Indian Journal of Entomology 84 (Spl. Issue): 61-76 (2022) eRef.No. 22929 DoI: 10.55446/IJE.2022.915

MANAGEMENT OF INSECT BORNE HUMAN DISEASES – A CASE STUDY ON NOVEL BIO-LARVICIDE FOR MOSQUITO BORNE DISEASES INCLUDING DENGUE

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ABSTRACT

In India National Vector Borne Diseases Control programme is an umbrella organization for management and control of six out of eight insect-borne human diseases, viz., Malaria, Lymphatic Filariasis (LF), Kala-azar, Dengue/ Chikungunya, and Japanese Encephalitis. Of these, India is committed for elimination of the first three diseases from the country. 8.6% of India's total population belongs to tribal community yet contribute 21% of *Plasmodium falciparum* infection and 29% of malaria-related deaths. There is an urgent need to implement novel strategies to overcome insecticide resistance in *Anopheles culicifacies* that transmit 60-70% of malaria cases in India. One such strategy is to use *Chilodonella uncinata*, an indigenous, maternally transmitted, facultative protozoan bio-larvicide with many biological control properties against mosquito vectors. In view of the above, if India really aims to achieve malaria elimination by 2030, there is an urgent need that tribal regions are given more attention.

Key words: Malaria, lymphatic Filariasis, Kala-azar, Dengue/Chikungunya, Japanese encephalitis, *Chilodonella uncinata,* bio-larvicide

Vectors are living organisms that can transmit infectious pathogens between humans, or from animals to humans. Vector-borne diseases (VBDs) are human illnesses caused by parasites, viruses and bacteria that are transmitted by vectors and account for more than 17% of all infectious diseases, causing more than 700 000 deaths annually. Many of these vectors are bloodsucking insects. Most common insects that pass on disease to human are mosquitoes, sand flies, ticks, and fleas. For example, mosquitoes are known for spreading the Dengue fever, Chikungunya fever, Malaria, Lymphatic Filariasis and Japanese encephalitis. Sand flies are known to spread Leishmaniasis or Kala-azar. Ticks are known to spread Kyasanur forest disease and Crimean-Congo haemorrhagic fever. Fleas are known to spread Bubonic and Pneumonic Plague. In India National Vector Borne Disease Control Programme (NVBDCP) is an umbrella programme for prevention and control of VBDs namely Malaria, Japanese Encephalitis (JE), Dengue, Chikungunya, Kala-azar and Lymphatic Filariasis (LF). Out of these six diseases, three diseases namely Kala-azar, LF and [Malaria] are targeted for elimination. The transmission of VBDs depends on prevalence of infective vectors and human-vector contact, which is further influenced by vector bionomics, ecological and social factors like climate, sleeping habits of human, type of vector, density and biting habit of vectors, migration of human population and development activities. Integrated Vector Management under NVBDCP includes Indoor Residual Spraying (IRS) in selected high-risk areas; Long Lasting Insecticidal Nets (LLINs) in high malaria endemic areas; use of larvi-vorous fish, anti-larval measures in urban areas including bio-larvicides and minor environmental engineering and source reduction for prevention of vector breeding (Anonymous, 2019).

MALARIA

Malaria is an entirely preventable and treatable vector-borne disease. Its transmission occurs in 99 countries, with an estimated 3.3 billion people at risk (Nema and Ghosh, 2022). Global initiative of WHO during 1950's and early 1960's to eradicate malaria also brought malaria under firm control in India and almost on the verge of eradication. But it returned to the country with a vengeance in the late 1970s. Today, malaria and other vector-borne diseases are the most

widespread cause of death, disability and economic loss in India especially among the poor who have limited access to timely and effective treatment. In 2009, some analysts estimate that the total number of malaria cases in India could well range between 60-75 million each year as a large proportion of fever patients preferring to seek private health care (WHO, 2010a). India has committed to eliminate malaria by 2030 in line with the global developments in achieving the elimination of malaria in different countries, The National Framework for Elimination of Malaria in India was released on 16 February, 2016 (NVBDCP, 2107a). Six *Anopheles* species, *Anopheles culicifacies*, *An. stephensi*, *An dirus*, *An. fluviatilis*, *An. minimus*, and *An. sundaicus* are primary vectors transmitting malaria in different eco-geographical regions of India, while *An. annularis*, *An. philippinensis* and *An. varuna* are vector of local importance. *An. culicifacies* alone is responsible for 60–70% of malaria in India. The species breeds in wide range of habitats, viz. irrigation tanks, rock pools, rain water pools, river bed pools, river margins (Dev and Sharma, 2013) and newly transplanted paddy fields in rice agro-ecosystem. *An. stephensi* transmits malaria in urban areas. Overhead tanks are the preferred breeding habitats for this species followed by cemented containers, drums, underground tanks and plastic pots. For decades malaria has remained stable in north-eastern states due to various factor, including presence of 3 vector species, viz. *An. dirus*, *An. fluviatilis* and *An. minimus*. Of these, *An. minimus* breeding in plains and slow flowing streams/ streamlets was detected with sporozoites in every month of the year, while *An. fluviatilis was* positive in winter months from hills/foothills and *An. dirus* breeding in forested areas detected with sporozoite in wet season (Dev et al., 2003). In India *Plasmodium vivax* (*P. vivax*) and *Plasmodium falciparum* (*P. falciparum*) are responsible for most human malaria. *P. falciparum* is the variety which is responsible for almost all the deaths due to malaria. *P vivax* causes debilitating illness. Malaria cases are mainly found among the Indian ethnic tribal population in Madhya Pradesh, Chhattisgarh, Jharkhand, Orissa, and the entire north-eastern region, where malnutrition poses a serious threat (WHO, 2021a). Direct correlation exists between these diseases since malnutrition peaks during the rainy season when malaria cases spurt (Das et al., 2018). 8.6% of India's total population belongs to tribal communities, yet contribute 21% of *Plasmodium falciparum* infections and 29% of malaria-related deaths (Sharma et al., 2015). Therefore, if India really aims to achieve malaria elimination by 2030 it is essential that tribal regions are given more attention and the populations get easy access to healthy balanced diet, safe drinking water and improved sanitation facility (Nema and Ghosh, 2022).

Under NVBDCP, India, vector control has been playing an important role in disease management. In order to control adult mosquitoes in rural areas of the country indoor spraying with residual insecticides (IRS) and Long-Lasting Insecticide Nets (LLINs) are being used. In urban areas, where vector breeding is in defined and confined habitats, larval control using chemical insecticides, bacterial pesticides and larvivorous fish is the applied strategy. LLINs are being extensively distributed in the north-eastern states and in forested areas of the states in Central India. However, use of synthetic insecticides for >4 decades in indoor residual spray and long-lasting insecticidal nets for fairly long period has resulted in widespread resistance in *An. culicifascies* and changes in their behaviour (Subbarao et al., 2019), there is an urgent need to implement novel strategies to overcome resistance (WHO, 2012).

Novel Strategies for Control of Mosquito Borne Diseases Including Malaria: Three novel approaches that have shown considerable promise in controlling mosquito population in recent years are: 1) the genetic control of *Ae. aegypti* mosquitoes; 2) the development of mosquitoes that are resistant to arbovirus infection; and 3) use of *Chilodonella uncinata,* a facultative endoparasitic ciliate with many biological control properties against mosquito vectors of human diseases.

The genetic control strategy: Known as RIDL (Release of Insects carrying Dominant Lethal genes)

and involves in mass rearing of *Ae. aegypti* that have been genetically modified so that the sperm cells of males carry a lethal gene. When those male mosquitoes mate with wild females, their offspring die (Phuc et al., 2007). This approach is innovative and potentially powerful. To be effective on a large scale, it could be necessary to constantly release modified mosquitoes; otherwise, unmodified mosquitoes from surrounding areas would move into the area and replenish the population.

*Use of Wolbachia: A*n obligatory intracellular endosymbiotic bacterium is used to prevent arboviruses replicating within the mosquito. Three *Wolbachia*-based control strategies have been proposed, viz. i) One is suppression of mosquito populations by large-scale releases of males incompatible with native females which requires repeated releases; ii) Transform wild mosquito populations with *Wolbachia* that shortens mosquito life, indirectly preventing viral maturation/ transmission; and iii) Use of *Wolbachia* that block viral transmission. Despite these manifold effects, relatively little is known about the underlying mechanisms (Frentiu et al., 2010), in part because *Wolbachia* cannot be cultured *in vitro*. What effect either RIDL or *Wolbachia* will have on arboviral transmission and epidemiology in the field remains uncertain. An important benefit of these environmentally friendly, species-specific approaches is the reduced dependence on insecticides—an increasingly important feature of future disease vector control (Yakob and Thomas, 2016).

Biocontrol through Chilodonella uncinate: In 1999, pathogenic property of a protozoan *Ch. uncinata* (Fig. 1) was accidentally discovered in Japanese Encephalitis (JE) vector larvae (*Culex tritaeniorhynchus*) (Fig. 2) growing in paddy fields of Sonepat District, Haryana state of India. *Ch. uncinata* was isolated from these infected larvae, colonized and a basic culture strain including a preliminary sand formulation was prepared at the National Centre of Disease Control (NCDC), Delhi. Since the knowledge was new to science, National and International patent applications were filed on "Microbial Control Agent for mosquito vectors of human diseases" (Inventor Dr Bina Pani Das; Co-applicants: Department of Biotechnology (DBT), Ministry of Science & Technology and NCDC (Erstwhile National Institute of Communicable Diseases), DGHS, Ministry of Health & Family Welfare) supported by DBT in 2001 (Das, 2003; 2006; 2008; 2011; 2012; 2015). In 2005 laboratory Bioassay were carried out at (i) Vector Control Research Station (VCRC), Pondicherry, ICMR with south Indian strain of *Ch. uncinata* isolated from infected *Cx. tritaeniorhynchus* larvae collected from Madurai (ii) at NCDC, Delhi with north Indian strain from Haryana against lab reared *An. stephensi, Ae. aegypti* and *Cx. quinquefasciatus* which revealed all the test larvae to be susceptible. *An. stephensi* was most susceptible against the culture strain as well as formulation with the active ingredient (*Ch uncinata)* isolated from *Culex* larvae from paddy field. These studies clearly demonstrated how an event noted in the natural habitat can be brought to the laboratory, refined and found to be a potential bio-larvicide capable of killing mosquito vectors of human diseases (Das, 2008). Seven countries have granted this patent. These countries with patent application # and granting dates are: Bangladesh (Patent # 1003897, dt.08.08.2005); U.S.A. (Patent # 7141245 dt. 28.11.2006); Australia (Patent # 2002217423, dt.28.06.2007); Sri Lanka (Patent # 13134, dt.11.12.2007); Vietnam (Patent # 6774 dt. 31.12.07); Philippines (Patent # 1-2003 - 500738 dt.01.08.08); India (Patent # 292015, dt. 23.01.2018) (Das 2008; 2013; 2019; Das and Tuli 2019). Events that lead to the invention leading to filing of national and international patent applications were documented by Das (2019). Follow up studies (2002-07) in many districts of Northern India revealed: i) *Ch. uncinata* is a facultative protozoan parasite that is naturally found in *Culex* mosquito larvae growing in some paddy fields, village ponds, etc.; ii) These are maternally inherited that is these parasites are passed on from infected female mosquitoes to her offspring; iii) Surprisingly, these protozoan parasites are neither available in every paddy fields, nor they are available in

man-made water reservoirs holding fresh or rain water (common breeding places of *Aedes aegypti* vector of dengue/Chikungunya) in urban and peri-urban areas. But wherever abundance of these parasites is very high, the area remains free from Japanese encephalitis (JE); iv) Unlike *Bacillus thuringiensis* var *israilensis* (the only microbial bio-larvicide used under Urban Malaria Scheme), that must be swallowed by the host mosquito larvae to cause death, *Ch uncinata* gets into the host body by piercing through host skin (head, thorax, abdomen, siphon) to cause death in host larvae. *Ch uncinata* in dormant stage is available in a sand formulation and packed in sachet "Infusion bag" (Fig. 3) based on type of wrapping paper used) which on dipping in affected water will revive the organism (the microbial agent). Laboratory evaluation with both the cultured strain and its formulation carried out at four institutes (VCRC; NCDC; Jamia Millia Islamia University, New Delhi and Ross LifeScience Limited) revealed that the infusion bag formulation impacted delayed development in mosquito larvae exposed to formulation; efficacy of this protozoan (*Ch uncinata*) biolarvicide is not dose dependent as least dose produced maximum mortality with minimum post exposure. *An. stephensi* larvae were most sensitive followed by *Cx. quinquefasciatus* and *Ae. aegypti. Ch. uncinata* infusion bag formulation is easy to store, transport and treat with a shelf life of >18 months resulting in satisfactory efficacy against *An. stephensi* larvae with LT_{50} (5.16) and LT_{90} (7.69) (pl. check these values; looks inverted) values (in days) noted at 0.25 g even after 6 months of storage. Satisfactory efficacy was noted with LT_{50} and LT_{90} values 3.93 and 6.27 (in days) respectively against *Ae. aegypti* at 0.5 g tea bag formulation (Das et al., 2016). 30 g infusion bag formulation of this bio larvicide (*Ch. uncinate* BP 610-2016 strain) provided 3 months control (75-100% inhibition of adult immergence) in *Ae. aegypti* in a half-filled 40liter domestic water storage tub (kept under peri-domestic area), one of the most preferred breeding sources of this species in NCT, Delhi during dengue transmission season that normally extends from August to November (Das, 2017). Residual efficacy of *Ch. uncinata* infusion bag formulation under field condition was evaluated in desert coolers and cemented tank in a slum and a posh locality in Delhi during June-October. The study revealed one time application of 80.0g resulted 100% control of *Ae aegypti* breeding for 8-9.5 weeks in both coolers and cemented tanks in posh locality. In slum area, limited study of 3 weeks @ 80.0g in a cooler impacted 100% control of mosquito breeding (Das and Tuli, 2019).

JAPANESE ENCEPHALITIS

Japanese encephalitis (JE), a mosquito borne zoonotic disease, is the leading cause of viral encephalitis in 14 Asian countries due to its epidemic potential, high fatality rate and increased possibility of lifelong disability in patients, mostly children between 1-15 years of age, who recover from this dreadful disease. There is no specific anti-viral medicine available against JE virus and cases are managed symptomatically. The JE virus is maintained in animals: pigs, birds (cattle egrets, pond herons etc) which act as the natural hosts. Pigs act as amplifier hosts in the transmission cycle, while man is 'dead end host". Vector mosquito *Culex* Vishnui group is able to transmit JE virus to a healthy person after biting an infected host with an incubation period ranging from 5 to 14 days. The JE affected states of India comprise of Andhra Pradesh, Assam, Bihar, Haryana, Karnataka, Kerala, Maharashtra, Manipur, Tamil Nadu, Orissa, Uttar Pradesh and West Bengal (Kabilan et al., 2004). Because of eco-epidemiological complexity, JE poses a serious challenge in terms of prevention and control. In order to reduce the disease burden as well as preventing mortality, morbidity and disability to a great extent Government of India has formulated a multipronged strategy in five most JE endemic states (NVBDCP- Operational guidelines 2010).

Problems faced while investigating AES/ JE outbreak in Northern India: Of the thousand suspected JE deaths in India annually, more than 75% is contributed by Northern India wherein disease transmission failed to be explained based on entomological evidence due to inadequate mosquito

surveillance tool used in determining JE vector density. In order to overcome the above problem, "BPD hop cage method a simple, cost effective, and operationally feasible surveillance tool was specially designed to collect predominantly day resting adult *Culex tritaeniorhynchus* mosquitoes, the principal JE vector species in the country from land and aquatic vegetation. Hop cage is a standard mosquito cage measuring 30 x 30 x 30 cm (Fig.4). For collecting resting mosquitoes from land vegetation, folded mosquito cage was allowed to hop through the shady vegetation near the ground (Fig. 5) and also low-level ground vegetation by a series of quick forward, backward, up and down movements through a distance of 5 feet (length wise) for about 2 minutes (Das, 2013a). This led to the trapping of mosquitoes in the cage. One side open sleeve of the cage is then immediately folded in order to prevent the trapped mosquitoes from escaping. This surveillance tool has helped to study nearly every aspect of JE vector bionomics and establish entomological evidences of JE outbreaks occurring in the country upon its use since 2003 (Das, 2013b,c,d; Das et al., 2004a).

Box 1

Mosquito density measurement by hop cage: Hop cage has to be used 10 times while collecting day-resting mosquitoes from land as well as aquatic vegetation and the mosquito density was measured as average number of female mosquitoes collected Per Ten Hop Cages (PTHC) by the following formula:

$$\text{Mosquito density (PTHC)} = \frac{\text{Total numbers of female mosquitoes collected}}{\text{Total numbers of hops made on vegetation}} \times 10$$

Each hop on vegetation covers an area of 1 sq. foot. The larger the area of the vegetation covered by hopping, the better representation of the mosquito density (Das, 2009).

JE vector control/management strategies: Japanese encephalitis continues to be a national problem, not because of poverty but because of lack of awareness. JE control is possible through protection of humans and pigs, and reduction of adult vector (mosquito) population. Control strategies can be drawn and implemented to protect humans and pigs, and to reduce adult vector mosquito population below a thresh hold level to minimize man-vector contact.

*1. Strengthening of IEC (Information Education and Communication) component at the District/PHC level to motivate people to achieve the following***:** i) Use of various physical and chemical methods for prevention of mosquito bite like mosquito repellents when outdoors, burning of dry leaves (preferably neem) during evening hours, etc. ii) Use of full sleeve cloths, trousers etc. to minimize mosquito bite, iii) Mosquito proof piggeries should be built away from the human habitations, iv) Piggeries should be sprayed with an appropriate insecticide to reduce the vector density and to break the transmission cycle, v) To eliminate adult resting sites (extensive low level ground vegetation in jowar) of important JE vector (*Cx. tritaeniorhynchus)* (Das, 2013)

2. *Reduction of vector breeding source***:** Eco-friendly methods to control vector breeding include: i) Treating paddy nursery and other breeding sources of the vector species with a suitable bio-larvicide capable of recycling in the breeding sources of the vector, not unduly sensitive to ultra-violate radiation and vagaries of agricultural pesticides and can disperse in the environment via transovarian transmission. It may be mentioned that the active ingredient of *Ch. uncinata* BP 610 formulation, is a good biological control agent (Das, 2008; 2013a; 2017). Field studies (Das 2013b) on ecology of JE vectors in Safiabad village (Sonepat District: Haryana state of India), a non-endemic area, revealed *Ch. uncinata* induces natural check on the density of infective JE vector (*Cx. tritaeniorhynchus*) population with majority already developed inhibition in taking blood feed during peak JE transmission season and the area so far remained free from JE though other parameters for an impending JE outbreak of the disease remained the same with very high JE

vector abundance, plenty of pigs and water birds in the area. Therefore, this novel biocontrol agent is best suited to control *Cx. tritaeniorhynchus* breeding in paddy fields that hold water for months together. Das (2003) reported during July 2000, *An. stephensi var. mysoriensis* was the only mosquito larvae collected from 14 paddy nursery plots from an extensively paddy cultivated area and out of 152 fourth instar larvae collected 16 (10.54%) were severely infected with *Ch. uncinata*. These parasites seem to have invaded the ovaries of surviving female mosquitoes emerging out these nursery plots to make them parasitically castrated to exhibit ovipositional behaviour and thereby actively dispersed these parasites through deposition into water of newly transplanted paddy fields, the main JE vector (*Cx tritaeniorhynchus*) breeding habitat in the area. As a result, the infectivity rate (% of larvae infected with *Ch. uncinata*) of *Cx. tritaeniorhynchus* was 80.43% in transplanted paddy fields and *An. stephensi var. mysoriensis* larvae were never recorded from these transplanted fields (Table 1). In JE endemic areas more extensive field studies are required to know the impact of using *Ch. uncinata* sand formulation in paddy nursery plots on the abundance of *Cx. tritaeniorhynchus* in the area. ii) Placing larvivorous fish in paddy fields as these hold water for over 3 months.

3. Control of indoor resting adult mosquitoes: Considering the fact that under high density situation the zoophilic vector species is likely to become an indiscriminate feeder leading to increase in man-mosquito contact and likely transmission of JE virus to human population, and JE virus infection was detected from vector mosquitoes collected from NDRI Cattle yard, Karnal Town, Haryana just 10 days before the onset of JE cases in the area (Das et al., 2005). Therefore, it is advisable, as an emergency control measure, to undertake thermal fogging with malathion (technical) in human dwelling in known endemic villages during September, October and first half of November to have a significant decrease in man-vector contact to prevent disease transmission.

4. *Reduction in man-mosquito contact:* Since *Culex* mosquitoes preferably feed on cattle, which act as "dampers" in the natural cycle of JE virus, cattle may be used to divert infected mosquitoes from humans. Other measures to reduce the risk of being bitten by infected mosquitoes may be adopted like: i) Minimizing the time spent outdoors in the evening, ii) Wearing clothing that leaves minimal skin exposed, iii) Liberal use of mosquito repellents, iv) Using long lasting insecticide impregnated curtains in doors and windows, iv) burning of dry neem leaves during evening hours.

5. *Protection of pigs*: i) Keeping pigs in mosquito proof piggeries, and ii) It may be made compulsory to confine pigs during night hours in their pigsties or in the community pig sheds. Even, if legislation is required it may be passed.

6. *Vaccination*: In JE endemic district all children <15 years are to be covered under mass vaccination programme for JE with >90.0% coverage (NVBDCP Operational Guidelines, 2010).

DENGUE FEVER/ DENGUE HAEMORRHAGIC FEVER

Dengue fever (DF) and Dengue haemorrhagic fever (DHF) is considered as the most widespread vector-borne infectious disease of humans, existing in around 125 tropical and subtropical countries worldwide (Singh and Taylor-Rabinson, 2017). Both *Aedes aegypti* and *Ae albopictus* are involved in transmission. Today, more than 2.5 billion people in these countries are at risk of infection (Bhatt et al., 2013). In Southeast Asia, which bears the brunt of the global disease burden, dengue is a leading cause of hospitalisation and death among children in most countries (WHO, 2010b). At the end of the last century, India has faced resurgence of many infectious diseases, of which dengue is one of the most important in terms of morbidity and mortality. The first confirmed outbreak occurred in Kolkatta in 1963-1964 (Sarkar et al., 1964; Chatterjee et al., 1965). It took almost 30 years for dengue to eventually spread throughout the entire country, resulting in the first major nationwide

outbreak of DHF in the year 1996 (Prabhakar et al., 1997; Dar et al., 1999; Agarwal et al., 1999). Dengue in India has established its root. It is now endemic and almost hyper endemic in our population (Gupta and Ballani, 2014). Principal factors which contribute to the spread of dengue in India include rapid and unplanned urbanization, human population growth, inadequate municipal services and increased use of non-biodegrable household products.

NVBDCP under the Directorate of Health Services, Government of India is the nodal agency for implementation of activities for prevention and control of vector-borne diseases including dengue across the country. According to the NVBDCP number of dengue cases in 2017 was the highest in a decade (NVBDCP, 2017b). The International Health Regulations 1969 (WHO, 1986) envisage that every port and its adjoining area within a perimeter of 400 metres should be kept free from immature and adult stages of *Ae. aegypti*, the vector of DHF and yellow fever. In order to ensure this, active mosquito surveillance and vector control measures within the prescribed limits are in place at every port/airport in India. However, NCDC, Delhi undertakes cross check to find out if there is a need for further strengthening of vector control measures in these areas: e.g., cross check studies at Kolkata port/airport and Kozhikode airport (Das et al., 2000; Das et al., 2004b). In the absence of a safe and effective vaccine for dengue viruses, vector control is the method to prevent viral disease. An effective vector control programme will require an increase in expenditure, new strategies to lower and limit the *Ae. aegypti* population (Ooi et al., 2006). This is particularly evident for anthropophilic species such as *Ae. aegypti*, which typically bite at dawn and dusk, breed in densely populated urban and semi-urban areas (Wilder-Smith and Gubler, 2008) in desert coolers of houses and in multi-storeyed building, discarded tyres, disposable cups, open tanks, water storage pots and construction sites. Larviciding using temephos, an organophosphate compound, is recommended by WHO since early 1970s for the control of container-breeding *Aedes* mosquitoes. In India, although there is no specific control strategy for the control of dengue vectors, since 1980 temephos and *Bacillus thuringiensis var israelensis* (*Bti*), a biological control agent used under Urban Malaria Scheme are recommended for the control of *Aedes* mosquitoes. However, *Bti* does not recycle in the environment requiring weekly application in most habitats (Mittal, 2003), increasing the end cost in the process. Study on insecticide susceptibility status revealed the possible development of resistance against temephos in the larvae of *Ae. aegypti* in some areas in Delhi (Singh et al., 2014). Temephos was found to be mutagenic in two out of three assays at concentrations similar to those applied in household water reservoirs (Aiub et al., 2002).

Although several spraying methods including space spraying of insecticide with ultra-low volume technology are in use over the last 40 years, vector control has failed to prevent outbreaks from occurring and to avert an expansion of the geographical distribution of dengue (Gubler, 2011; Singh and Taylor-Rabinson, 2017). Very few biological control agents are commercially available for the control of mosquito vectors of human diseases. Those that exist, failed to maintain “initial success” in reducing vector population. In view of the above, researchers in recent years are looking for microbiological agents that are not only pathogenic to mosquito larvae including *Ae. Aegypti,* but also satisfy four basic criteria, viz. tolerant to desiccation; ability to recycle in the environment; amenable to local production and maintenance and safe for humans and the environment. The study carried out in Delhi (2008) by NCDC revealed that more than 50% of the breeding places of dengue vectors are contributed by desert room coolers because they hold water for long period. These coolers are predominantly used by the residents in slum area in the city. 6343 slums with approximately 10.20 Lacks households were estimated to be in existence in urban Delhi in 2012. Field evaluation of *Ch. uncinata* infusion bag formulation against *Ae. aegypgti* in Delhi revealed that this protozoan bio-larvicide is a better option to check Dengue/Chikungunya vector breeding

as a target dose of 80.0g infusion bag formulation of *Ch. uncinata* produced long duration of control of *Ae aegypti* breeding in these coolers in urban areas (Das and Tuli, 2019). Important messages for Dengue prevention/management include: i) covering all water holding containers & tanks with tight lids; ii) emptying, cleaning by scrubbing and drying desert room coolers at least once a week before refilling; iii) disposing & destroying all unused containers, junk materials, tyres, coconuts shells etc.; iv) sheltering stored tyres from rains; v) installing mosquito screening on windows, doors and other entry points; vi) wearing full sleeved clothing, using mosquito nets (day time) and repellents.

CHIKUNGUNYA

Chikungunya is a debilitating non-fatal viral illness caused by Chikungunya virus. Symptoms of Chikungunya fever are most often clinically indistinguishable from those observed in dengue fever. However, unlike dengue, haemorrhagic manifestations are rare and shock is not observed in Chikungunya virus infection. It is characterized by fever with severe joint pain (arthralgia) and rash. Joint pains sometimes persist for a long time even after the disease is cured. Chikungunya outbreaks typically result in large number of cases but deaths are rarely encountered. There is neither any vaccine nor drugs available to cure the Chikungunya infection and cases are managed symptomatically. The disease re-emerged in the country after a gap of three decades. In India major epidemic of Chikungunya fever was reported during 60s and 70s from isolated places of five states: West Bengal (Kolkata); Tamil Nadu (Pondicherry and Chennai); Andhra Pradesh (Rajahmundry, Vishakapatnam and Kakinada); Madhya Pradesh (Sagar) and Maharashtra (Nagpur and Barsi). During 2006 out of 35 States/ UTs, 16 were affected. In subsequent years cases were reported almost regularly. Chikungunya is also transmitted by *Aedes* mosquito. Both *Ae. aegypti* and *Ae. albopictus* can transmit the disease. Humans are considered to be the major source or reservoir of Chikungunya virus. Therefore, the female mosquitoes usually transmit the disease by biting infected persons and then biting others. *Ae. aegypti* played the major role in transmitting the disease in all the states except Kerala, where *Ae. albopictus* played the major role. *Ae. albopictus* breeding was detected in latex collecting cups of rubber plantations, shoot-off leaves of areca palm, fruit shells, leaf axils, tree holes etc. Since same vector is involved in the transmission of Dengue and Chikungunya strategies for transmission risk reduction by vector control are also the same. *Ae. aegypti* uses a wide range of confined larval habitats, both man-made and natural. These containers such as discarded tyres, flower pots, old water drums, family water trough, water storage vessels and plastic food containers collect rain water and become the source of breeding of *Aedes* mosquitoes **(**NVBDCP). Methods to control this mosquito includes: *1. Personal prophylactic measures***:** Use of mosquito repellent creams, liquids, coils, mats etc.; Wearing of full sleeve shirts and full pants with socks; Use of bed nets for sleeping infants and old family members during day time to prevent mosquito bite. *2. Biological control:* Use of larvivorous fishes in ornamental tanks, fountains, etc. Use of bio larvicides. *3. Chemical control:* Use of chemical larvicides like Temephos in big breeding containers; Aerosol space spray during day time. *4. Environmental management & source reduction*: Detection & elimination of mosquito breeding sources; Management of roof tops, porticos and sunshades; Proper covering of stored water; Reliable water supply; Observation of weekly dry day. *5. Health education:* Impart knowledge to common people regarding the disease and vector through various media sources like T.V., Radio, Cinema slides, etc. *6. Community participation:* sensitizing and involving the community for detection of *Aedes* breeding places and their elimination. For effective community participation, people are informed about Chikungunya and the fact that major epidemics can be prevented by taking effective preventive measures by community itself. Therefore, considerable efforts have been made through advocacy and social mobilization for community education and awareness (NVBDCP-Guidelines).

LYMPHATIC FILARIASIS

Lymphatic filariasis (LF), commonly known as elephantiasis, is a painful and profoundly disfiguring disease. The disease affects over 120 million people in 72 countries throughout the tropics and sub-tropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America. India has 40% of the world's LF cases (Ramaiah et al., 2000). Survey conducted in 2000 revealed that about half of the people in India were at risk of contracting LF (Sabesan et al., 2000). Lymphatic filariasis is caused by infection with nematode (roundworms) parasites that are transmitted through the bites of infected female mosquitoes. These worms (larvae) are deposited on the human skin at the point of mosquito bite, from where they enter the human body. The larvae then migrate to the lymphatic vessels where they develop into adult worms and disrupt lymphatic function. In India, mosquitoes of the genera *Culex* and *Mansonia* transmit the parasites from person to person. 99.4% of the cases are caused by the species - *Wuchereria bancrofti* whereas *Brugia malayi* is responsible for 0.6% of the problem (NVBDCP, 2017d). *Culex quinquefasciatus* is the vector of *W. bancrofti* in the mainland. In the national health policy-2002, India proposed to eliminate filaria from India by 2015 which was later extended to 2021 (Singh et al., 2016). For this Maas Drug Administration (MDA) was started in year 2004 The drug treatment will only work if 60-80% of people from large regions take this treatment once a year for five years.

Vector control/management

Vector control/management is not a part of national filaria health policy. However, in affected large urban areas recurrent anti-larval measures in polluted waters where *Cx quinquefasciatus* breeds, such as sewage and sullage water collections including cess pools, cess pits, drains and septic tanks is recommended at weekly interval. Environment friendly methods including source reduction by filling ditches, pits, low lying areas, deweeding, desilting, etc. along with chemotherapy (MDA) will certainly increase the chances of elimination of LF from the country.

KALA-AZAR OR VISCERAL LEISHMANIASIS

Kala-azar or Visceral leishmaniasis is a parasitic disease caused by *Leishmania donovani* and transmitted by the sandfly *Phlebotomus argentipes*. The disease is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. If left untreated, visceral leishmaniasis can be fatal in over 95% of cases. Most cases occur in Brazil, East Africa and India. An estimated 50,000 to 90,000 new cases occur worldwide annually. Kala-azar remains one of the top parasitic diseases for outbreak and mortality potential. In 2019, more than 90% of new cases reported to WHO occurred in 10 countries: Brazil, Eritrea, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan (Daily update, 2021). There are three types of leishmaniasis found in India: i) Visceral leishmaniasis, which is commonly known as Kala-azar in India and affects multiple organs and is fatal in over 95% of the cases, if left untreated, ii) Cutaneous leishmaniasis, which causes skin sores and is the most common form and iii) post-kala azar dermal leishmaniasis or PKDL. All 4 Kala-azar endemic states are required to report cases to the NVBDCP every month, even if there are zero cases. The four states are: Bihar (33 districts, 458 blocks), Jharkhand (4 districts, 33 blocks), West Bengal (11 districts, 120 blocks) and Uttar Pradesh (6 districts, 22 blocks).

After entrusting the NVBDCP with the task of coordinating control of all vector-borne diseases, India created the National Health Mission in 2013 to target the elimination of Kala-azar as a public health problem. Elimination is defined in Tripartite Memorandum of Understanding among India, Bangladesh and Nepal to achieve Kala-azar elimination from the South-East Asia Region (SEAR) as reducing the annual incidence of Kala-azar to less than 1 case per 10,000 population at the district level in Nepal and at sub-district level in India and Bangladesh. Bihar's Muzaffarpur district has been reporting new cases of Kala-azar, raising serious doubt on the state government's efforts to eliminate the disease in the state by 2022. Since 2010 Bihar has already missed the Kala-azar elimination target four times, viz., the first deadline was 2010 followed

by 2015, 2017 and 2020 due to the government's failure to eliminate Kala-azar. Reasons for Missing the Deadline: i) Lack of Direction: Elimination programmes lack direction and Kala-azar returns year after year, ii) Widespread Poverty: It was mostly the poor belonging to the Dalits, other Backward Communities and Muslims, who are the main victims of the disease. Poverty is an increased risk factor as is poor housing and domestic sanitary conditions (such as a lack of waste management or open sewerage). These increase sandfly breeding and resting sites, as well as their access to humans. Sandflies are attracted to crowded housing which provides a good source of blood-meals. Human behaviour, such as sleeping outside or on the ground, may also increase the risk. Other factors include malnutrition, population mobility and environmental and climate changes. However, according to official data a trend of decline in the number of Kala-azar cases recorded in Bihar: there were 23,084 cases in 2010, and by 2020, there were 2,712 cases.

Vector control interventions

In endemic villages that have reported cases of Kala-azar over the past 3 years, 2 rounds of indoor residual spraying are being applied. Due to the development of resistance in sandfly vectors to DDT, the NVBDCP introduced a synthetic pyrethroid (Alpha-cypermethrin 5% wettable powder formulation) for indoor residual spraying in 2015. It kills the sandflies that land on sprayed wall surfaces. Every year, 35–38 million people at risk of Kala-azar are covered by the spray campaign. This intervention has contributed to a major reduction in disease incidence (WHO, 2021b). The current strategy is to do IRS twice a year in all houses (upto six feet height) and complete coverage of cattle sheds in villages which had a Kala-azar case reported in the last 3 years including the current year supplemented with focused IRS in villages reporting KA cases. Two rounds of spray, 1st round during February - March when sand fly is fairly active, and 2nd round during May – June to control sand fly population supplemented with focused IRS in the villages reporting the cases (NVBDCP, 2017c).

TICK-BORNE DISEASES

Tick-borne diseases in India: Ticks are distributed worldwide and can harbour and transmit a range of pathogenic microorganisms that affect livestock and humans (Sonenshine, 1991). Two highly infectious tick-borne virus zoonotic diseases in India, Kyasanur Forest Disease (KFD) and Crimean–Congo Haemorrhagic Fever (CCHF), are notifiable in India and are associated with high mortality rates. KFD and CCHF are both of high importance for public health in India, as cases are observed almost every year in Karnataka and Gujarat states, respectively.

Kyasanur forest disease: The KFD virus (KFDV) is a member of the genus Flavivirus and family Flaviviridae. It was first recognized in 1957, when an illness occurred concomitantly in monkeys and in humans. KFDV is transmitted to the wild monkeys through the bites of infected *H. spinigera* ticks (Work and Trapido, 1957). After infection, KFDV is transmitted to other ticks feeding on the infected animals. Infection causes severe febrile illness in some monkeys. When infected monkeys die, the ticks drop from their body, thereby generating hotspots of infectious ticks that further spread the virus (Mourya et al., 2014). Since 1957, the estimated incidence of KFD in India has been 400–500 cases per year (Kasabi et al., 2013). *Control:* Infected nymphs and larvae are shed in the forest, mainly by the monkeys, rats, shrews, porcupines, squirrels, and probably a few birds that form enzootic foci. Destruction of infected ticks would necessitate control of ticks throughout the entire forested area but is not technically and economically feasible. Under these circumstances, the prevention of tick bites using repellents should be considered (Banerjee, 1990).

*Crimean–Congo Haemorrhagic Fever***:** The Crimean–Congo Haemorrhagic Fever Virus (CCHFV) is also considered as an important zoonotic virus, owing to its wide distribution and ability to cause disease in humans, where it causes a high mortality rate. CCHF is distributed in Asia, Africa and some part of Europe. *Hyalomma* spp. ticks are the main vectors.

The existence of CCHF in India was first confirmed in 2011 in Gujarat state. Mode of transmission of CCHF virus: Humans become infected through tick bites, by contact with a CCHF-infected patient during the acute phase of infection, or by contact with secretions, blood or tissues from viraemic livestock (Mourya et al., 2012). Risk groups include individuals who are exposed to ticks (mainly farmers, shepherds and veterinarians) and persons who come in close contact with CCHF patients. In 2013 CCHF outbreak in Amreli district, as well as positive tick, animal and human samples in various areas of Gujarat state, suggested that the virus is widespread in Gujarat state, India (Yadav et al., 2013). Tick bites are best prevented by people avoiding tick-infested areas or by wearing long trousers that are tucked into boots. Tick bites can be prevented by application of a topical repellent to exposed skin and treatment of clothing with insecticide, which gives nearly 100% protection (Mourya et al., 2014).

PLAGUE

Plague is caused by infection with *Yersinia pestis*, a bacterium carried by rodents and transmitted by fleas commonly found in parts of Asia, Africa, and North and South America (Barnes, 1982; Poland et al., 1989). Humans can be infected through the bite of infected vector fleas; unprotected contact with infectious bodily fluids or contaminated materials; the inhalation of respiratory droplets/small particles from a patient with pneumonic plague. There are two main forms of plague infection, depending on the route of infection: Bubonic plague and Pneumonic plague. Bubonic plague is the most common form of plague and is caused by the bite of an infected flea. Plague bacillus, *Yersinia pestis*, enters at the bite and travels through the lymphatic system to the nearest lymph node where it replicates itself. The lymph node then becomes inflamed, tense and painful, and is called a 'bubo'. At advanced stages of the infection the inflamed lymph nodes can turn into open sores filled with pus. Human to human transmission of bubonic plague is rare. Bubonic plague can advance and spread to the lungs, which is the more severe type of plague called pneumonic plague. Pneumonic plague, or lung-based plague, is the most virulent form of plague. Incubation can be as short as 24 hours. Any person with pneumonic plague may transmit the disease via droplets to other humans. Untreated pneumonic plague, if not diagnosed and treated early, can be fatal. However, recovery rates are high if detected and treated in time (within 24 hours of onset of symptoms). Preventive measures include informing people when zoonotic plague is present in their environment and advising them to take precautions against flea bites and not to handle animal carcasses. Generally, people should be advised to avoid direct contact with infected body fluids and tissues. When handling potentially infected patients and collecting specimens, standard precautions should apply. WHO does not recommend vaccination, except for high-risk groups (such as laboratory personnel who are constantly exposed to the risk of contamination, and health care workers).

Managing plague outbreaks: Find and stop the source of infection: A localized outbreak of bubonic plague occurred in village Dangud (population 332), district Uttar Kashi, Uttaranchal, India in the second week of October 2004. Eight cases were considered outbreak based on their clinical and epidemiological characteristics; 3 (27.3%) of them died within 48 hours of developing illness. All the 3 fatal cases and five surviving cases had enlargement of inguinal lymph nodes. None of them had pneumonia. The age of the cases ranged from 23-70 years and both sexes were affected. No such illness was reported from adjoining villages. The outbreak was fully contained within two weeks of its onset by supervised comprehensive chemoprophylaxis using tetracycline. A total of approximately 1250 persons were given chemoprophylaxis in three villages. This investigation highlights that with high index of suspicion the disease can be diagnosed early and mounting of supervised comprehensive response can prevent the disease to proceed to pneumonic stage where man to man transmission gets established and outbreak assumes larger dimensions (Mittal et al., 2004).

This outbreak and the occurrence of earlier outbreaks of plague in Surat (Gujarat) and Beed (Maharashtra) in 1994 and in district Shimla (Himachal Pradesh) in 2002 confirm that plague infection continue to exist in sylvatic foci in many parts of India which is transmitted to humans occasionally. Thus, there is a strong need for the States to monitor the plague activity in known sylvatic foci regularly and have a system of surveillance to facilitate prompt diagnosis and treatment of cases to control the disease.

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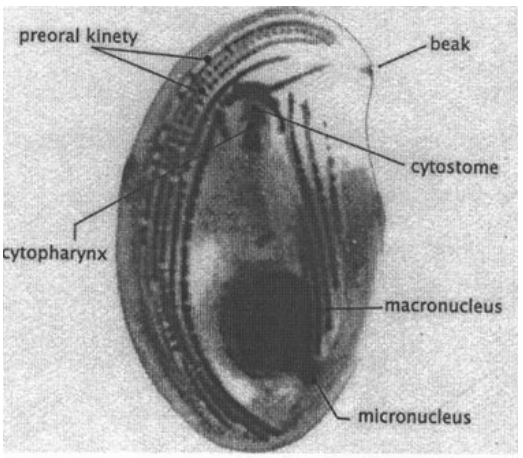

Fig. 1. *Chilodonella uncinata* (Ehrenberg) 1838 [Adapted from Das, 2003]

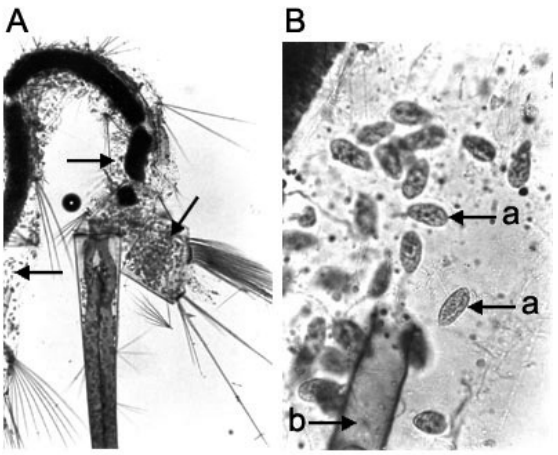

Fig. 2. Wild caught transparent dead JE vector larva (*Cx. tritaeniorhynchus*).
A, fourth instar larva: arrow showing endoparasites (*Ch. uncinata*). B, Same in higher magnification: a, endoparasites. b, disintegrated alimentary canal (Adapted from Das, 2003)

Fig. 3. *Chilodonella uncinata* infusion bag formulation (in sealed pouch to retain moisture) containing 20 g formulation (Adapted from Das and Tuli, 2019)

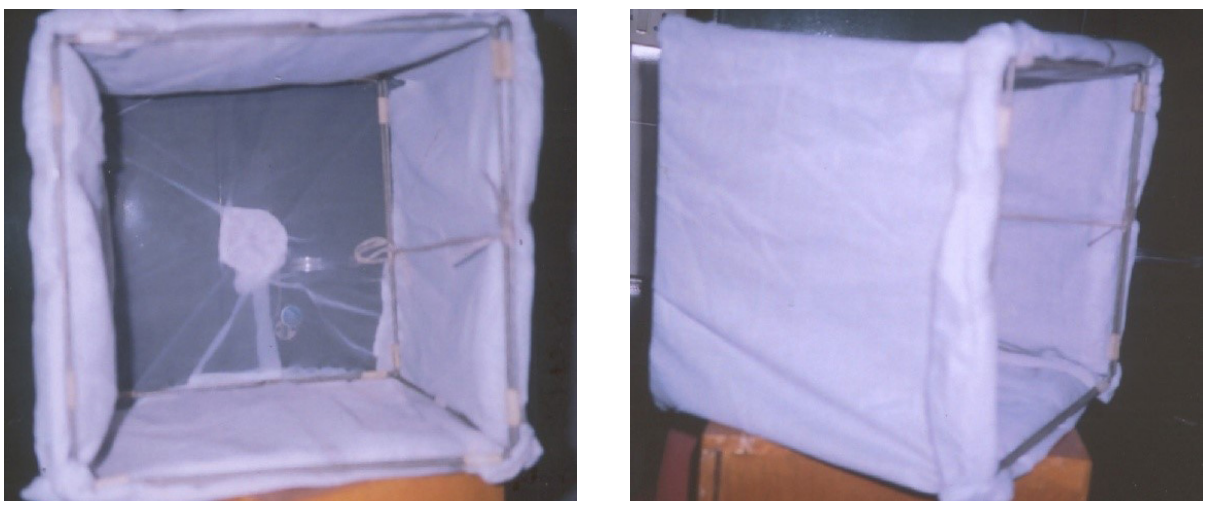

Fig. 4. Hop cage: A, side view. B, front view (Adapted from Das 13 Chap 2)

Fig. 5. Collection of mosquitoes resting on secondary ground vegetation following BPD hop cage method (Adapted from Das 2013 Chap 2)

Invited Review Presented at the 3rd National Symposium
Entomology 2022: Innovation and Entrepreneurship, held during 8-10 December at Hyderabad, India
Online published (Preview) in www.entosocindia.org eRef. No. 22929