Internship Training

at

Smart Analyst India Pvt. Ltd.

Analysis of Clinical Trial Registry Data: A Case for Dengue Fever

By

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Under the Guidance of

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Apoorva Mehta

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List of Abbreviations

API - Active Pharmaceutical Ingredient

BD & L - Business Development And Licensing

CDC- Centers for Disease Control

CH- Consumer Healthcare

CTRI- Clinical Trial Registry of India

DHF -Dengue Hemorrhagic Fever

FDA- Food and Drug Administration

GSK- GlaxoSmithKline

HEOR - Health Evidence And Outcomes Research

ICMR- Indian Council of Medical Research

ICTRP- International Clinical Trial Registry Platform

MoA- Mechanism of Action

MoU- Memorandum of Understanding

NIH - National Institutes of Health

NVBDCP- National Vector Borne Disease Control Programme

R&D – Research and Development

rNPV - Risk Adjusted Net Present Value

RWE- Real World Evidence

SAIPL- Smart Analyst India Private Limited

TPP- Target Product Profile

USA- United States of America

WHO- World Health Organisation

SECTION 1 - INTERNSHIP REPORT

1.1 INTRODUCTION

Smart Analyst India Private Limited (SAIPL) is a subsidiary of Smart Analyst Inc. located in New York, USA. It is a business management consulting firm that provides comprehensive, integrated solutions based on a deep understanding of the science, the market, and the key business decisions for its clients. Smart Analyst has worked with 17 out of the 20 top global pharma companies as part of its client portfolio. The organisation deploys agile, cross-functional project teams that are responsive to client needs. Recently, the company has been acquired by UDG Healthcare. UDG Healthcare plc, formerly United Drug, is a Dublin-based international company and partner to the healthcare industry, providing clinical, commercial, communication and packaging services. It is listed on the London Stock Exchange. The experienced team of experts also use proprietary strategic frameworks to help biopharma companies make key decisions at the Disease, Asset, and Portfolio levels. The organisation also provides insights into consumer healthcare (CH) and health evidence and outcomes research (HEOR)

The key services provided are listed as under:

1.1.2 DISEASE STRATEGY

1.1.2.1 STRATEGIC DISEASE PRIORITIZATION

Prioritization of diseases within a franchise area based on scientific attractiveness, commercial attractiveness, and innovation attractiveness

1.1.2.2 DISCOVERY AND COMMERCIAL ALIGNMENT

Determine what early programs to pursue; and gain alignment between Discovery and Commercial aspirations

1.1.2.3 INTEGRATED DISEASE STRATEGY

5-10 year future disease strategy perspective to support investment decisions, including key targets, Mechanisms of Action (MOAs), treatment evolution, and internal/external asset mix

1.1.3 ASSET STRATEGY

1.1.3.1 OPPORTUNITY PRIORITIZATION

Evaluate and drive prioritization decisions across multiple granular patient segment opportunities for early assets or for lifecycle planning

1.1.3.2 VALUE PROPOSITION

Clinical and Payer benefit thresholds and evidence required for success; help drive asset go/no-go decisions

1.1.3.3 LABEL AND PRE-POSITIONING AND MESSAGING

Simulating the label as value driver; developing asset pre-positioning

1.1.3.4 COMMERCIAL ASSESSMENT, FORECASTING AND VALUATION

Commercial and TPP assessment to understand forecast drivers, forecast range, and rNPV (Risk Adjusted Net Present Value)

1.1.3.5 PATIENT JOURNEY MAPPING

Understand the patient journey to identify leverage points and influencers

1.1.3.6 TARGET PRODUCT PROFILE (TPP) DEVELOPMENT AND TESTING

Identification and validation of meaningful differentiators

1.1.3.7 REGIONAL PRIORITIES

Identification of asset strategy for a specific country or group of countries; unique considerations in emerging markets

1.1.3.8 HEALTH ECONOMICS

Disease modelling for scenario planning, economic justification, and real world evidence

1.1.3 PORTFOLIO STRATEGY

Portfolio Trade-offs and Optimization: Program correlations and risk-return trade-offs to optimize portfolio value

1.1.4 BUSINESS DEVELOPMENT STRATEGY

1.1.4.1 FILLING PORTFOLIO GAPS THROUGH BUSINESS DEVELOPMENT AND LICENSING (BD&L)

Screening, prioritization, and in-depth commercial assessment and independent valuation of opportunities

1.1.5 CONSUMER HEALTHCARE

1.1.5.1 AREAS OF EXPERTISE

Nutritionals and Naturals including TCM and Ayurveda, Pain Management, Cough Cold & Respiratory, Medicated and Non-medicated Skin Care, Gastrointestinal, Eye Care, Foot Care, Oral Care, Men and Women's Health.

1.1.5.2 INNOVATION SUPPORT FOR NEW PRODUCT DEVELOPMENT

- Identify Untapped Market Opportunities - Category Adjacencies, Channel Opportunities
- Detailed Global Market and Category Landscape Analysis
- Prioritization of Markets and Categories; Identifying Unoccupied White Spaces
- Competitive Analysis and Brand / Company 'Deep Dives'
- New and Emerging Science and Technology Trackers
- Track and Evaluate Emerging Scientific & Medical Literature - Determine Impact on Product Claims
- Identify Developments in Product Packaging Design
- Analysis of Trends and Drivers of Category and Brand Growth
- Identify Unmet Consumer Needs
- Global Regulatory Environment and Clinical Claims Support

1.1.5.2 MEDICAL AND SCIENTIFIC ANALYSES TO SUPPORT MEDICAL AFFAIRS AND R&D ACTIVITIES

- Ingredient and API (Active Pharmaceutical Ingredient) Dossier Development
- Identification and Vetting of Technical and Research Centers of Excellence
- Identification of Technical Subject Matter Experts

1.1.5.3 PRESCRIPTION (Rx) TO OTC SWITCH

- Identification of Rx to OTC Switch Candidates
- Learning and Insights from Analog Case Studies to inform inputs for Switch Forecast Analyses
- Insights into 'Difficult to Switch' Rx Categories and 'How to Win'

1.1.5.4 MODELING

- Global Market Cluster Analysis
- Forecast Modeling

1.1.5.5 PRIMARY MARKET RESEARCH

- Large Database of Category and Retail Experts and Healthcare Professionals

1.1.5.6 CORPORATE DEVELOPMENT

- Identifying Corporate Acquisition Targets in Global Markets
- Providing Independent Third Party 'New' Market and Category Assessments to inform M & A decisions

1.1.6 HEALTH ECONOMICS AND OUTCOME RESEARCH

The organisation supports bio-pharma companies with real world evidence and economic modelling to maximize product access and value.

- SmartAnalyst utilizes deep disease and domain knowledge to design and deliver successful projects for their clients.

- The organisation takes a holistic approach to Market Access, with the ability to combine patient, payer, and physician insights and work with clients to develop economic evidence to demonstrate the value of their products.
- The organisation has also developed and utilized innovative methodologies, such as dynamic disease modeling to forecast epidemiology of complex diseases.

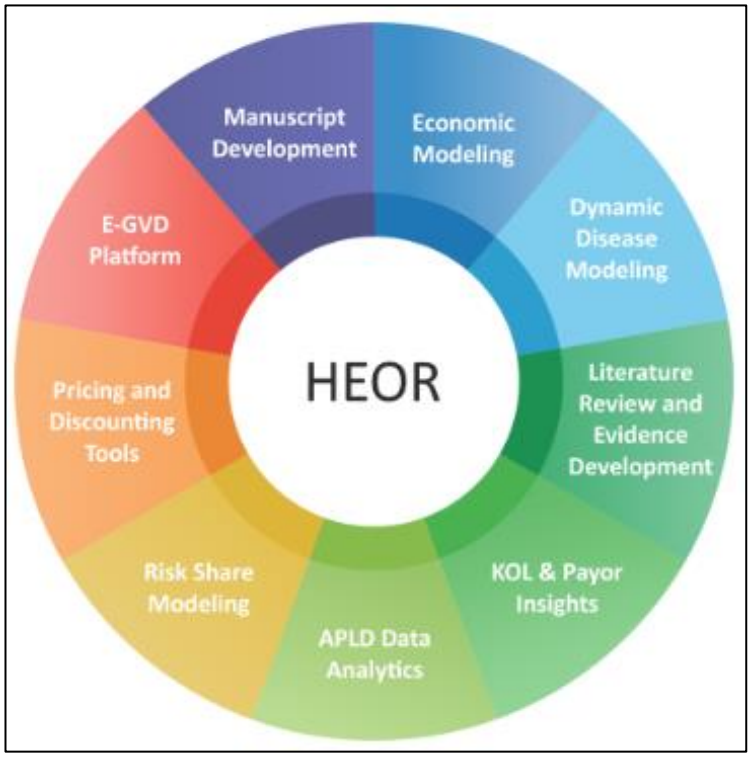

Figure 1.1 HEOR Offerings by Smart Analyst India Pvt Ltd.

Some of the key features of HEOR at the organisation are

- Domain expertise in a variety of therapeutic areas, including complex areas such as oncology
- Data agnostic - ability to employ leading retrospective patient level databases across the globe

- Flexibility and focus on the client experience - a collaborative working relationship
- Extensive track record of success with a highly skilled research team

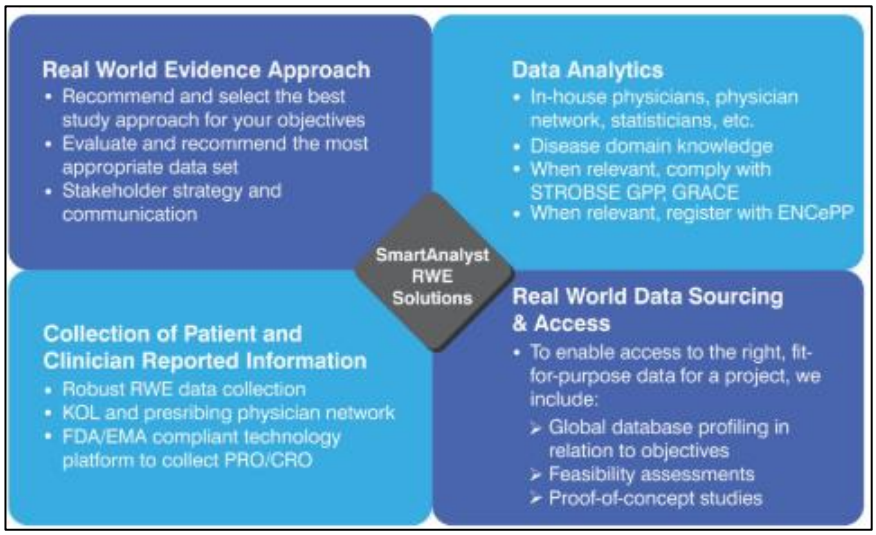

Figure 1.2 Key Real World Evidence Solutions Offered by Smart Analyst

The organisation's capabilities in Health Economics Modelling include:

- Longitudinal Data Analysis
- Cost-effectiveness Analysis
- Risk Sharing Analysis
- Budget Impact Models
- Comparative Effectiveness Models

1.2 ORGANISATION MISSION

The core mission is to drive Pipeline and Portfolio Value for Pharma and Bio-Pharma Companies. The organisation is focused on the following key issues in the pharma and Bio-pharma space

1.2.1 IDENTIFYING AND COMMERCIALIZING THE NEXT GENERATION OF INNOVATIVE THERAPIES

What innovative therapies should be developed to improve future patient outcomes and garner market success?

1.2.2 DRIVING EVIDENCE OF IMPROVED PATIENT OUTCOMES TO SUPPORT ACCESS AND REIMBURSEMENT

What compelling clinical and cost benefit evidence is likely required to get advantageous reimbursement and access to patients?

1.3 GLOBAL LOCATIONS

1.3.1 GLOBAL HEADQUARTERS: (New York, USA)

9 East 38th Street, 8th Floor,

New York 10016

1.3.2 EUROPE: (London, UK)

12 Hammersmith Grove,

London, W6 7AP

1.3.3 ASIA PACIFIC: (Gurgaon, INDIA)

14th Floor, Tower D, Cyber Green,

DLF City Phase-III,

Gurgaon 122002, Haryana, India

1.3.4 REGISTERED OFFICE

90/31 B, IST FLOOR, MALVIYA NAGAR

NEW DELHI - 110017, India IN

1.4 ORGANISATIONAL STRUCTURE

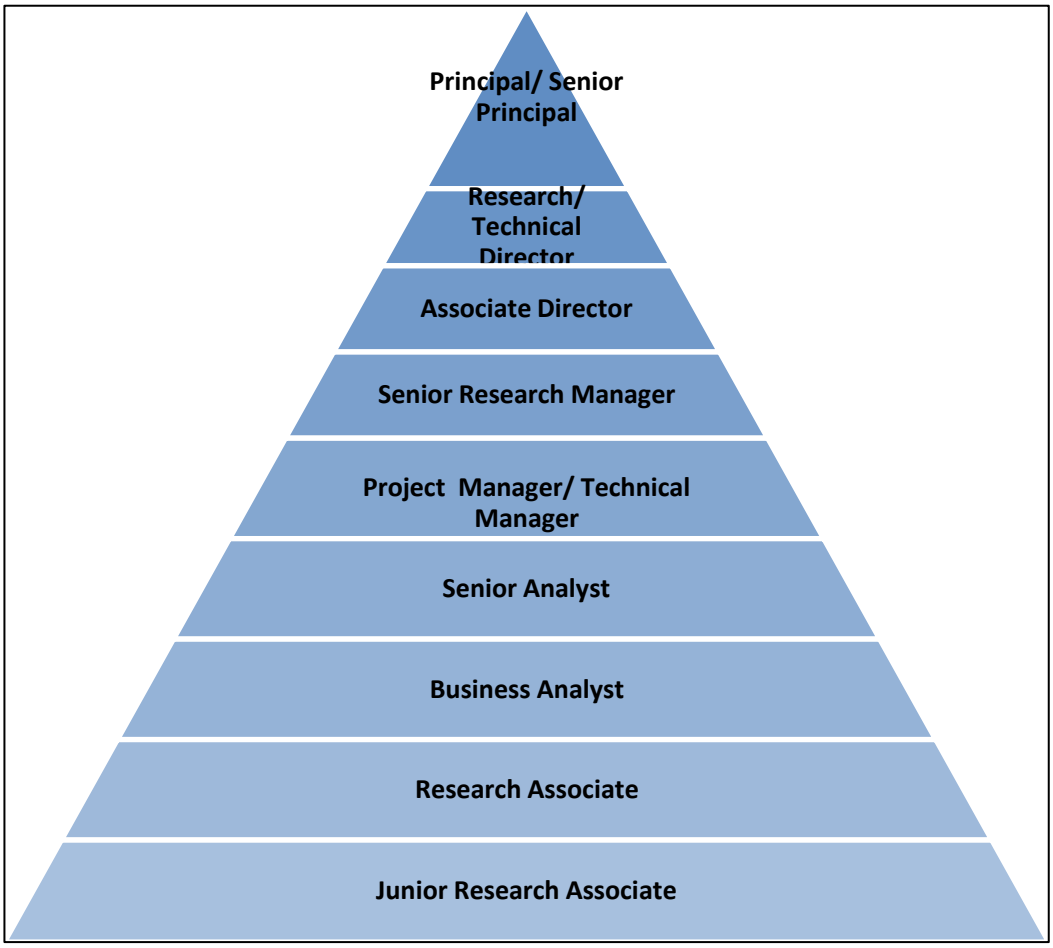

Figure 1.3 Pyramid depicting organisational Structure

1.5 LEARNINGS FROM THE SPECIALTY THERAPEUTICS TEAM

- Role of Business Analyst within the organisation
- Culture of the organisation
- Exploring industry databases and secondary research
- Competetive intelligence
- Target Product Profiles and Target Opportunity Profiles
- Primary Market Research
- How to navigate Clinical Trial Registries
- Interpreting Clinical Trial Results
- Systematic Literature Review methodology
- How to prepare complex and elaborate Excel sheets, Powerpoint slides etc.

SECTION 2- DISSERTATION REPORT

An Analysis of Clinical Trial Registry Data- A Case for Dengue Fever

2.1 Introduction

Dengue is the world's fastest-growing infectious disease, afflicting up to 400 million people worldwide, causing half a million life-threatening infections and development of DHF (Dengue Hemorrhagic Fever) and killing up to 25,000 people, mostly children, each year.

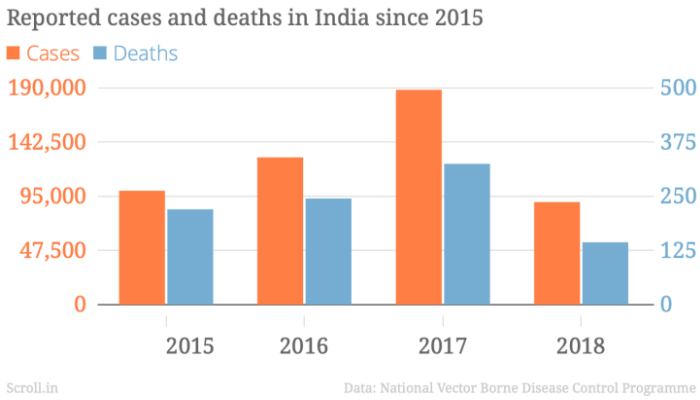

Figure 2.1 Trend for Dengue Cases and deaths in India from 2015- July 2018 (Source: NVBDCP Data by Scroll.in)

Although several drug candidates for Dengue fever have been evaluated in randomized controlled trials, none has been highly effective and at present, early recognition of severe dengue and timely supportive care are the only means are used to reduce mortality. Although dengue is rare in continental USA, it is very frequent in the Latin America and Samoa regions and increased inter-continental travel is also a threat for the spread of Dengue in the warmer, Latin America. Currently, no vaccine is available for use in India and the global need for a more efficacious, safe and robust vaccine for dengue and the search for a universal Dengue vaccine remains elusive. An effective vaccine could be worth more than $1 billion globally, according to industry analysts.

Several vaccine candidates are in development and have moved from the pre-clinical to the clinical trial stage. Clinical trial registries provide publicly available information on the registration of any clinical trial, its intended endpoints of study, it's progress, and ideally, it's results. The WHO maintains the ICTRP (International Clinical Trial Registry Platform), where all clinical trials are mandated to be registered before commencement. It also draws data from nine country specific Primary Registries, which maintain region/country specific clinical trial records. Clinical Trial Registry of India (CTRI) is the platform wherein all clinical trials to be carried out in India are mandatorily registered.

This study was carried out with the objective of collating and analyzing the present drug candidates for dengue fever that are in development using clinical trial registry data. Furthermore, timely registration and fair and unbiased reporting of results forms a cornerstone of evidence based medicine, as they form the basis for approval of any new pharmacotherapy around the world. To that end, the compliance of these records to WHO clinical trial registration and reporting standards has also been analyzed.

2.2 Rationale of Study

This study has been carried out to understand the global and Indian Dengue vaccine development landscape. A portion of this report was prepared as part of competitive intelligence exercise for a potential bio-pharma client interested in venturing into infectious disease research and development. Dengue fever was selected as the target health indication.

2.3 Review of Literature

Several studies have analysed clinical trial registry data as means of evidence synthesis-

- Liu et al. (2018) have analysed intervention trials of acupuncture and moxibustion
- Bolshete (2017) has analysed the registration status of all AYUSH trials as part of CTRI
- Sakate et al (2018) have analysed rare disease drug development using data from European Clinical Trial Registry, Japan Primary Registries Network and Clinicaltrial.gov

Several studies have also explained the vaccine development scenario in detail-

- Swaminathan (2019), has provided a comprehensive overview of vaccine technology in development
- Another recent comprehensive example is Cummings et al (2018), wherein a drug development pipeline for Alziehmer's has been generated

2.4 Research Question

What is the scope of emerging and available preventive pharmacotherapy for dengue fever?

2.5 Objectives

(i) To construct a global Dengue vaccine development pipeline

(ii) To describe approved vaccines for Dengue, if any

2.5.1 Specific Objectives

(i) To understand the Dengue vaccine development scenario, identify opportunities for Dengue vaccine development and propose recommendations for India

2.6 Methodology

2.6.1 Study design: Registry based Cross-sectional study

2.6.2 Data Type: Secondary data

2.6.3 Data Source: Clinical Trial Registry data from ICTRP, CTRI and Clinicaltrials.gov; clinical trial results published in indexed journals, research articles, reports, book chapters, website and press notifications, among other publicly available secondary data

2.6.4 Search terms: 'dengue, 'dengue'/'dengue haemorrhagic fever'/ 'severe dengue'**.**

2.6.5 Data Retrieval: Online

2.6.6 Time Period: Registry Entries since beginning of time were included in this exercise (2003-present)

2.6.7 Search and Retrieval Strategy: All ICTRP, CTRI and Clinicaltrials.gov clinical trial registration entries with the keyword 'dengue' were retrieved online and cross referenced by NCT ID and/or title to remove duplicates, following which only interventional drug trial entries were included in the analysis. The detailed approach for this retrieval is as follows:-

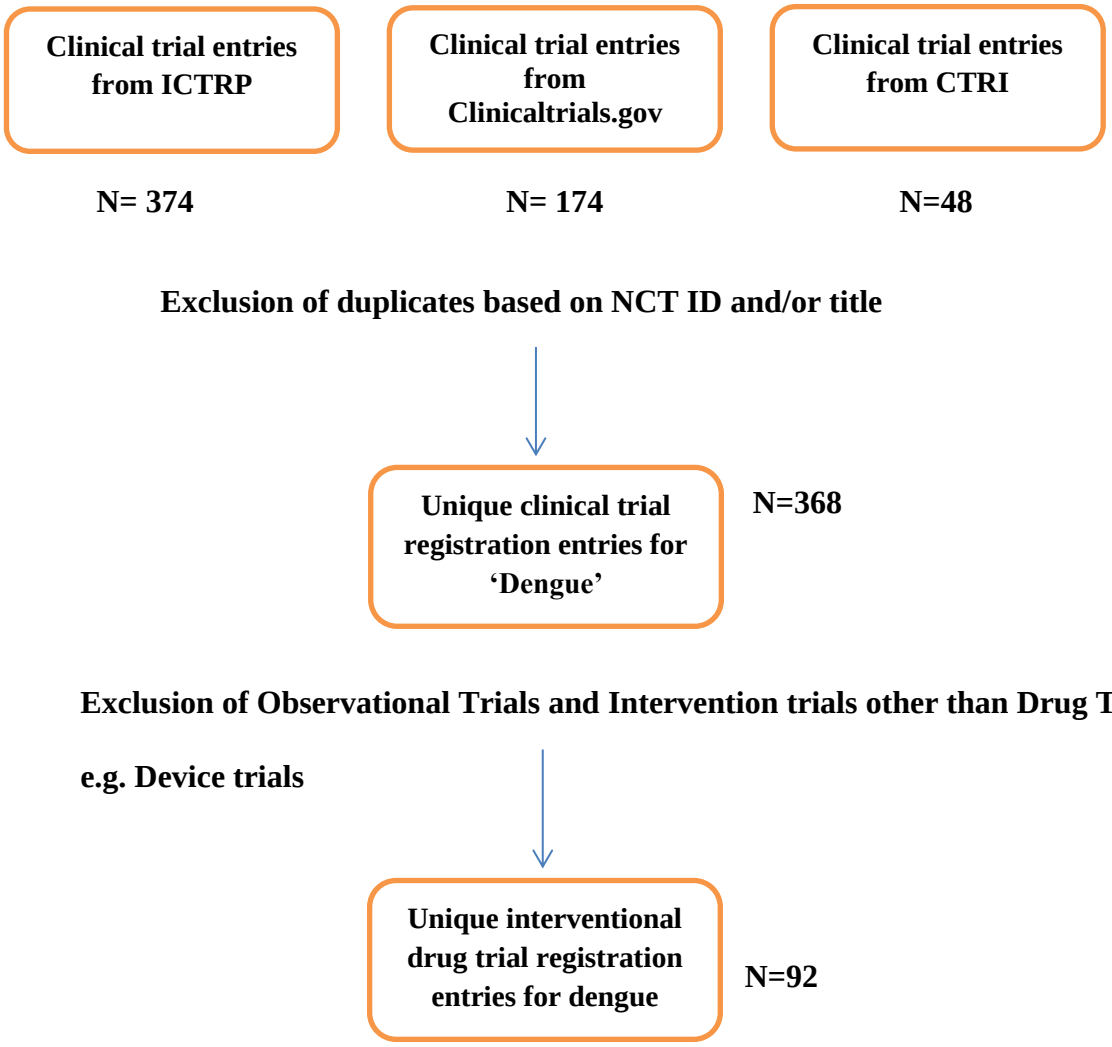

Figure 2.2 Detailed methodology for retrieval of Clinical Trial registry entries for analysis

2.6.8 Methodology for developing vaccine Pipeline: From this dataset, descriptive analysis was used and only vaccine candidate trials were included for this analysis (Drug trials involving Ayurveda, homeopathy, new dosing regimen etc were excluded) Trials that did not meet primary endpoints were also excluded for generating vaccine pipeline. Only 'pivotal' trials that met the required criteria for vaccine candidate approval for next step were included for generating the vaccine pipeline. The rest of the analysis has been carried out on dataset N=92

2.7 Results and Discussion

This exercise was carried out mainly as part of the first step towards opportunity assessment for a potential global bio pharma R&D company looking to invest in infectious disease R &D development. The overall strategy for market analysis is as follows:

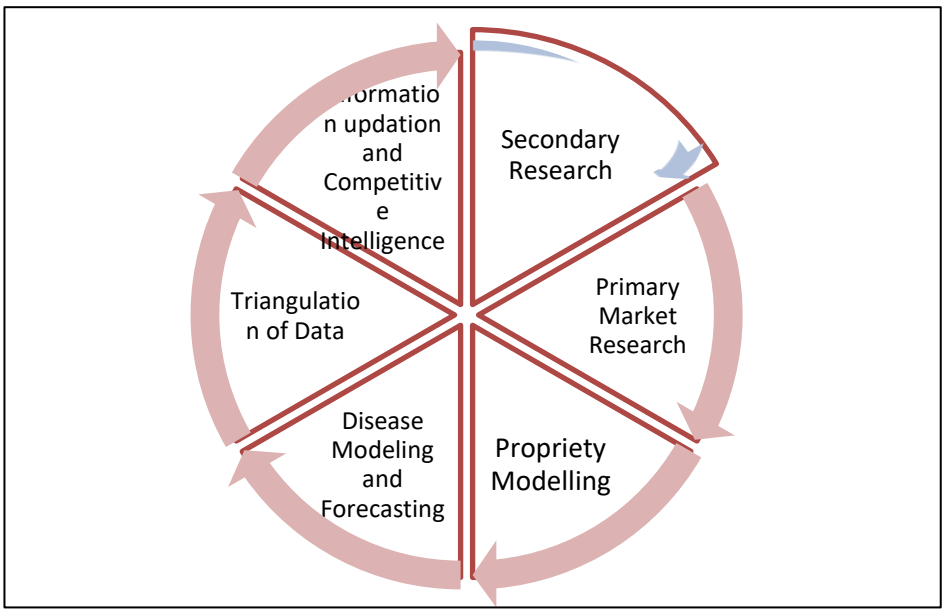

Figure 2.3 Research Methodology for Market Opportunity Assessments

2.7.1 Analysis of Clinical Trial Registry Data

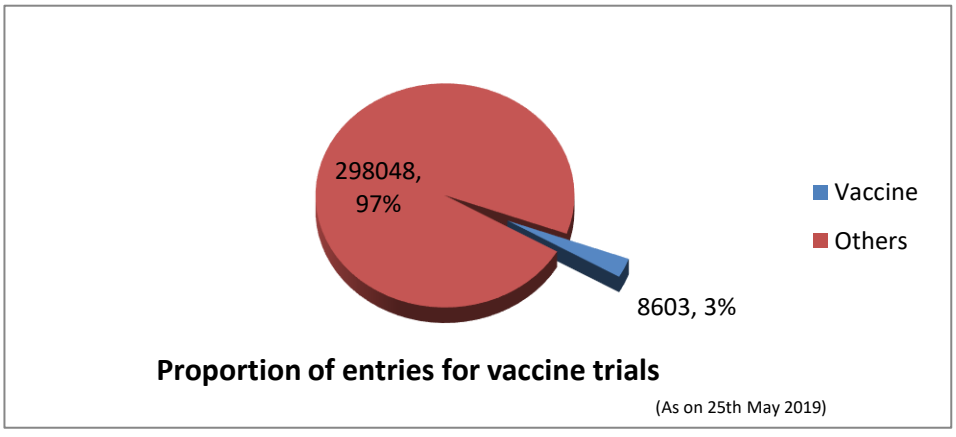

Figure 2.4 Figure depicting entries for vaccine trials as porprtion of all trial entries

Vaccine trials form only a very small percentage (3%) of all registered clinical trials. It is well documented that the research and development for safe and efficacious vaccines is far more time consuming, costly and faces more regulatory hurdles than other drug trials and clinical trial registration data follows the same trend in that aspect. Further, the market for vaccines is much narrower and restrictive than that of drugs, making vaccine trials a measly proportion of all clinical trials registered.

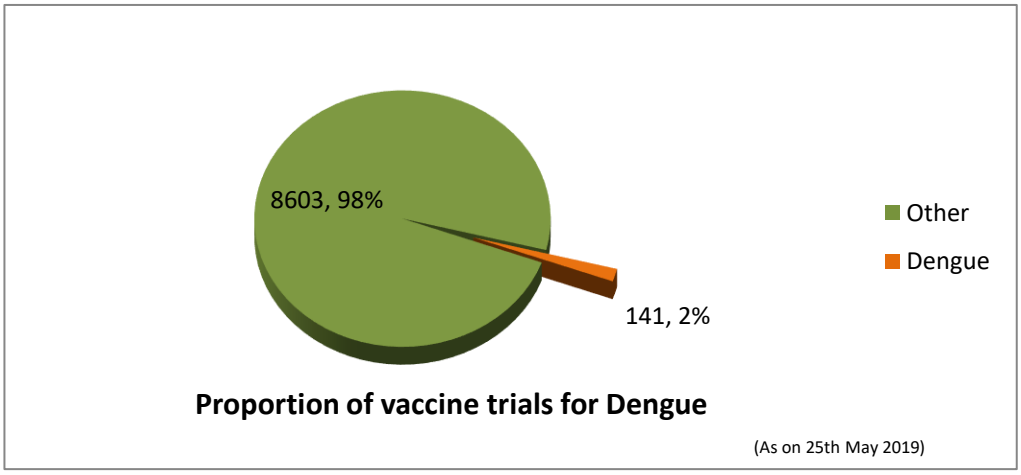

Figure 2.5 Figure depicting entries for vaccine trials for Dengue as porprtion of all vaccine trial entries

Within clinical trial entries for vaccines, Dengue accounts for only 2% of trial registrations. This is a low percentage for an infectious disease that has doubled in risk over the last

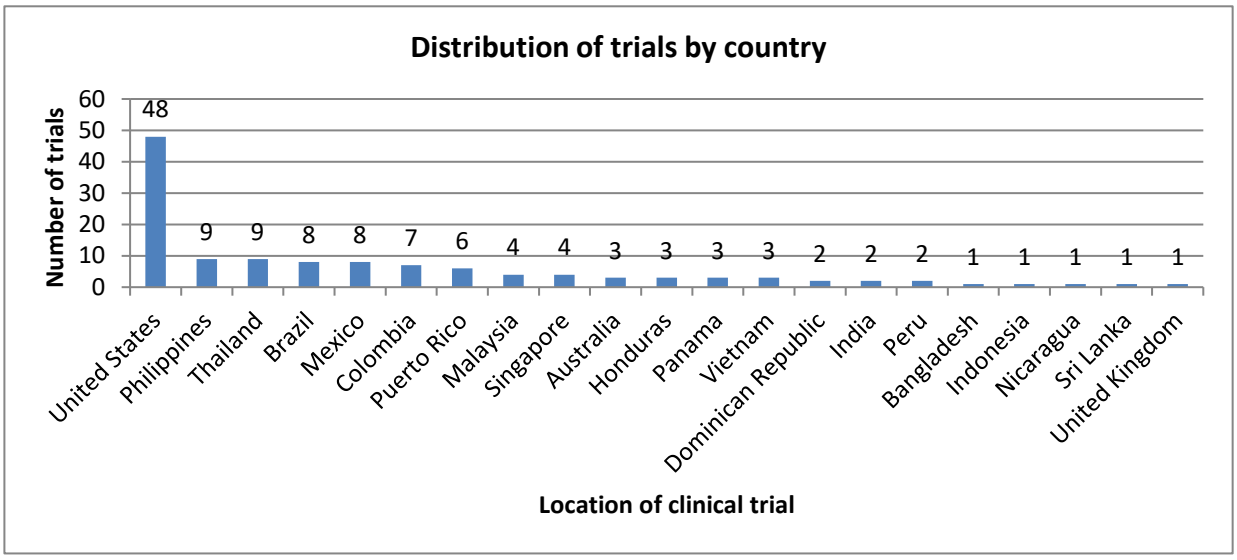

Figure 2.6 Figure depicting distribution of dengue trial entries entries by country

This trend is consistent with proportion of R & D expenditure on healthcare by country.

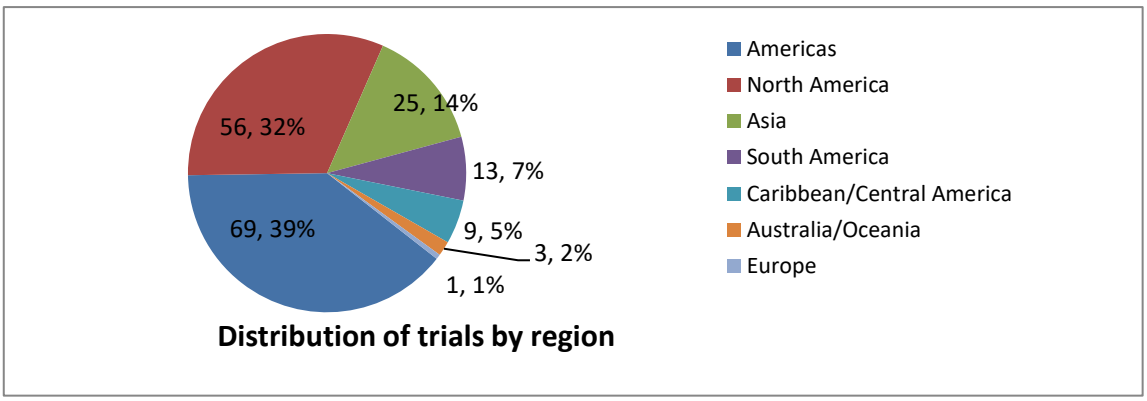

Figure 2.7 Figure depicting distribution ofdengue trial entries entries by region

As per estimates by ABVP, in 2016, USA spent approximately 58% of its healthcare budget on R&D and conducting clinical studies comprises a significant part of the same. The approval of any medical intervention by the FDA, USA, therefore also sets a regulatory precedence for licensing and approval in other countries and locations. The only drawback, particularly in case of dengue, is the lack of true dengue serotype population in continental USA, as is found in endemic areas such as in Latin America and South Asian countries. This change in the study population is likely to alter results and trials are increasingly looking at inclusion of laboratory confirmed seropositive cases as volunteers.

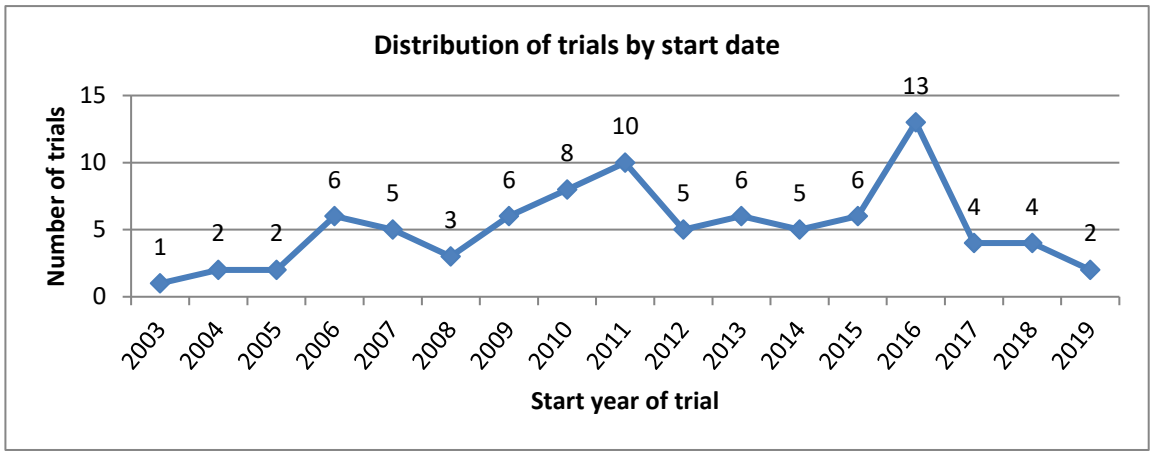

Figure 2.8 Figure depicting trend of clinical trial entries registered over time

These charts shows that clinical trials have been consistently commencing every year since 2003 and have only increased in number since then, indicating the continued interest of pharmaceutical sponsors and government agencies in the development of a dengue vaccine. The sudden peaks of increase in clinical trial commencement in the year 2011 and 2016 can be speculated to be responses to global outbreaks, however a detailed year wise analysis would be required to ascertain a specific reason for these increased peaks, if any.

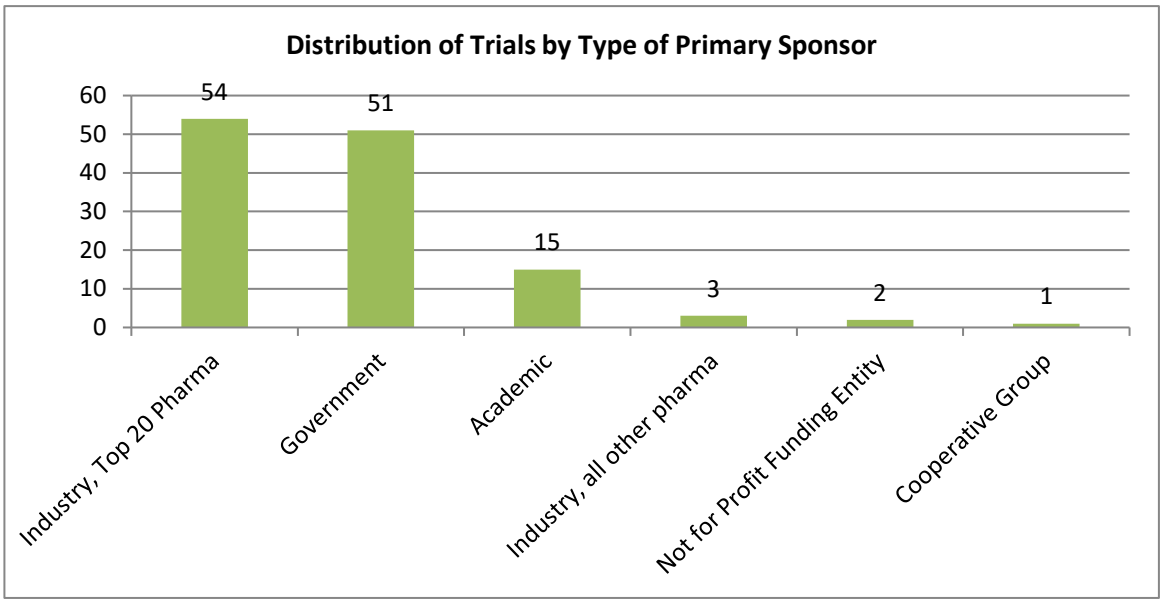

Figure 2.9 Figure depicting distribution of dengue trial entries by type of primary sponsor

This graph shows the distribution of sponsorship for the trials. Top 20 global pharmaceutical companies (Sanofi Pasteur, Takeda Pharmaceuticals, GlaxoSmithKline, Merck Sharpe and Dohlme) and government sponsored trials (National Institutes of Health(NIH), Centers for Disease Control, Indian Council of Medical Research) account for the maximum number of trials of dengue, followed by those sponsored by academic trials (Mahidol University, Johns Hopkins University, among others). It is important to note that we cannot directly conclude about the amount invested by each category or organisation based simply on the number of clinical trials sponsored by them. For example, Bill and Melinda Gates foundation is the third largest funder [26] for dengue research, globally, however, only a single clinical trial has been sponsored by them. Is is important to note that funding in R &D research could be Pre-Clinical, which is not reflected in the clinical trial registry data.

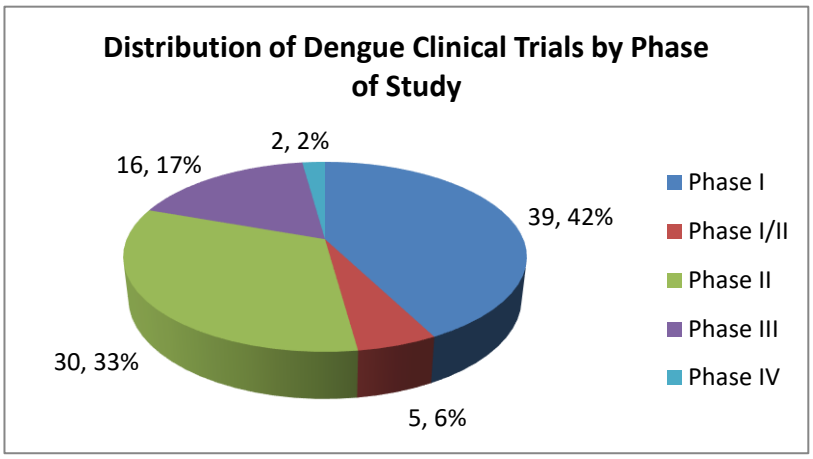

Figure 2.10 Figure depicting distribution of dengue trial entries entries by Phase of study

This result shows that maximum proportions of clinical trials are either in Phase I or in Phase II. It simply implies that it will take a long time before any of these candidates is able to make it Phase IV, in the likelihood of their success. As we know that probability of success for moving from one stage of study to the next progressively decreases, therefore, further impetus should be given to pre-clinical research in Dengue fever.

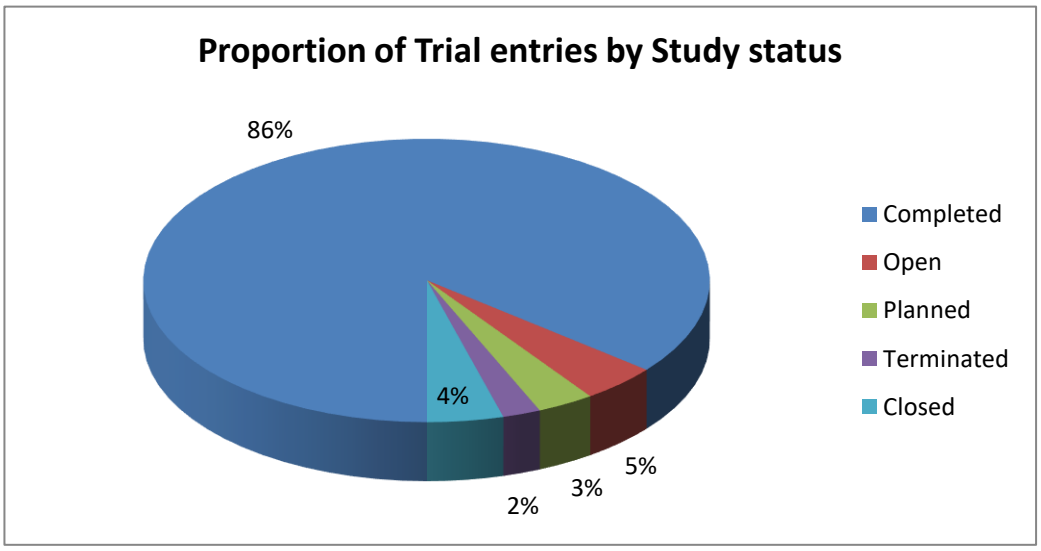

Figure 2.11 Figure depicting distribution of dengue trial entries entries by status of study

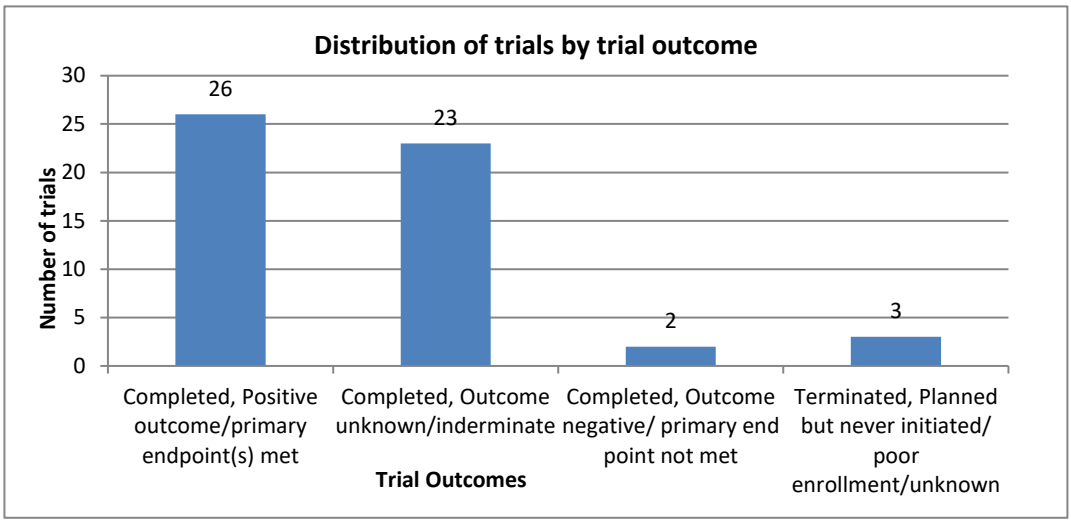

Figure 2.12 Figure depicting distribution of dengue trial entries entries by status of study

Figures 2.9 and 2.10 indicate that in a significant proportion of trials primary end point was met indicating success of carefully crafted trial design and an increased likelihood of success of tested therapy. However at the same time a significant proportion of trials, although completed, have their outcome listed as unknown/indeterminate. This is a reflection of non-compliance of sponsors to the WHO guidelines on trial result reporting. In other words, this is a reflection of the lack of transparency and accountability shown by sponsors. WHO guidelines mandate that trial results be published by sponsor on the registry website 12 months after study completion and in any case within 24 months. By not updating the clinical trial results on the clinical trial platform, hampers in the way of transparency and accessibility of clinical research data for the general public.

2.7.2 Evaluation of Approved Vaccines for Dengue

Only a single vaccine that has been licensed for preventive therapy which is Dengvaxia (CYD-TDV), developed and marketed by Sanofi Pasteur, France. It was first licensed for use in Mexico in 2015, following which it received marketing approval in several countries. As of today, Dengvaxia is licensed for use in 20 countries, including 10 countries in Latin America and Asia. Late in 2017, the European Commission approved the vaccine for use in dengue endemic parts of Europe — mainly offshore territories, such as the Caribbean islands of Martinique and Guadeloupe. The approval allows for use of the vaccine in people ages 9 to 45 who have previously had at least one dengue infection.

In 2016, the World Health Organisation had recommended the vaccine for all children aged nine to 16, based on early results of several large clinical trials conducted by Sanofi around the world. However, these studies did show that some children who had not been exposed to dengue went on to develop severe forms of the disease after receiving the vaccine.

On WHO's recommendation, the Philippines incorporated the vaccine in mass school immunisation programme covering over 1,00,000 children in 2016. However, a year later, Sanofi released new data showing the vaccine heightened the risk of hospitalisation and plasma leakage syndrome, in which blood vessels start to leak plasma. It is speculated that the death of more than 100 children was a direct result of this immunisation. This brought the Philippines' immunisation drive to an abrupt halt.

On 1st of May 2019, despite the safety concerns and the permanent halting the sale distribution and marketing of Dengvaxia by the National Health Authorities of the vaccine in Philippines, the FDA has approved the vaccine for use in the USA. The

vaccine has been approved for use with several limitations such as it can only be administered to individuals aged 9 to 16 living in parts of the United States where the dengue virus is endemic such as in Puerto Rico and a few other U.S. offshore territories and protectorates. Furthermore, the vaccine can only be given to children and teens who have had one previous laboratory-confirmed case of dengue.

Pre-Qualification Status by WHO

WHO vaccine pre-qualification programme ensures safe and effective supply of vaccines for distribution as part of immunisation programmes by member states and by organisations such as GAVI, UN agencies, etc. At present, Dengvaxia has not been pre-qualified for use by WHO.

India's position on preventive Dengue Vaccine

India had turned down the request by Sanofi to market the Dengvaxia vaccine in 2017 as it requested for waiving off the Phase 3 trials on Indian volunteers, and requested for direct marketing in the county. In the wake of the crises in Philippines, it was a wise public health policy decision. At the same time, India does not have a strongly enforced adult vaccination policy and inclusion of a partially effective, preventive vaccine in the Universal Immunisation programme seems unlikely even after due debate and consideration.

Clinical Efficacy of the Vaccine

The vaccine has a clinical efficacy of at best ~76% [in seropositive children] [23]

2.7.3 Vaccine/drug pipeline

A pipeline refers to the portfolio of drug or vaccine candidates in development by a pharmaceutical company. A similar portfolio can be created for any disease or medical condition by descriptive analysis of clinical trial registry data. It is a dynamic document as clinical trial registries get updated every day with newer trial registrations. It provides a holistic overview of the stakeholders in the drug development process and the relative position of each of their competing candidate along the drug development timeline. The pipeline for Dengue vaccine candidates has been generated in Table 2.2 (as on 25th May2019

Table 2.1 Global Dengue Vaccine Development Pipeline with associated Clinical Trials and Estimated Completion dates

VACCINE CANDIDATE NAMES/INTERVENTION ARM	PRIMARY SPONSOR	VACCINE PARAMETERS	CLINICAL TRIAL ID(S)	PRESENT STATUS	ESTIMATED/ACTUAL COMPLETION DATE	TRIAL SITES
TetraVax-DV-TV003 (also known as Butantan DV)	Butantan Institute	Tetravalent Dengue Vaccine; attenuated; subcutaneous	NCT02406729	Phase III, Recruiting	December 2025	Brazil
	Panacea Biotec Ltd		CTRI/2017/02/007923	Phase I/II, IEC under review	Not provided	India
TAK-003	Takeda Pharmaceuticals		NCT02747927	Phase III, a press release states that Primary end point has been met in January 2019	December 2021	Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand
?	GlaxoSmithKline		NCT00239577	Phase II, completed	June 2007	USA
T-DEN F17, T-DEN F-19	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT00370682	Phase II, completed	February 2008	Thailand
Dengue tetravalent Vaccine F17 Pre transfection, Dengue tetravalent Vaccine F17 Post transfection, Dengue tetravalent Vaccine F19 Post transfection	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT00350337	Phase II, completed	March 2008	USA
T-DEN-Post-Transfection F17, T-DEN-Post-Transfection F19	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT00468858	Phase II, completed	April 2010	Puerto Rico
Dengue Vaccine Formulation 17	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT00384670	Phase I/II, completed	May 2004	Thailand

DEN vaccine candidate, F17	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)	Tetravalent Dengue Vaccine; attenuated; subcutaneous	NCT00322049	Phase I/II, completed	June 2009	Thailand
TDENV-PIV with AS03B adjuvant	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)	Tetravalent dengue virus purified inactivated vaccine	NCT02421367	Phase I, Recruiting	June 2019	USA
TDENV-PIV	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT01666652	Phase I, completed	November 2017	USA
TDENV-PIV	GlaxoSmithKline (in association with Walter Reed Army Research Institute, USA)		NCT01702857	Phase I, completed	March 2017	Puerto Rico
TDENV-PIV and TDENV-LAV F17	U.S. Army Medical Research and Materiel Command	Tetravalent attenuated vaccine and inactivated vaccine both	NCT03141138	Phase I, Active but not recruiting	January 2022	USA
TDENV-PIV and TDENV-LAV F17	U.S. Army Medical Research and Materiel Command		NCT02239614	Phase I, completed	February 2017	USA
TVDV	U.S. Army Medical Research and Materiel Command	Tetravalent DNA Vaccine; intramuscular	NCT01502358	Phase I, completed	December 2013	USA
V180	National Institute of Allergy and Infectious Diseases (NIAID) in collaboration with Merck Sharp & Dohme Corp	Tetravalent recombinant subunit dengue vaccine; intramuscular	NCT02450838	Phase I, completed	October 2015	USA
	Merck Sharp & Dohme Corp		NCT01477580	Phase I, completed	December 2014	Not provided
Dengueshield	Serum Institute of India Pvt. Ltd in collaboration with PPD	Dengue monoclonal antibody; intravenous	NCT03883620	Phase 1, Recruiting	October 2019	Australia

2.7.4 Insights from the pipeline

Overall, the Dengue vaccine pipeline is very sparse and candidates are spaced far apart along the clinical development timeline. Larger numbers of candidates are still awaiting progress into Phase II and Phase III. There are a total of four distinct type of vaccine candidates – The tetravalent live attenuated vaccine, the tetravalent DNA vaccine, the recombinant subunit vaccine and lastly monoclonal antibody therapy. At present, the most robust competition is going to come from TAK-003(Takeda pharmaceuticals) that has recently (January 2019) announced that it has met the primary end point for dengue in its Phase 3 pivotal trial. It would now take, anywhere between 1-.2.5 years to obtain FDA approval for the same (on an average) and if Takeda possesses a priority review voucher (such as one for tropical disease), it would likely get a fastrack designation and approval hearing within 10 months. It will likely be the biggest challenge for other pharma companies as it has first mover advantage and likely to be favoured by regulatory bodies all over the world due to superior safety data over the approved Dengvaxia.

Another major player in the pipeline is GlaxoSmithKline (GSK), in conjunction with Army Research Institute USA. However, most candidate assets have not moved forward into Phase II and III in the last 1-3 years. This could be due to regulatory delays or due to company realignment and de-prioritisation in light of developments in competitor assets.

2.7.4.1 Insights for India

Two Indian companies – Panacea Biotech Pvt. Ltd. and Serum Institute of India are also carrying out Phase I/II studies for dengue vaccine candidates under non-exclusive technology transfer agreements with National Institutes of Health (NIH), USA and PPD Pharmaceuticals respectively. Although Panacea biotech has got approval and planned

trials in India, Serum Institute of India had earlier planned trials in Singapore, but now has started recruitment in Australia. This throws some light on the tightly regulated clinical trial approval frameworks in India, wherein it is difficult to obtain approval for an experimental therapy, such as monoclonal therapy for Dengue. The likely reason(s) for approval of Panacea Biotech is due to the MoU between NIH and GoI and associated technology transfer for TV-003 candidate.

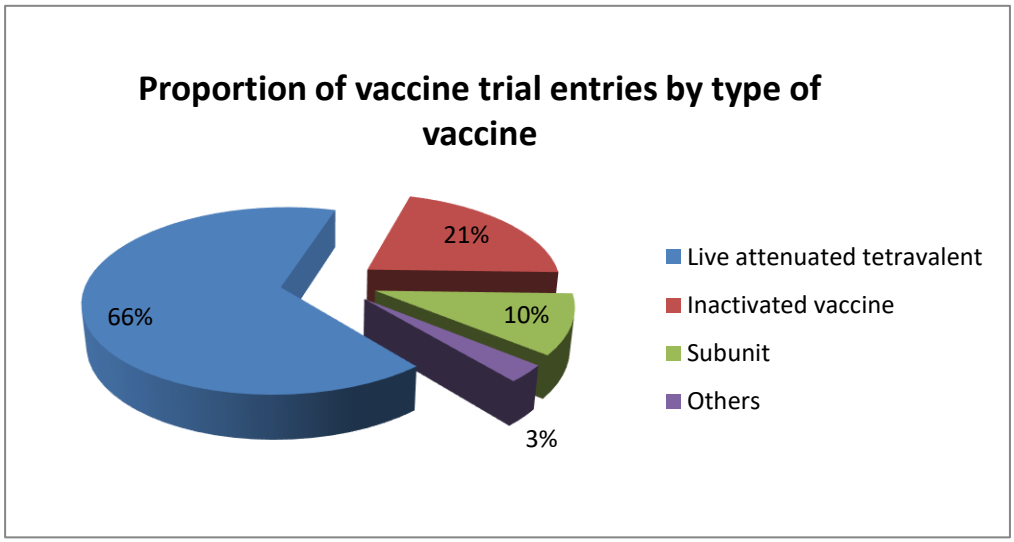

Figure 2.13 Figure depicting proportion of vaccine trial entries by type of vaccine

Within vaccine trial entries, the maximum proportion belongs to live attenuated tetravalent vaccines. This can be explained by two main reasons- out of all vaccine types available the LAV technology is considered to be the safest and stable at the molecular level. In other words, it is easy to handle. Additionally, several variants of it are owned by different pharmaceutical companies, thereby increasing the number of trial entries for this vaccine type.

Summary of insights:

- TAK-003 candidate is the now the only major competition to existing Dengvaxia globally
- Only two vaccine development programs are India based- Panacea Biotech and Serum Institute India
- Vaccine candidates are moving along slowly the development pipeline, and most candidates are in early to middle phase of development. This can be attributed ot regulatory delays, variation in sponsor interest or other reasons that need to be investigated further.

2.8 Recommendations for India

The Clinical Trial Registry of India is hosted by the National Institute of Medical Statistics, ICMR is one of the nine primary registries around the world, from which data is regularly uploaded on a weekly basis into the ICTRP, WHO. It was analysed that a significant proportion of dengue clinical trials (44%) have been registered retrospectively, i.e. after the enrolment of the first patient. This suggests that medical practioners and sponsors are not following the WHO guidelines on prospective trial registration. Similarly, although there are no explicit guidelines on registration of Observational Clinical Trials and their registration is only recommended, a significant proportion (31%) of dengue trials on CTRI are observational. This suggests that knowledge about the CTRI registry and it's processes are well understood, however better implementation of the same is required. This could include trial registration related trainings for medical and healthcare professionals, as well as education and knowledge transfer to them regarding the larger implication for open data, transparency, ethics and evidence base for meta-data research.

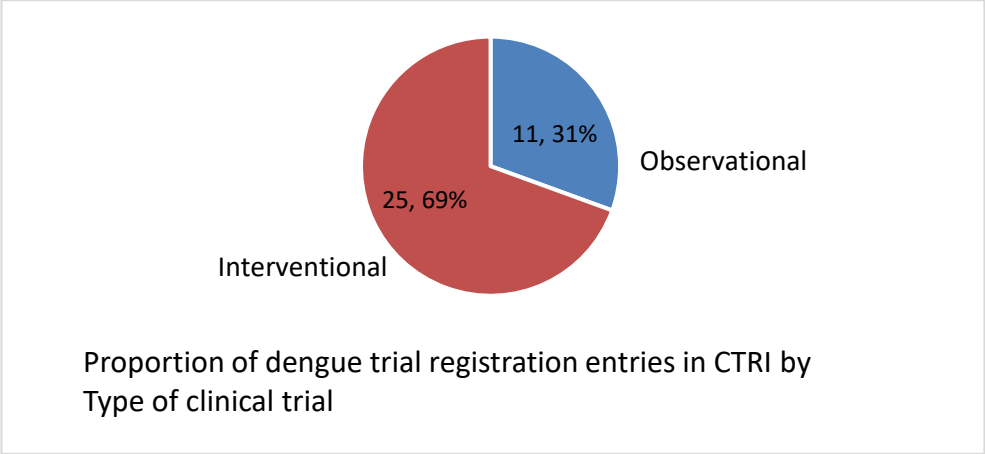

Figure 2.14 Figure depicting proportion of dengue trial entries in CTRI by type (Observational versus interventional)

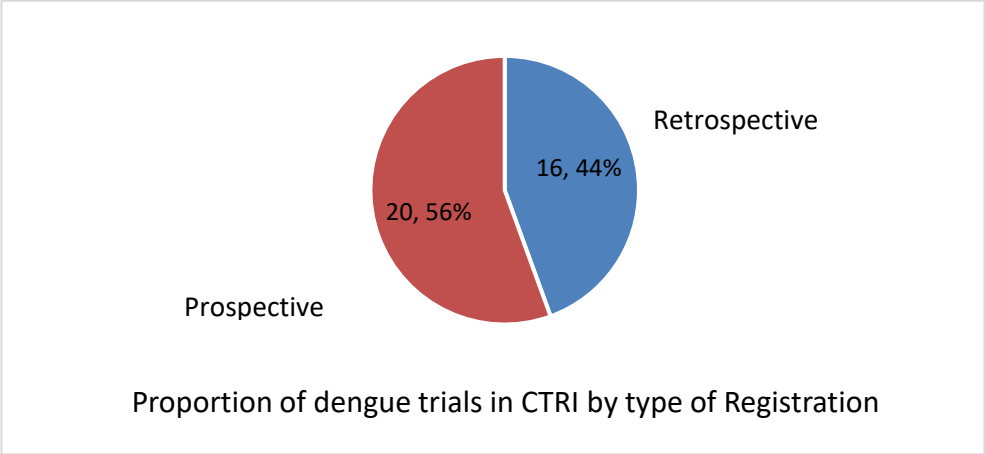

Figure 2.15 Figure depicting proportion of dengue trial entries in CTRI by type of registration (prospective versus retrospective)

In India, in- licensing for domestic manufacture and trials is the way forward as is the case with Serum Institute and Panacea Biotech. India should further expand in this direction, as procuring vaccine in bulk is also cost intensive. Therefore we need to utilise our already present, GCP compliant manufacturing bases to manufacture an in house vaccine and also test in our indigenous population before licensing it for use.

As long as a vaccine does not have >90% or 100% efficacy for an infectious disease, it cannot be used as the sole method of prevention. India needs to continue to keep up its vector control, surveillance and IEC methods for dengue control.

After analysis of the clinical trial registry, several Ayush compounds are in clinical trial of but their efficacy remains questionable. Although their registration or clinical trials are not required, due to their variable and non-standardised efficacy parameters, their uptake remains a challenge. India can also invest in these candidates as a topic of research.

Lastly India should invest more in pre-clinical research and drug discovery programs, particularly for diseases that endemic to our country.

Summary of Recommendations:

As India contributes to approximately 1/3rd the burden of Dengue in the world, India can have the following way forward in it's own Dengue vaccine development:-

- Indian pharma companies can invest in in-licensing agreements for the manufacture and testing of Dengue vaccines in India through technology transfer
- Set up strong, GCP compliant manufacturing units, in line with the 'make in India' vision of the government
- Streamline the clinical trial regulatory process (starting from registration step) to facilitate speedy and ethical clinical trials within the country
- India must invest and promote pre-clinical R&D; options such as In-silico drug development offer a unique cost advantage

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