

(REVIEW ARTICLE)



## Scoping review on impact of mosquito - borne diseases of man and animals and use of potential bacterial larvicidal agents to control mosquito vectors

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### Abstract

Mosquito vector-borne disease which accounts for the transmission of many deadly diseases like dengue, zika, chikungunya, Rift Valley fever, malaria, West Nile fever, heartworm, lumpy skin disease is one of the major causes of mortality, morbidity, and economic loss to human and animal communities. Though there have been several interventions like insecticide-treated nets, spatial repellents, indoor pesticide sprays to control adult mosquitoes, it only remains effective for short time, possibly leading to faster replacement of the adults by immature only achieving lesser mosquito population reduction. Extensive use of synthetic insecticides leads to resistance, affects non-target organisms and cause ecological imbalance. While recognizing the limitations of the synthetic and adulticide-based mosquito control methods, alternatively, microbial larvicidal agents are more feasible, target-specific, environment-friendly, low application rates, and moderate costs when compared with other vector control measures. This review highlights the microbial larvicidal agents as a most promising tool in vector control management to prevent disease transmission and discusses the major mosquito-borne diseases affecting humans and other animals.

**Keywords:** Vector-borne disease; Mosquito vectors; Synthetic insecticides; Bacterial larvicides; Vector control

### 1. Introduction

Vectors are organisms that act as carriers to transmit deadly parasites and pathogens which lead to the spreading of infectious diseases to humans and other animals [1]. Most of the important vectors come under the Phylum Arthropoda. They include mosquitoes, mites, sand flies, ticks, black flies, and triatomine bugs which transmit the pathogens by bites to the host. Among these insect vectors, mosquitoes are the most threatening vector responsible for the transmission of many dreadful diseases like dengue, West Nile disease, chikungunya, malaria, Japanese encephalitis, zika, Rift valley fever, lumpy skin disease, heartworm, etc. that affect humans and animals [2].

With more than 3500 species under 112 genera in the *Culicidae* family, only three genera of mosquitoes namely *Aedes*, *Culex*, and *Anopheles* is accountable for vectoring major mosquito-borne diseases [3]. These mosquito vectors suck blood from the infected host and ingest the pathogen/parasite. Subsequently, when the mosquito bites and feeds on another person it will transmit the pathogen to him [4].

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### 1.1. Mosquito Ecology

Throughout their lifecycle, mosquito undergoes four different stages (egg, larvae, pupae and adult) of development that has distinct morphology and habits. Mosquitoes need stagnant water bodies for breeding like fresh water, brackish water, salt swamps, and sewage water and also in containers holding water - old tires, and tree holes. [5].

Female mosquitoes need a blood meal before laying eggs and therefore feed by biting and sucking the host (humans/animals). Most male mosquitoes survive on the nectars of flowers. The female mosquito is capable of laying hundreds of eggs. The egg hatches in two to three days and develop into larvae which feed on microorganisms and organic detritus for about a week. Then they develop into pupae which stop feeding but are very active. After 2 to 3 days, they develop into adult mosquitoes [5].

Increased urbanization and industrialization along with climate change have facilitated the site for mosquito breeding profoundly. Improper practice of water management is the chief cause of rapid uncontrolled mosquito breeding [6].

The population of mosquitoes decreases with increasing altitude and increases at lower coastal elevations [7][8]. Larval abundance is found to be higher in breeding grounds with aquatic nitrates, ammonia, and area of shrubs of a certain height. Larval profusion is negatively correlated with pH and area of flowering shrub.

Sometimes, mosquitoes develop different approaches to acclimatize to high levels of salinity and tolerance to this factor differs among species. As salinity and conductivity increase diversity of the species in the breeding ground decreases this consequently results in an abundance of salinity-tolerant mosquito species like *Ae. Albopictus* [9]. While breeding, the female mosquito avoids water bodies that already have predators and choose to be in water bodies with certain physiochemical characteristics and microorganism [10]. Sometimes they also prefer certain aquatic plant habitats like Bromeliads which can be good breeding sites [9].

Heterogeneous patterns of mosquito-borne disease transmission at various places are evident as the biotic (microorganisms, vegetation, animals) and abiotic factors (salinity, concentration of nitrate, chloride, ammonia, nitrite, sulfate, calcium, and phosphate, turbidity, pH, water hardness, humidity, light, temperature, precipitation, elevation, conductivity in breeding grounds) of the environment varies in the breeding ground. These variations influence the abundance and competence of the mosquito. [11] [12] [13] [9]. Identifying these hotspots and predicting habitats plays a crucial role in planning and executing immature mosquito control practices [14].

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## 2. Mosquito-borne diseases (MBDs) in Man

World Health Organization (WHO) estimates that more than 17% of all infectious diseases are due to disease-causing vectors, accounting for more than 700,000 human deaths annually. These diseases are caused by different pathogens which are transmitted by different mosquito vectors. Some of the diseases like lymphatic filariasis, Zika virus, chikungunya and leishmaniasis may result in life-long morbidity, inability and sometimes stigmatization [15]. The following table shows the diseases caused by mosquitoes in man (Table 1).

### 2.1. Malaria

With more than 241 million cases in 2020 and 227 million cases in 2019 reported, malaria is seen as a major mosquito-borne disease. Most of the cases are accounted from sub-Saharan Africa. Approximately, half of the human population in the world was exposed to malaria [16]. It is caused by a protozoan parasite of *Plasmodium* species particularly *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*; *P. falciparum* is the most lethal of all. It is transmitted during the bite of infected *Anopheles* mosquitoes. The sporozoites in the saliva of the mosquito enter into the vertebrate host during the blood meal and they undergo several different stages of development. [17].

The disease can be classified as uncomplicated or severe. The initial symptoms are headache, fever and chill and may later lead to severe complications that are tough to apprehend. *P. falciparum* malaria can advance into acute infection identified as malignant malaria and lead to death within a day if left untreated. Severe impacts in the epidemic area are seen in mothers and their infants. For instance, malaria leads to low birthweight of babies in pregnant mothers and maternal death. Decreased intellectual development and poor academic performance are reported in children. Antimalarial drugs and symptomatic treatment are the present practice to deal with malarial infections. However, there is a growing resistance to antimalarial drugs, so there is significant awareness in preventing infection in the first instance. [17].

**Table 1** The Vector borne diseases caused by mosquitoes in man

Diseases	Mosquito vector species	Types of pathogen
Chikungunya	<i>Aedes sp.</i>	virus
Dengue	<i>Aedes sp.</i>	virus
Rift Valley fever	<i>Aedes and Culex sp.</i>	virus
Yellow fever	<i>Aedes sp.</i>	virus
Zika	<i>Aedes sp.</i>	virus
Japanese encephalitis	<i>Culex sp.</i>	virus
West Nile fever	<i>Culex sp.</i>	virus
Eastern equine encephalitis	<i>Culex sp. and Aedes sp.</i>	virus
La Crosse encephalitis	<i>Aedes sp.</i>	virus
St. Louis encephalitis	<i>Culex sp.</i>	virus
Snowshoe Hare Virus disease	<i>Aedes sp.</i>	arbovirus
Jamestown Canyon Virus Disease	<i>Culex sp.</i>	virus
Lymphatic filariasis	<i>Culex sp., Aedes sp. and Mansonia sp.</i>	parasite
Malaria	<i>Anopheles sp.</i>	parasite

## 2.2. Dengue

With more than 5 million cases reported in 2019 alone, dengue is considered as the most dreaded mosquito borne disease after malaria. Dengue is caused by the dengue virus (serotypes – DENV1, 2, 3 and 4) that belongs to Flavivirus group and is transmitted by *Aedes* mosquito. After blood meal from dengue infected person, the virus gains entry and multiplies into the gut of mosquito. Later circulates in the salivary glands and is spread during subsequent blood meal in different hosts throughout the mosquito's lifespan. [18].

High transmission is found in Asian children of ages 5 to 15 followed by American tropics of ages 19-40. They are known for their fever, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Primary symptoms are moderate flu type illness lasting over a week and in some cases the disease can be serious. Treatments are symptomatically managed. Mass vaccination for dengue is expensive. [19]

## 2.3. Chikungunya

Chikungunya is caused by Chikungunya virus (CHIKV) belonging to *Togaviridae* family. It is transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquito species. Chikungunya symptoms are fever, rash and severe aches in muscles and joints. Their peculiar arthritis may last for month to years. It is mostly seen in elderly and new born. Outbreaks are mostly reported from Asia and Africa. It has two types of transmission cycles: urban (man-mosquito-man transmission) and sylvatic (animal-mosquito-man) [20].

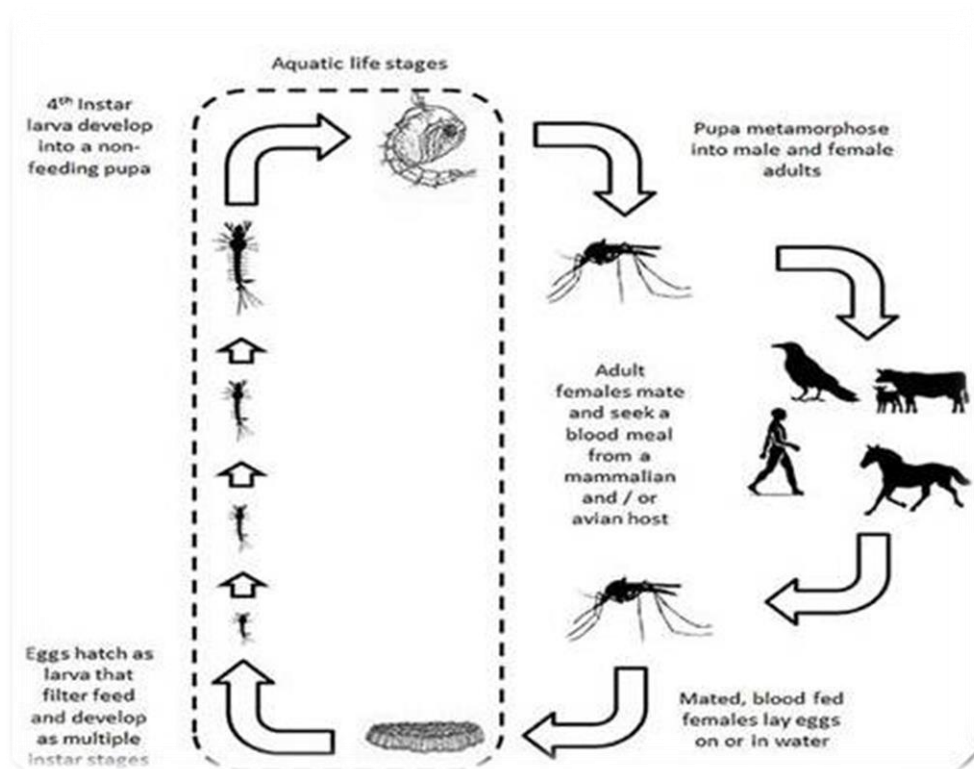
## 2.4. Zika

Zika is a viral disease transmitted by *Aedes* vectors. Sometimes the infections are asymptomatic. Symptoms include fever, headache, rashes, and joint pain. During pregnancy, the infected mother may give birth to newborns with birth anomalies like microcephaly. In adults it may lead to Guillain-Barré syndrome (GBS). The disease gained popularity due to outbreak in Brazil in 2016. In 2016, America documented more than 1 million cases of congenital anomalies; newborn deaths particularly during early pregnant women are affected in their early pregnancy. [21].

## 3. Mosquito-borne diseases in Livestock

According to the World Organisation for Animal Health (OIE), one-fourth of the terrestrial vertebrate pathogens of concern are vector borne [23]. Several of them are of international trade importance. 29 percent of 593 known mammalian viruses are vector-borne viruses. These viruses have thrice the host range compared to non-vector-borne

viruses. VBDs of humans and animal health importance are studied more, which pose unique challenges in determining and eradicating VBDs. They are associated with animal host factor; sometimes multiple animal host are involved for a particular VBD (Figure 1) [24]. Mosquitoes take blood meal from a range of livestock causing itching, blood loss, decreased productivity and even death at times [22]. They affect the dairy, poultry, piggery and other livestock business leading to economic loss and public health concern of cross transmission of pathogen from animals to humans.



**Figure 1** Diagrammatic representation of mosquito lifecycle [22]

Tembusu virus (TMUV) transmitted by mosquito vector in chicks affects poultry farming as they cause stunted growth and encephalitis. Likewise, Israel Turkey encephalitis virus (ITV) causes neuro - paralysis in turkeys (*Melaeagris gallipavo*). Japanese encephalitis virus (JEV) has hosts in both human and livestock. In pigs, JEV causes miscarriage and death in young piglets. [22]

Diseases like *Francisella tularensis* affecting rodents and rabbits; and lumpy skin disease affecting the cattle are transmitted by multiple vectors like ticks, fleas, mosquitoes through multiple hosts are also noted for their unique transmission of these VBDs. [25]

Some of the major MBDs in livestock are:

### 3.1. Heartworm

Heartworm is of veterinary importance, affecting dogs and cats worldwide. It is caused by parasitic worms *Difilaria immitis* and *Difilaria repens*. Mosquitoes during their blood meal from the infected animal draw immature microfilariae that circulate in the bloodstream and subsequently transmitted to other hosts. Later the immature microfilariae develop into adult filarial worms that live in the heart and pulmonary arteries. These worms can grow up to 31cm long, compromises the integrity of the cardiac walls leading to reduced cardiac efficiency to the lungs, coughing, weakness and eventually heart failure. Treatments for heartworm are costly and agonizing for the animals. [26]

### 3.2. Rift Valley Fever (RVF)

RVF is a viral disease of livestock importance as it affects animals like sheep, camels, cattle, goat, and buffaloes transmitted through mosquito vectors. They also affect man. Many outbreaks in African countries are reported and they spread to Arabian Peninsula in 2000 due to translocation of infected animals. Initially, fever is observed, then jaundice leading to liver failure and hemorrhage. In some RVF epidemic outbreaks, severe mortality of up to 90% was accounted

in juvenile stage of the animals. Neonatal anomalies, deaths in new-born and mass abortion at all levels of pregnancy were observed in sheep and cattle. Recently, hemorrhagic type of RVF has emerged with sudden death in mature animals like cattle. [27]

### 3.3. Equine Encephalitis

Worldwide many zoonotic alpha viruses cause encephalitis in humans, horses, dogs, pigs, llamas, alpacas and in birds like emu, pheasants. They are jointly called as the equine encephalitides, comprising mainly of three viruses Western Equine Encephalitis Virus (WEEV); Eastern Equine Encephalitis Virus (EEEV) and Venezuelan Equine Encephalitis Virus (VEEV) causing severe disease to wide range of hosts transmitted by different mosquito species. [22]

The EEE virus is endemic of the US, is a major cause of death in horses, whopping cranes, emus, etc. Symptoms in horse are fever, abnormal behavior of circling, lack of energy, muscle tremors, coma and death. In birds like emus and pheasants, the infected shows almost same symptoms as horses. The dead birds should be handled with caution as they lead to spreading of virus from body fluids. Western Equine Encephalomyelitis (WEE) virus infects the horses. VEE Virus is common in Mexico affecting the mules, horses and burros. The peculiar thing about VEE and DEE is that, in former mosquitoes transmit the virus within the equine community and in latter the mosquitoes transmit the virus from birds to horses. [22]

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## 4. Wildlife and MBDs

Mosquito-borne diseases in wildlife are complicated to eradicate as its reemergence is not determinable and is difficult to control. Higher risk of biodiversity loss threat has been faced by many isolated islands compared to mainlands due to the introduction of pathogens from infected migratory birds. For instance in Hawaii Island, only 21 out of 100 indigenous forest bird species lives. In this 12 species are kept in highly endangered list persisting in small groups due to many mosquito borne disease transmissions. [14]

Wildlife due to their isolation has more chances of introducing novel diseases which causes serious challenge to the avian and vertebrate community. In Galápagos islands, Plasmodium spp has been found in penguin. Whataroa virus that is spread across New Zealand is found to be introduced by the *Cx. pervigilans* and *Culiseta tonnoiri* in South Islands. Avianpox that causes skin lesions and avian malaria in wild birds leads to mass extinction. Thus, proper mosquito vector surveillance is vital for managing such disease causing pathogens. [14].

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## 5. Vector Control measures (integrated vector management)

The best method to combat most of the MBDs is to focus on controlling the mosquito vectors. Most mosquito control methods depend on controlling either larvae or adult mosquitoes. Approaches to control immatures rely on eliminating oviposition sites like containers that hold stagnant water, and use of larviciding agents; adult control methods mostly depend on pesticide sprays [28].

Larvicide focused mosquito control efforts maybe more successful than adulticide-focused mosquito control as the former (Larvicide) remains active for weeks to months [29], ensuring prolonged control of adult mosquito with a minimal labor expense, whereas the latter (adulticide) remains effective for a very minimal amount of time, possibly leading to faster replacement of the adults by immatures. This does likely reduce the occurrence of infection among adults, even though achieving only less mosquito population reduction and extensive use also leads to resistance to insecticide. [30].

Integrated vector management (IVM) is important as it involves larger coordination from many aspects of society. It has many components like health system, legal regulations, and educational awareness, capacity building, etc. [31]. The IVM is considered as best method for vector control.

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## 6. Synthetic insecticide

Present mosquito control practices are highly dependent on chemical insecticides [32], such as pyrethroids and insect growth regulators (pyriproxyfen, methoprene, diflubenzuron, novaluron). Most of the chemical insecticidal products are classified under these four classes as: pyrethroids (permethrin), organochlorines (DDT), organophosphates (temephos and fenthion) and carbamates.

Use of broad spectrum synthetic chemical control agents has certain downsides, such as effects on non-target organisms, development of insecticide resistance. Repetitive and high doses can lead to toxic effects on the environment and cause ecological imbalance. Thus, it is important to decrease the usage of chemicals and to devise environment friendly vector control products.

However, increasing awareness of its effect on environment has reverted the attention back to environmental and biological control measures [33]. Natural antagonists of mosquito larvae such as cyclopoids, copepods, mermithid nematodes, larvivorous fish, entamopathogenic fungi, plant extracts/semiochemicals and bacterial toxins (*Bti*; *Bs*, spinosad, spinetoram, abamectin) have been applied to control populations of disease vectors [34].

Specifically, bacterial biopesticides like *Bacillus thuringiensis israelensis* (*Bti*) and *Bacillus sphaericus* (*Bs*) has been most widely used for mosquito control [35] [36]. Nevertheless, there are fewer alternatives for better bacterial larvicides present currently.

## 7. Bacterial larvicides

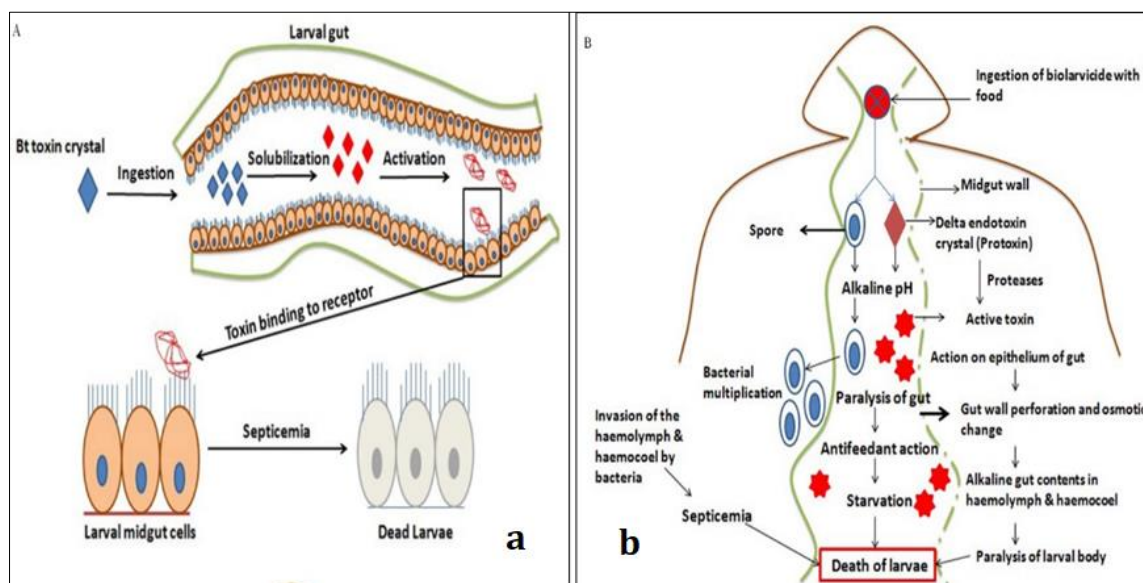
### 7.1. *Bacillus sphaericus* (*Bs*)

*Lysinibacillus sphaericus* (formerly known as *Bacillus sphaericus*) is a rod-shaped bacterium mostly found on soil. They produce spores in terminal or subterminal sporangium at the end of their vegetative cycle. During sporulation, some strains release intracellular protein toxin and parasporal crystalline toxins [37]

During sporulation, parasporal inclusions are formed in active *Bs* strains. They have two crystal binary toxins A and B that play the important role in larvicidal activity. Some strains in their vegetative state also release non crystal toxins such as *Mtx 1, 2, and 3*. The *Mtx* contribute to the larvicidal activity lesser than the binary toxins. [38].

Because of the simplicity of the binary crystal toxins in *Bs*, resistance was first reported in 1994 in Southern France, it showed an increased level of resistance to repeated treatments in field populations of *Culex pipiens L.* [39]. Later many reports on different stages of resistance to *Bs* both in lab reared and field mosquito populations followed from various countries. [40] [38].

### 7.2. *B. thuringiensis subsp. israelensis* (*Bti*)



**Figure 2** (a) Diagrammatic illustration of mode of action of *Bti* toxin; (b) Illustration showing mortality of mosquito larvae due to biolarvicides. [45]

*Bti* is a bacterium that during sporulation releases protein crystals that are highly toxic to mosquito larvae, it has been used worldwide in mosquito control for more than 25 years, and its specificity has been tested on many taxa. It is in the



feeding larval instars I-III that *Bti* is the most effective, in instar IV the feeding eventually stops before the larva enters the pupal stage. Very few studies have showed negative *Bti* related effects on the non-target organisms [41] [42].

Mode of action: The *Bti* has *Cry* toxins that are chiefly involving in solubilizing and proteolytic activation of protoxin by protease, interaction between receptors and active toxin and binding to the midgut epithelial cells. Thus, leading to the formation of lesions in the midgut cell membrane and causing the death of mosquito larva. Besides these, *Bti* also produces other toxins such as  $\alpha$ -exotoxin,  $\beta$ -exotoxins, hemolysins, enterotoxins, phospholipases, and chitinase. [43]. the multi toxin crystal composition of *Bti* is closely associated with the lesser evolution of resistance to the mosquito vectors. Commercial *Bti* formulations in liquid, dunks and powder are available for use (Figure 2a and 2b) [44].

### 7.3. Spinosad

*Saccharopolyspora spinose* is a bacterium that produces mosquitocidal compounds called as spinosads during their process of fermentation. It is used against different instars of mosquito larva. It is used to control vector like *Aedes sp.*, *Culex sp.* and *Anopheles sp.* of human and animal importance. And also recently it was permitted for using in drinking water reservoirs to control larval proliferation [46].

Some species of *Bacillus subtilis* shows both larvicidal and pupicidal properties against mosquitoes. They produce toxins in the vegetative state, whereas in *Bti* and *Bs* it is during the sporulative stage. These toxins have biosurfactant properties that help in mortality of the larvae [47]; *Bacillus circulans* is most effective as a larvicide in *Aedes aegypti* because of its high toxicity; *Clostridium bifermentans* is effective against *Anopheles sp.*; *Pseudomonas fluorescens* has larvicidal and pupicidal effect to *Culex*, *Anopheles* and *Aedes sps.* [48]; *Bacillus brevis* and *Bacillus alvei* have been demonstrated to produce larvicidal toxins. [49]; soil bacteria, *Chromobacterium* species have properties for controlling mosquitoes [50]. Furthermore, some species of *Xenorhabdus* and *Photorhabdus* exhibits mosquitocidal activity. Therefore, these microbial agents can also be incorporated in newer control strategies. [36]

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## 8. Conclusion

The review focuses on the greater need to control mosquito vectors as they are the key driver in the transmission of many vector borne diseases in humans, livestock and wildlife. Proper mosquito surveillance and timely control reduces the spill-over risk of disease transmission, decreases the economic burden to livestock industry in outbreaks and thereby reduces the potential harm in domestic animals and restricts the challenges of biodiversity in the wild. [22]. For many MBDs, disease control is difficult, so controlling the mosquito breeding is vital. Mosquitoes are able to adapt to newer environment and emerging resistance to synthetic pesticides. Use of bacterial larvicides like *Bacillus sphaericus* (*Bs*), *Bacillus thuringiensis* var. *israelensis* (*Bti*) are shown to control mosquitoes in a safe and eco-friendly way. The need to isolate novel bacterial larvicides is emphasized to tackle the emerging resistance in the mosquitoes.

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## Compliance with ethical standards

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### Disclosure of conflict of interest

The authors hereby declare that there is no conflict of interest.

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