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Innovations in Vector-Borne Diseases

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Abstract

Since the middle of the twentieth century, the world has made great progress fighting diseases transmitted by vectors such as mosquitoes, ticks and sandflies, particularly malaria. However, this progress is threatened by a surge in other vector-borne diseases such as dengue, Zika and chikungunya. Malaysia is particularly badly hit by these three diseases, despite having nearly eliminated malaria. The mosquitoes that transmit Zika and chikungunya are thriving due to increased global trade, rapid population growth and urbanisation.

Until recently there has been no effective treatments or vaccines for these three disease. Malaysia has therefore focused its efforts on vector control in order to prevent disease spread and transmission. Most resources have been dedicated to fogging, which involves spraying insecticide into residential areas to reduce the numbers of mosquitos. Despite its visibility and political attractiveness, there is little credible evidence that fogging is a cost-effective method of reducing dengue incidence. Other insecticide-based methods of vector control are limited by insecticide resistance, which is an increasing problem in Malaysia.

To fight back against the rise of vector-borne diseases in Malaysia, public health authorities will have to look to innovative technologies and solutions. This is likely to be a mixture of new vector control techniques and technologies and vaccines, several of which are now available for use by public health authorities. In December 2015, the first dengue vaccine, Dengvaxia (CYD-TDV) was licensed in Mexico for use in individuals 9–45 years living in endemic areas. CYD-TDV has since been licensed by nine other endemic countries including Singapore, Indonesia, Thailand, the Philippines, Mexico and Brazil. It is currently being studies the Malaysian Ministry of Health prior to a decision being made about including it in the national immunization programme, although clinical trials did take place in Malaysia. Given that vaccines produce economic and social benefits in excess of their initial cost, the government should strongly consider making vaccination a central part of Malaysia's dengue control and eradication strategy.

Introduction

Since the middle of the twentieth century, the world has made great progress fighting diseases transmitted by vectors such as mosquitoes, ticks and sandflies, particularly malaria. However, this progress is threatened by a surge in other vector-borne diseases such as dengue, Zika and cikungunya. Malaysia is particularly badly hit by these three diseases, despite having nearly eliminated malaria.

Given that until recently there have been no effective treatments or vaccines for these three diseases, Malaysia has focused its efforts on vector control in order to prevent disease spread and transmission. However, changes in land-use and human behaviour mean that traditional vector control methods are now unequal to the task of controlling the principle disease vector in Malaysia – the mosquito Aedes Aegyptae.

To fight back against the rise of vector-borne diseases in Malaysia, public health authorities will have to look to innovative technologies and solutions. This is likely to be a mixture of new vector control techniques and technologies and vaccines, several of which are now available for use by public health authorities.

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What are vector-borne diseases?

Vector-borne diseases are infections transmitted by the bite of infected arthropod species such as mosquitoes, ticks, fleas, black flies and sandflies. These species can carry infectious agents such as protozoa, bacteria and viruses, which carry and transmit numerous diseases to humans: malaria, leishmaniasis, dengue fever, yellow fever, West Nile Virus, Zika, Chikungunya and others.

Vector-borne diseases are most commonly found in tropical and sub tropical parts of the world, and in places where there is limited access to safe drinking water and sanitation. They account for more than 17% of all infectious disease, causing more than 1 million deaths annually. Malaria is the most deadly vector-borne disease, causing around 600,000 deaths per year, mostly children under 5. Despite the impact of malaria in terms of mortality, dengue fever is now the world's fastest growing vector-borne disease, with more than 2.5 billion people in over 100 countries at risk – a 30-fold increase in the incidence of the disease over the last 50 years. Other diseases such as Chagas disease, leishmaniasis and schistosomiasis affect hundreds of millions of people worldwide.

Vector-borne diseases are particularly prevalent in rural communities, but are increasingly affecting urban and peri-urban people as disease-carrying mosquitoes adapt to and thrive in these fast growing environments. Those lower down the socio-economic scale are particularly impacted, as a result of inadequate housing and poor living conditions. Malnourished people and those with weakened immunity are especially vulnerable.

[1] Interview, 18 March 2016

Increasing threat of vector-borne diseases

The world has made great progress in controlling vector-borne diseases since the mid-twentieth century through a mixture of poverty-alleviation, physical development and public health interventions. In 1900, 53% of the earth's land surface was at risk from malaria, but by 2002 this had fallen by half to 27% (Hay et al, 2004). As a result of these successes, the proportional contribution of vector-borne diseases to global mortality has fallen in recent years (Lozano et al, 2012). Nevertheless, in 2015, there were an estimated 438 000 malaria deaths worldwide, with 90% occurring in the WHO African Region and 7% in the WHO South-East Asia Region.

"Although malaria is decreasing at a global level, it is stable or increasing in specific geographic locations."

However, this progress seems to have halted. Although malaria is decreasing at a global level, it is stable or increasing in specific geographic locations. Some diseases, such as dengue, Chikungunya, Zika and the West Nile virus, are emerging in countries where they were previously unknown, and increasing in intensity in areas where they are endemic.

The global incidence of dengue, for instance, has grown dramatically around the world in recent decades, with one estimate putting it at around 390 million infections per year. More than 70% of the dengue global disease burden is in South-East Asia, Asia and the Western Pacific areas.

Following its first identification in Uganda in 1947, Zika has now increased its range to include Africa, the Americas, Asia and the Pacific. As of October 2016, 73 countries and territories have reported evidence of mosquito-borne Zika virus transmission since 2007 (67 with reports from 2015 onwards) (WHO, 2016).

There are four main factors driving increases in vector borne-diseases:

01 The rapid expansion of global travel and trade, enabling the geographic spread of pathogens and vectors. International trade in used car tires, for example, has seen the transportation of mosquitoes across borders and increases in dengue infection in previously non-endemic tropical urban environments (Gubler, 1998). Increased air travel, meanwhile, allows transportation of viruses to new cities, regions and continents where there is little or no effective mosquito control (Gubler, 2011).

02 Rapid population growth and urbanisation, which has resulted in more people living in close proximity to growing populations of mosquitoes and other vectors (Gubler, 2011)

03 Societal, cultural, and behavioral practices that encourage disease transmission; for example labouring outside at dawn and dusk, or sleeping in close proximity to livestock; and the proliferation of non-biodegradable consumer products such as cans and wrappers that make ideal vector breeding sites (Gubler, 1998).

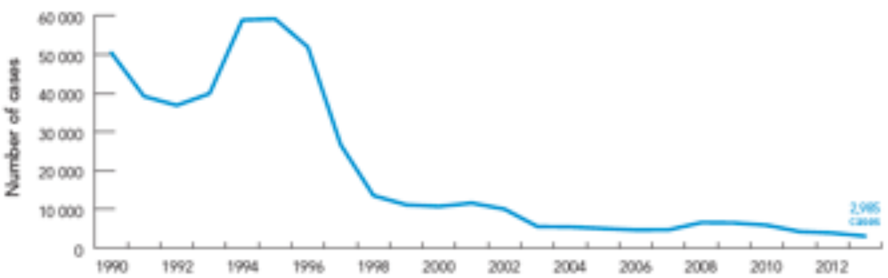
04 Decreased national government support for vector-borne control and surveillance.

Malaysia and vector-borne diseases

Despite the worrying global picture around vector-borne diseases, Malaysia has achieved some significant successes, most notably a 95 per cent reduction in reported malaria cases since 1995. Malaria in Malaysia is categorised in the pre-elimination phase by the World Health Organization (WHO).

This remarkable achievement has been attributed to increased access to improved diagnosis and treatment, nationwide distribution of insecticide-treated bed nets, and regular indoor residual spraying (WHO, 2015). In 2011, the national malaria program strategy was reoriented from control to elimination, and Malaysia is now working to eliminate malaria entirely by 2020.

Reported Malaria Cases*



Increased coverage of insecticide-treated nets and laboratory diagnostics as well as the extensive use of community health volunteers helped reduce Malaysia's malaria burden after a peak in the mid-1990s. Recent case reductions can be attributed to intensified surveillance among mobile populations.

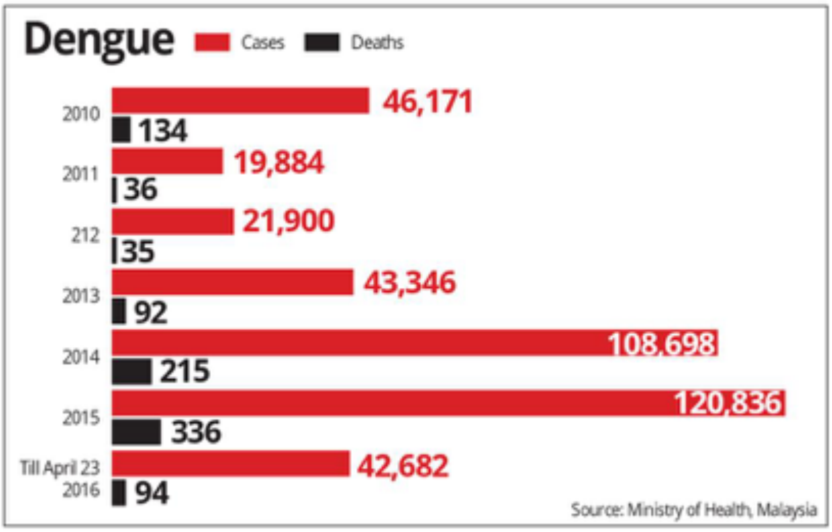
*Graph shows total reported cases from 1990–1999; as of 2000, only local cases are shown.

Source: World Health Organization, World Malaria Report 2014

While Malaysia is a world-leader in malaria control, it has not been so successful with dengue fever. Malaysia has continuously recorded an increased number of dengue cases every year since 1980 (Azami et al, 2011), with the average number of dengue cases surging by 14% per annum between 2000–2010. The country underwent a 250% increase in infections in 2014 alone (Mia et al, 2013) and the disease has been declared a major national health national threat in Malaysia (Er et al, 2010).

Dengue fever represents a significant economic burden with direct medical costs and costs related to productivity loss and premature mortality, amounting to US $102.2 million in 2009 - the equivalent of 0.05% of GDP (Shepard et al, 2010). This figure excludes the substantial costs of dengue prevention which consumed a further 0.3% of GDP in 2010 (Raviwharmman Packierisamy, et al, 2015).

Malaysia also faces challenges from other emerging vector-borne diseases, detecting its first locally infected Zika patient in September 2016, and at the time of writing, has recorded seven cases of infection. Zika has the potential to cause explosive epidemics, and appears to be associated with neurological conditions such as microcephaly in babies. Its principle vectors the mosquitos Aedes aegypti and Aedes Albopictus are abundant in Malaysia, placing the country at significant risk (Vythilingam, 2016).



Current technologies for fighting vector-borne diseases

Until very recently, there have been few treatments or preventative vaccines for vector-borne diseases, so the majority of global and national efforts to tackle vector-borne diseases have focused around prevention. Public health officials have deployed a number of technologies and methods to reduce vector numbers and to prevent vectors from making contact with humans. The following is a brief summary of these techniques and technologies, including an assessment of their effectiveness.

Long Lasting Insecticidal Nets and IRS

Insecticide treated bed nets (ITNs) are integral to many malaria control campaigns and their use is recommended by the World Health Organization. They are generally supplied without charge or subsidised, and their use is often promoted through mass campaigns (Willey et al, 2012). When used properly and distributed in sufficient numbers, they can be effective in preventing the transmission of vector-borne diseases. For example, ITNs have been pivotal in allowing Malaysia to approach malaria eradication (WHO, 2010). However, in many parts of the world coverage is too low due to a number of factors, including cost, logistics and training and supervision.

Indoor Residual Spraying (IRS)

IRS involves coating the interior walls of a dwelling with insecticide. It helps prevent transmission of disease by killing or repelling mosquitos as they come to rest on walls after a blood meal.

IRS with DDT was the primary malaria control method used during the Global Malaria Eradication Campaign (1955-1969). The campaign did not eradicate malaria but eliminated malaria in some areas and reduced it significantly in others. Since 2007, WHO has recommended IRS in conjunction with ITN use in highly endemic malaria areas.

To be effective at preventing disease transmission, IRS must be applied over 80% of households in an area. Cost is also an issue. The crude design of the majority of sprayers in operation mean that IRS' effectiveness is largely dependent on the diligence and skill of the individual operator (Knapp, Macdonald, Malone, Hamon, & Richardson, 2015) . Given that insecticide degrades over time, IRS must be viewed as an on-going commitment requiring long-term predictable financing. Such resources are not always available, especially in low and middle-income countries.

Outdoor spraying

Aerial spraying has been used during epidemics of dengue and yellow fever to control mosquito populations. This technique was also recently deployed in the United States to kill mosquitoes carrying the Zika virus. If used early enough, it can be used to control the outbreak before other mosquito control measures are introduced. The US Centers for Disease Control caution that aerial spraying must be used as part of a comprehensive vector control campaign that includes other methods such as larval breeding control, fogging and other forms of environmental management.

The practice of indiscriminate or wide-scale outdoor spraying is of questionable effectiveness since many mosquitoes may be inaccessible and would be unaffected (particularly those indoors) (Castle et al, 1999; Pereich et al, 2000). Additionally, there is often a long time lag between the reporting of infections and the commencement of spraying. This undermines the effectiveness of outdoor spraying, as epidemic transmission will have already occurred before the spraying can take place. This problem is particularly pronounced in rural and resource-constrained areas (Chang et al, 2011).

Fogging

Fogging or space spraying is widely used in the control of Chikungunya and dengue. It disperses insecticide into tiny droplets, which then kill flying insects and other vectors. The objective of fogging is to reduce the numbers of flying insects and pests, and interrupt transmission of disease. Although space spraying is the standard public health response to a dengue outbreak worldwide, and is recommended by WHO for this purpose (WHO, 2009) meta-analyses of national case studies have failed to identify convincing evidence that it is effective (Bowman et al, 2016; Perich et al, 2000). The main shortcoming with this method is that it can only prevent dengue transmission if it manages to immediately reduce the mosquito population below a certain threshold, most likely by 97% (Giglioli, 1979).

While space sprays can initially reduce adult mosquito populations rapidly, they require regular re-application to maintain control (Reiter & Gubler, 1997). Fogging, when undertaken by public health authorities, is also likely to leave infective mosquitoes already indoors unharmed. Poor maintenance and cleaning of fogging machines can also limit their effectiveness (Castle et al, 2000). Insufficient coverage of spraying and incorrect dosage of chemical insecticides coupled with poor public acceptance and compliance also undermine the effectiveness of space spraying (Chang et al, 2011). Space spraying is politically attractive as it is highly visible and gives reassuring signals to the population that the public health authorities are responding effectively to an outbreak (WHO SEARO, 1999), although it can give residents a false sense of security and discourage them from participating in community-based vector control methods, such as covering drains and water containers (Espinoza-Gomez et al, 2002).

Biological control

Vectors can also be controlled by introducing organisms that prey upon, parasitise or compete with them. Typically larvivourous fish and certain freshwater crustaceans are deployed to control the larvae of mosquitoes. Guppy fish are often introduced to freshwater wells, irrigation ditches and industrial tanks, where they have proven to be effective predators. Toxins from the bacterium Bacillus thuringiensis var. israelensis (Bti) can be applied to larvae breeding sites, which exclusively kill only mosquitoes, black flies, and midges. This latter method is integral to Malaysian dengue control efforts (MOH, 2011).

However, near complete eradication of larvae is necessary for effective disease control, so these methods must be used as part of an integrated strategy. It is also difficult to reach all the breeding sources consistently (Bowman, 2016).

Fogging

In many Asian countries, households often store water in outside containers, which are very difficult to protect from infestation by mosquitoes. In Malaysia breeding sites are often discarded and neglected containers rather than domestic water storage containers. Other potential breeding sites are containers found in parks, empty land, industry buildings, construction sites, and blocked cement drains and septic tanks. Removing and minimising these breeding sites, for example by covering drains, can reduce vector contact with humans. However, this kind of environmental management needs full participation of local communities, which requires sustained intervention by public health authorities.

Chemical treatment of breeding sites

Some species of mosquitos cannot be controlled by environmental management, so the use of chemical insecticides may be used to kill or retard the growth of larvae and prevent them growing into adult insects. Other less environmentally invasive methods can be used to treat larvae breeding sites, such as oils that break the surface tension of the water, thereby suffocating the larvae.

Chemical treatment of breeding sites can carry the risk of development of insecticide resistance and community dependence on expensive, centrally planned interventions. The cost of achieving sufficient coverage to effectively control mosquito populations using larval control methods is also a major challenge (Tusting et al, 2013).

Vector control – other considerations

Given the shortcomings and complexities of the above vector-control methods and technologies, the WHO recommends the simultaneous use of multiple methods – so-called integrated vector management (WHO, 2012). Vector control can be effective, but implementation must be done thoroughly, comprehensively, and be sustained. This requires constant intervention by government and the commitment of substantial funds over the long-term.

Insecticide treated bed nets (ITNs) are integral to many malaria An additional problem is that the effectiveness of the main methods of vector control is threatened by the rise of resistance by vectors to the various insecticides. Resistance is known to affect all major malaria vector species and all four recommended classes of insecticides. According to WHO, insecticide resistance is now such a problem, it threatens to undermine the significant progress in malaria vector control made since the early 2000s. Since 2010, a total of 60 countries have reported resistance to at least one class of the four classes of insecticide used in vector control , with a total of 49 of those countries reporting resistance to two or more classes.

Insecticide resistance is also a major problem for dengue control. Several studies have demonstrated successive increases in resistance to pyrethroid insecticides over time in dengue vectors, often following repeated applications of this for dengue control (di Cunha et al, 2005; Mecuria et al, 1991). This is significant because pyrethroids are the most effective and least expensive of the four classes of insecticide available for vector control. Insecticide resistance in dengue vectors has also been observed in Malaysia to the four major classes of insecticide, with the problem most severe in Kuala Lumpur (Ishak et al, 2015). This study found a moderate resistance to temephos in Penang, Kuala Lumpur, Johor Bharu and Kota Bharu, but widespread and multiple resistances in Aedes aegypti against pyrethroids, DDT and bendiocarb. Mosquitoes from Kuala Lumpur consistently had the highest resistance levels and was the only population showing a moderate resistance to malathion (91% mortality).

Another critical shortcoming in global vector control is a shortage of expertise. The worst affected countries have serious shortages of trained entomologists that can perform vector surveillance and design and implement control programmes. In some African countries there are only a handful of people with the requisite expertise.

Innovations in fighting vector-borne diseases

All these factors mean that the significant advances made in vector control around the world are now at risk. The shortcomings of current vector control methods technology are also becoming increasingly apparent with the increase geographical reach and incidence of dengue fever, Chikungunya and Zika (Gubler, 2012). Vector control technology has remained essentially static for several decades and is in need of significant innovation if it is to meet current challenges (Knapp et al, 2015).

New technologies are particularly required to control the Aedes aegypti species of mosquito, the primary vector of zika, Chikungunya and dengue. Unlike the mosquitoes that transmit malaria, this mosquito thrives in urban environments that lack sanitation, feeds in the daytime, does not fly long distances and breeds in a wide variety of water containers (Honorio et al, 2009). Innovative control methods and technologies must take account of this behaviour, be cheap, easy to use and overcome emerging problems with insecticide resistance. Fortunately, there are several promising technologies under development that may meet these criteria:

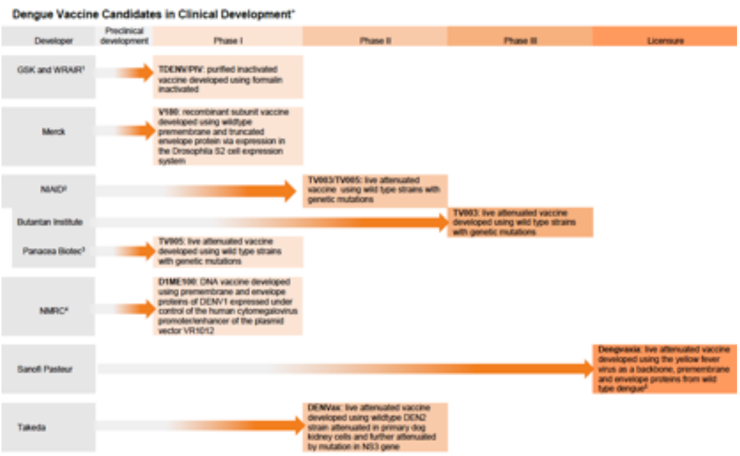
- Innovative insect repellents, which will improve the effectiveness of indoor residual spraying
- Infecting mosquitoes with Wolbachia and releasing them into the wild. This bacteria blocks dengue virus replication.
- Decreasing the Aedes Aegypti population through genetic modification (GM), specifically by causing the mosquitoes to transmit a defective gene to their offspring, rendering them infertile. Field trials of this technology took place in Malaysia in 2010 and 2011, managed by the Institute of Medical Research and British-based biotech company Oxitec Ltd. Around 6,000 male GM Aedes aegypti mosquitoes were released at an uninhabited forested area near Bentong, Pahang. However, in 2015 the Ministry of Health halted proceedings as the initial study showed the technology to be cost ineffective.
- Attractant-Bait Lethal Ovitraps (ALOT) which are lethal traps designed to collect Aedes aegypti eggs and kill female mosquitoes visiting the traps
- Pyriproxifen traps which contain a larvicide that the mosquito then transfers to its egg-laying site.
- Attractive toxic sugar baits (ATSB) which kills sugar feeding male mosquitos, thereby reducing breeding opportunities for females.
- The use of aerial drones not only for vector surveillance but also to deliver insecticide.

Vaccines

While such innovations will improve future vector control and potentially mitigate the spread and impact of vector-borne diseases, there is a growing consensus that eliminating diseases can only be achieved by integrating vector control with vaccines (Achee et al, 2015). By conferring immunity upon individuals, vaccines present the prospect of disease eradication by interrupting the transmission cycle and promoting herd immunity.

Although there are dozens of vaccines available for infectious diseases, there are only a handful for vector-borne diseases, including those for Japanese encephalitis, tick-borne encephalitis and yellow fever. However, significant efforts and resources have been put into vaccines for malaria and dengue over the last thirty years, which finally appear to be coming to fruition:

- The first malaria vaccine, Mosquirix (RTS,S/AS01) completed phase III clinical trials in 2015, with WHO recommending in 2016 that large-scale pilot implementations be undertaken before adoption in national immunisation strategies. In 2015, there were 31 other malaria vaccine candidates, although the vast majority are in early stage phase I clinical trials. Only three are in Phase 2 clinical trials (Birkett, 2015).
- Progress is more rapid for dengue. In December 2015, the first dengue vaccine, Dengvaxia (CYD-TDV) was licensed in Mexico for use in individuals 9–45 years living in endemic areas. CYD-TDV has since been licensed by nine other endemic countries including Singapore, Indonesia, Thailand, the Philippines, Mexico and Brazil. It is currently being studies the Malaysian Ministry of Health prior to a decision being made about including it in the national immunisation programme, although clinical trials did take place in Malaysia (Hadinegero et al, 2015). Another promising lead is the TV003 candidate, currently in Phase 3 clinical trials which has so far proved highly effective in preventing dengue fever (Vannice et al, 2015). The current status of dengue vaccine pipeline is shown in figure x.
- For Chikungunya, there are currently more than 15 vaccine candidates currently in preclinical and clinical development (Ahola et al, 2015)
- 14 vaccine candidates are currently under investigation for Zika (WHO, 2016).



Discussion

Vector-borne diseases continue to be one of the greatest causes of disease in tropical settings around the world. While Malaysia has made enormous strides against malaria, the rapid growth in dengue incidence and the arrival of Zika demonstrates that current vector control approaches are failing, and new thinking is needed in the fight against mosquitoes and the diseases they carry.

Traditional vector-control methods have proven to be effective in the Malaysian fight against malaria. However, the unique behaviour of the principal vector of dengue, zika and Chikungunya - the aedes aegypti mosquito - has defied traditional methods, especially when combined with Malaysia's increasing urbanisation and changes in climatic patterns – both of which favour the mosquito. Malaysia also appears to be suffering a worsening problem with insecticide resistance, which may render many of the traditional aede aegypti control methods obsolete in the near future. Given the resource-intensity and shortcomings of current technologies and techniques, relatively wealthy countries such as Malaysia should prioritise the adoption of technological innovations in the fight against vector-borne disease. Some new methods of vector control hold real promise in mitigating outbreaks, although other ideas such as GM mosquitoes look likely to have less potential. Both new and old vector control technologies, however, are resource intensive, requiring sustained intervention by public health authorities.

Given this backdrop, it is fortunate that new, innovative vaccines against vector-borne diseases are now available, with more potentially coming on-stream in the coming years. Vaccines can be used in combination with vector-control techniques to move beyond disease control towards elimination, with its myriad social and economic benefits. Malaysia has been a regional leader on vaccination with immunisation against a wide range of infectious diseases (including the HPV vaccine against cervical cancer) provided free of charge within the public health system since the 1950s. This is a major factor behind the country's high performance in child heath.

Vaccines have long been recognised as one of the most cost-effective public health interventions available. While early economic research narrowly focused on the savings to governments of averted medical costs that arise from vaccination, it is now well understood that spending on childhood immunisation programmes also promotes national economic growth and poverty reduction (Bloom & Canning, 2000). Successful vaccination programmes drive economic and social development by making workforces more productive, which in turn drives economic growth, increases the tax base and reduces public spending on disease management. These mechanisms through which vaccination can drive economic and social development are briefly enumerated in Table 2 (adapted from Bärnighausen et al, 2011).

Benefit	Description of benefit	Macroeconomic and fiscal impact
Health gains	Reduction in mortality	Increased labour supply and tax base
Health-care cost savings	Savings in medical expenditures as disease incidence is reduced	Reduce public expenditure on health for vaccine treatable conditions
Care-related productivity gains	Parents need not care for sick children, saving productive work time	Increased labour supply and tax base
Outcome-related productivity gains	Increased productivity because vaccination improves cognition, physical strength and school attainment	Increased productivity, and consequently wage growth
Behaviour-related productivity gains	Changes to household behaviour due to improved child health and survival	Changes in fertility, improved education and workforce participation
Community externalities	Unvaccinated people benefit from individuals being vaccinated; less antimicrobial resistance	All of the above

Given that vaccines are generally given in one or two doses and produce economic and social benefits in excess of their initial cost, they should be a central part of Malaysia's vector-borne disease control and eradication strategy. In the meantime, the government should investigate innovations in vector control technologies are part of its integrated approach to disease control.

Malaysia has been a past regional leader in public health, with considerable successes against malaria and vaccine-preventable diseases. As new technologies come on-stream to tackle vector borne diseases, Malaysia should capitalise on these past successes by adopting innovations as quickly as possible – this is the only viable path towards the elimination of vector-borne diseases in the country.

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