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Review Article

Tropical Diseases

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Tropical diseases encompass all diseases that occur solely or principally in the tropics. In practice the term is often taken to refer to infectious diseases that thrive in hot humid conditions. Tropical diseases affect large population, are potentially preventable, affect economically backward communities and are neglected.

In past two decades with funding from national and global agencies, new drugs, vaccines, diagnostics have been developed tested and some of the diseases are identified for elimination.

This review focuses on diseases relevant to India viz., malaria, leishmaniasis, lymphatic filariasis and dengue and work done on epidemiology, policy, diagnostic tests, drug resistance, clinical trials, pharmacovigilance, new drugs and vaccines, in India.

Significant contributions have been made by India by carrying out clinical trials on new drugs, developing treatment guidelines for control and elimination of malaria (resistant falciparum, *P. vivax* relapse) leishmaniasis (liposomal amphotericin, combination with miltefosine for VL and PKDL) and filariasis (mass drug administration of DEC and ABZ).

Liposomal amphotericin developed in India has been evaluated clinically and marketed for visceral leshmaniasis. A novel trioxane antimalarial developed by CDRI has undergone phase I study. Arterolane piperaquine developed in India is marketed for falciparum and vivax malaria. Another drug for dengue is undergoing clinical trials. Several in vitro and preclinical studies on medicinal plants, synthetic chemicals, nanoparticles have also been carried out and await further development.

Keywords: Epidemiology; Drug Resistance; Clinical Trials; Drug Development; New Drugs

Introduction

Tropical diseases encompass all diseases that occur solely or principally in the tropics. In practice the term is often taken to refer to infectious diseases that thrive in hot humid conditions, such as malaria, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, chagas disease, African frypanosomiasis, and dengue (WHO Health topics, Tropical diseases).

Tropical diseases affect large population and are potentially preventable, affect economically backward communities, and are neglected. In the past few decades with the initiative and funding from WHO, Governments and other donors, new drugs, vaccines, diagnostic tools have been developed and immunological responses investigated. Leishmaniasis, filariasis and malaria have been identified for elimination.

In this update, tropical diseases relevant to India-viz., malaria, leishmaniasis, lymphatic filariasis and dengue are covered.

Methodology

For preparing this manuscript PubMed and Google scholar were searched for articles with key words tropical disease, specific disease, pharmacology and India, with filter applied for year of publication from 2012-2017.

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PubMed and Google scholar search gave initial hit publications, titles of which were perused to get potentially eligible, abstracts of which were seen to finally get publication of interest

Initial hits- 31,220

Potentially eligible-592

Finally included-173

Most of the publications are from research institutes, few are from medical and pharmacy colleges.

Publications for each disease are grouped according to publications on epidemiology, incidence, prevalence, policy, susceptibility to disease, diagnostic and prognostic tests, drug resistance, clinical trials, pharmacovigilance, prescribing practices, quality of marketed products, new drugs and vaccines.

To achieve control and elimination, besides chemotherapy, chemoprevention and immunological approaches, concerted efforts to control vector and protect subjects from insect bite are needed simultaneously. Work done in India for vector control and personal protection is not covered in this review.

Malaria

Epidemiology, Incidence, Prevalence and Policy

P. vivax has been the focus of attention due to its relapsing nature and recent observations about the complications it produces.

The epidemiology of *P. vivax* malaria, response to treatment of acute attack with chloroquine and preventing relapse with primaquine and bulaquine has been reviewed (Anvikar *et al*., 2016). As *P. vivax* cannot be reliably differentiated from recrudescence or reinfection, recurrence rates were assessed. There is variation in relapse patterns both across and within states. Strains of differing patterns of relapse can coexist, complicating transmission and control measures. For e.g., in Delhi, Group I tropical type, is most common with relapse between 1month and 3 month, also present are Group II and III (temperate) types with relapse between 3-5 and 6-7 months respectively. In Mumbai the relapse pattern is predominantly Group I tropical type.

Choloroquine resistance was sporadically reported but mostly there is 100% response. G6PD deficiency varies from absent to 27.1% among Angami Naga tribe. Multiple G6PD genotypes including severe variant G6PD Mediterranean exist, though there are only few reports of acute haemolytic anaemia (Anvikar *et al*., 2016).

Roy et at applied a *P. vivax* transmission model to surveillance data from a semiarid region in Northwest India. The results quantify the striking dependence of *P. vivax* on relapses for its survival supporting the feasibility of regional elimination using antirelapse treatment and emphasize need for replacing primaquine. (Roy *et al.*, 2013)

Jain studied severe *P. vivax* malaria in tertiary healthcare facility in Jabalpur. Severe vivax was found in 11% out of 198 vivax cases, cerebral malaria and seizure, respiratory distress, severe anaemia each seen in 32% cases (Jain *et al*., 2013).

In prospective observational study in referral hospital in northern India, from Jan, 2012-Dec, 2012, clinical features of *P. vivax* were similar to *P. falciparum*, two patients died of cerebral malaria and ARDS. Children were treated with IV artesunate followed by artemethar-lumefantrine. Microscopy and PLDH based rapid diagnostic test (RDT) was used for diagnosing malaria (Gehlawat *et al*., 2013)

Out of 110 patients of *P. vivax* admitted in medical college hospitals in Chandigarh and Gujarat 19 had severe disease, there was wide variation in treatment given. All patients survived, one child of cerebral malaria had sequale (Singh *et al*., 2013).

The antimalarial policy in India was reviewed. Various unresolved challenges in the use of Artemisinin Combination Therapy (ACT), gametocytocidal and antirelapse use of primaquine, and preventing malaria during pregnancy were pointed out (Anvikar *et al.*, 2014).

An analysis of data from 21 therapeutic efficacy trials done in India during 2009-2010 showed that P. falciparum gametocytemia was present in 18% of patients and contribute substantially to the reservoir for potential transmission (Shah *et al.*, 2013).

Artesunate + Sulfadoxinepyrimethamine (AS+SP) treatment failure was found to be widespread in Northeast India. Based on these results Artemether+Lumefantrine were selected for subnational drug policy for India (Mishra *et al*., 2014).

A state level analysis of NVBDCP data showed that ten states/UT with 30% or more tribal population comprising only 3% of total population, contributed to 14% of total malaria.

Districts with 30% or more tribal population comprising of about 8% country's population contributed to 46% of total cases, 70% falciparum and 47% malarial deaths in the country (Sharma *et al*., 2015).

Pathak *et al.* noted in Mumbai and Rourkela region, clinical malaria exhibited an adult male bias, which was not seen in children ≤10 year and discussed possible roles of sex hormone, vector exposure, co-infections and other factors in this enhanced susceptibility of males (Pathak *et al*., 2012).

Jha studied human mannose binding lectin encoded by the MBL 2 gene variation and malaria susceptibility in Indian population and found that MBL 2*LXPA increases malaria risk while MBL 2*LXPA haplotypes confers protection (Jha *et al*., 2014).

The complement receptor 1 variant in severe malaria (SM) has been studied (Panda *et al*., 2012) and it was concluded that the homozygous polymorphisms of CR1 intron 27 and exon 22 (TT and GG) and alleles (T and G) that are associated with low expression of CR1 on red blood cells conferred significant protection against cerebral malaria (CM), multiorgan dysfunction (MOD) and malarial deaths. Combined analysis showed significant association of blood group B/ intron 27-AA/exon 22-AA with susceptibility to SM (CM and MOD) (Panda *et al*., 2012).

Individuals infected with *P. falciparum* and healthy controls were studied and significant role for GSTM 1 deletion in complicated malaria (ODDs. ratio 3.8, 1.9-7.4) Polymorphism in GSTP 1, SOD1 and CAT gene was found may be associated with malaria susceptibility, whereas SOD 3 polymorphism may play a role in malarial resistance (Fernandes *et al*., 2015).

The challenges in tackling malaria problem has been reviewed (Bharti and Ganguly, 2013). They emphasized that to achieve early case detection, diagnosis and prompt treatment (EDPT) rapid diagnostic tests of high sensitivity, specificity are needed.

There is also need to tackle issue of illegal manufacturing and cross border trafficking of fake or counterfeit drugs with inter country collaboration, use of pharmacovigilance and biochemical tests like GPHF- Minilab® dye test Kit developed by the Global Pharma Health fund for checking the quality of antimalarials such as artesunate (Bharti and Ganguly 2013).

Clinical profile and management of malaria in pediatric age group has been studied (Nayak *et al*. 2014). In a tertiary care hospital in Manglore 0-5 years age were more affected and *P. vivax* was major parasite type (Nayak *et al*., 2014).

Diagnostic Tools and Pathogenesis

Singh evaluated in the field and noted that Rapid Diagnostic tests (RDTs) are useful even at high temperature but quality should be regulated and monitored closely (Singh *et al*., 2013).

Sri Krishna and others showed that in 8 malaria endemic states in India, mixed plasmodium spp. infections were detected by PCR in 17.4% of blood samples in which microscopy had shown to contain only *P. falciparum*. The quality of microscopy needs to improve (Krishna *et al*., 2015).

Patients with acute undifferentiated fever were studied (Hanshuus *et al*., 2016) in seven secondary community level hospitals and was PCR positive in 19 % cases of which P. falciparum and *P. vivax* and mixed infection was 46%, 38%, and 11% respectively. Microscopy sensitivity was 29%, specificity 98%, RDT sensitivity was 24% and specificity 99% (Hanshuus *et al*., 2016).

Real time micro PCR point of care device developed by Bigtec lab. Banglore has limit of sensitivity of<5 parasites/µl, sensitivity 99%. It was claimed to be suitable for diagnosis, active surveillance and epidemiological intervention (Nair *et al*., 2016).

The results of study by Sahu showed that compared to microscopy ParaHIT-f had sensitivity

63.6% specificity 98.9%. Its sensitivity was 47.8% at low parasitaemia of 4-40 parasites/µl (Sahu *et al.*, 2015).

Sahu *et al*. summarized current understanding of cerebral malaria pathogenesis, compiled an array of new biomarkers and tools available for diagnosis and research and described emerging therapeutic approaches to tackle this pathology effectively (Sahu *et al*., 2015).

Das *et al*. studied genotyping of *P. vivax* by minisatellite marker and showed that CH1 T1 M13779 can be a potential minisatellite marker for differentiating relapse and new infection (Das *et al.*, 2016).

Drug Resistance

A systematic review of antimalarial drug resistance of *P. falciparum* in India, changes over time and space showed the increase in chloroquine resistance over the years and also geographical spread.

Sulfadoxine pyrimethamine resistance increased from 7.7% during 1984-96 period to 25.9% in 1997-2007, most studies were done in north eastern states and Arunachal Pradesh on the Chinese Burmese borders had the highest rate of treatment failure. This is very relevant to monitoring and policy for considering the effectiveness of treatment with artesunate plus sulfadoxine pyrimethamine which is the recommended ACT in the National program (Shah *et al*. 2011).

Amit Kumar genotyped 173 field isolates and found rise in resistant SP (sulphadoxine-pyrimethamine) alleles from very low frequencies in 1994 to steady rise in year 2000 and maintaining this trend in year 2013, even after change in malaria treatment policy (Kumar *et al*., 2015).

P. falciparum field isolates in Ujjain Madhya Pradesh had sulphapyrimethamine resistance associated *pfdhfr* 108 N and 59R alleles in 96% and 90% and *pfdhps* 437 G in 9%, double mutant in 82%, triple mutant in 8%, chloroquine resistance associated *pfcrt* 76T in 94%. *pfmdr1* S 1034+N 1042+D1246 in 97% samples. Efficacy of chloroquine was poor, and there is reduced susceptibility to SP (Pathak *et al*., 2014).

Drug resistance genes dihydrofolate reductase and dihydropteroate synthase in *P. falciparum* had double mutations in low transmission area while upto sextuple mutation were present in high transmission area in various states (Sharma *et al*., 2015).

Mutation in PfK-13 in strongly linked to artemisinin resistance. In 384 samples (from an efficacy study) PCR amplified and sequenced from codon 427 to 727, nonsynonymous mutations were found in 4 patients from north-eastern states but this did not correlate with treatment failure (Mishra *et al*., 2015).

Gupta *et al*. studied ABCB1membrane transport genes that code for P-glycoprotein and noted that multiple mechanisms such as genetic and epigenetic variations within a key gene may play a role in malarial susceptibility and response to antimalarial drugs in the population (Gupta *et al*., 2017).

Clinical Trials, Observational Studies, Pharmacokinetics, Pharmacovigilance

Clinical trials to evaluate efficacy, safety, pharmacokinetics of ACT and of different doses of primaquine have been carried out in different parts of the country.

Data on patients in primary health centres is sparse.

Response to a standard doses of chloroquine, primaquine 210mg over 14 days was studied in *P. vivax* cases in primary health centres in Karnataka and cases were followed up for 28 days. 3% had G6PD deficiency (<30% normal mean activity) They received primaquine 45mg once a week, one patient got dark brown urination which subsided on discontinuating primaquine. All patients showed adequate clinical and parasitological response. Nested PCR showed 28% cases were mixed vivax and falciparum (Saravu *et al*., 2016).

To explore use of azithromycin (AZ) and chloroquine (CQ), a double blind, randomized, non-inferiority study comparing AZ 1gm+CQ 600mg daily for 3 days or CQ+ sulfadoxine pyrimethamine (SP), was carried out in adult uncomplicated falciparum malaria patients. Parasite clearance rate was 84% with AZ CQ and 94% with CQ SP respectively (Kshirsagar *et al*., 2017 accepted).

A comparison of artesunate amodiaquine (ASAQ) fixed dose combination with amodiaquine (AQ) for treatment of P. falciparum malaria in patients aged 6 months-60 years of age showed PCR corrected cure rate in intent to treatment population to be 97.51% in ASAQ and 88.65% in AQ arm. There were 2 early treatment failures in AQ arm. (Anvikar *et al*., 2012)

In a Phase II multicentric open label study in children aged 6 months to 12 years with acute uncomplicated P. falciparum, efficacy and safety of fixed dose combination of arterolane maleate and piperaquine phosphate dispersible tablets was studied. PCR corrected adequate clinical and parasitological response was achieved in 100% of cases with fever clearance time and parasitological clearance time being 10 hr. and 24 hr. respectively. Most frequent adverse events (AES) were vomiting which was mild to moderate and resolved without sequalae. No changes in QT prolongation were seen (Toure *et al.,* 2015).

In Phase 3 double blind randomized study of arterolane maleate piperaquine phosphate (AM+PQP) vs artemether-lumefantrine (AL) for P. falciparum in adolescent and adult patients in Asia and Africa, AM+PQP showed comparable safety and efficacy to AL with high clinical and parasitological response and rapid parasitological clearance (Toure *et al.,* 2016).

Study for therapeutic efficacy of artemether lumefantrine for treatment of falciparum malaria from three highly malarious states in malaria patients, had one late clinical failure and two late parasitological failures (Bharti *et al.,* 2016).

A single ascending dose safety and pharmacokinetic study of 97/78 a novel trioxane developed by CDRI was carried out in healthy volunteer. It was well tolerated, t ½, MRT, AUCof the active metabolite was calculated and now further studies are awaited (Shafiq *et al.,* 2014).

In 2009-2010 prospective study in 25 sentinel sites 98.8% efficacy for AS+SP was noted. Double mutation in *dhfr* was found in 68.4% genotyped isolate. A daily dose of AS<3 mg/kg, age less than 5 and fever at enrolment was associated with increased risk of failure. Chloroquine was 100% effective in *P. vivax* (Mishra *et al.,* 2012).

In Jalpalguri district significant failure of ASSP was noted with *pfdhfr,* I(51)R(59)N(108) and *pfdhps* G(437) and/or E(540) mutation (Saha *et al.,* 2012).

Rajgor studied antirelapse efficacy of various primaquine regimens for P. vivax in Mumbai and found that recurrence rate was 16.39, 8.07, 10.07, 6.62 per cent in control (no primaquine), 15 mg/day for 14 days, 30 mg/day 7 days, and 30 mg/day 14 days regimen. The concordance between different methods *viz* month of recurrence and PCR RFLP and PCR sequencing for distinguishing relapse from re-infection was low. Probable resistance to PQ warrants continuous monitoring and caution in interpreting results of re-infection, relapse. (Rajgor *et al*., 2014)

Efficacy of 14 days PQ regimen (0.25 mg/kg/day) in adult with 15 months long follow up was studied in Udupi district. Of 144 participants, 24.6 % got recurrence with median duration of recurrence 3.1 months (1.2-15.1 months). Patients with history of *P. vivax* malaria had higher risk of recurrence (Kumar *et al.,* 2016).

In a multicentric (one centre India) double blind 2b study of tafenoquine, antihypnozoite efficacy was evident for reduction in homologous recurrence of *P.vivax* but not heterologous recurrence (Beck *et al.,* 2016).

Therapeutic *in vivo* efficacy of chloroquine alone or in combination with primaquine against *P. vivax* malaria in Kolkata, West Bengal, India and polymorphism of pvmdr1 and pvcrt 0 genes. Y976 F mutation was not detected in any isolate. *pvmdr1* gene had 8 non-synonymous mutation B which were new. Chloroquine was effective though day 3 positivity was observed in 5.3% cases (Ganguly *et al.,* 2013).

Valecha studied arterolane piperaquine vs chloroquine in acute uncomplicated *P. vivax* in a phase III, multicentric open label study and found comparable efficacy (Valecha *et al.,* 2016).

Population pharmacokinetics of mefloquine administered as a fixed dose combination of artesunate mefloquine in Indian patients for the treatment of acute complicated *P. falciparum* malaria was similar to Thai patients (Jullien *et al.,* 2014).

Lumefantrine concentration and treatment outcome in *P. falciparum* cases in Orissa treated with artemisinin lumefantrine was studied. One hundred per cent patients had adequate clinical and parasitological response despite high inter individual variation in lumefantrine concentration (Valecha *et al*., 2012).

Kadam studied pharmacokinetics of chloroquine in malnourished children, compared with normally nourished children with malaria and observed that there was wide inter individual variability in the levels of drug and metabolite but the difference between groups was not significant (Kadam *et al*., 2016).

500 patients of malaria were studied and it was noted that nearly half complained of ADR, though there was no serious ADR (Belhekar *et al*., 2012).

ADR reporting beliefs of healthcare professionals were assessed and compared and it was noted the need for specific targeted in service education with hands on training on ADR monitoring and reporting to boost real time pharmacovigilance in India was noted (Gupta *et al*., 2014).

Targets, New Drugs, Vaccines, Mechanism of Action

Various plants from traditional and tribal medicine, synthetic chemicals and drug delivery systems have been studied. Targets for vaccines and for developing new drugs have also been investigated. Animal model for Acute Respiratory Distress Syndrome has been developed and effect of surfactants tested (Hagawane *et al*., 2016).

Aqueous extract of Traditional Plant-based Malaria Prophylactic drug 74, given twice a week for 14 weeks compared to control (no drug) group had significantly fewer cases of malaria (12.3% compared to 26.6%) (Nagendrappa *et al*., 2017).

Dry rind of *Punica granatum* was shown to have effect on hemoprotozoa and also anti-inflammatory action (Bhattacharya *et al*., 2013).

Traditional medicines used against fever were studied and promising antiplasmodial activity in *Aegle marmelos, Lantana camara, Leucas aspera, Momordica charantia, Phyllanthus amarus, Piper nigrum* was observed (Kamaraj *et al*., 2012).

Nine medicinal plants used by Karens of Andaman Nicobar Islands were investigated and *Z. spectabilis, S. wallichiana, C. pulcherrima* and *Amomum* sp. demonstrated significant antimalarial activity with no toxicity on erythrocytes (Chander *et al*., 2015).

Chander also found antimalarial activity in methanolic extract of *J. syringi folium, D. andamanica, C. indicum, P. tithymaloides* used traditionally by Nicobarese tribes (Chander *et al*., 2016).

Clinical activity of *N. arbor tristis* was studied and the effect of the paste of 5 fresh leaves, given thrice a day for a week in twenty patients was evaluated.

N. arbor tristis showed disease modifying activity, early clinical recovery, decline in TNF-á and a gradual parasite clearance (Godse *et al*., 2016).

Kumari showed that *Nyctanthes arbor tristis* (Harshringar) leaf extract and RPHPLC purified fractions had promising activity against chloroquine sensitive and chloroquine resistant strains (Kumari *et al*., 2012).

Antimalarial activity of ethanolic bark extract of *A. lebbeck* against chloroquine resistant and sensitive strains was tested and high selective index and ED_{50} of < 100 mg/kg against *P. berghei* was found (Kalia *et al*., 2015).

It was found that ethanolic extract of *O. sanctum* had significant activity against *P. falciparum* (Inbaneson *et al*., 2012).

A literature search was done and Vaidya/Hakim and lay people were interviewed and it was seen that 51 plants belonging to 27 families, plant root decoction are mostly used. Most popular plants are *Adhatoda vasica, Cassia fistula* and *Swertia Chirata* (Qayum *et al*., 2016).

Aminake synthesized hybrid molecules with covalent fusion of azidothymidine (AZT) and dihydroartemisinin (DHA) tetraoxane or a 4 aminoquinoline derivative and found antiplasmodial activity and activity against HIV in compound 7, but it is metabolized by O-dealkylation hence inactive in mice (Aminake *et al*., 2012).

Artemether Lumefantrine nanostructured lipid carriers for oral malaria therapy was studied and enhanced efficacy at 1/5 the standard dose and dosing frequency daily instead of twice a day in mouse model was found (Prabhu *et al.,* 2016).

Goyal reviewed essential redox active processes and their components in malaria parasite and enlisted currently used redox-active antimalarials, their mode of action and pharmacotherapeutic implications (Goyal *et al*., 2012).

Potential drug targets in malarial parasite were reviewed (Arora and Banerjee, 2012).

Genetic variation in the *P. falciparum* circumsporozoite protein in India and its relevance to RTS, S malaria Vaccine was studied. Genetic diversity in samples collected over 5 year prospectively was studied. For RTS, S malaria vaccine candidate, naturally occurring polymorphism at the vaccine candidate loci are critical determinants of efficacy. The study provides an insight into it (Zeeshan *et al.,* 2012).

The Duffy (FY) antigens act as receptors for chemokines as well as for *P. vivax* to invade RBCs. Occurrence of FY*A allele is correlated with decreased susceptibility to *P. vivax*. Results of this study by Chittoria show the correlation with FY*A and role of natural selection (Chittoria *et al*., 2012).

Deletion of asparagine synthetase delays asexual and liver stage development as parasite life cycle has an absolute requirement for asparagine which could be targeted to prevent malaria transmission and liver infection (Nagaraj *et al.,* 2015).

Thus it is seen that investigators have identified several plants with potential for antimalarial activity. What is needed is investigating effect of purified characterized extracts (phytopharmaceutical) or active molecules from the plants and testing activity on resistant strains and for anti relapse activity.

Conclusion and Way Forward

Clinical studies done in India have been of considerable use for policy making and individual patient care. e.g., artemether, lumefantrine was recommended in Northeast India based on widespread ASSP treatment failure observed. Epidemiological studies have highlighted the burden of malaria in tribal population resulting in policy of focusing on malaria in tribal region; studies on *P. vivax* have highlighted the geographical variation in relapses, ethnic variation in G6PD deficiency, genotypes and that *P. vivax* can present with severe manifestations.

Studies on efficacy of different doses of primaquine were useful to recommend National policy of 14 day treatment with primaquine. Methodological issue of differentiating relapse from re-infection has been taken up in some studies but it continues to pose a challenge. Changes in resistance pattern in P. falciparum malaria over time and geographical areas has been well demonstrated through clinical and genetic studies and is a warning to avoid overuse and irrational use of antimalarials.

Work on drug development especially from plant sources holds promise. We need drugs which are effective against artemisinin resistant strains of *P. falciparum*, alternative to primaquine, that is safe in G6PD deficiency and effective with short course. Complicated/severe malaria can be avoided by early diagnosis and treatment. Hence sensitive, specific, point of care diagnostic tests are needed. Severe malaria still has high mortality and research into pathogenesis and drugs that can be used to treat complication of severe malaria like ARDS (Acute Respiratory Distress Syndrome) are needed.

Leishmaniasis

Incidence Prevalence Policy

Kala Azar (Visceral Leishmaniasis) VL is a major public health problem in four states of India. The disease has been targeted for elimination by 2017. Elimination is defined as reduction in the annual incidence of Kala Azar to less than 1 case per 10,000 populations at the sub district level.

Over time, cases have shown a decline from 24212 cases with 93 deaths in 2009 to 8223 cases and nine deaths in 2015.

Sodium stibogluconate was main drug in the National program in 1990's. However there was increasing resistance. Miltefosine an oral drug was introduced. Amphotericin though very effective was toxic. Liposomal amphotericin with considerably reduced toxicity was introduced.

There are several challenges in control and elimination of VL such as rational use of drugs and understanding Post Kala Azar Dermal Leishmaniasis (PKDL).

Predictors from three transmission models were compared and it was concluded from all models that *L. donovani* transmission will continue after 2020 and surveillance and control measures need to remain in place until longer term aim of breaking transmission is attained (Rutte *et al*., 2017).

To halt increasing unresponsiveness to drugs it has been highlighted that various steps need to be taken such as rational dosing, and duration, identify markers of resistance, use of effective combinations, immunotherapy, management of HIV/VL confection and PKDL (Sundar *et al*., 2014).

The need for pharmacovigilance and economic alternatives to ambisome has been commented upon (Kshirsagar, 2014 a). Different liposomal formulations of amphotericin vary in efficacy and safety due to difference in composition, particle size and manufacturing process. There is need for preclinical animal pharmacokinetic, safety, efficacy and clinical data besides pharmaceutical characterisation for liposomal formulation which may be similar but not same to regulatory approved marketed products like ambisome or fungisome (Kshirsagar, 2014 b).

The clinical, epidemiological, parasitological and immunological perspective of PKDL has been reviewed and hypotheses developed relating to role of antimonial drugs, UV induced skin damage, re-infection, organ specific failure of memory T cell response and genetic susceptibility of host, to explain development of PKDL (Mukhopadhyay *et al*., 2014).

Clinically suspected cases of PKDL were investigated with *rk-39* strip, microscopy and *PCR/q* PCR. 20% of cases of PKDL had no history of VL. Diagnostic sensitivity was 32-36% with microscopy, 96-100% with *PCR/q* PCR. Compliance to treatment was 85% with miltefosine and 15% with antimonial. Relapse rate with miltefosine was 13.2% (Ramesh *et al*., 2015a).

Cutaneous Leishmaniasis is endemic in Bikaner region situated in Thar Desert in Rajasthan. Clinical features of preschool children (0-5 year of age) has been described. *L. tropica* is usual causative species. Intralegional sodium stibogluconate is well tolerated. Other therapies that are effective are oral rifampicin, oral dapsone, radio frequency, heat therapy and combination of three therapies (Agarwal *et al*., 2014).

Diagnostic, Prognostic Tests and Tools

The current status and challenges in various diagnostic tools for diagnosis of VL have been discussed and their applications assessed in resource poor settings (Singh and Sundhar, 2015).

In one study, serological test, DTH or conventional PCR or quantitative PCR have been used to detect asymptomatic or early infection and as predictor of progression to symptomatic disease, 34.7% of 1469 healthy individuals living in endemic area were PCR positive. There was poor agreement with serology testing and in subjects who developed symptomatic VL after 12 months (Sudarshan *et al*., 2014).

Singh evaluated *rk-39* strip and with some modification it showed sensitivity of 100% in serum while in urine, it was 96% with specificity 100% (Singh *et al*., 2013).

rKE 16 antigen based rapid test flow through test (KEFT) was comparable to *rk-39* and better than lateral flow test (KELF) (Vaish *et al*., 2012).

Drug Resistance

Two patients of VL were studied, whose blood buffy coat grew *L. donovani*. Both isolates had good IC_{50} value for amphotericin (0.07, 0.1 µg/ml), one isolate was refractory to antimony sb^{III} with IC_{50} more than 200 µm, one had 36.7µm, but both had miltefosine IC_{50}>100µm, 10 fold higher than standard strain DD8 with IC_{50} 6.8 µm. Genetic analysis showed SNP_{354}Tyr ↔ Phe and $_{1078}$Phe↔ Tyr in LdMT gene (Srivastava *et al*., 2017).

In J 774A.1 macrophage cell line, increased tolerance with high ED_{90} value for miltefosine and paromomycin in isolates from a patient from high endemic region was noted (Prajapati *et al*., 2012a).

It was found that *in vitro* susceptibility of VL isolates from relapsed VL and PKDL cases had lower susceptibility than pre-treatment isolates, PKDL

isolates were more tolerant to miltefosine (MIL) compared to VL isolates. All were uniformly susceptible to paromomycin. Mutations in the LdMT and LDRos3 genes that previously correlated with experimental resistance to MIL were not present for the field isolates (Bhandari *et al*., 2012).

Deep studied *L. donavani* pre-treatment (*LdPreTx*) isolates and post treatment isolates (*LdRelapse*) from VL and PKDL patients that relapsed and parasites made experimentally resistant to MIL (LdM30) and found higher IC_{50} and lower MIL accumulation in *LdRelapse* parasites compared to *LdPreTx* (Deep *et al*., 2017).

Functional studies were carried out to determine activity of the efflux pumps in antimonial resistant clinical isolate from India. Molecular characterization of thiol levels was also carried out and was found over expression of gene coding of Y glutamylcysteine synthetase was found thereby establishing that thiols are key determinants was found of antimonial resistance. Sb^{III}/thiol conjugates can be sequestered by ABC transporter multidrug resistance protein A (MRPA) into intracellular organelles and pumped out by an uncharacterized transporter (Singh *et al*., 2014).

Mitogen activated protein kinase 1 single allele replacement mutant exhibited increased resistance to sb^{III}, it negatively regulates the expression of pglycoprotein type efflux pump in the parasite. The decrease in efflux pump activity with an increase in LdMAPK1 activity may result in increased antimony accumulation in the parasite, making it more vulnerable to the drug (Garg and Goyal, 2015).

Clinical Trials and Observational Studies

A 2007 observational cohort study in Bihar of 251 patients with VL, treated with 20 mg/kg IV. Ambisome demonstrated 98% cure rate at 6 month between July 2007 & Aug 2012. Medicines Sans Frontiers (MSF) and Rajendra Prasad Memorial Research Institute (RMRI), implemented a VL treatment project in Bihar. IV ambisome was given in 4 dose of 5 mg/kg over 4-40 days. The observational cohort study by Burza *et al*. describes 8749 patients with laboratory confirmed primary VL treated over 5 year period. 1396 were treated at primary health centre, 7189 in hospital and 164 in camps. Initial cure rate was 99.3%, 0.3% defaulted 0.4% died 1.8% were HIV co-infected, 0.6% were TB co-infected. 0.1% discontinued due to allergy and 0.3 % were readmitted due to PKDL.

Risk factors for late presentation were female sex, age ≥15 years. Of the 984 patients treated, 827 were traced, 20 (2.4%) relapsed with mean time to relapse was 9.6 ± 3 months (Burza *et al*., 2014a).

In a further study, Burza noted that 1.4% of initially cured 8537 patients relapsed with median time of relapse 10 months. Male sex, age >5 and ≤ 45 year, decrease in spleen size at the time of discharge of < 0.5cm/day and shorter duration of symptoms prior to seeking treatment were significantly associated with relapse (Burza *et al*., 2014 b).

Amongst patients treated with 20 mg/kg liposomal amphotericin (Ambisome), 0.3% had passively returned with PKDL. Median time to developing PKDL (1.2 years) was shorter compared to conventional VL treatment (Burza *et al*., 2014 c).

In 71 parasitologically proven VL patients, efficacy of miltefosine given as per NVBDCP guidelines, was 93% and no adverse effects were observed during study period (Patra *et al*., 2012).

Sundar studied in 567 patients effect of miltefosine and concluded that compared to phase III trial that led to registration of drug a decade ago, there is a substantial increase in failure rate of oral miltefosine for treatment of VL in India (Sundar *et al*., 2012).

Confirmed PKDL cases were treated with miltefosine 50 mg twice a day for 90 days (regimen 1) or 50 mg thrice day for 60 days (regimen 2). Of the 73 treatment completed cases, 11 cases relapsed by end of 18 months, significantly higher in regimen 2 (31%) vs (10.5%) in regimen 1. Parasite load pre-treatment was significantly higher in patients that relapsed. *In vitro* susceptibility of isolates after relapse was significantly (2 fold) lower compared to pre-treatment isolates (Ramesh *et al*., 2015b).

Fungisome (Indian Liposomal amphotericin) 5mg/kg daily for 2 days and 7.5 mg/kg daily for 2 days had initial cure rate of 100% at 1 mt. At 6 mt it was 90% with 10 mg/kg and 100% with 15 mg/kg. There was no SAE (Goswami *et al*., 2016).

Retrospective analysis of HIV-VL co-infected cases treated between July 2012 and Sept. 2014 with 30 mg/kg IV liposomal amphotericin, given as 6 equal dose, with 14 days of 100 mg/day oral miltefosine was carried out in 102 patients. They had all cause cumulative mortality, relapse at 18 months 16.6% and 13.9% resp. Not initiating ART and concurrent tuberculosis were independent risk factors for mortality (Mahajan *et al*., 2015).

New Drugs and Vaccines

Several workers have reviewed/summarized developments in the diagnosis and approaches to anti-leshmanisal drug discovery and development, (Bhargava and Singh, 2012), compounds isolated from various natural sources that are worth screening as anti-leishmanial drug candidates (Tiwari *et al*., 2017) important biochemical and enzymatic machinery that could be used as putative drug targets for anti-leishmanial drug (Singh *et al*., 2012) and successes and failures of genetically modified organisms used in vaccination (Chhajer and Ali, 2014).

Original research publications during 2012-2017 periods are described below.

Ten weeks post infection BALB/c mice were orally given hexane fraction of Artemisia Annua leaves (AAL) and seeds (AAS). There was significant reduction in parasitic burden, strong DTH response, increased *Th 1* response and induction of immunological memory. It could be an adjunct therapy for VL (Islamuddin *et al*., 2015).

Studies were done with CpG ODN 2006 (synthetic oligodeoxynucletide containing unmethylated cytosine phosphate guanine) CpG motif mimic microbial DNA and are recognised as toll-like receptors 9 on cells and stimulate innate immune response) 0.4 mg/kg single dose as free and liposomal form with or without miltefosine for 5 days in infected hamster mice was studied. The combination with liposomal form showed the best inhibition of parasite multiplication and biased *Th 1* response (Shivahare *et al*., 2014).

Oil in water emulsion of Eugenol showed significant antileishmanial effect *in vitro* and when given IP daily for 10 days caused significant decrease in DTH and fall in disease associated Th2 cytokines and potentiated *Th1* response (Islamuddin *et al*., 2016).

Carbon nanotubes functionalized with amphotericin administered orally resulted in 99% inhibition of parasite growth following 5 day course at 15 mg/kg body weight in hamster model (Prajapati *et al*., 2012b).

Nanoliposomal artemisinin with mean particle diameter of 83$\pm$ 16 nm reduced intracellular infection of *L. donovani ex vivo* and in murine model inhibited infection in liver and spleen and modulated immunity towards protective *Th1* type response (Want *et al*., 2017).

Phosphatidylcholine PC dimethyldioctadecyl ammonium bromide (DDAB) SSG was found to alleviate SSG sensitive and resistant *L. donovani* infection in BALB/c mice, probably due to better interaction with parasite membrane (Sinha *et al*., 2015).

Ursolic acid loaded N-octyl-chitosan surface decorated nanostructured lipid carrier system was prepared for delivery to macrophages for VL, characterised, was found to be more active than free form and *in vivo* study showed parasite burden could be suppressed by 98.75% (Das *et al*., 2017).

Alginate coated Nano capsule were prepared and loaded with doxorubicin, compared against nano-emulsion containing doxorubicin and it was found that it had better uptake greater efficacy against intra-macrophagic amastigotes, better efficacy on parasite burden in leishmania infected hamster and enhanced apoptotic efficacy (Kansal *et al*., 2014).

A series of novel aminoquinaldine derivatives, a new class active *in vitro* and *in vivo*, when given IP and orally in BALB/c murine model with sodium antimony gluconate sensitive and resistant *L. donovani*, were investigated. PP9 and PP10 compounds were promising lead compounds with potential for treating VL with oral route (Palit *et al*., 2012).

Mishra has taken a target based therapeutic approach. Two isobenzofuranone compounds were synthesized and characterized in BALB/c mouse model. They showed potent antilieishmanial effect in antimony sensitive and resistant parasites and also

induced Th 1 cytokine response (Mishra *et al*., 2014). They also studied a new amphiphilic formulation of amphotericin B (kalsome TM 10) and found it to be significantly safer that amphotericin B deoxycholate and was effective in mouse models (Mishra *et al*., 2013).

Computational and biophysical studies revealed that paromomycin/miltefosine interact with TLR9 inducing TLR9 dependent NF-KB promoter activity through MyD88 and functional maturation of DCs (Das *et al*., 2014).

B Nitrostyrenes compounds were found to be active *in vitro* (comparable to AMB) against promastigotes and amastigotes (Shafi *et al*., 2016).

It was also noted that 2NB *2 nitro-N-*(*pyridine-2ylmethyl*) benzene sulphonamide was active against promastigotes and intracellular amastigotes and it also increased efficacy of amphotericin against amphotericin resistant *L. donovani* (Dikshit *et al*., 2016).

Vaccines

VL vaccine scenario has recently been reviewed. Although in recent years a large body of researchers have concentrated their efforts, only three vaccines candidates have gone for clinical trials. Killed vaccine in Brazil for immunotherapy, live attenuated vaccine for humans in Uzbekistan and one for dogs. There are half a dozen in pipeline. Leish III F failed to protect, its phase I was done in India (Srivastava *et al*., 2016).

rLD Sir 2RP has been studied as a vaccine candidate against VL and naive hamsters when vaccinated with it were found to resist the *L. donovani* challenge to the tune of 75% with increased in *IgG2* antibody level, which is indicative of *Th1* type of protective response (Baharia *et al*., 2015).

Kaur *et al*. examined the protective efficacy of DNA vaccine based on gp63 and Hsp 76 against murine visceral leishmaniasis. Inbred BALB/C mice were immunized s.c. twice at an interval of 3 weeks with PC DNA 3.1 (+) encoding epitopes of gp63 and Hsp 76. Immunized animals had significant reduction in parasite burden, heightened DTH response and elevated *Th 1* cytokines and reduced *1gG1* and *IL-10* levels (Kaur *et al*., 2016).

Conclusion and Way Forward

Visceral Leishmaniasis is targeted for elimination in India by 2017.

Studies done in India have contributed to the elimination program. Liposomal amphotericin developed in India has been shown to be effective in VL with 2 days treatment.

PKDL cases are considered as reservoirs hence preventing and managing them is important for the elimination program. Patients treated with liposomal amphotericin ambisome have low relapse rate and development of PKDL is low. Clinical trial on PKDL patients have shown that long duration of treatment is required with miltefosine.

Current treatments for VL and PKDL though effective are prolonged and require parenteral administration. Miltefosine treatment though oral is prolonged and development of resistance is a problem. There is need for newer drugs. As stated above there are several publications/studies on new drug development from India. However at present none seem to fit the public health requirement as suitable alternative or addition to current treatment. Studies are needed to develop products which are effective orally, requiring short duration of treatment, active against sensitive and resistant strains, safe to be administered to diseased asymptomatic carriers, PKDL cases and effective in HIV/VL co-infected cases, women and children. There is need for basic work on asymptomatic carriers, their conversion to VL, PKDL disease and diagnostics to differentiate between infected and diseased, cured and likely to relapse. Drugs that will target such conversion are needed. Clinical trials with existing drugs/combinations that will shorten treatment especially for PKDL could be an immediate short term strategy.

Lymphatic Filariasis

Epidemiology, Mass Drug Administration Incidence, Prevalence, Policy

The goal of global program to eliminate lymphatic filariasis (GPELF) launched in 2000 is to eliminate the disease as a public health problem by 2020. The programme aims to achieve the goal by interrupting transmission through annual single dose mass drug

administration (MDA) of albendazole (ABZ) fixed dose 400 mg with or without diethylcarbamazine cirtrate (DEC) 6mg/kg for 5-6 years. India contributes to nearly 1/3rd of global burden of LF and a program was initiated on a pilot basis in 13 of the 250 endemic districts, implementation units (I.U.) during 1996-1997 with DEC alone and thereafter with DEC+ABZ. The program has been gradually scaled up to reach all the 250 endemic districts spread over 20 states and union territories, covering 421 of the 590 million people at risk in 2007. The impact of the program is to be monitored in at least one sentinel and one spot check site for microfilaremica (MF). It has been reported that in 192 of the 250 implementation units (IU) MF prevalence has reached <1%, the recommended threshold for proceeding with further epidemiological assessment, which is required prior to making a decision to stop or continue MDA.

Model based on empirical observations has been used and it was concluded that during 2000-2012 the mass drug administration program has made remarkable progress. A total of 6.37 billon treatments were offered and 4.45 the billon treatments consumed, 96.7 million LF cases, including 79.2 million mf carriers, 18.7 million hydrocele cases, and 5.49 million lymphedema cases have been prevented or cured (Ramaiah and Ottesen, 2014).

Mathematical modelling of lymphatic filaras is elimination programmes in India has been carried out to predict required duration of mass drug administration and post treatment level of infection indicators.

Using a model variant for Indian setting it was observed that the required duration of annual MDA increases with higher baseline endemicity and lower coverage. To achieve elimination in high transmission area and high infection levels, MDA must be continued longer than in low endemic communities (Jambulingam *et al*., 2016).

Babu *et al*. systematically reviewed published studies on coverage and compliance with MDA in India. They identified 36 published papers. Coverage varied from 48.8-98.8%, compliance from 20.8-93.7% and there were potentially correctable causes (Babu and Babu, 2014).

The effect of eight rounds of mass drug administration has been studied in primary health centres in Thanjavur district and it was noted that although overall the effect was satisfactory, wherever the coverage was more than 70%, existence of hotspots and clustering of infection are indicative of need for good surveillance and action strategy, with evidence based sampling strategy and evaluation of unit size for Transmission Assessment Survey (TAS) (Swaminathan *et al*., 2012).

Drug distribution coverage, compliance and effective coverage in Burdwan district in West Bengal was found to be 48.76%, 70.02% and 34.16% resp. Authors concluded that there is urgent need to improve compliance with drug intake through strengthening the awareness program (Roy *et al*., 2013).

In an independent survey in endemic area of Gujrat it was seen that during MDA, drug coverage was 81-88%, epidemiological coverage 77-89%, directly observed consumption increased from 58% in 2010 to 82% in 2015. Current Mf rate was less than one in all implementation units (IUs) with 68% decrease from baseline year 2005 to year 2015 (Modi *et al*., 2017).

Assessment of coverage, compliance and side effects of MDA in Bankura district, West Bengal showed drug compliance rate, effective coverage to be lower in urban than rural area. Fear of side effects was the main reason for noncompliance. Reported side effects were few, mild and transient. Poor social mobilization, lack of knowledge about disease and program were major areas of concern (Ghosh *et al*., 2013).

Study on barriers to coverage and compliance to MDA in Odisha showed that only a quarter of the 99% who received drugs, actually consumed DEC ABZ. Cause of noncompliance was mostly fear of side effect, lack of awareness of benefits of MDA and non-attendance of health staff (Hussain *et al*., 2014).

It has been observed that there was high rate of acquiring infection by children born to LF infected mothers than uninfected mothers even though mf rate had come down to < 1% after implementing ten round of MDA. Authors concluded that to attain target of eliminating LF, the current MDA program should give emphasis on covering the women of child bearing age

and recommended that supervised MDA should be incorporated in Adolescent reproductive and sexual health program ARSH (Bal *et al*., 2015).

They also showed that maternal filarial infection influences the development of regulatory T cells in children from infancy to early childhood (Bal *et al*., 2016).

A plan of action has been discussed to use DEC fortified salt for diurnally subperiodic filariasis for Nicobar district (Shriram *et al*., 2015).

Some studies have investigated productivity loss due to lymphatic filariasis. Productivity loss due to lymphedema in previous 30 days was estimated to be 6.4 days (Lenk *et al*., 2016).

A research priority setting process has been organized as described in James Lind Alliance guidebook and it identified seven priority areas to achieve effective morbidity control of lymphedema including due to LF (Narahari *et al*., 2017).

Pathogenesis and Diagnostic Tests

Molecular mechanisms underlying the pathogenesis of disease and quantitative immune response patterns differentiating patients with overt from subclinical manifestation has been reviewed. This will enable design of effective pharmacological inhibitors and pathogenesis specific interventions aimed at the early stage of the disease before major lymphatic function have been chronically affected (Chakraborty *et al*., 2013).

The predominant immunological feature in LF is an antigen specific *Th2* response and a muted *Th1* response. This is crucial for the maintenance of the sustained, long standing infection with high parasite densities (Babu and Nutman, 2017).

Study of plasma levels of various markers-circulating microbial products such as LPS and markers associated with microbial translocation, in four groups of individuals-chronic pathology individuals with or without active filarial infection, asymptomatic filarial infected individuals and uninfected endemic normal individuals showed that circulating levels of LPS, acute phase proteins and certain cytokines are significantly elevated in filarial disease with active infection but not in other groups indicating that it is correlated with filarial lymphatic pathology (Anuradha *et al*., 2012).

Vishal evaluated rapid blood sample collection in the detection of circulating filarial antigen for epidemiological survey by rwbsxp-1 capture assay and showed that it gave 7.32% increased positive results (Vishal *et al*., 2014).

Clinical Trials and Observational Studies

The effect of higher and more frequent dosing of ABZ with fixed 300 mg dose of DEC was studied and it was found that microfilaria decreased more rapidly with higher or more frequent dosing without any increase in ADR (Kar *et al*., 2015).

Britto studied in a double blind randomized control trial (RCT), 146 asymptomatic *W. bancrofti* infected individuals, effects of DEC 300 mg + Doxycycline 100 mg co-administered or DEC 300 mg+ ABZ 400mg co-administered or DEC 300 mg+ABZ 400 mg given sequentially DEC 300 mg ABZ sequential treatment had better efficacy in microfilaria clearance though effect on antigenemia was comparable (Britto *et al*., 2015).

Study in mf positive patients found no difference between effect of DEC(6mg/kg) and DEC (6mg/kg) + ABZ 400 mg on safety and micro filaria (judged by peripheral smear and nucleopore filter method) and adult worm (judged by circulating filarial antigen card test and ultrasonography). Study consisted of three annual rounds of DEC or DEC ABZ in double blind randomized controlled trial (Kshirsagar *et al*., 2017 accepted). They concluded that there is not much effect on adult worm with three yearly administration of DEC or DEC ABZ. However other workers did find effect, specially when given for more than 3 rounds and in children.

Thomas compared three quality of life instruments in LF DLQI, WHO DAS 2.0, and LF SQQ. The study provides insight into use of tools and shows that LF SQQ performed best. (Thomas *et al.*, 2014).

New Drugs and Vaccines

Researchers have studied medicinal plants, synthetic chemicals and drug delivery systems for antifilarial activity.

Ursolic acid a major constituent of *Eucalyptus tereticornis* was lethal *in vitro* to microfilara and female adult worm of *B. Malayi* as observed by motility assay. In silico PK and drug likeness studies showed UA has drug like properties. *In vivo* in *B. Malayi* M coucha model (natural infection), UA showed 54% macrofilaricidal and 56% adult worm sterility and unchanged microfilaremia. Thus it is a promising widely available natural lead for developing macrofilaricidal drug (Kalani *et al*., 2014).

From ethanolic extracts of aerial parts of *T. distichum*, four molecules were isolated, structure determined. A 001 was effective in killing adult worm and microfilaria of *B. Malayi in vitro* in MTT assay. Diterpenoid K003 produced 100% reduction in motility of microfilaria and adult worm and >80% inhibition in MTT reduction potential of adult female worms. In *B. Malayi*, *M. Coucha* model, K003 killed 54% of adult worms and 36% female worm were rendered sterile (Kushwaha*et al*., 2016).

This indicates that labdane diterpenoid molecules may provide valuable lead to design and development of new macrofilaricidal agents.

Yadav reported antifilarial activity of diarylheptanoids from Alnus nepalensis leaves. Out of 4 compounds tested one showed antifilarial activity *in vitro* and *in vivo* studies in Host-parasite model i.e., *B-Malayi-M. unguictatus* model (Yadav*et al*., 2013).

Ultrafine PLGA nanoparticles of Doxycycline hydrochloride were constructed and it's preferential lymphatic targeting, greater *in vivo* antifilarial activity compared to doxycycline solution as gauged by tests in *B. malayi* infected *M. Coucha* model, were found (Singh *et al*., 2016).

Nanoparticles of silver, elicited significant loss in microfilarial motility (obtained from infected jird) (Singh *et al*., 2012).

Proteome subtractive approach was used to screen possible therapeutic targets in Wolbachia of *Brugia Malayi*. Authors also did literature search and presented the data in a user friendly database Filo Base (Sharma and Kumar, 2016).

The available drugs and their targets, novel targets, websources and databases were summarized to re-examine and develop new drugs using bioinformatics (Sharma *et al*., 2013).

Natural sources having antifilarial potential have been summarized (Mendam *et al*., 2015).

Mukherjee reported new metabolic targets to identify new antimetabolic drugs (Mukherjee *et al*., 2016).

Trehalose 6- phosphate phosphatase of *Brugia malayi* represents an attractive vaccine target as it is absent in mammals. Immunization with the recombinant protein caused 78% decrease in microfilaremia and 71% decrease in adult worm establishment and sterilizaiton of recovered live female (Kushwaha *et al*., 2013).

Vaccination in mice with trivalent HAT vaccine as HAT protein alone or as heterologous prime boost vaccine conferred significant protection (95%) against *B. Malayi* L3 challenge suggesting that trivalent HAT fusion protein is a promising prophylactic vaccine against LF infection in humans (Dakshinamoorthy *et al*., 2013).

Conclusions and the Way Forward

To achieve the goal of elimination by 2020 mass drug administration needs to be continued for much longer duration in high transmission and high infection area. An important conclusion from the studies done has been that there is low coverage and poor compliance in some areas due to potentially correctable causes. Important causes of noncompliance were found to be fear of side effects, lack of awareness of benefits of MDA and insufficient involvement of health staff.

In the search for drugs with effect on adult worm and rapid and long lasting effect on microfilaria, doxycycline with DEC, Albendazole with DEC in different schedules were investigated. However methods to detect adult worm viz., antigenemia, ultrasound have not given consistent specificity and sensitivity.

There is need to develop biomarkers for detecting adult worm and lymphatic system pathology.

Several workers have shown promising results especially of effect on adult worm with compounds from plants.

However further work is needed to identify most promising compounds and conduct studies, on toxicity testing and in vivo animal models, to study them further in humans.

In recent years triple drug combination of DEC+ABZ+Ivermectin has shown very promising results and should be considered as comparator for any further studies.

Filariasis infection is noted in early childhood. Current mass drug administration program excludes children below 2yr & 5yr and pregnant women. There is a great need to show safety of drugs in children and develop formulation suitable for children.

Dengue

Dengue virus belonging to family *Flaviviridae* having four subtypes, spread by the bite of infected *Aedes* mosquito, causes a wide spectrum of illness from mild asymptomatic illness to severe dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). A multinational study estimated that there were 390 million cases worldwide 1/3rd in India. Of the 390 million, 1/4th manifest clinically, most cases are undetected (Bhatt, 2013). Gupta *et al*. reviewed in 2012, work done by various groups of scientists in India focusing mainly on epidemiology, clinical presentation, experimental studies on immune response, pathogenesis and diagnosis in DV infection (Gupta *et al*., 2012).The manifestation of "expanded dengue" with unusual manifestations has been reviewed (Kadam *et al*., 2016). Work during 2012-2017 is reviewed below:

Clinical Trials and Observational Studies

List of dengue drug trials identified from WHO International Clinical Trials Registry platform web portal using search term "dengue" on Dec 31st, 2015 was reviewed. None of the handful of drugs tested so far has yielded encouraging results. There is need for tools to predict "high risk" patients early on (Beesetti *et al*., 2016).

Immunogenicity and safety of recombinant live attenuated tetravalent dengue vaccine (CYD-TDV) given at 0,6,12 months was studied in healthy adults in India. In a randomized observer blind placebo controlled phase II trial, immunogenicity was assessed by using a 50% plaque reduction neutralization test (PRNT50) at baseline and at-28 days after each study injection. Sero positivity rates with each serotype, increased with geometric mean titres being 2.38 to 6.11-fold higher after 3rd injection compared to baseline. There were no serious adverse events (Dubey *et al*., 2016).

Reddy compared effect of furosemide with furosemide + ventilation, ventilation alone in 1 month-18 years old children with ARDS with dengue IgM positivity. They found significant survival difference between groups and pre and post intervention arterial blood gases and concluded that diuretic infusion improves outcome in dengue with ARDS (Reddy *et al*., 2014).

Single dose of anti D 50 µg/kg was found to increase significantly patients (60%) with platelet count over 50,000/mm^3 compared to 6.7% in control group and reduced platelet concentrate infusion need and improvement in bleeding manifestations (Pannu *et al*., 2017)

A systematic review and meta-analysis of efficacy and safety of *Carica Papaya* leaf extract in dengue, showed that in four studies in 439 patients given *Carica Papaya* leaf extract, there was increase in platelet count, decrease in hospitalization days. There was no significant difference between *C. Papaya* and control group (Charan *et al*., 2016).

Dengue causes platelet activation and thrombocytopenia in patients.

C. Papaya leaf extract was studied to evaluate if its action is directly on platelets and if the extract can specifically inhibit the platelet aggregation during dengue viral infection in vitro. Platelet aggregation was significantly reduced when leaf extract pre-incubuted with dengue plasma was added to control platelet rich plasma but no such effect was seen when it was incubated with control plasma. Upon addition of leaf extract to dengue PRP and control PRP significant reduction in platelet aggregation was seen. They concluded that leaf extract has dengue specific neutralizing effect on dengue viral infected plasma that may exert a protective role on platelets (Chinnappan *et al*., 2016), preventing aggregation and reduction in platelets.

Sarala et al also reviewed studies done on Papaya extract, one animal study, one case report,

three case series and two RCT, and concluded that although many lack adequate information, there is a possibility that Papaya leaf extract could be an important option for future (Sarala and Paknikar, 2014).

New Drugs, Vaccines, Preclinical Studies

Some earlier preclinical work has been reviewed (Gupta, 2012). Pre-feeding mice with trivalent chromium picolinate (CrP) in drinking water could abolish the adverse effects of DV infection on most of the haematological parameters (srivastava *et al.*, 2007) *Hippophae rhamnoides* (seabuckthorn SBT) leaf extract has been shown to have a significant anti dengue activity (Jain *et al*., 2008).

The development and current status of dengue vaccine was reviewed (Marimuthu and Ravinder, 2016).

Among the ten proteins (structural and non-structural) encoded by dengue viral genome, NS2B-NS3 protease is an ideal target. It is responsible for the processing of poly protein that is required for genome replication of the virus.

Different inhibitors reported against dengue proteases have been reviewed (Timiri *et al*., 2016).

Salidroside main bioactive compound of *Rhodiola rosea* was evaluated for its antiviral potential against DENV. It potently inhibited DENV infection by decreasing DENV envelope protein expression more than tenfold. It also induced expression of IFN-α, NK cells and CD 8^+ T cells in human PBMCs (Sharma *et al*., 2016).

NS2B-NS3 protease (pro) of dengue virus (DENV) is the prime therapeutic target for the development of anti-dengue drug. Neem plant (*Azadirachta indica*) has shown potential antiviral activity. Dwivedi etal with molecular docking study showed that nimbin, desacetylnimbin and desacetylsalannin have good binding affinity with DENV NS2B-NS3 pro while azadirachtin and salannin had no affinity (Dwivedi *et al*., 2016).

Ethyl 4-(4-methylphenyl)-4-pentonoate from *Vetiveria Zizanoides* was also shown, to inhibit dengue NS2B-NS3 protease and prevent viral assembly in docking analysis (Lavanya *et al*., 2016).

In a bioassay-guided screening approach, indigenous herbals were evaluated by Sood *et al*. Alcoholic extract of *Cissampelos pareira* Linn (Cipa extract) was found to be potent inhibitor of all four DENVs in cell based assay, assessed in terms of viral NS1 antigen secretion using ELISA as well as viral replication based on plaque assay. Virus yield reduction assay showed that *Cipa* extract could decrease viral titres by an order of magnitude. The extract also conferred significant protection against DENV infection in AG129 mouse model. It had no adverse effects on platelet counts and RBC viability. It had antipyretic activity in wistar rats, down regulated TNF-α and had no toxic effect in wistar rats at doses as high as 2gm/kg (Sood *et al*., 2015).

Rhodiola that significantly promoted ISG, RIG-I and MDA5 gene expression and an antiviral immune response against dengue virus infection has been identified. *Rhodiola* induced, (IFN)β and other cytokines in infected cells. Number of NK cells was increased in dengue virus infected human PBMCs. It can be a novel therapeutic strategy (Diwaker *et al*., 2014).

Mahadevan and Palraj reviewed available literature on Siddha Herbal Formulations (Kudineer) on management of dengue. Symptoms of *Pitha suram* described in Siddha are comparable with symptoms of dengue. Antiviral, anti-inflammatory and immune modulator pharmacological actions of ingredients of *Siddha Kudineer* formulations used in treatment of dengue are summarized (Mahadevan and Palraj, 2016).

Ramya evaluated effect against dengue virus of actinobacterially synthesized selenium particle. Streptomyces minutiscleroticus M 10 A 62 isolated from a magnesite mine has the ability to synthesize selenium nanoparticles (SeNPs) extracellularly. It was characterized and found to have good antiviral activity in vitro against Dengue virus (Ramya *et al*., 2015).

A benzimidazole derivative MB21 was found to be most potent in inhibiting the cloned protease (IC_{50}= 5.95 μM). It also inhibited all 4 serotypes of dengue viruses in infected cells in culture, based on analysis of virus antigen synthesis and infectious virus production. It did not have any cytotoxicity (Raut *et al*., 2015).

A 3D modelling of dengue virus NS4B (non-structural protein-4B) and virtual screening of selected compound showed N-(p-tolylmethyl)-3-[(3-pyridylmethylamino)methyl] benzamide (TPB) had significant binding characteristics (Satheesh *et al*., 2014).

β-0G pocket a cavity in the flavivirus envelope (E) protein has been identified as a promising site for the design of antiviral agents that interfere with virus entry into the host cell.

Jadav evaluated hybrid compounds in virus cell based assay and found a molecule with an EC50 of 1.32±0.41 µM against dengue virus serotype 2 (Jadav *et al*., 2015).

Amodiaquine inhibited DEN V2 infectivity measured by plaque assay with EC50 and EC90 values of 1.08 ±0.09 µMand 2.69± 0.47 µM and DEN V2 RNA replication measured by Renilla luciferase reporter assay (Boonyasuppayakorn *et al*., 2014).

Parida selected panduratin molecule, designed 65 novel compounds, did virtual screening and docking studies for NS3 inhibitor activity by targeting protein-protein interacting sites of dengue virus (Parida *et al*., 2013).

Dengue viral-dependent RNA polymerase inhibitor was identified using computational fragment based approaches and molecular dynamic study (Anusuya *et al*., 2016).

Synthesis and molecular modelling studies on novel sulphonamide derivatives as NS2B-NS3 protease inhibitor has been carried out (Timiri *et al*., 2015).

Magnetic nanoparticles inhibited at 2-8 µg/ml DEN-2 replication inhibiting the expression of the envelop (E) protein (Murugan *et al*., 2017).

The bioactivity of Bruguiera cylindrica synthesized characterized silver nanoparticles (AgNP) has been studied. It inhibited production of dengue viral envelope protein *in vero* cells and downregulated the expression of dengue viral E gene (Murugan *et al*., 2015).

Ag NP has been synthesized using *Moringa oleifera* seeds extract as reducing and stabilizing agent. It showed in vitro antiviral activity against DEN-2 infecting vero cells (Sujitha *et al*., 2015).

Conclusions and the Way Forward

Clinically of the 50-100 million patients infected with dengue, 500000 develop manifestation of dengue haemorrhagic and dengue shock syndrome fever. There is need to develop tests to predict these "high risk" patients.

Perusal of publication on new drug development for dengue shows that a variety of new chemicals, and plants are investigated in molecular docking studies, cell based assays and mouse model. NS2B-NS3 protease of dengue virus is prime target for drug development. Alcoholic extract of *Cissampelos pareira* Linn is in advanced stage of development.

Dengue vaccine developed indigenously and one marketed internationally are being investigated for protective immunity. Clinical studies on dengue vaccine and promising drugs are greatly needed.

Vaccine research is indeed greatly needed for dengue control and treatment.

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