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Prevention and Control of *Aedes aegypti*-borne Diseases: Lesson Learned from Past Successes and Failures

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HISTORY

Historically, *Aedes aegypti* has been one of the most important mosquito vectors of human disease. A native of Africa, it was introduced to the Americas in the 1600s by the slave trade, and became highly domesticated, adapted to humans, and a highly efficient vector of epidemic yellow fever and dengue. As the shipping industry expanded in the 18th and 19th centuries, *Ae. aegypti* was transported around the world, infesting port cities and then moving inland along routes of transportation (Gubler, 1997). The result was major epidemics of dengue in Asian and American countries. Fortunately, for reasons that are unrelated to dengue but not yet fully understood, yellow fever epidemics never occurred in Asia (Curtis and Reuben, 2007). Dengue epidemics occurred at infrequent intervals because the viruses and mosquito vectors depended on sailing ships to move them between continents. During World War II, however, transmission intensified as both the Allied and Japanese armies spread the viruses and *Ae. aegypti* throughout the Asian and Pacific regions. Dengue fever was a major cause of casualties in both armies in these theatres; it was at this time that the dengue viruses were first isolated (Kimura and Hotta, 1944; Sabin and Schlesinger, 1945).

PAST SUCCESSES

The first success in controlling an *Ae. aegypti*-transmitted disease was the control of yellow fever in Cuba in 1904. This was followed by controlling the same disease in Panama, which allowed the Panama Canal to be built and completed in 1912. More successes came in Brazil in the 1930s, and in the American region after World War II, when *Ae. aegypti* was eliminated from 23 countries in Central and South America between 1946 and 1970, effectively preventing epidemic yellow fever and dengue (Soper *et al.*, 1943; Schliessman and Calheiros, 1974). Unfortunately, this success, plus successes with malaria and other infectious diseases resulted in the war on infectious disease being declared won in 1969 (Henderson, 1993) and issued in a 30 year period of complacency and apathy. During this time resources were re-directed to other competing public health priorities and vector-borne infectious disease control infrastructure deteriorated in most countries of the world.

PAST FAILURES

Coincident with the dramatic change in public health policy in the early 1970s was propagation of the myth that new technology could be used to more effectively control mosquitoes and prevent diseases without investment in the infrastructure and the hard work associated with successful campaigns in the past. The concept of space spraying of insecticides using the new ultra low volume technology was initiated in the early 1970s as the recommended method to control Ae. aeqypti (Lofqren, 1970; Pant, 1983; Mount, 1985). Needless to say, this strategy, which has been recommended for over 40 years, has been a complete failure (Gubler, 1989; Newton and Reiter, 1992). Since 1970, the whole of the tropical world has become hyperendemic for dengue as both the viruses and the mosquito vectors have been spread by modern transportation. The number of reported cases of dengue/dengue hemorrhagic fever reported to WHO annually has increased dramatically during this time (Gubler, 2011). Currently, all four dengue virus serotypes have a global distribution in the tropics, mirroring the distribution of Ae. aeqypti. Recent studies have estimated that over 3.6 billion people live in areas of risk for dengue transmission, and that every year, there are 50 to 230 million infections (depending on epidemic activity), tens of millions of cases of dengue fever and millions of cases of dengue hemorrhagic fever (Beatty, *et al* 2008). In 2011, dengue is the most important arboviral disease of humans and one of the most important tropical emerging infectious diseases globally. In Southeast Asia, which bears the brunt of the global disease burden, dengue is a leading cause of hospitalisation

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and death among children in most countries (WHO, 2010). Clearly, whatever it is that we have been doing to prevent and control this disease, it has not worked. It is time to try something new.

The reasons for the 20th century pandemic of dengue are many and diverse, including apathy, redirection of resources, and changing lifestyles. If the popular press and some scientists are to be believed, climate change has been a major factor, but there is no good evidence to support this claim. In fact, there have been only four major drivers of this dramatic increase in incidence and geographic expansion of dengue: 1) population growth in tropical developing countries, 2) unprecedented urban growth in those same countries, 3) lack of effective mosquito control in tropical urban centers, and 4) globalisation. Economic growth has been a major driver of both urbanisation and globalisation. The tropical urban environment, with its crowded human populations living in unhygienic conditions (inadequate housing, water, sewage and waste management systems) in intimate association with equally large *Ae. aegypti* populations, provided the ideal conditions for increased dengue transmission. These large urban centres spawn epidemic virus strains that are transported via modern transportation to other urban centers where mosquito control is equally bad (Gubler *et al.*, 1979; Cummings *et al.*, 2004; Gubler, 2004).

In the past 40 years, there have been only two successes in preventing epidemic dengue by controlling *Ae. aegypti*, first in Singapore from 1973 to 1989, and second in Cuba from 1982 to 1997. Both are island countries and vertically structured programmes were used with a strong emphasis on larval control (Chan, 1985; Armada and Figueredo, 1986). Both programmes ultimately failed because of the increased epidemic activity in surrounding endemic countries in the respective regions and the pressure of imported dengue from those countries. A major factor in the Cuba programme's failure was economic distress after the Soviet Union collapsed; when Soviet financial aid to Cuba stopped, the *Ae. aegypti* control programme deteriorated. Interestingly, however, the Singapore failure was driven by economic growth and the importation of hundreds of thousands of migrant workers from dengue endemic countries, combined with a very strong tourist industry and decreasing herd immunity (Ooi *et al.*, 2006). The result has been outbreaks of dengue despite the fact that *Ae. aegypti* control has been maintained. The rest of the dengue endemic world essentially did nothing to control dengue, paying only lip service and very little economic support for their national programmes (Gubler, 2005).

LESSONS LEARNED

So what are the lessons learned from the past 60 years of increasing incidence and expanding geographic distribution of dengue? There are many, but the most important is that space spraying, as commonly conducted in most countries, does not have any impact on dengue transmission. We must acknowledge that what most countries have been doing to control *Ae. aegypti* has not worked. Unfortunately, however, we have a whole generation of dengue operational control personnel who know nothing but space spraying with insecticides that have no residual activity. A second lesson learned is that community-based control programmes alone do not work either. Community involvement and ownership are necessary for long-term sustainability, but it takes years to achieve efficacy, as demonstrated by the seatbelt and anti-smoking campaigns of the past 40 years. A third lesson is that the vertically structured, paramilitary type programmes used so effectively in the *Ae. aegypti* eradication programme do work, and that a residual insecticide like DDT can be very useful in controlling the *Ae. aegypti* adults emerging from the cryptic or hidden breeding sites that are so difficult to control. Unfortunately, as we also learned from the *Ae. aegypti* eradication campaigns, vertically structured control programmes are not sustainable. Moreover DDT is not acceptable in today's world. Fourth, we have learned that effective *Ae. aegypti* control will never be achieved until dengue endemic countries invest in the public health infrastructure needed to control the disease using their own resources instead of relying on international funding agencies for support. Even though most dengue endemic countries list dengue as one of their top health priorities, very few have invested in effective control programmes. A fifth lesson is that a combination of global trends and lack of effective mosquito control have been the principal drivers of the dramatic expansion of epidemic dengue in the past 40 years. The massive unplanned urban growth in many tropical countries has made the control of *Ae. aegypti* very difficult in the absence of new tools. A final lesson learned is that no single approach to *Ae. aegypti* control will provide success when used in isolation. The ecological variation found in large tropical cities requires an integrated approach to controlling *Ae. aegypti*, the methods used depending on the city and the ecology. Effective *Ae. aegypti* control will likely require a combination top-down and bottom-up approach that integrates chemical, biological, genetic and community-based control methods, as well as effective use of dengue vaccines, drugs and therapeutic antibodies (Gubler, 2011). Although topics such as yellow fever, chikungunya, and the secondary dengue vector *Ae. albopictus* are outside the scope of this paper, it would be worthwhile to take a holistic approach by considering them alongside the strategy to combat dengue and its primary vector *Ae. aegypti*.

PROSPECTS FOR THE FUTURE

The good news is that progress has been made in recent years in developing new tools in all of these areas. For the first time in decades, efforts are being made to develop new insecticides that will provide residual activity (McCall and Kittayapong, 2007). These will have to include new classes

of chemicals that can be alternated in their use to prevent resistance from developing in the mosquito. Similarly, good progress has been made in the biological control of *Ae. aegypti*. Copepods have been used to eliminate and/or control *Ae. aegypti* in parts of Vietnam (Kay and Vin, 2005), and Bti is widely used for larval control. Even more promising are strains of *Wolbachia* that have been adapted to *Ae. aegypti*, which seem to give it the ability to effectively reduce transmission by increasing resistance to dengue infection in *Ae. aegypti* as well as by decreasing the life span of the adult female mosquito (McMeniman and O'Neil, 2010; Hoffmann *et al*., 2011; Walker *et al*., 2011). Finally, the use of genetically modified mosquitoes also appears very promising. The RIDL (release of insects with a dominant lethal) technology uses a strain of *Ae. aegypti* which has been genetically modified to include a repressible lethal trait that sterilises the male mosquito (Alphey *et al*., 2010). The sterile male release method has been used successfully to control screw worm, fruit fly and boll weevil populations in the Americas, and shows great promise for *Ae. aegypti*. This approach, which has negligible or no risk to humans or the environment (Beech *et al*., 2009; Vasan, 2010), is currently undergoing trials in the Cayman Islands, Malaysia and Brazil; the US, Singapore, India and Brunei are also considering trials. Other forms of transgenic mosquito are also under development, but are not as far along. The most promising is the KR-UD (killer rescue-under dominance), two gene systems that confer protection against virus infection, thus preventing transmission of the virus to humans. (Wise de Valdez *et al*., 2011)

There has also been good progress in developing a dengue vaccine in recent years. Currently there are six tetravalent vaccines in the pipeline including three live attenuated candidates, one in phase III efficacy trials, and two in phase I clinical trials, as well as inactivated, subunit and DNA candidate vaccines, all in phase I trials (Gubler, 2011). It is anticipated that one of these vaccines will be licensed as early as 2014. Similarly good progress has been made in developing antiviral drugs and therapeutic antibodies.

CONCLUSION

To reverse the trends of increased incidence and geographic expansion of epidemic dengue, we will need to use all of the tools that are available to us, both old and new. This includes integrated use of chemical, biological and genetic control tools for *Ae. aegypti*, combined with a top-down bottom-up strategy that includes the use of vaccines and drugs as they come online. While the ethical issues of using genetically modified mosquitoes as a part of this integrated strategy are important and should be thoroughly investigated, they should not be allowed to prevent the use of genetic control approaches that have very low or negligible risk to the environment and humans. The same applies to the dengue vaccines and therapeutic antibodies in the pipeline, most of which are also genetically modified.

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