Impediments of reporting dengue cases in India

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**ABSTRACT**

Dengue has emerged as one of the most important mosquito-borne, fatal flaviviral disease, apparently expanding as a global health problem. An estimated 3.6 billion people are at risk for dengue, with 50 million infections per year occurring across 100 countries globally. The annual number of dengue fever cases in India is many times higher than it is officially reported. This under reporting would play a major role in the government’s decision-making. Underestimating of the disease in India encumbers its people from taking preventive measures, discourages efforts to ensnare the sources of the disease and deliberate efforts for vaccine research. In this article, we highlight the probable impediments of under reporting leading to its impact on national and global public health and also offer key remedies to effectively address the issues across the clinics to the community level.

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**Introduction**

Dengue is a self-limited, flu-like systemic arboviral disease transmitted between humans by \textit{Aedes} mosquitoes. An estimated 3.6 billion people are at risk for dengue\textsuperscript{[1]}, with 50 million infections per year occurring across 100 countries globally\textsuperscript{[2]}. Global increase in urbanisation has facilitated endemicity of dengue, especially in Asia and parts of South America\textsuperscript{[3]}. India experiences cyclic epidemics of dengue over the years and the infection imposes for the leading cause of hospitalisation and death among children in the country\textsuperscript{[4]}. Concurrent infection in some patients with multiple serotypes of dengue resulted from co-circulation of several serotypes of the virus in India\textsuperscript{[5]}. Unplanned urban development, poor water storage, sub-standard sanitary conditions, increasing international travels and rising role in global economy could account for growing public health problem of dengue in India. A recent review has reported that India alone contributes to 34% (about 33 million infections) of the total global threat of dengue leading to hyper-endemicity, prevailing mostly in urban areas\textsuperscript{[6]}. Notably, India reported an annual average of 20,474 dengue cases and 132 deaths by the disease in 2006–2012\textsuperscript{[7]}. Indian Health Ministry reported more than 138 Indian people killed by the dengue virus during the first 10 months of 2013, with more than 55,000 cases recorded across the country. According to the National Vector Borne Disease Control Programme (NVBDCP) data, the worst affected areas in India in 2015 were Delhi, Punjab, Haryana, Gujrat, Karnataka and Kerala with a range of about 4000–15,000 cases and 9–60 deaths\textsuperscript{[7]}. However, the wide spread problem of under reporting of dengue cases from India has come into focus very

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recently and the real burden of dengue in the country is heavily ignored [5,8]. Interestingly, a recent study reports that an average of six million people a year in India had a symptomatic illness between 2006 and 2012 with dengue [5]. Shepard et al. retrospectively collected data from 10 medical colleges across five regions of the country. The study reports annual average of 5,778,406 clinically diagnosed dengue cases during 2006–12; which is about 282 times greater than what is reported by the Indian Ministry of Health [5]. The NVBDCP data shows increase of case reporting in 2015 compared to the previous year in several states; viz. Arunachal Pradesh, Haryana, Punjab, Uttar Pradesh etc. [7].

**Fallacies in WHO case definition?**

Dengue patients present with myriad of symptom profile; the commonest being non-specific fever, similar to other viral infections. Quite a significant number of people in India get infected with dengue virus every year, especially during epidemics posing a serious threat to the health system with regard to their preparedness in controlling this menace. Therefore, it is imperative to define and categorize dengue symptoms for early diagnosis and helping clinicians to recognize a case for reporting. The WHO case definition is the important tool for public health surveillance studies for early intervention and hence can significantly reduce morbidity and mortality. However, some researchers have reported of fallacies in the WHO case definition [9,10]. In India, this definition holds great significance as health resources are very limited especially in remote areas and clinicians rely deeply on clinical diagnosis aided by some basic laboratory tests. Notably, the WHO definition is not straightforward and relies on tests that reflected the situation in south east Asia in the 1960s [9]. With the advent of time, the application of this case definition required performance of different and repeated clinical tests (haematocrit, platelets, radiographs, serum albumin or protein, microscopic analysis of urine). This poses critical challenges for highly populated countries like India, with limited resources of trained health professionals, referral laboratories, accessibility to radiological support, and facilities to detect DHF by haematocrit and plasma leakage signs. Therefore, it was suggested that when the WHO case detection criteria are strictly followed, many severe cases, including those that involve shock and fatality, may be overlooked [11]. However, this may impact numbers for DHF, but not of DF. This is also evident from studies that 18% of severe dengue did not fulfil all four criteria considered necessary for the diagnosis of DHF by WHO, whereas over-inflation of the DHF figures was found when WHO provisional classification scheme was used [12]. The newer version of WHO case definition will permit for more sensitive management of the severe disease and allowing comparison of data across all regions [13,14]. Clinicians in the Pan American Health Organization (PAHO), Caribbean Epidemiology Center (CAREC) and World Health Organization (WHO) have also developed alternative classifications to guide proper clinical management [15]. Considering the limited laboratory facilities catering to the vast population and geographical extent in India, the WHO/PAHO/CAREC modified classification (discussed in the next section) [15] can be effectively implemented in India to aid correct identification of cases, effective surveillance and disease management.

However, it is also noteworthy to mention that the WHO case definition helps in classification of the disease and its management strategies rather than directly impacting the reporting process. Majority of the dengue burden is due to DF; however, DHF only accounts for 5–20% of the total cases. Proper clinical judgement, extensive training and awareness of the disease among clinicians, along with prompt laboratory detection is more important in the reporting process rather than the WHO case definition which is mainly focussed for the management of the types. However, passive surveillance using case definitions would lack specificity due to similarity of dengue fever with several other fever [discussed below].

**Problems in laboratory diagnosis**

Diagnosis by the clinician is the most important aspect that accounts for case reporting in India. The problem compounds as the clinical symptoms of dengue disease vary case by case. According to the WHO/PAHO guidelines, one clinical manoeuvre (tourniquet test) and two laboratory studies (platelet counts and hematocrit) should be performed for the diagnosis of dengue haemorrhagic fever in general laboratory settings [15]. In endemic areas, physicians do not conclusively diagnose dengue based on specific laboratory criteria, but instead use the dengue classical triad of symptoms of fever, rash and headache, a positive tourniquet test and the dengue classical triad observed in the complete blood count [Thrombocytopenia (platelet = 65,000), atypical lymphocytosis (atypical lymphocyte = 8%) and haemoconcentration (Hct = 47%)] [16]. However, the problems with tourniquet test had also contributed to the underreporting. A positive Tourniquet test (TT) reflects haemorrhagic tendency and capillary fragility. In several observational outbreak studies, the sensitivity of the TT in DHF varied from as low as 0% [17] to 57% [18]. Notably, studies of Phuong et al. and Lucas et al. reported variable results for positive TT between DHF (47% and 27% positive, respectively) and DF (30% and 26% positive, respectively) [12,19]. Moreover, percent positive TT was also noted in dengue-like febrile illnesses, e.g. 21% [18], 12% [19] and 5% [12]. Interestingly, previous reports suggest that no haemorrhagic tendencies have been observed in 32–46% of DHF cases in India [20,21]. Therefore, inclusion of positive TT could underestimate dengue occurrences in India. A modified TT with an elastic cuff was suggested [22], which can be easily adapted by the Indian clinicians for better reporting of DHF. Either TT positive or negative, the clinician should be well trained to suspect dengue and report both DF and DHF. However, only depending on clinical diagnosis would not suffice the needs of holistic reporting. Viruses can evolve by gaining random mutations to subvert the host immune system and remain undetectable. Dengue virus is also not an exception; mostly when the infections are asymptomatic or apparent presenting as fevers of unknown origin.

Inclusion of increased haematocrit and decreasing platelet count in diagnostic criteria can also lead to misdiagnosis especially where laboratory diagnosis of dengue is difficult to conduct. The diagnosis of dengue haemorrhagic fever in the Indian population with the rise of haematocrit does not help much due to the high prevalence of anaemia [23]. Variable results for thrombocytopenia in DHF had been repeatedly reported; ranging from 8.8% in Indonesia [24], 48% in Sri Lanka [19], 54% in Bangladesh [25], 70% in India [26] and 78% in Cuba [27] outbreak studies. These great ranges of variability can result in false reporting of dengue cases due to non-specific haemorrhagic conditions. Of note, several studies suggest that dengue cases can also be misdiagnosed as other tropical diseases [28–31], as concurrent infection of dengue with other infections is possible. Studies from India also confirm this fact [32]. A study of 118 cases, who fulfilled the clinical WHO criteria for DF/DHF, were evaluated for serological evidence of dengue, hantavirus, chikungunya, Rickettsia typhi, Rickettsia tsutsugamushi, rubella virus, influenza A virus, and Leptospira. Results suggested that only 49% were serologically tested positive for dengue infection, while the rest were dengue-negative [28]. Therefore, differential diagnosis of dengue fever from other forms of fever in Influenza, acute viral exanthems (Measles, Rubella), Leptospirosis, several forms of purpura or viral haemorrhagic diseases,

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septicemia and acute meningococcemia, has been widely proposed in the WHO/Paho guidelines [15]. On the other hand, dengue IgM antibodies also cross-react with other flaviviruses [Japanese encephalitis, St. Louis encephalitis and yellow fever] occurring in the same endemic zone [33,34], which is very common in India. Differentiation of dengue infection from other infectious diseases may require management with specific anti-microbial therapy [35]. These complicated conditions need to be defined more elaborately to aid the correct differential diagnosis, timely management and reporting of cases.

The use of good dengue diagnostic tools is critical for laboratory confirmation of DHF/DSS, counting the number of case fatalities, establishing which strains are involved, and to calculate the total incidence following epidemics. According to the Pan American Health Organization (PAHO) guidelines, 80% of all dengue cases have detectable IgM antibody by day five of illness, and 93–99% of cases have detectable IgM by day six to ten of illness, which may then remain detectable for over 90 days [15]. However, the abundant use of spurious, non-validated serological tests with variable sensitivity and specificity [36,37], leads to lack of adherence to test algorithms, increase the load of under diagnosed cases and under reporting [5]. Recently developed molecular tools for dengue diagnosis like Nucleic acid sequence based amplification assay (NASBA) can also be utilised, provided that the cost can be provided by the Indian government as these tests are expensive. Studies suggest that antigen detection through virus isolation and RT-PCR were the most sensitive tests during the early period of illness whereas beyond third day, IgM antibody detection was found to be the most sensitive method of dengue diagnosis [38].

Differences in laboratory diagnostic methods for confirmation of dengue add up to the problem of under reporting in India. Therefore, stringent quality control regulations are needed to be followed by the government for enabling these tests to be evaluated by the WHO-approved laboratories under the global network of dengue laboratories programme. Instead of using variable diagnostic rules, we should strictly follow the CDC testing algorithm for diagnosis and reporting of dengue cases in India at specialisation referral laboratories. Taken together, a combination of different tests should be introduced following the CDC algorithm for testing and reporting dengue cases in India [39] and the suggested algorithm should be as follows: (a) a positive real-time PCR result is a definite proof of current infection and it also confirms the infecting serotype, (b) IgM antibody capture ELISA [MAC ELISA], (c) IgG ELISA can be used for the detection of a past dengue infection, (d) NS1 ELISA can detect acute dengue infections and (e) Plaque Reduction and Neutralization Test (PRNT) must be used when specific serological diagnostic is required.

**Diagnostic facility network**

Evidently the National Vector borne Disease Control Programme (NVBDCP) captures only 0.35% of the clinically diagnosed dengue cases in India [5]. This is important to mention that NVBDCP only reports the laboratory confirmed dengue cases. It is plausible that significant under reporting of highly endemic dengue can occur owing to this decision of laboratory-based surveillance with about 1 billion population. Therefore, an alternate option can be developing a robust specialised laboratory network in India to predict, detect, investigate, monitor and evaluate dengue outbreaks and timely management of cases. Only a fixed percent of suspected cases can help to extrapolate the estimated case load of the country.

Another option could be to design a state-wise surveillance model with random selection of about 15–20 sentinel villages from each district. Human sera can be randomly collected monthly from inhabitants and subjected to serological and/or molecular detection for the presence of anti-dengue antibodies. A district level sentinel laboratory with clinicians can better monitor any outbreak to cater to the high population load. This can be a more practical approach in improving reporting in India. Notably, to scale up the efforts, there are now 350 Sentinel Surveillance hospitals across India with laboratory support for dengue diagnostics linked to a network of 14 Apex Referral laboratories that have advanced diagnostic facilities for back up support. In recent years, several new rapid diagnostic techniques have been developed for dengue diagnosis. The rapid test kits used in India are manufactured by different manufacturers’, viz. Panbio, Standard Diagnostics, J. Mitra, Reckon diagnostics etc. and have variable sensitivities and specificities [40]. As per this study, only the Panbio IgM capture RDT was found to be reliable to be used for dengue outbreaks. However, an ‘ideal’ dengue test, as advocated by WHO expert group, is yet to be reported for case management, outbreak investigations and surveillance purposes [41]. Several commercial kits are available in India for serological testing with wide variable sensitivity and specificity. The widely used serological tests in India, dengue IgM or IgG, are not a direct diagnosis of the presence of the virus, but rather the measurement of host response. The most suitable option would be to use Panbio IgM ELISA kits and in-house MAC ELISA testing simultaneously for testing of dengue. An in-house reference laboratory can also be set up to monitor the tests of the sentinel sites and also validate the surveillance data.

However, in India, antibodies to all epitopes display varying degrees of cross-reactivity across the dengue serotypes and other flaviviruses residing in the same location [33,34], increasing the limitation for these serological testing. Furthermore, nonspecific results are also observed in patients due to previous exposure to malaria, leptospirosis etc. febrile diseases. Therefore, it is important to find out the vector potential and prevalence of hemeagglutination inhibiting antibodies against flaviviruses through regular periodic serosurveys to gauge the risk of the infection in an area. However, lack of quality control and quality assurance of laboratory investigations, erroneous specimen collection and transportation leads to inconsistent data across clinics, aggravating the problem further. Undoubtedly, human errors can occur when the workload is high during phases of epidemics in poor quality laboratories in community healthcare centres or district-level PHCs.

The diagnosis of dengue infection is generally confirmed by a variety of commercial or in-house serological protocols. The need to survey the accuracy of dengue serological diagnostics, through QA/QC process, is very important for reporting in a country. Therefore, an organised external quality assurance set-up of dengue serological practice in diagnostic laboratories is required to evaluate the scope of improvement for detection sensitivity of anti-dengue virus IgM antibodies against the commercial antibody capture ELISA tests.

**Surveillance network**

According to the WHO, “Surveillance is the corner stone of public health security” [42]. Quality and timely information are essential for its prevention and control of dengue. However, infrastructural limitations impede effective surveillance in many developing countries, including India. Access to timely and reliable epidemiologic and entomologic information is necessary for decision making process and facilitate the dealings between the participating stakeholders. The new International Health Regulations (IHR, 2005) requires detection of elevated disease and death rates, instant implementation of control measures, and reporting any event to WHO representing public health emergency of international concern [43].
In most developing countries, human, laboratory, and infrastructure limitations impede effective surveillance. Unfortunately, these countries do not meet core surveillance and response capacities for dengue [44]. The lack of several operative components and control programmes is the most important shortcoming in dengue control in India. The sensitivity of NS1 by ELISA is higher (60–75%) compared with NS1 RDT (38–715%) [45]. This has been noted that non-government corporate hospitals in India merely diagnose dengue by Rapid tests (RDTs) which has been questioned and not approved by the NVBDCP. Thus, over 80% of dengue patients, reporting at private hospital remained under reported to the national surveillance system [8].

Recently, the routine dengue surveillance systems in six countries (Brazil, Bolivia, Cambodia, Indonesia, Maldives and Thailand) were evaluated [46]. All routine reporting systems were found to be useful for trend monitoring and national planning. Interestingly, use of alert signals or additional surveillance components to increase timeliness or sensitivity (e.g. as sentinel sites or syndromic surveillance components) had great capacity for early outbreak detection. Recently, a web-based, geographically enabled, dengue integral surveillance system (Dengue-GIS) was developed for the nation-wide collection, integration, analysis and reporting of georeferenced epidemiologic, entomologic, and control interventions data in Mexico [47]. This GIS-based model system for dengue surveillance helps to integrate the interoperable platform for gathering basic information for problem appraisal and devise future planning for controlling the disease. This type of web-based, electronic data management and data sharing platform can be adapted by India for preventing under reporting of cases by effective surveillance of dengue in the country. Moreover, situation awareness can be achieved by the novel approach of “syndromic surveillance” that uses pre-diagnostic data, non-specific presentations and statistical algorithms to detect epidemics earlier than the traditional surveillance systems leading to wider public health benefits [48]. Increase in case reporting in dengue can be anticipated by traditional surveillance programme followed by a broad deliberative process of syndromic surveillance and publication of statistical projections. Moreover, the Indian system can also follow the PAHO/WHO ‘Integrated Management Strategy for Dengue prevention and control (IMS-Dengue)’ [15] that consists of successive application of laboratory participation in support of the epidemiological study of dengue outbreaks. The widely approved IMS-Dengue strategy is designed to integrate key components for dengue prevention and control, viz. social communication, epidemiological surveillance, laboratory diagnosis, environment management, clinical case management, and Integrated Vector Management, at the national, sub-regional and regional levels [15].

Conclusion

Under reporting of cases also seems to be politically manipulated to forge effectiveness of control programmes [49]. With this type of practices and lack of wide-spread effective sentinel surveillance, the problem cannot be fully evaluated and controlled. For addressing these problems, the Indian government should strictly follow the recommendations of dengue surveillance experts. The recommendations are: (i) reporting of dengue cases to the government should be made mandatory in all dengue endemic countries; (ii) electronic reporting systems should be developed and used at all areas; (iii) the government dengue surveillance data should include age-stratified data of incidence, hospitalisation rates and deaths; (iv) additional system sensitivity checking studies should be performed; (v) diagnostic laboratories should share expertise and data; (vi) dengue antigen tests should be used in patients with fever for four days or less, whereas antibody tests should be used after day 4 to diagnose dengue; and (vii) the national surveillance systems should aim for early detection and prediction of dengue outbreaks [50]. Part of the purpose of a surveillance system is to indicate how the situation in one year compares with that in other years. Therefore, this goal requires consistency and stability in the system. In recommending improvements to inform vaccine introduction, it is also important to find if a crosswalk could be developed between historical data, which would be needed for comparison, and possible new data could be achieved.

In recommending a series of improvements to the surveillance system, we would also suggest mandatory reporting that exists in many endemic countries. However, enforcement is particularly challenging for ambulatory cases and in the private sector. Dengue is typically an urban disease in India. Of interest, the annual dengue epidemic coincides with the beginning of India’s busiest tourist season. The dengue vaccine development programme is underway and the unique pathogen–host interaction complicates the process. Moreover, adequate reliable country-specific disease surveillance data is the major requirement for assessing the situation prior to introduction of vaccine to a community and monitoring for its effectiveness and safety after introduction. Whatever the true dengue burden in India, there is consensus on the fact that the numbers are rising. The severe problem of under reporting of dengue cases will lead to severe problems in introduction of a vaccine in India. Quality dengue surveillance data are very important for estimating dengue disease burden and to measure the impact of preventive intervention [51,52]. Exact national dengue burden is important to inform the decision makers of vaccine price and could also enable proper negotiations between stakeholders when considering the incorporation of the dengue vaccine into the National Immunization Program. Therefore, assessing the true burden of dengue cases in India should be a priority of the government. The government should choose some type of systematic sampling of health facilities with statistically designed weighting factors to adjust for under reporting. A cross-sectional study was conducted in India among persons visiting a tertiary care hospital and systematic sampling procedure of health facilities was adopted [53]. The study findings suggest that future campaigns should involve health education through active involvement of health workers and community representatives, with the use of mass media and health education programmes for community awareness. Thus, understanding people’s perception and their practices could help in identifying target areas and in formulating strategies to combat dengue outbreaks. The NVBDCP also plans to raise awareness of the disease and vector through media channels including TV, radio, and cinema. Communities are working together to identify spots that encourage unabated reproduction of the vector Aedes. Periodicity in dengue occurrence is dependent on vector biology. During non-transmission season, the virus may be maintained in nature by vector mosquitoes through transovarial transmission or in some ‘hidden reservoirs’ [54]. Therefore, it is also equally important to run an effective entomological surveillance and search for all possible reservoirs in India.

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Conflict of interest

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