated IgG response is observed in contrast to a decreased IgM.
It has been seen that a first infection by a certain serotype induces prolonged homotypic immunity, and also provides transient immunity against heterologous serotypes, which has been partly explained by the conformational similarity of glycoprotein E. among DENVs, as described above.
This broadly means that a second infection with the homologous serotype is therefore unlikely.
A second infection by a heterologous serotype, on the other hand, can cause an intensified antibody dependent enhancement (AED) response, which in turn translates exacerbated inflammation, with consequences deleterious pathophysiology.
It is postulated that this AED occurs because despite the fact that in the first infection there is production of neutralizing antibodies (capacity that remains over time thanks to memory B cells), when infection by a heterologous serotype occurs, the secreted IgG they do not succeed neutralize this virus with molecularly distinct characteristics.
These antibodies, instead of producing an adequate opsonization and suppression, bind to the heterologous virus, subsequently to the macrophage or monocyte through the Fc# receptor, which instead of generating the elimination of the pathogen, favors its endocytosis without inactivating it, thereby potentiating its ability to complete its cycle.
The exacerbated inflammatory reaction that was mentioned has an immunity component.

Cell Phone.

RELATIONSHIP BETWEEN DENGUE AND SEVERE DENGUE (COMPLICATED)

ALARM SIGNS IN DENGUE

- Dolor abdominal interno y sostenido (o la palpación)
- Vómitos persistentes
- Sangramiento de mucosas o hemorragias espontáneas
  - Petequias, equimosis, hematomas
  - Gingivorragia, sangrado nasal
  - Vómitos con sangre
  - Heces negruzcas o con sangre evidente
  - Menstruación excesiva / sangrado vaginal
- Acumulación clínica de líquidos (ascitis, derrame pleural)
- Cambio de fiebre a hipotermia con sudoración profusa, postración o lipotimia
- Cambios del estados mental: Letargia / intranquilidad
- Dolor precordial
- Hepatomegalia > 2cm (adultos)
- Trombocitopenia < 100.000/mm³

It has been postulated that memory CD8+ T cells maintain an adequate response when infected by homologous serotypes at their first exposure.
However, with heterologous serotypes, it presents increased secretion of interleukins, which is not as effective in eliminating the virus and perpetuates the proinflammatory cycle.
Activation of complement and autoantibodies.
The complement system provides a first line of defense against pathogens.
Its activation is present both in the first and in subsequent infections.
In patients they are Dengue Shock Syndrome, during the defervescence time, when Clinically, capillary leakage and redistribution of fluids are becoming evident, it has been demonstrated high levels of C3a and C5a products in plasma, followed by consumption accelerated and marked reduction of complement.
Different mechanisms have been postulated, one of the most important being direct activation by non-structural protein 1.
It has been shown that the NS1 protein has a direct action on the complement, generating activation of the membrane attack complex, both in its secreted phase and when it is expressed by infected cells.
This protein not only has effects at the complement level.
It has been determined that the immunological reaction that triggers specific anti NS1 antibodies can result in an attack on the host's own elements.
The endothelium and platelets are the ones that are most affected by this process, since in their membrane they express antigens with structural similarities to said protein.
Once infection of these cellular elements occurs, the attack of the immune system is also justified by recognition of viral antigens, therefore "autoimmunity" is not the only process involved.

Increased capillary permeability and extravasation

The characteristic capillary permeability of the severe clinical pictures caused by Dengue has a multifactorial origin.

There is evidence to suggest that there is endothelial activation, with vacuolization and clefts at the interendothelial junctions, as a consequence of DENV 1 infection.

The condition of the endothelium per se plays an important role due to the cytotoxic immunity directed towards the infected cells, with consequent apoptosis or necrosis that favors the disruption of capillary integrity.

The function of the glycocalyx is the restrictive selection of molecules, according to their charge, size and shape.

The cytokine storm generates modification of the glycocalyx and tight junctions, thereby favoring hyperpermeability and eventual capillary leakage.

In addition, during dengue fever hypoalbuminemia and proteinuria can be observed, which together with the increased permeability of the glycocalyx favor fluid extravasation.

All these processes together are responsible for the formation of third spaces (ascites, pleural effusion), and edema (intestinal, pulmonary, cerebral), and consequently tissue hypoperfusion.

Thrombocytopenia and impaired coagulation homeostasis

Thrombocytopenia is a consistent phenomenon in both mild and severe clinical episodes.

It is mainly due to two mechanisms.

The first is bone marrow suppression (which also explains part of the leukopenia), and second, the autoimmune effect by cross-reaction with antibodies against the protein NS1.

NS1 has the ability to bind to prothrombin, decreasing its activation and causing alteration of coagulation haemostasis, in addition to being able to trigger signal transduction in some cells, thereby increasing the secretion of cytokines and generate a greater proinflammatory state.

Gastrointestinal disturbances

Liver noxa has been seen to be related to processes of apoptosis in hepatocytes induced by DENV, rather than to necrosis phenomena.

This generates an increase in transaminases without a significant elevation in bilirubin.

The ascites that occurs in cases of severe dengue and dengue shock syndrome is due more to extravasation due to increased capillary permeability than to hepatitis. properly, since it is not usually so severe.

In the same way, coagulopathy is more related to inflammatory phenomena, the interaction of prothrombin with NS1, than with liver disease.

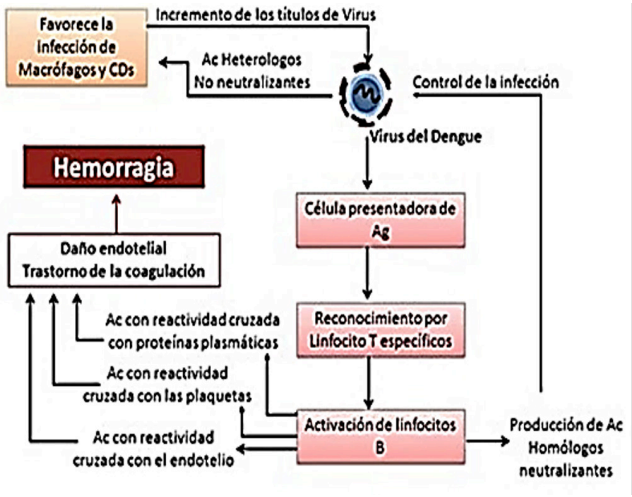
It not only generates liver disease, since the gastrointestinal manifestations are present in 70% of patients with symptomatic Dengue infection.

Of these the most frequent are nausea and vomiting, however others such as diarrhea and abdominal pain occur, and in more exceptional cases, pancreatitis and cholecystitis.

In adults these symptoms have been determined to be related to upper gastrointestinal bleeding; On the other hand, in children, the gastrointestinal manifestations are related to the severity of the condition, they are more frequent in dengue hemorrhagic fever and dengue shock syndrome.

However, this is an epidemiological correlation; no pathophysiological theory has yet been described in the literature.

IMMUNOLOGICAL EFFECTS IN DENGUE INFECTION



Neurological alterations

Neurological alterations due to dengue virus are rare, only present in 1% to 5% in some series.

Despite the fact that cases of neurological alterations related to DENV infection were already reported since 1976, and that indirect evidence such as intrathecal production of specific immunoglobulins against the virus was found since the 1990s, it was not until 2007 that it was demonstrated by assay. biological neurotropism of DENV as a direct cause of leptomeningitis and encephalitis in mice.

The hypotheses established by the literature involve three pathogenic mechanisms.

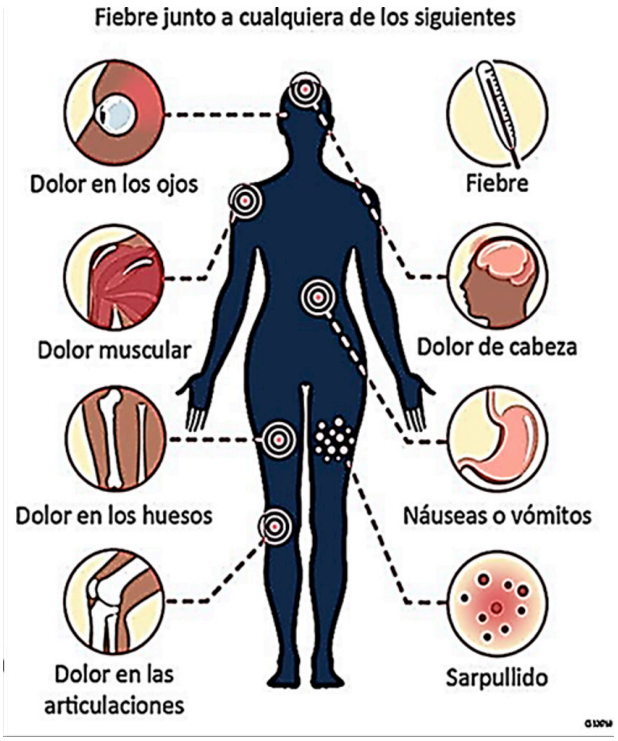
main.

The neutrotropism mentioned above, as responsible for encephalitis, meningitis, myositis and myelitis.

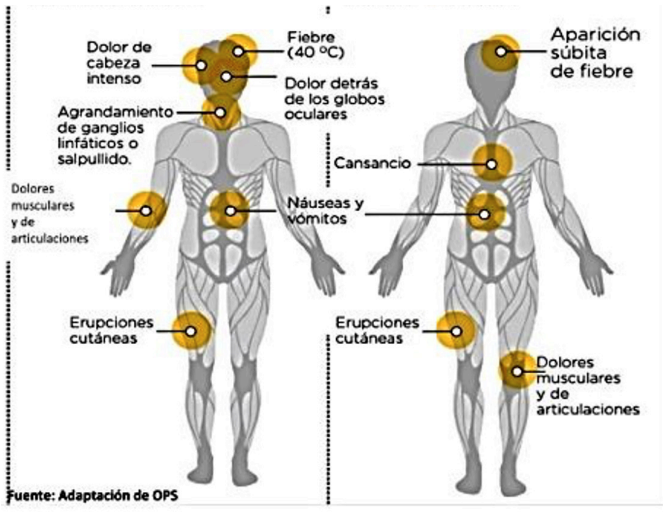
Systemic complications resulting in encephalopathy and hypokalemic paralysis, such as hypotension, cerebral edema, microvascular or frank hemorrhage, hyponatremia, and failure hepatic fulminant.

In addition, a picture of immune-mediated post-infectious encephalomyelitis could present, which also includes Guillain Barré syndrome and optic neuritis.
Although, in theory, a person could suffer from dengue up to four times throughout their life
(one for each serotype), so far only up to three infections have been confirmed in
the same individual.
Any serotype can cause severe forms of the disease, although serotypes 2 and 3
have been associated with the largest number of serious cases and deaths.

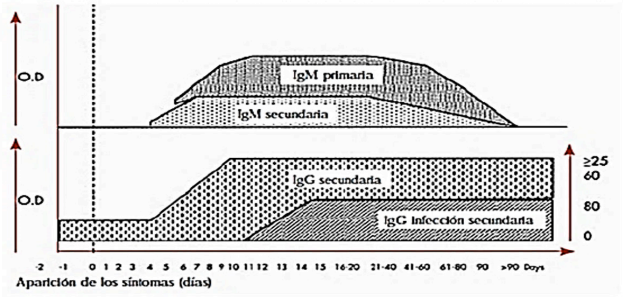
CLINICAL FINDINGS IN DENGUE

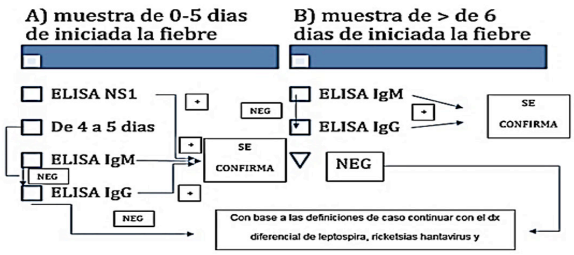


SIMILARITIES AND DIFFERENCES BETWEEN THE DENGUE CLINIC (LEFT) AND CHIKUNGUNYA (RIGHT)



SEQUENCE OF APPEARANCE OF ANTIBODIES
SEQUENCE OF LABORATORY FINDINGS





Dengue and vaccines

As we already explained, immunoamplification is the cause of cases of complicated/severe dengue (dengue shock and dengue hemorrhagic fever).
It occurs when an individual, with Ac. against a dengue serotype, comes into contact with one of the other serotypes.
This was brought to the fore – regarding the risk of multivalent experimental vaccines – when Sanofi tested the Dengvaxia vaccine.
The phase III study was heavily criticized for not mentioning potential risks and removing them from the list of serious side effects.
Despite this, the vaccine was accepted by the WHO as "theoretically promising", and its use was approved in the Philippines (2019).
There, more than 600 deaths were detected in children who received the vaccine, which is why it was permanently banned in that country, and the case is still being investigated by the Public Prosecutor's Office.

CONCEPTS ABOUT IVERMECTIN

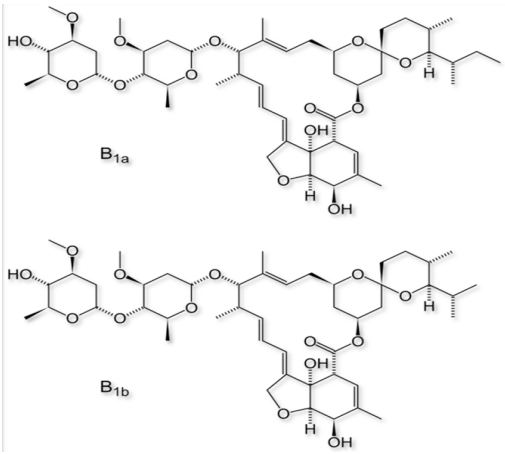
Ivermectin is an antiparasitic (endodecticidal), with nematicidal and ectoparasiticidal properties.
It is a macrocyclic lactone derived from the avermectins, a group of highly active endodecticidal antiparasitic agents isolated by fermentation from the soil microorganism Streptomyces avermitilis.
It was discovered in 1960 in Japan by Satoshi Omura.
In 1981, William C. Campbell began the studies that allowed its veterinary use.

Both received the Nobel Prize in Physiology and Medicine in 2015.
In 1985, the French demonstrated its usefulness in onchocerciasis in Africa.
It was approved in 1997 by the FDA for strongyliasis and crusted scabies, in patients with AIDS.
Ivermectin is a semisynthetic analogue of Avermectin B1a (Abamectin).
It is composed of a mixture containing at least 80-90% 22,23-dihydroavermectin B1a and 10-20% 22,23-dihydroavermectin B1b.
The two homologues (B1a and B1b) differ only by a methyl group (CH2).
Ivermectin is 22,23-dihydroavermectin B1.
Several avermectins are known today:

- Ivermectin
- Abamectin
- Doramectin
- Moxidectin
- Emamectin
- Nemadectin
- Eprinomectin
- Selamectin

Of all of them, the only one indicated and tested in humans is Ivermectin.
Ivermectin is a white to yellowish white crystalline powder, insoluble in water, but soluble in methanol and 95% ethanol.(8)
In Human Medicine, it has been used in children from 5 years of age onwards, for the management of ecto and enteroparasitosis.
Ivermectin is generally well tolerated and adverse reactions are generally minor and rare.
Most of the adverse reactions have been associated with the treatment of filariasis that could be related to an immunological reaction due to the death of the parasites, as occurs with the Mazzotti reaction in onchocerciasis.
In a double-blind, randomized, placebo-controlled study in 68 adults, Ivermectin doses of 30 to 60 mg three times a week were tested in one group and 90 to 120 mg in a single dose in another group, without Significant side effects will be observed, demonstrating the tolerance and safety of the medication.
pediatric precautions
Most studies recommend not using Ivermectin in children who weigh less than 15 kilos or who are less than two years of age, since the blood-brain barrier may be less developed than in older children.
However, in other studies, Ivermectin has been used from one year of age or in children weighing more than 10 kilos without significant side effects.
Many studies have shown that the safety and efficacy of Ivermectin administration in children are similar to those observed in adults.
geriatric precautions
There are not many studies that include patients older than 65 years; however, when treating geriatric patients with scabies who were treated with conventional topical therapies without improvement, oral Ivermectin could be used successfully and with minimal side effects that could be attributed to the use of the medication.
No increased mortality has been shown in geriatric patients receiving treatment with oral ivermectin.

CHEMICAL STRUCTURE OF AVERMECTINS



Orally, and in humans, it does not cross the blood-brain barrier.
It is contraindicated in pregnancy.
Recently, its virucidal effects on flaviviruses have been compiled: Dengue, Zika, Chikungunya, etc.
Chikungunya virus (CHV) is an arbovirus of the Alphavirus genus, which has infected millions of people since its re-emergence in the last decade.
To test the efficacy of around 3000 compounds, a stable replica of HCV included in a BHK cell line was used, with a luciferase used as a reporter.
Ivermerctin (EC%=0.6 microM) inhibited viral replication in a dose-dependent manner.
They were also active against the flavivirus that causes malaria.
In studies carried out in farm animals, the administration of ivermectin caused the death of the mosquitoes that infect them, in a dose-dependent manner.
This is applicable to mosquitoes of the Anopheles, Culex and Aedes genera.
The current status of ivermectin continues to surprise and excite scientists.
It has been confirmed that ivermectin is closely related to the immune system, acting as an immunomodulatory agent.
Reuse and repositioning of ivermectin
It has been shown to control a whole new range of diseases.

For example, orbital myiasis, trichinosis, malaria, leishmaniasis, African trypanosomiasis, asthma, epilepsy, viral diseases (eg, human immunodeficiency virus [HIV], dengue fever, encephalitis), bacterial diseases (tuberculosis and Buruli ulcer), oncological diseases (breast cancer, leukemia, glioblastoma, cervical cancer, gastric cancer, ovarian cancer, colon cancer, melanoma and lung cancer).

Ivermectin may become an exceptional drug in the future, as it may be effective for:

diseases (diabetes, hypercholesterolemia, insulin resistance, obesity, hypertriglyceridemia and hyperglycemia).

Diseases mediated by the NR1H4 farnesoid X receptor (atherosclerosis), fatty liver, cholestasis and gallstones, inflammation and cancer.

Viruses such as HIV, Human Cytomegalovirus (HCMV), Epstein-Barr Virus (EBV), Human Papillomavirus (HPV), etc.

Ivermectin and Dengue

Ivermectin has already demonstrated its efficacy in reducing dengue viral load, in a dose-dependent manner.

Ivermectin has a proven antiviral effect against other single-stranded RNA viruses such as dengue or yellow fever, against which it has succeeded in inhibiting their replication in vitro.

In addition, it has an immunomodulatory role that is interesting to evaluate, since it has been seen that one of the great problems of the dengue virus is immunoamplification.

The disappearance of the clinical picture -when it is administered early- occurs in less than 72 hours.

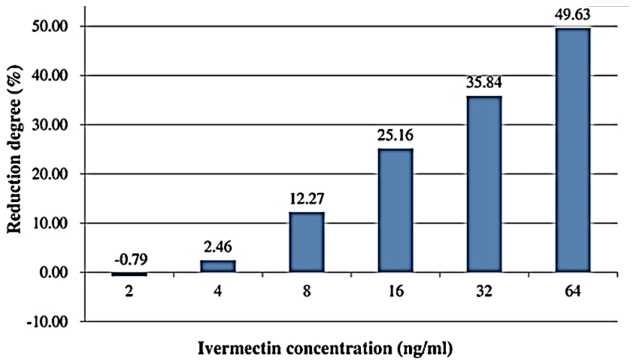
Likewise, subjects receiving prophylactic doses of IVM will not contract dengue, even when inoculated through the bite of Aedes mosquitoes, which confirms the viricidal effect of the compound.

What's more, these mosquitoes will die after such a bite, at a rate 6 times greater than their normal life cycle.

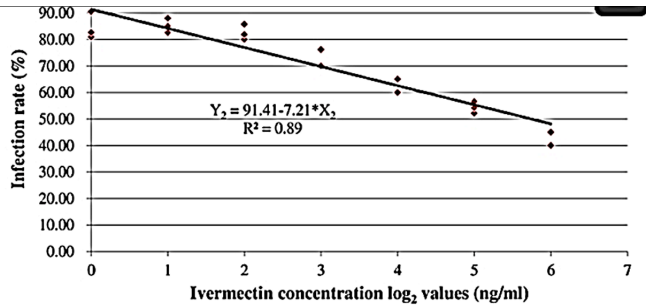
This was observed in farm animals, which received IVM to avoid mosquito-borne diseases (Culex, Anopheles, Aedes, etc.).

Given this finding, the effect was replicated in human volunteers, with equal success.

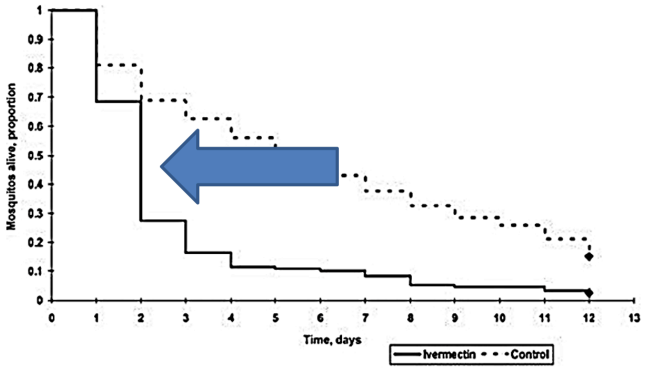
REGRESTIVE CORRELATION BETWEEN INFECTION RATES AND LOG2 VALUES OF IVM CONCENTRATION



COMPARISON BETWEEN ADMINISTRATION OF IVM TO MOSQUITOES AND REDUCTION OF DENGUE SEROTYPE 2 RNA



SURVIVAL OF MOSQUITOES AFTER FEEDING FROM PEOPLE WITH AND WITHOUT IVM



Yang S et al., identified that the ivermectin molecule can prevent important factors of the viral replication cycle from entering the nucleus; for example, in the case of HIV, it was observed that ivermectin inhibits the entry of integrase into the cell nucleus.

In dengue, ivermectin could inhibit the entry of the dengue NS5 protein into the host nucleus.

Subsequently, these investigators reported the precise point of impact of ivermectin. To prevent the passage of integrase and NS5 to the cell nucleus, ivermectin would target a host protein, located in the cytoplasm of cells, the IMPα/ß1 protein, which is responsible for transporting these molecules to the nucleus of the cell. host cell.

PROPHYLAXIS SCHEME WITH IVERMECTIN

IVM, 0.3 mg per kilo of weight, after a high-fat meal.
Repeat this scheme twice a week.

TREATMENT SCHEME WITH IVERMECTIN

CASES DOSE FREQUENCY DURATION
Mild 0.4 mg/Kg once a day for 5 days
Severe 0.6 mg/kg once a day for 7 days

CONCLUSIONS / RECOMMENDATIONS

Dengue and its related arboviral diseases (Zika and Chikungunya) continue to increase in the Americas.

The economic weight that they imply is becoming higher and higher, as is the number of fatalities (not missible in monetary terms).

There was -to date- no protection measure other than junk removal and the use of repellents.

The arrival on the scene of A. albopictus has reduced the effectiveness of peridomiciliary care, as well as the seasonal incidence.

Ivermectin has already been tested -successfully- in this type of pathology.

Its use is economical, its response is extremely satisfactory (both in prophylaxis and in treatment), and its safety has been proven in billions of doses administered in other continents.

For all of the above, we emphasize the use of ivermectin (according to the schemes proposed above), to overcome this scourge.

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