ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Statistical Analysis of State wise Dengue Data in India.

Shreenidhi R, Vidya VS, Ramanathan K, and Shanthi V*.

Industrial Biotechnology Division, School of Bio Sciences and Technology VIT University, Vellore-632014, Tamil Nadu, India.

ABSTRACT

Dengue fever is a viral disease of the tropics, transmitted by mosquitoes causing sudden fever and acute pain in the joints. The statistical data on Dengue was seen in detail, with respect to its pathogenesis and epidemiology. We have also discussed the life cycle of the vector that bears the *Flavivirus*. Experimental drugs were listed out in this paper, which may cure this deadly disease. Also, a natural therapy, in the form of papaya leaf juice has been identified and discussed in the paper. Mutations found in the virus have been discussed, and has emphasized the need to find a cure. Computational applications towards analysing the number of Dengue cases and deaths have been found and are used to keep a check on how the disease spreads. Graphical representation on the variation of the number of cases and deaths with respect to the disease helps to understand the most vulnerable states in India towards the Dengue virus, as well as how medical care has improved over the years, bringing the number of reported cases down. The article has tried to come up with a concise detailing of Dengue infection, its mechanism, its drugs and their specific targets, its databases and the drug resistance mutations. The main facts and figures, as to which countries of the world are affected by this disease, as well as number of cases that were reported to WHO was also discussed.

Keywords: Dengue, Drug Targets, Mechanism, Mutations

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Dengue fever DF is an infection caused by single-stranded RNA *Flavivirus* found in the infected *Aedes* mosquito. It has flu-like properties and affects most infants, children and young adults (WHO Dengue report, 2014).

It is characterized by the rapid onset of fever in combination with severe headache, retro-orbital pain, myalgia, arthralgia, gastrointestinal discomfort, and usually rash. Minor hemorrhagic manifestations may occur in the form of petechiae, epistaxis, and gingival bleeding. Leukopenia is a common finding, whereas thrombocytopenia may occasionally be observed in Dengue fever, especially in those with hemorrhagic signs. The World Health Organization (WHO) classifies Dengue Hemorrhagic Fever (DHF) in four grades (I to IV). DHF grades I and II represent relatively mild cases without shock, whereas grade III and IV cases are more severe and accompanied by shock (Martina et al., 2015).

EPIDEMIOLOGY

This disease was first described in 1780 and the Virus was isolated in 1944. Dengue virus infection is the most common arthropod-borne disease worldwide with an increasing incidence in the tropical regions of Asia, Africa, Central and South America. The global prevalence has grown dramatically in the recent decades. The disease is endemic in more than 100 countries in Africa, America, the Eastern Mediterranean, South-east Asia and the Western pacific, in which South-east Asia and the Western pacific being severely affected. Incidence of dengue has grown substantially around the world, leaving 40% of the people susceptible to the disease. It is seen that around 50-100 million dengue infections occur every year**.**

Not only is the number of cases increasing as the disease spreads to new areas, but explosive outbreaks are occurring. The threat of a possible outbreak of dengue fever now exists in Europe and local transmission of dengue was reported for the first time in France and Croatia in 2010 and imported cases were detected in three other European countries. In 2012, an outbreak of dengue on Madeira Islands of Portugal resulted in over 2000 cases and imported cases were detected in 10 other (the picture depicts the number of cases reported and countries affected from 1955 to 2007) countries in Europe apart from mainland Portugal (WHO Dengue Guidelines, 2009).

Figure 1.2 Average annual number of dengue fever (DF) and dengue haemorrhagic fever (DHF) cases reported to WHO, and of countries reporting dengue, 1955–2007

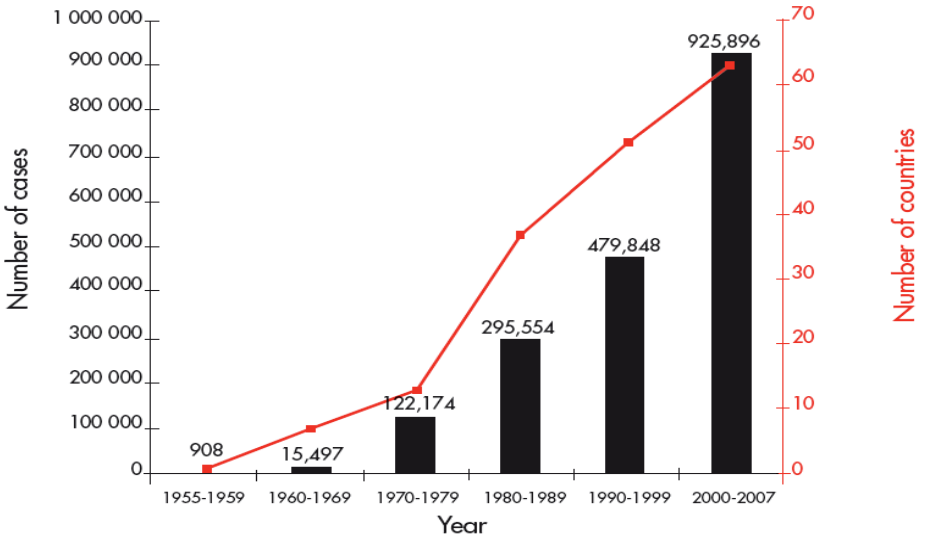


Figure 1: Dengue Cases reported to WHO, 1955- 2007 (WHO Dengue report, 2014)

An estimated 500 000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die(WHO Dengue Guidelines, 2009).

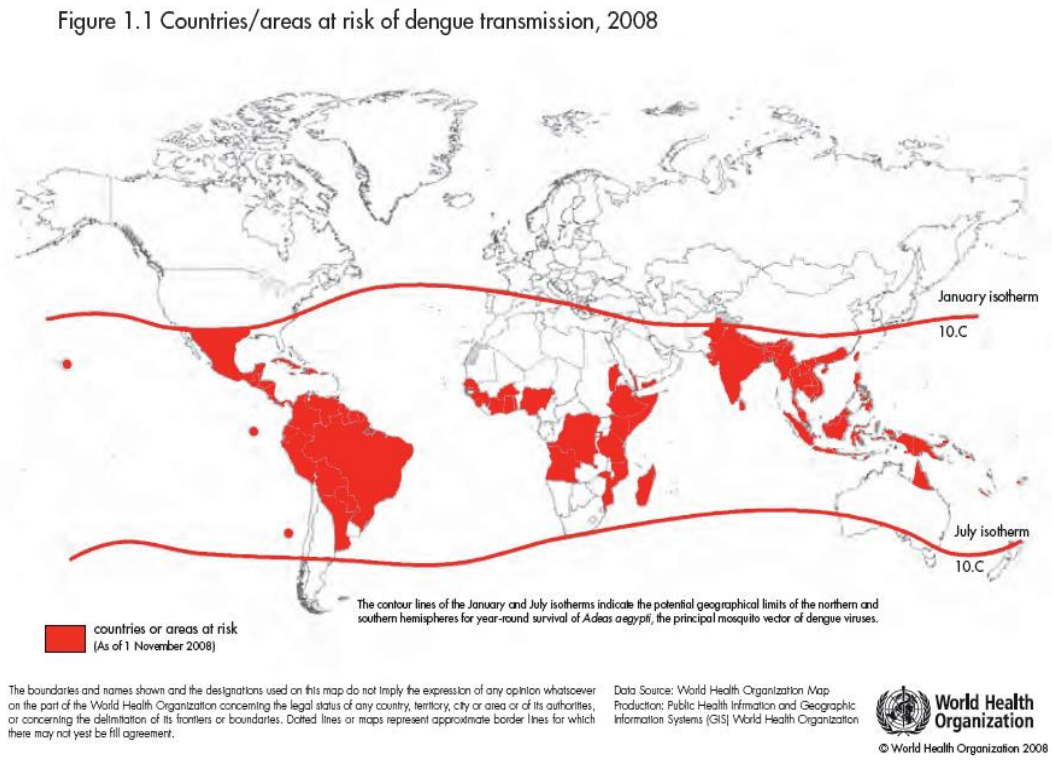
ISSN: 0975-8585

PATHOGENESIS

Primary fever maybe asymptomatic or may result in dengue fever. This is generally a self-limiting illness which occurs after an incubation period of 4 to 8 days. It has symptoms such as fever, aches and arthralgia which can progress to arthritis (Drug Targets Database for Dengue). In this situation, clinical differentiation from other viral illness may not be possible and need for supportive treatment is required.

DENGUE HAEMORRHAGIC FEVER

Figure 2: Countries with higher probability of transmission of Dengue (WHO Dengue report, 2014)



DHF is a potentially deadly complication. The incubation period is unknown but is likely to be similar to that of dengue fever. It commences with high fever and many of the symptoms of dengue, but with extreme lethargy and drowsiness (Drug Targets Database for Dengue).

Mechanism of Interaction:

Dengue is a vector borne disease, and is carried by the *Aedes*mosquito. This female mosquito only bites a human being around the evening time, and thus causes the virus to affect the human body (Abonyi, et al., 2009).

In order to cause infection, a virus must be able to bind to a somatic cell surface. This means that the virus has to bind with specific receptors by producing special proteins. Monocytes and macrophages are the principle target for dengue viruses. The virus E-protein mediates this attachment to the cells, but the nature of the host cell receptors remains elusive.

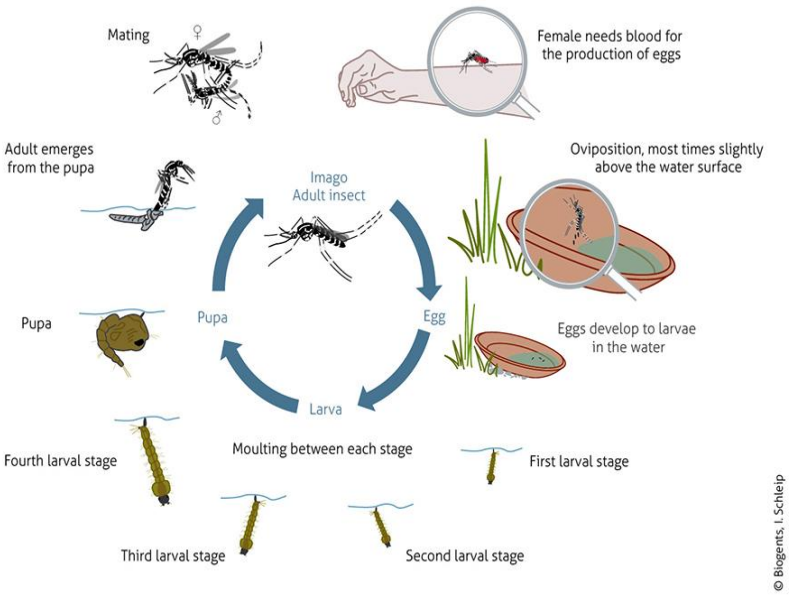
The major receptors to this virus are proteins, Fc receptors, which are specific proteins found on the surface of certain cells like B- lymphocytes, macrophages, neutrophils, glycosaminoglycans and lipopolysaccharide binding CD14- associated molecules. The initial step in dengue virus contamination is adsorption and penetration. The attachment to the cell wall is temperature dependent process occurs at both 37°C and 40°C. The viral penetration only proceeds at 37°C. The penetration occurs by membrane fusion in mosquito or by receptor- mediated endocytosis in monocytes. In the presence of sub-neutralizing amounts of

antibody, Fc Receptors alsomediate attachment and uptake of dengue viruses into certain cells such as macrophages and monocytes The antibody dependent mechanism (ADE) plays a role in the development in DHFand the Dengue Shock Syndrome (DSS).

Dengue as such has no significant course of treatment. Severe complications arise from dengue haemorrhage fever, and can only be controlled by careful clinical practices and experienced physicians(Kala CP, 2012).

The Life Cycle of Tiger Mosquito:

Figure 3: Life cycle of Tiger mosquito



The life cycle of the Asian tiger mosquito and the Yellow fever mosquito are very similar. The eggs are resistant to heat and dryness and are deposited in natural and artificial containers subject to flooding(Campbell et al., 2008). When eggs are covered by water, the larvae hatch. They hang at the surface of the water and breathe through a snorkel-like siphon at the tip of the abdomen. There are four larval stages that feed on organic material that they filter out of the water with their mouthparts. The fourth-stage larva changes into a pupa that hangs at the surface of the water and breathes air through two snorkel-like siphons at the front end. The pupa is a non-feeding stage where the mosquito changes from the larval form into an adult insect, or imago. The adult mosquito emerges from the pupa and normally feeds on sweet plant juices and nectar to meet their energy requirement Only female mosquitoes feed on blood, which they need to produce their eggs.(Chen, Yaping, et al., 1997).

Drugs Used To Combat Dengue:

As we know already, the Dengue fever is a life threatening disease caused by the Dengue virus (*Flavivirus*) that is borne and transmitted by the *Aedes* mosquito. There is no medicine or vaccine against the virus so far that is clinically approved of, but the effect of 'Papaya (*Carica papaya L.*) leaf juice' in curing the disease has proven to be very efficient in combating the disease by increasing the platelet count (Kala CP, 2012).Hence once during the outbreaks, the Tamil Nadu State Government requested the usage of Papaya leaf juice for its population.

The low platelet count in blood is uniquely attributed to the Dengue fever which leads to high fever, severe muscle pain, sudden bleeding and joint pains. Therefore, improvement in platelet counts after therapy by application of ethno medicines such as papaya leaf juice is considered a positive outlook. Platelets are vital

components in blood as they provide both structural and molecular function in blood clotting (Campbell, N. A. et al., 2008).

The methodology of effective drug usage:

The usage of papaya leaf juice against Dengue fever is a traditional belief among the population. The people collect fresh papaya leaf and extract the juice by crushing and squeezing. Only the leafy part is collected not the sap or stalk. The extracted juice is then filtered to avoid uncrushed fibres of the leaf. One leaf gives about one tablespoon of juice. The patients are given 2 tablespoons of papaya leaf juice with an interval of 5 to 6 hours per day. The leaf should not be boiled or cooked; only the raw freshly crushed juice is to be used.

Besides leaf juice of papaya, there are reports indicating that the extract of some other flowering species, such as *Vitexnegundo, Azadirachtaindica* and *Artemisia annua* contains properties to work against the viruses (Abonyi, et al., 2009). Some lower plant species including lichens and algae exhibit inhibitory activity against some type of viruses.

Dengue virus is a human pathogen that has re-emerged as an increasingly important public health threat. We found that the cellular receptor utilized by dengue envelope protein to bind to target cells is a highly sulphated type of heparan sulphate. Heparin, highly sulphated heparan sulphate, and the polysulphonate pharmaceutical Suramin effectively prevented dengue virus infection of target cells, indicating that the envelope protein-target cell receptor interaction is a critical determinant of infectivity. The dengue envelope protein sequence includes two putative glycosaminoglycan-binding motifs at the carboxy terminus; the first could be structurally modelled and formed an unusual extended binding surface of basic amino acids. Similar motifs were also identified in the envelope proteins of other flaviviridae. Developing pharmaceuticals that inhibit target cell binding may be an effective strategy for treating *flavivirus* infections (Chen, Yaping, et al., 1997).

Experimental Drugs Used:

Drug Bank Accession Number	Drug Type	Generic Name	Molecular Weight
EXPT00452	Experimental Drug	Alpha-L-Fucose	164.158g/mol
EXPT00721	Experimental Drug	Beta-D-Mannose	180.157 g/mol
EXPT02113	Experimental Drug	Alpha-D-Mannose	180.157 g/mol
EXPT00737	Experimental Drug	B-Octylglucoside	292.372 g/mol

As there is no proven drug as of yet that can eradicate, or clear the symptoms of Dengue, there is still some research that is going on to find the appropriate drug which can fight against the virus.

Targets of Drugs Used:

Drug targeting is mainly known as targeting a specific tissue of the human body. This helps in the recovery of the ill person by the ingestion of the drug found. The target here means the specific pathway of metabolism in the body that gets inhibited or activated due to the introduction of the drug. As the specific of the virus is unknown, and the indication of the virus infection is unknown; there are a lot of experimental drugs- but no particular drug to cure the disease yet.

Mutations In The Dengue Virus And A Novel Approach Towards It:

The mosquito-borne dengue virus has mutated several times over the years, leading to five outbreaks of the disease in the Capital (New Delhi) since 1996. This comes at a time when scientists from All India Institute of Medical Sciences (AIIMS) and National Centre for Disease Control (NCDC) were preparing tests to identify 2012's dengue strain (Dr.ShobhaBroor, 2012).

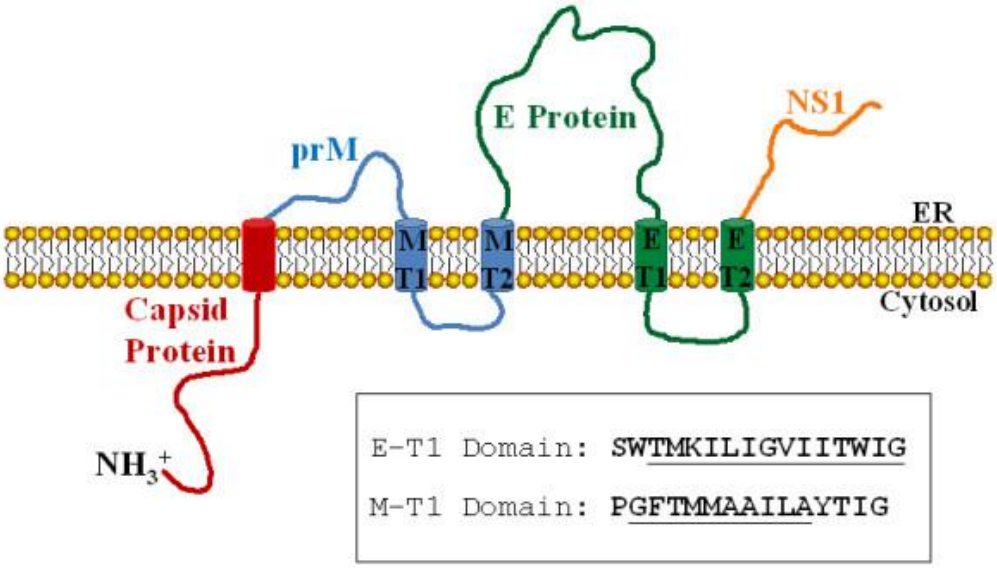
ISSN: 0975-8585

There are four strains of the virus, commonly categorised as dengue-I, II, III and IV. It is a myth that the virulence of the disease is determined by the strain. Any strain can lead to aggressive forms of the disease. Since most people don't have immunity against new strains, a greater number are affected. Doctors have reported that there is a mutation at the molecular level in the virus, which did not change the way the virus infected (Romano, Camila Malta, et al., 2013). They described how the dengue virus (DENV) undergoes mutations at a much slower pace than originally imagined, increasing the chances of finding an effective vaccine against this virus.

The scientists reached this conclusion by sequencing the complete genome of thousands of viral particles that were found in ten blood samples from patients who were diagnosed during the epidemic that hit the tropical areas in 2010(Romano, Camila Malta, et al., 2013).

A strategy has been developed by which host-range mutants of Dengue virus can be constructed by generating deletions in the trans membrane domain (TMD) of the E glycoprotein. The host-range mutants produced and selected favoured growth in the insect hosts. Mouse trials were conducted to determine if these mutants could initiate an immune response in an *in vivo* system (Smith, Katherine M., et al., 2011).

Figure 4: Complete genome of thousands of viral particles found in 19 blood samples during the epidemic that hit the tropical region in 2010 (Romano, Camila Malta, et al., 2013)



Novel host-range mutants were created that have preferential growth in insect cells and impaired infectivity in mammalian cells. This method for creating live, attenuated viral mutants that generate safe and effective immunity may be applied to many other insect-borne viral diseases for which no current effective therapies exist (Smith, Katherine M., et al., 2011).

Computational Applications towards Dengue:

Researchers have come up with using social media networks as a method of analysis- to compare the amount of dengue statistics officially reported, and otherwise. The correlation between the two was found. Researchers believe that this is required to study the evolution of dengue studies.(Gomide, Janaína, et al., 2011).

There are also applications available on Mobile Devices, which can help a person to diagnose their susceptibility towards dengue, by following a questionnaire. This also helps doctors to easily treat the early stages in the patient (West, Darrell, 2012).

Statistical Data:

ISSN: 0975-8585

The following figures (5-9) show the statistics of Dengue cases and deaths over the years, between the years 1997 till 2013 taken from (Ministry of Health and Family Welfare, Indiahealthstat database). It is clearly seen that with improvement in medical care facilities, less number of Dengue deaths were reported. However, with the increase in population over the years, there is an increase in number of Dengue cases.

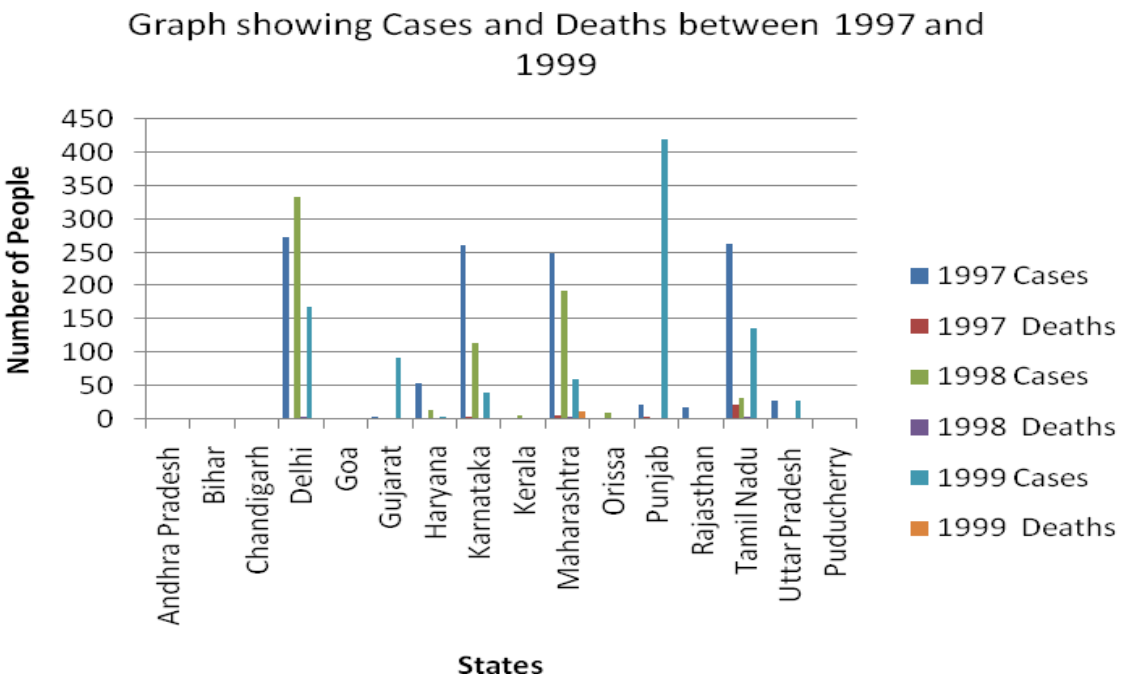


Figure 5: Graph showing Cases and Deaths between 1997 and 1999

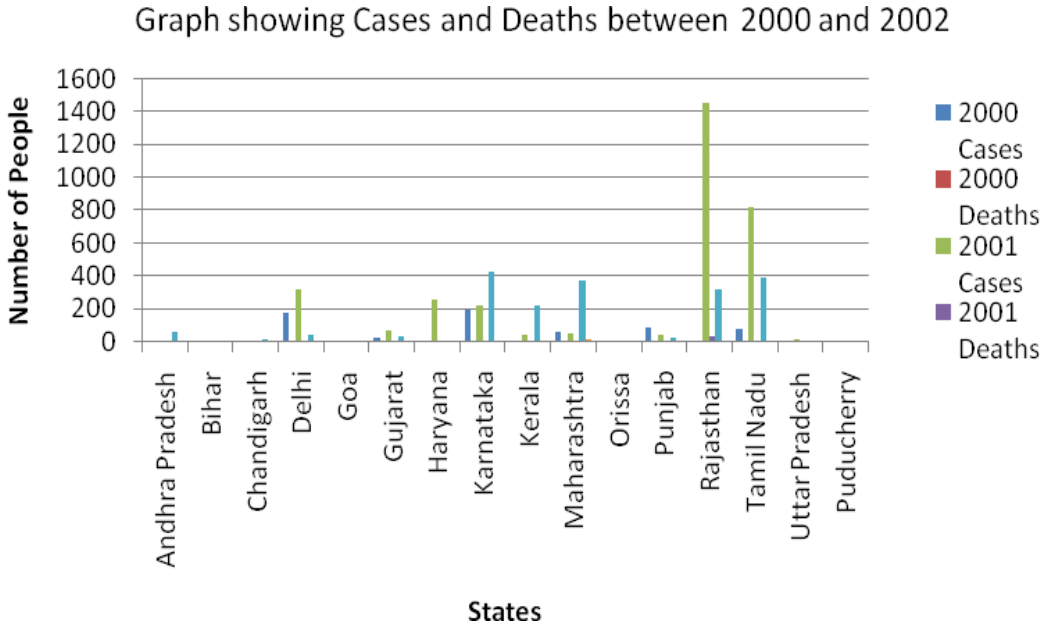


Figure 6: Graph showing Cases and Deaths between 2000 and 2002

ISSN: 0975-8585

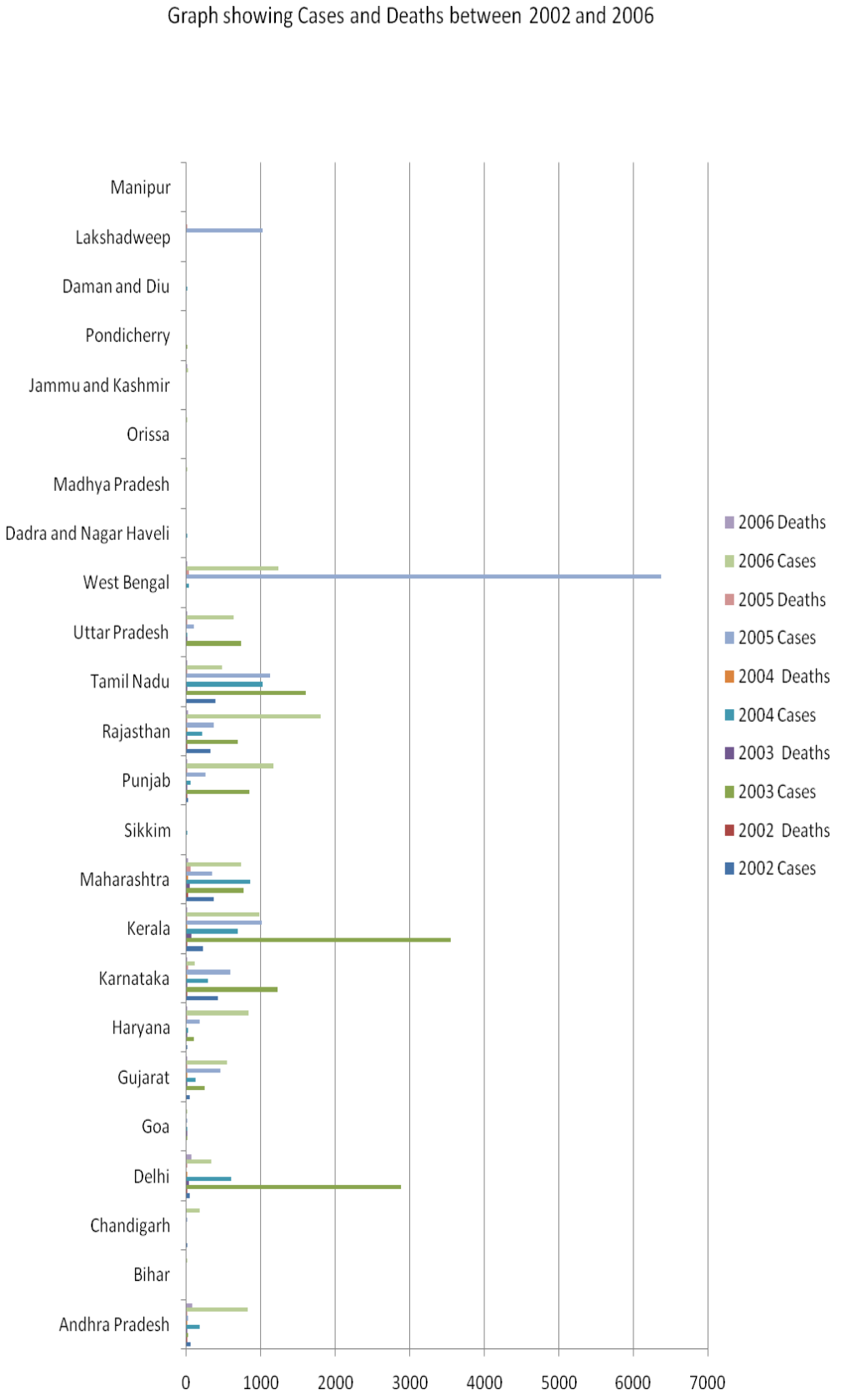


Figure 7: Graph showing Cases and Deaths between 2002 and 2006

ISSN: 0975-8585

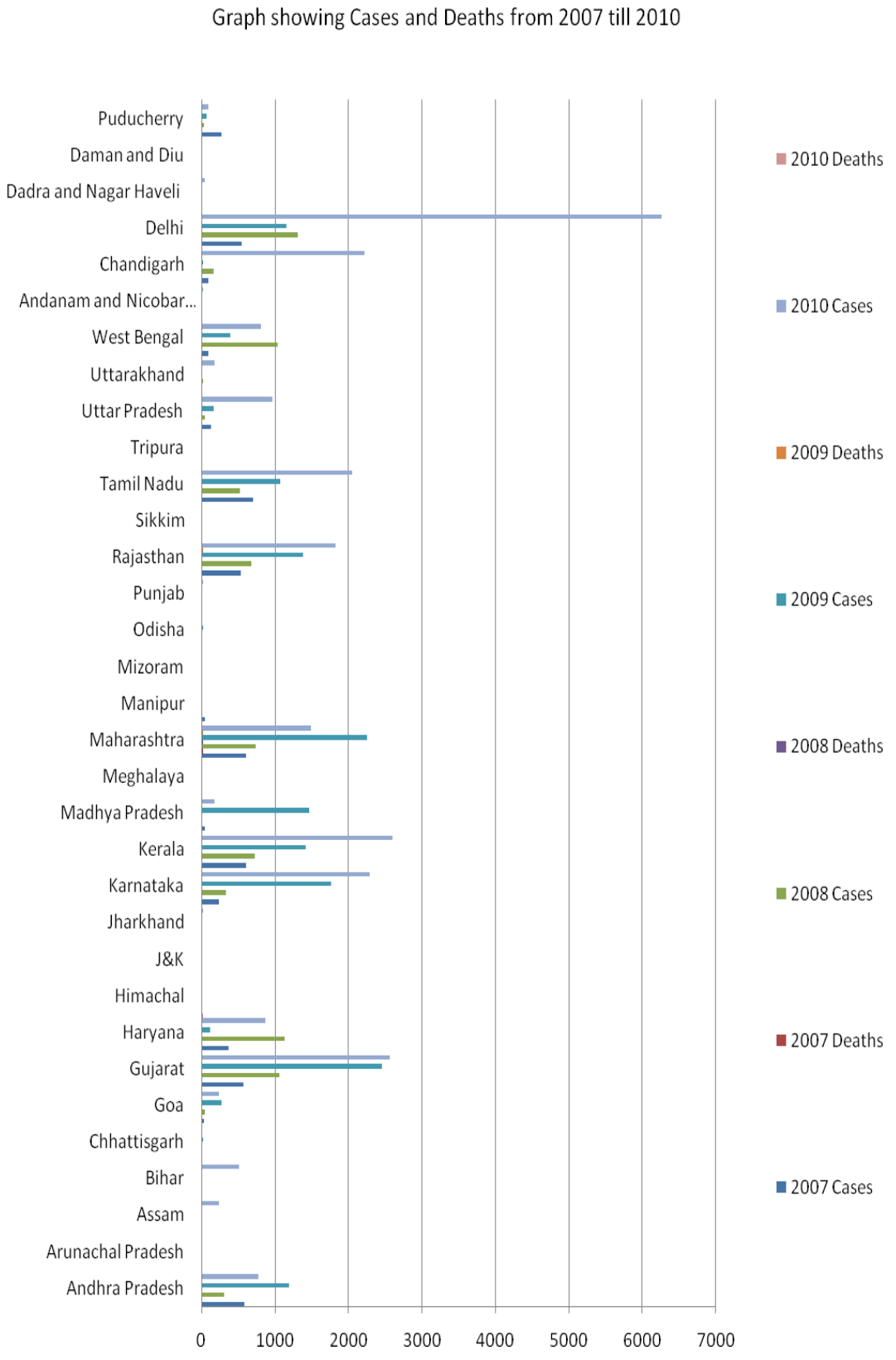


Figure 8: Graph showing Cases and Deaths between 2007 and 2010

ISSN: 0975-8585

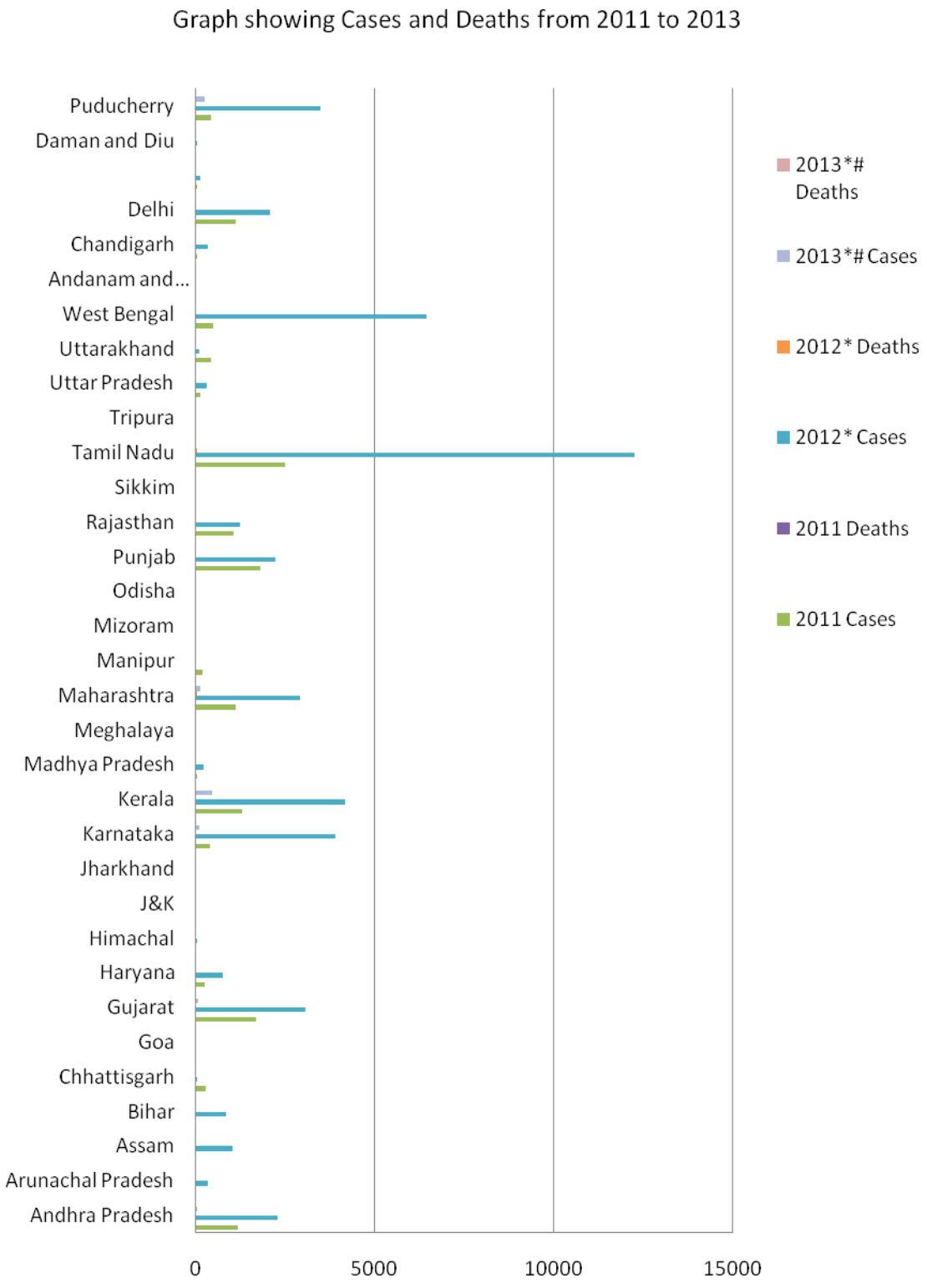


Figure 9: Graph showing Cases and Deaths from 2011 to 2013

Analysis:

The highest cases have been noted in West Bengal and Tamil Nadu over the years. West Bengal had outbreaks in 2002 to 2006 period while Tamil Nadu had it after that, quite recently. It can be clearly noted that

there have been continuous outbreaks state after state over the years. Also it is quite evident that numbers of deaths are less than cases admitted. Over the years, although there isn't any specific drug against Dengue, it is seem thatcases of the death has fallen due to the experience in handling this disease and the worst case scenario being death. Here it is to be noted that 'diagnosis' of the disease plays a very important role.

CONCLUSION

Dengue as a deadly epidemic has been discussed here with the past statistics. The severity of the disease is a threat that demands treatment of higher standards. But so far there has been no commercialised drug in use for Dengue. Still during the outbreaks of Dengue, there was a natural cure (papaya leaf juice) that was suggested to the people. Also some of the experimental drugs in use and their drug targets were summarised. The viral mutations have been given importance in this paper, because they might prove to be a potential source for future 'attenuated vaccines' against Dengue. We found the idea of using social networks as a method of analysis on the statistics of Dengue interesting. The state-wise dengue outbreaks in India give clear evidence that India is always in the crib of a Dengue outbreak and is in immediate need of medicines against Dengue.

ACKNOWLEDGEMENTS

The authors thank the management of Vellore Institute of Technology, for the constant encouragement, help and support to carry out this work.

REFERENCES

[1] WHO, Dengue and severe dengue, Fact sheet Number 117. 2014, 5(1), 1–37

[2] Martina, Byron EE, Penelope Koraka, and Albert DME Osterhaus. Dengue virus pathogenesis: an integrated view.*Clinical microbiology reviews.* 2009, 564-581.

[3] World Health Organisation. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control-New Edition 2009.

[4] Shardiwal, Rakesh K, and ShaluMagar. DengueDT-DB Drug Targets Database for Dengue. *Bioinformatics.org*. 2007.

[5] Kala, Chandra Prakash. Leaf juice of Carica papaya L. *A remedy of dengue fever. Med Aromat Plants*. 2012, 2167-0412.

[6] Abonyi, D.O., Adikwu, M. U., Esimone, C. O., and Ibezim, E. C.Plants as sources of antiviral agents. African Journal of Biotechnology. 2009, 3989-3994.

[7] Campbell, N. A., Reece, J. B., Urry L. A., Cain, S. A., Wasserman, S. A., Minnorsky P.V., et al. Biology. 8th Ed. London: Pearson. 2008.

[8] Chen, Yaping, et al. Dengue virus infectivity depends on envelope protein binding to target cell heparansulfate. *Nature medicine* 1997, (3.8) 866-871.

[9] Smith, Katherine M et al. Structural Mutants of Dengue Virus 2 Transmembrane Domains Exhibit Host-Range Phenotype.*Virology Journal* (8), 2011, 289.

[10] Romano Camila Malta, Michael Lauck, Felipe S. Salvador, Celia Rodrigues Lima, Lucy S. Villas-Boas, EvaldoStanislau A. Araújo, José Eduardo Levi, Claudio Sergio Pannuti, David O'Connor, and Esper Georges Kallas. Inter-and intra-host viral diversity in a large seasonal DENV2 outbreak. *PloS one* (8.8) 2013.

[11] Dr.ShobhaBroor, Head of Microbiology, AIIMS, City anchor: Mutation of virus gives dengue strains deadlier sting. Newspaper: Indian Express- New Delhi, Wed Oct 24, 2012

[12] GomideJanaína, Adriano Veloso, Wagner Meira Jr., Virgílio Almeida, FabrícioBenevenuto, Fernanda Ferraz and Mauro Teixeira. Dengue surveillance based on a computational model of spatio-temporal locality of Twitter. *Proceedings of the 3rd International Web Science Conference*. ACM, 2011.

[13] West, Darrell. How mobile devices are transforming healthcare.*Issues in technology innovation* (18)2012, 1-14.

[14] Courtesy: Ministry of Health & Family Welfare, from India health stat database. <http://www.indiahealthstat.com/default.aspx>