Perspective-1

NEED FOR INVENTIONS, INNOVATIONS AND DISCOVERIES IN VECTOR CONTROL

B.K. Tyagi[1*] and Rina Tilak[2]

[1]SpoRIC, VIT University, Vellore - 632014, TN, India
[2]Department of Community Medicine, AFMC, Pune (MS), India

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Vector Control is presently at cross-roads, with the vector-borne diseases constituting a colossal 17% of all illnesses due to communicable infections in the world. Some of the world's most devastating vector-borne diseases (VBDs) are transmitted to people by blood-sucking arthropods, particularly mosquitoes. Mostly these VBDs are rampant in tropical and subtropical disease endemic countries (DECs) where they affect billions of people globally and are of serious public health concern. Population growth, poorly managed urbanization, the greater incursion of human activities into natural ecosystems, and the transition and expansion of the geographical distribution of vectors due to climatic changes have contributed to an unprecedented growth in several VBDs,

***Corresponding Author:**
Dr B.K. Tyagi; Email: abktyagi@gmail.com

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particularly dengue and malaria. This situation has been aggravated by the accidental spread of vectors and pathogens through increased global travel, and the collapse of vector control in public health programmes.

The conventional methods of controlling disease vectors, for example mosquito populations, which involve insecticide fogging, aerosol space spraying, larviciding, indoor residual insecticide spray have proved largely ineffective in reducing vector density. This is principally because mosquitoes have developed resistance to insecticides, but also because the insecticides are costly and environmentally hazardous. This crisis has prompted scientists to develop alternative safe methodologies or tools that can effectively control diseases such as dengue and malaria without exposing human to health hazards and environment to degradation. With the successful development of genetically modified (GM) crops and a few GM insects through the sterile insect technique (SIT) to control pests on fruit and agriculture produce, these new tools use genetic engineering to control some disease vectors and pests.[1-3] Several of them, such as the technology known as Release of Insects carrying a Dominant Lethal (RIDL™) gene against the dengue vector, *Aedes aegypti*; the endosymbiont *Wolbachia*-driven cytoplasmic incompatibility to induce feminization and cessation of reproduction of pathogen in the host's body; and, introduction of CRISPR/Cas9 technology to design a pest genome at will have shown great promise in rapidly reducing or replacing the vector population, thereby also reducing disease transmission in endemic areas.[4-7]

The genetic engineering of insects or arthropods is not a recent invention in the scientific world. For a long time now, many countries have used it successfully against agricultural pests and disease vectors. Scientists and researchers have started using the same technology against insect vectors of human diseases by either suppressing or replacing vector populations with genetically modified vectors (GMVs), thus making the insect vectors unable to reproduce or transmit pathogens.

In the last two decades, researchers around the world have focused on developing genetically modified mosquitoes (GMMs) as an effective strategy to control transmission of VBDs.[8] The strategy has focused either on reducing the overall number of target mosquitoes to levels unable to support pathogen transmission (population suppression), or on introducing a genetic modification that renders the local mosquito population unable to transmit the pathogen (population replacement). Under the population suppression strategy, SIT was at the forefront during 1960–1970s with release trials of sterile male mosquitoes. The WHO's Indian SIT project launched in 1970 with the establishment of "Genetic Control of Mosquitoes Unit" under the Indian Council of Medical Research (ICMR), witnessed a large number of highly significant research information published. The project was a frontrunner in mining the data on the technology which is based on the principle of large scale production, sex separation, sterilization, and subsequent release of sizeable quantities of sterile male mosquitoes into targeted populations where they mate and produce non-viable offspring. Although this method was effective against some agricultural pests, it had limited impact on controlling disease vectors because of the high costs involved. Many of the necessities in the technology perfection have now been overcome, and the WHO has recently launched a massive vector control programme through SIT in Bangladesh.

RIDL is a similar approach to SIT but with several improvements in that it offers solutions to issues experienced with SIT such as sex separation and sterilization by irradiation. With this approach, GMMs carrying a dominant lethal gene are introduced into the field to mate and pass the gene onto their progeny. As a result, the female progeny die either as larvae/pupae or as adults without genetic repressor to survive or they are unable to fly. Thus, the female is unable to act as a vector, mate, seek a host or escape from predators. Many countries/regions like Cayman Islands, Brazil and United States have permitted the technology for control of the dengue vector, *Aedes aegypti*. Another technique in GM technology is RNA interference (RNAi) aimed at improving the mosquitoes' natural defense against viruses and suppressing virus replication. Research is also underway into homing endonuclease genes (HEGs), site-specific so-called selfish genetic elements to examine ways to eliminate (i) the gene required for disease transmission, (ii) the gene involved in survival and reproduction, and (iii) the sex-determining gene. Another leading approach under the population replacement strategy is Maternal-Effect Dominant Embryonic Arrest (Medea) which is a synthetic selfish genetic element first discovered in a species of flour beetle, *Tribolium castaneum*. Medea is able to spread through a population causing the death of all offspring of heterozygous females that do not inherit the allele. Studies have found that *Wolbachia* act as a natural agent in suppressing disease by making the vectors resistant to human pathogens. Some strains of *Wolbachia* can influence fecundity or oogenesis arresting the development of embryos whereas life-shortening strains of *Wolbachia* can dramatically reduce the longevity of adult female mosquitoes.

Apart from these techniques, there are some new strategies in the pipeline such as the use of site- specific DNA lesion, transcription activator-like effector or nucleases (TALENs), and studies related to the microbial midgut of mosquito population. These are still in the initial stages of development and require further study. The future belongs to a combined lab+field based inventions, innovations and discoveries, where ecological, social, regulatory, legal, economic and ethical implications have been amply addressed prior to the execution of the technology.

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