Partnership for Dengue Control

Workshop to Develop a Research Agenda for Assessing Vector Control to Prevent Dengue

Annecy, France
2-3 February 2015
EXECUTIVE SUMMARY

The general consensus among dengue control experts is that use of any one intervention by itself is unlikely to effectively control dengue. Thus, the Partnership for Dengue Control (PDC) has pursued the strategy of combining new dengue vaccines with vector control. An initial workshop on the status of new dengue control strategies was held in November 2013. Here we report on a follow-up workshop that reviews currently available dengue control tools/strategies and provides expert opinion on the most effective control strategies that target the primary urban dengue vector, *Aedes aegypti*, and can be utilized now in combination with vaccination. Promising vector control candidates that are in development were also identified for future trials.

The workshop consisted of three phases. First, a questionnaire was used to obtain expert opinion on the relative effectiveness of vector control interventions. Second, reviews of major dengue and malaria control interventions, dengue epidemiology, dengue vaccines, and trial design were presented. Third, a recommendation on currently available vector control strategies that should be coupled with dengue vaccination was presented. The vector control questionnaire (matrix) measured opinion on efficacy, the ability of the intervention to provide sustainable control of adult *Ae. aegypti* populations, having an impact on dengue transmission, and the logistics involved in the intervention (costs, safety, labor, acceptability to health workers and the public). Of currently available methods, indoor residual spraying (termed targeted IRS - TIRS - to distinguish it from malaria IRS interventions) was thought most efficacious although insecticide resistance would reduce efficacy in certain situations and must be prospectively evaluated. TIRS involves targeted spraying of dark surfaces and areas inside premises where *Ae. aegypti* harbor; e.g., inside closets, under tables, and dark objects such as suitcases. Logistics of TIRS is relatively high due to the laborious nature of treating inside houses. Indoor and outdoor space sprays involving thermal and ULV fogging were not judged effective due to the transient nature of control. Larval control by itself was deemed ineffective and should be combined with adult control. Finally, spatial repellents (vapor active synthetic pyrethroids such as transluthrin and metofluthrin) show high promise, but lack evidence of impact on vector populations and dengue transmission. New formulations of existing pesticides (eg, deltamethrin, pirimiphos methyl [Actellic]) and some lethal ovitraps show potential for several months of control and could be used to decrease vector populations before the dengue transmission season.

Populations of *Ae. aegypti* are often physiologically resistant to insecticides. This can have a serious impact on efficacy of the intervention, especially those using synthetic pyrethroid insecticides. Control of larvae and adults should employ different classes of insecticides to minimize the development of resistance. Vector control intervention sites must be screened for resistance in populations of *Ae. aegypti* to a range of insecticides (such as the synthetic pyrethroids deltamethrin and permethrin) to determine those that are feasible for use in a trial. Indeed, it is likely that a trial using synthetic pyrethroids in a TIRS program could not be conducted in many dengue endemic areas due to insecticide resistance.

Spatial repellents are volatile insecticides that confuse mosquitoes, reduce biting, and, with higher doses, kill mosquitoes. Paper and plastic emanators placed inside rooms would have public appeal, although high cost, limited longevity of control and impact of insecticide resistance could reduce efficacy. New lethal ovitraps incorporating adhesives (Autocidal Gravid Trap; AGO) have been shown to reduce female *Ae. aegypti* populations by up to 80%. Traps require servicing every 2 months. A series of AGO ‘killing stations’ maintained throughout the year could effectively control resistant mosquitoes. Insecticide treated screens also show promise in areas where houses (typically block or stucco) have small windows that force mosquitoes to make frequent contact with the treated screen.

Use of *Wolbachia* and the release of insects with a dominant lethal gene (RIDL) both involve the rearing and release of laboratory reared *Ae. aegypti* that mate with wild populations. In the case of *Wolbachia*, the wild population is gradually infected with a strain of the bacterium *Wolbachia* *pipiens*, which reduces the capacity for female *Ae. aegypti* to transmit dengue viruses. In RIDL, the mosquitoes are genetically modified (GM), and released sterile males mate with wild females,
inducing sterility. Sustained releases of RIDL males can reduce and potentially eliminate local populations. Gaining public acceptance for releases of GM sterile males mosquitoes is a critical issue. Trials with RIDL are currently under way in several countries. While Wolbachia has been successfully established at several field sites in Cairns Australia, randomized controlled trials (RCTs) providing evidence of prevention of dengue transmission have not been conducted. Due to the complex nature of the intervention, where Wolbachia establishment may vary between clusters, alternative trial designs have been proposed. These include step-wedge and measures of virus prevalence in mosquitoes. The use of Wolbachia and RIDL are not mutually exclusive.

Vector control interventions have been successfully used to control malaria in many areas. The development and uptake of IRS and long-lasting insecticide treated nets (LLIN) has been driven by efficacy validation with epidemiological endpoint trials, typically RCTs. Even then, most (ca. 95%) published vector control studies targeting Anopheles do not meet formal criteria (randomization, suitable control arm, no epi-endpoint data, etc.) for inclusion in Cochrane-type reviews of evidence. Malaria control funding agencies have developed a review scheme based on evidence (systematic reviews; Vector Control Advisory Group assessment) from robust, controlled trials to support procurement of funds for control programs.

The gold-standard trial design is an RCT using randomization of clusters. This approach minimizes confounding factors because as many variables as possible will be controlled in each trial group, allowing clear conclusions to be made regarding the effect (or lack thereof) of the intervention. Alternative designs, such as the step-wedge design, may be used when a true placebo that would prevent use of a disease control intervention, could not be used. The movement of people can result in infection risk outside of clusters, which would contaminate treatment and control arms and confound results. Human movement will, therefore, need to be accounted for in the trial design. Trials should include initial baseline data and sufficiently long post-treatment assessment to account for variability in seasonal and annual variation in DENV transmission. A pilot trial is recommended to work out methodology and impact of specific vector control methods on target species.

The current Sanofi tetravalent dengue vaccine offers significant but incomplete protection against the 4 dengue serotypes. Phase 3 trials indicate that the vaccine offers highest protection against DENV-4 and DENV-3, lower efficacy against DENV-1 and relatively poor efficacy against DENV-2. The overall efficacy of the vaccine was 56-61%. High efficacy was obtained against severe disease and hospitalizations (> 80%) and was highest in older age cohorts that were previously exposed to DENV. Trial design to test vaccine plus vector control should incorporate transmission risk strata with random assignment of treatment and control within strata. As noted above, movement of people can confound results and should be addressed in the trial design. Metrics to be measured should emphasize epidemiologic outcomes (confirmed clinically apparent dengue illness), entomological data (larval and especially adult female Ae. aegypti populations), and environmental factors (housing type, window screening, etc.).

Although very few proper RCTs for dengue control have been carried out, those trials that have been conducted highlight important for future assessments. Government dengue control programs will likely conduct vector control within the trial site, including the control areas. This cannot ethically be prevented, and it is recommended that trial program leaders engage with local authorities to understand and potentially reduce impacts on the trial. Buffer areas should be established around treatment clusters to reduce dilution of vector control by mosquito immigration from outside the treatment area. Timing of the intervention is critical, and should begin prior to the annual seasonal increase in DENV transmission. With effort and good community engagement, coverage rates can reach 90%.

The working group concluded that TIRS is the best available strategy to control urban populations of Ae. aegypti and prevent dengue. While there is evidence TIRS significantly reduces populations of adult Ae. aegypti, and a GIS based study showed TIRS protected against dengue transmission, RCTs with epidemiological-endpoint data have not been conducted. The working group also recommended that TIRS be combined with larval control using a residual product of a different insecticidal class; e.g., the insect growth regulators s-methoprene or pyriproxyfen. It is important that field sites for a
potential RCT be identified. Country, regional and local health workers and regulators will need to be consulted and supportive, with permits for use of the interventions obtained. Community engagement of residents will be needed and should be ongoing. Preliminary studies will need to document dengue incidence, the vector and its abundance, insecticide resistance especially towards SPs used in TIRS, efficacy, and local acceptance of TIRS against vector populations. The proposed interventions can then be used to design a formal RCT in combination with vaccine. Treatment and control cluster sample size and the location of clusters should be determined and mapped a priori. Baseline virology and vector sampling should be established and run for at least 1 year before the interventions are started and the intervention should last at least 2 transmission seasons. Research into promising new formulations (e.g., long lasting microencapsulated Actellic) and insecticides (e.g., metofluthrin) that could enhance or replace TIRS should be supported.