REVIEW ARTICLE

Dengue in India: Recent Advances, Prognostic Concerns and Future Considerations - A Review

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ABSTRACT

The last semi centennial has witnessed Dengue's expansion and escalation into all WHO regions, through the progressive build-up of hyperendemicity, to become the most important mosquito-borne disease in the world. India reports the fourth highest incidence of Dengue in the world, 14 cases per 100,000 population, after Brazil, Malaysia and Mexico. However, in 2014, a complexly designed study showed that India's Dengue case rate is severely under-reported and estimated it to be probably higher than Brazil's 291/100,000. India will, in all probability, experience many more outbreaks of Dengue as hyperendemicity gets established in our 4000-odd smaller cities and towns in the years to come.

We have characterized the available weapons against Dengue as 3Is – Insecticides, Immunologicals and Innovations. We have reviewed India's budgetary allocations for Dengue control and surveillance in the past five years. We compare this with expenditures in other Asian countries. While India's central allocation on all vector-borne diseases as part of 12th five-year plan was 0.36 USD per capita, Mexico, Malaysia , Brazil and Singapore spent 0.76, 3, 5 and 10 USDs per capita for Dengue surveillance and vector control in the same period. Even if we double this estimate of India's central allocation on all vector-borne diseases (0.72 USD per capita), accounting for an equal contribution from states, it is lower than the total cost of illness per capita for Dengue in the country (0.88 USDs per capita).

Eradication of Dengue virus is theoretically possible before it establishes itself completely in the mosquito-vector and human populations. We have argued for improved surveillance as a necessary backdrop for dengue control strategies. With good infrastructure and manpower, these strategies could be up scaled in the future for eradication of the Dengue virus. We conclude with recommendations for a future systemic strategy that synthesizes surveillance and control measures to achieve zero-infestation of humans and mosquitoes by the Dengue virus.,

Key Words: Dengue in India, Hyperendemicity of Dengue, Vector-borne diseases surveillance, Innovations for Dengue, Immunologicals for Dengue, Expenditure and Cost of Dengue

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Introduction

The existence of the Dengue virus has been acknowledged for nearly 400 years now. The earliest reported outbreaks of Dengue were from the Caribbean islands of Martinique and Guadeloupe in 1635.[1] In the 18th and 19th centuries, the American and Asian continents experienced pandemics of Dengue.[2,3] But the disease usually remained limited to soldiers of invading armies and other travelers, and did not affect local populations. As a result, even during the 19th century, Dengue was thought to be a sporadic disease with intermittent epidemics.[4]

It was only after the 1980s that Dengue emerged in its 'full glory'. Movement of refugees, vehicles, storage containers and rapid urbanization facilitated its geographical expansion. Since its appearance in the Philippines in 1954,[4] there has been an astronomical rise in Dengue cases reported annually to the WHO, from 908 in the 1950s to 2.2 million in 2010.[5] India accounted for only 1.3% of these cases (28,292) in 2010.[6] However, this was challenged by a study in 2013, which argued that the actual incidence of Dengue in the country is probably 282 times more than that captured and reported by the surveillance system![7] In 2017, India reported 14 cases and 0.02 deaths per 100,000 population.[6] But applying the 'adjustment factor' calculated by Shepard et al,[7] raises the case rate

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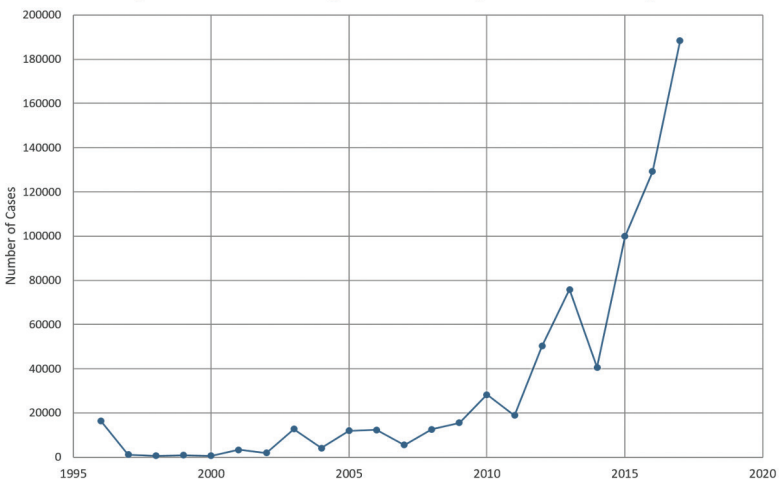

Figure 1. Trendline of Dengue cases in India (NVBDCP 1996-2017)

to 477 per 100,000 population, almost twice the case load in Brazil (292 per 100,000),[8] the country with the highest dengue incidence in the world.[9] As seen in **figure 1,** official estimates of Dengue incidence in the country, which were less than 20,000 cases per year before 2009, have now magnified by 10 times in the last decade.

We conducted a descriptive literature review to understand the recent advances in prevention and control methods for Dengue, and the financial outlay on Dengue in India and other endemic countries. This paper is based on our reflections from this review and an elementary comparative analysis of the costs and expenditures on Dengue in India vis-à-vis other endemic countries.

Intensification of disease transmission in India - Hyper-endemicity

Important to the pathology of Dengue disease is the concept of hyperendemicity -- a situation in which two or more of 4 different serotypes of dengue virus (DENV-1 to DENV-4) coexist in increasing proportions of Aedes mosquitoes within a given area, for e.g. within a ward of a city. With increasing density of infected mosquitoes, the probability of more serious dengue infection with more than one serotype keeps increasing, thus building up hyper-endemicity in our wards and cities over the years.[10,11] Older populations accumulate immunity to multiple serotypes. The severe forms of the disease then shift towards younger populations as was witnessed in Brazil in the last decade, where an unusually higher fatality was recorded in children less than one year.[12] Good case management has enabled dengue burdened countries of South-east Asia and the Americas to reduce their overall dengue fatalities.[13]

Vellore district in Tamil Nadu, India, was the earliest region in the world, to report the presence of all four virus serotypes[3] in humans and mosquitoes in the 1960s. By 2000s, more than half of India reported Dengue Hemorrhagic Fever and Dengue Shock Syndrome, indicating a build-up of hyperendemicity in the country.[14,15]

However, co-circulation of all four serotypes within an area is not actively searched for by the National Vector Borne Diseases Control Program (NVBDCP).

The routine fever monitoring and sentinel laboratory surveillance of the NVBDCP records the rising cases in all parts of the country. But, there is no proactive surveillance to detect circulating viruses before they cause outbreaks among unexposed populations in mofussil towns and villages. Despite the recorded exponential increase in cases as detected by 646 sentinel laboratories using ELISA testing,[16] publications of co-circulation from Indian cities are few and far-between -- in 2003 from the capital city of Delhi,[17] and more recently from Jabalpur[18] and Bhubaneshwar.[19]

Weapons in our armory against Dengue, their deploy-ability and effectiveness

Presently, clinical treatment for Dengue is only symptomatic; no specific treatment exists for the disease. We broadly classify our weapons against Dengue, presently in-use and in various stages of experimentation and production, into three 'I's – Insecticides, Immunologicals and Innovations.

Insecticides

Insecticides are mainly deployed in two ways: for individual level personal protection (repellants, treated nets) and population level mass application (treatment of breeding sites, residual spraying, fogging). One major drawback of dependence on insecticides as a long-term strategy is the mosquito's ability to quickly develop resistance to every new insecticide molecule, which is passed down generations.[20,21] However, the advantage of insecticides as a control measure in India is a practical one -- of familiarity. A long history of malaria control programs has led to the establishment of systems that are familiar with insecticides and their deployment. Insecticides would have been effective as a control method if we could use them to destroy the virus-bearing mosquitoes before they caused the outbreak. At present, we use these insecticides extensively after an outbreak has been detected. Even if we were to use larval and adult surveillance to indicate an earlier time point for insecticide application, literature suggests that this approach does not provide good indicators of impending outbreaks.[5]

Insecticides are not likely to bring complete resolution to the problem of mosquito-borne viruses.[22] A case in point is Singapore, with the highest funded Aedes control program in the world since the 1970s. In spite of achieving sustained suppression of Aedes population over last many decades through insecticides, Singapore has recorded repeated outbreaks of Dengue.[23] This probably means that

despite best efforts with insecticides, complete cessation of Dengue transmission is not possible.

Immunologicals

Among the immunologicals are vaccines and monoclonal antibodies. The most promising is an adult vaccine, called Dengvaxia, which produces immunity against all four serotypes of the virus.[24] The Indian government has not yet approved its use. Also, there are some issues around affordability, as the manufacturers price it at the higher end of profitability.[25] The Indian government had rejected the request for waiver of a large scale trial of Dengvaxia, but had agreed for market authorization, provided phase IV trials were carried out.[26] The second immunological in the horizon, Monoclonal antibodies, VIS513, has not yet undergone human trials and therefore, will probably become available for clinical practice only after 5-10 more years.[27–29] However, papaya plant extracts are already in extensive use although they haven't yet been validated.[30]

Essentially, immunologicals too would not break the dengue transmission cycle, since they are brought into use after human infection has occurred.

Innovations

A variety of anti-mosquito measures are being innovated all over the world. Researchers have been experimenting with and creating small-scale solutions such as repellents, attracticides, biocontrol agents, street lamp traps, baits and ovitraps.

Two promising techniques, with medium to large scale population effect, are the release of genetically modified sterile male mosquitoes,[31] and of Wolbachia-infected mosquitoes.[32] These have been tried in east Asia, Australia and Brazil.[32–34] While the former aims to bring down Aedes mosquito population by inhibiting their multiplication, the latter aims to bring down infestation of Aedes mosquitoes by dengue and other pathogenic viruses through inhibition of virus replication.[35]

The latter Wolbachia technique has gained traction in recent times through the World Mosquito Program. This program, envisages the introduction of Wolbachia-infected Aedes aegypti into wild Aedes populations. The resulting progeny become less infectious, thereby breaking the transmission cycle.[36,37] Since its launch in 2011 in Australia, the World Mosquito Program, has expanded its work to 12 countries, including India, Brazil, Colombia, Mexico, Indonesia, Vietnam, Sri Lanka, Fiji, Vanuatu, Kiribati and New Caledonia.[38] A recent large-scale trial in Townsville, Northern Australia, has reported complete cessation of dengue transmission, since Oct 2014.[32] In India, the program has partnered with the Indian Council of Medical Research (ICMR) and an initial research phase is being conducted at the ICMR's Vector Control Research Centre (VCRC) in Puducherry, South India.[39]

Researchers have argued that there is a need to consider the probable harmful evolutionary, environmental and ethical effects of such interventions.[40,41] However, initial risk assessments done for the program in Australia[42] and Vietnam[43] show an overall negligible risk of such harm. Continued surveillance over such new strategies is essential. In short, while insecticides and immunologicals will not completely arrest dengue transmission, innovations need to be tested and proved for their effectiveness.

Dengue in India's future: comparison of costs and expenditure for Dengue prevention and control

So how does our future with the Dengue virus look? Both human and mosquito populations in India will be increasingly infected by more and more serotypes of the virus. As hyperendemicity gets established in 4000 odd medium and small towns in the country, we can expect a higher number of cases and casualties, especially among children. Neither the insecticides presently in use,[20–22] nor the immunologicals in our horizon will dent this. But a large-scale intervention like Wolbachia-infected mosquitoes can potentially eliminate and later eradicate the Dengue virus. Small pox and polio viruses have been ideal candidates for eradication in the past century, because only humans served as reservoirs for these viruses. Now, Dengue viruses are rapidly establishing themselves in mosquito and human populations in the tropics. With the right tools and monitoring, dengue viruses could be possibly eradicated before they entrench themselves fully in mosquito and human populations. This would require that surveillance and control strategies are effected speedily enough to catch up with the ongoing spread of the virus into unexposed populations. However, future risk of re-introduction into humans from zoonotic sources would remain.[4]

Need for building robust surveillance systems to evaluate methods for prevention and control of Dengue

We are on a learning curve for strategies for prevention and control of Dengue. Our present systems are only stumbling over one outbreak episode after another in all parts of the country. We need to build integrated surveillance, prevention and control systems that would periodically generate regional maps of prevalence of dengue infection in humans and mosquitoes based on available diagnostic tools. By using such maps to apply specific interventions in specific regions over specified time periods, this system would help to evaluate their costs and effectiveness. This would further help to identify appropriate local strategies, e.g. what combination of mosquito traps, attracticides, vaccine, and/or Wolbachia-infected mosquitoes works best at varied levels of virus infection in mosquitoes and humans? Based on their effectiveness, we would be able to choose the most appropriate strategy for specific areas and make the right expenditure decisions. The two key tools which would greatly enhance our ability to pick and choose the best area specific strategies are quick and cheap

Table 1. Comparison of India's allocated expenditure on Dengue control with actual expenditures other endemic countries

Country (study duration)	Dengue case rate (per 100,000 population)	Illness cost of Dengue		India	
		Per year ($ mill)	Per capita per year $	Per year ($ mill)	Per capita per year $
Singapore [2000-09][47]	14	67.1	14.99	50.0	10.02
Malaysia [2007-10][48]	167	54.9	2.06	78.1	2.93
Brazil [2000-07][8]	291	878.2[49]	4.64[49]	1000[51]	5.13[51]
Mexico [2010-11][50]	26	87.0	0.80	83.0	0.76
India [2012-17]	14[6]	1110.0[7]	0.88[7]	# 30.33[52]	# 0.025[52]

This amount, Rs. 810.6 crores, was the allocation towards annual prevention and control of Dengue and Chikungunya from 2012-17 from the total central health budget. A later parliamentary committee report showed that only half of the budget allocated towards Health had been disbursed.[52]

field level diagnostic kits that can detect dengue virus infection -- firstly in humans, and secondly in mosquitoes. While rapid diagnostics are being developed to detect serotype specific IgM in human saliva,[44] the pathway to a similar diagnostic method in mosquitoes is still distant.[45] These tools would help us assess the prevalence of infected human and mosquito populations before and after application of control strategies and thus the cost-effectiveness of these strategies. This would help us over time to construct a coordinated action plan to eradicate the Dengue virus.

Comparison of India's expenditure on Dengue control with other countries

Expenditure on dengue surveillance and control measures in other endemic countries is not commensurate with the severity of their disease burden, but does come close to the illness costs (direct and indirect expenditure on ambulatory and in-patient cases) in these countries. **(Table 1)** Singapore has the least Dengue case rate. But, it records the highest per capita illness cost and also the highest expenditure on dengue surveillance and vector control. Despite a large expenditure and good vector control, permanent cessation of dengue epidemics has proven to be impossible for Singapore.[46,47] Other countries like, Malaysia,[48] Brazil,[49] and Mexico[50] have spent nearly as much as their per capita illness cost on Dengue surveillance and vector control. **(Table 1)**

In comparison, India's expenditure on all vector borne diseases put together has been much lower than its illness costs for dengue alone. India allocated a budget for Dengue and Chikungunya for the first time in its 12th Five Year Plan (FYP), an amount of Rs. 810.61 crores for 2012-17.[53] This amounted to an annual allocation of Rs. 162.12 ($0.026 per capita per year, at 2012 exchange value). The allocation for all other vector-borne diseases (malaria, filaria, kala-azar and Japanese encephalitis) was Rs. 1976.5 crores ($0.33 per capita per year). Thus, the total central allocation on all vector-borne diseases in the 12th FYP summed up to $0.356 per head per year.[52] This is well below the overall annual economic cost of dengue fever alone, which was estimated to have been $0.88/capita[7] in 2012. Based on the past history of matching expenditure by the state government of Gujarat in 2007-08,[54] even if we assumed that states and local bodies contributed an equal matching amount towards vector borne infections, the total expenditure ($0.712) would still be lower than the annual economic cost of Dengue alone at $0.88/head.[7]

The total allocation on Ayushman Bharat for 2018-19 is $770 million, $0.57 per head (for entire population).[55] Documents produced by the Niti Aayog demonstrate a fierce commitment to the creation of the National Health Analytics Framework, the virtual environment, necessary to provide Universal Health Coverage. Within this document are also affirmations of future "horizontal expansibility" of this framework for disease surveillance and predicting epidemics.[56] However, no budgetary details for future prevention and control or surveillance needs, akin to FYPs, are available.

Conclusion

Our present systems and strategies for dengue prevention and control are reactive, and are designed to be applied post facto, after an outbreak happens when the virus is already established. We need to shift the foundations of our response systems towards the ability for proactive strikes, before cases appear in communities. For this, the Dengue virus should be at the centre of the response plan, not Dengue cases. We should map the relative density of the virus in mosquitoes and humans across various geographies in the country and use the available strategies to strike pre-emptively. We believe that this requires strong surveillance -- an interconnected network of locally-generated-and-owned-surveillance platforms across the country. Creation of human resources and laboratory capacity for surveillance of viruses in human and vector populations will require substantial and sustained investments.

Without preventive surveillance systems in place, we would continue to advocate only improved clinical care for already diseased patients (as is the strategy at present), while dengue (and other viruses like Chikungunya and Zika) continue to expand their territories to occupy and infect more and more mosquito and human populations.

Key Messages:

- India probably has the highest burden of dengue in the world, but spends much less than other endemic countries on control and surveillance.
- Policy makers need to plan for a long-term goal of reducing infestation of humans and mosquitoes with the dengue virus, not just tiding over outbreaks. This calls

for a combination strategy of producing regional disease transmission maps for the whole country and methodical introduction and study of various strategies for control.

- Even the highest estimate of allocation for Dengue prevention of $ 0.05 per capita per year is well below the overall annual economic cost of $ 0.88 per capita.

Conflict of Interest: None declared

Authors' contributions

VI was responsible for the conception, design and initial draft of this study. KB, SAC, AS, VK, VSD and BS contributed to the literature review and analysis. VI, VK and VSD reviewed the manuscript and edited the final draft along with SAC and AS. All authors have approved the final version.

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