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The interplay of vaccination and vector control on small dengue networks

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HIGHLIGHTS

- Genetic variants of SIT provide alternative control solutions for dengue spread.
- Vaccination and vector control can be combined to control dengue on small networks.
- Reduced vector control or imperfectly efficacious vaccines will impact dengue spread.
- Control method failings can be mitigated by using alternative control strategy.

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ABSTRACT

Dengue fever is a major public health issue affecting billions of people in over 100 countries across the globe. This challenge is growing as the invasive mosquito vectors, *Aedes aegypti* and *Aedes albopictus*, expand their distributions and increase their population sizes. Hence there is an increasing need to devise effective control methods that can contain dengue outbreaks. Here we construct an epidemiological model for virus transmission between vectors and hosts on a network of host populations distributed among city and town patches, and investigate disease control through vaccination and vector control using variants of the sterile insect technique (SIT). Analysis of the basic reproductive number and simulations indicate that host movement across this small network influences the severity of epidemics. Both vaccination and vector control strategies are investigated as methods of disease containment and our results indicate that these controls can be made more effective with mixed strategy solutions. We predict that reduced lethality through poor SIT methods or imperfectly efficacious vaccines will impact efforts to control disease spread. In particular, weakly efficacious vaccination strategies against multiple virus serotype diversity may be counter productive to disease control efforts. Even so, failings of one method may be mitigated by supplementing it with an alternative control strategy. Generally, our network approach encourages decision making to consider connected populations, to emphasise that successful control methods must effectively suppress dengue epidemics at this landscape scale.

1. Introduction

Dengue fever is a significant disease that is estimated to affect two and a half billion people (Whitehorn and Farrar, 2010). Weak control programmes, large scale movement of asymptomatic carriers and expanding populations of *Aedes aegypti* present a mounting challenge that is spreading across the tropics (WHO, 2015). This public health issue has rapidly escalated; before 1970 only nine countries recorded severe dengue cases, now more than 125 countries are classified as dengue endemic, with almost 400 million infections globally every year (Murray et al., 2013).

Once human hosts are bitten by a dengue-carrying vector, viral infection can lead to fever symptoms which persist for approximately one week. Following this an immune response is mounted to clear the infection, at which point hosts enter a period of cross-immunity to all serotypes (Gibbons and Vaughn, 2002). It is worth noting that an issue with dengue control is that three-quarters of annual dengue infections are asymptomatic, but hosts continue to infect mosquitoes whilst going about their daily routines (Duong et al., 2015). A more severe version of the disease manifests as dengue haemorrhagic fever. This particular quirk of dengue virus infections is the result of an immunological phenomenon called antibody dependent enhancement (Gubler, 1998). This occurs

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when antibodies that have been produced in response to one serotype actually facilitate rapid cell entry for a different serotype of the virus, leading to faster host body invasion and more severe secondary infections.

The dengue virus is a member of the flavivirus family, with other notable members causing West Nile disease, Zika, yellow fever and chikungunya (Amaku et al., 2011). Multiple serotypes of dengue virus exist, with the latest classified, DENV-5, having only recently been discovered (Normile, 2013). Due to antibody-dependent enhancement, virulence of one dengue serotype is enhanced where it co-occurs with another serotype and can successfully invade the same host. This can make predicting the epidemiological outcome of local serotype diversity challenging (Feng and Velasco-Hernández, 1997).

Dengue virus is spread between humans through infected female mosquito bites. The principal vector of dengue, the invasive species *A. aegypti*, is distributed throughout tropical regions (Capinha et al., 2014). This vector is successful in colonising high density human populations, and often adult mosquitoes do not disperse very far, with evidence that some inhabit single households throughout their lives (Stoddard et al., 2013). Although there is some evidence that insecticide treated bed-nets (Lenhart et al., 2008) and curtains (Quintero et al., 2015) may have some protective qualities, as a diurnal vector, the female mosquitoes primarily bite humans and transmit the virus during daylight hours (Canyon et al., 1999). This presents a challenge to dengue management as hosts will be bitten during the day as they move around a landscape thus facilitating rapid movement of the virus.

A. aegypti saw a large resurgence at the end of the 20th century and populations continue to grow and increase the global burden of dengue fever following ineffectual control programmes (Gubler, 2002) and rapid urbanisation. The expansion of human settlements simultaneously generates still water breeding sites for *A. aegypti*, provides housing which shelters adult insects and clusters blood meal food sources into a densely populated locale (Gubler, 2011). These conditions are ideal for this urban mosquito to thrive and facilitate dengue outbreaks. This reoccurrence may also have a climate change dimension. As annual temperatures increase in temperate ecosystems, it is likely that *A. aegypti* will follow a shifting climate envelope and further increase the number of humans at risk of this disease (Hales et al., 2002).

A second mosquito, *Aedes albopictus*, is becoming an ever more prevalent vector and is currently the most invasive mosquito (Benedict et al., 2007), capable of spreading multiple diseases as it expands in its global distribution (Medlock et al., 2012). More alarmingly, this vector is also resilient to cooler climates which is facilitating rapid colonisation of temperate regions and subsequent disease transmission of diseases typically confined to the tropics (Rezza, 2012). For example, the 2007 outbreak of chikungunya in Italy, where a strain originating in India was able to spread through the region by invasive *A. albopictus* mosquito bites (Rezza et al., 2007).

Historically, vector control has been the primary approach used to suppress dengue outbreaks. Simply put, reducing mosquito densities can reduce the transmission of the disease as insect densities fall below an entomological threshold limiting the spread of the disease. With increasing interest in control measures, vaccine research is also under way to combat dengue. For example, a chimeric, live-attenuated yellow fever-dengue composite vaccine is currently in phase II b trials (Thavara et al., 2014). However currently there is no vaccine that effectively immunises against every dengue serotype. In fact, the WHO (2015) advocates a combined dengue control approach to make optimal use of available resources within Integrated Vector Management programmes. To this end, our broad aim is to explore vector control and vaccination strategies both in isolation and in combination, for the control of dengue.

Sterile insect technique (SIT) is a biological form of vector control in which sterile insects are released into the environment, compete with wild type insects for mates, and lower the population size through failed reproductive events. We explore a variant on this classic approach to SIT and investigate the use of self-limiting genetic constructs (Alphey et al., 2011). Disease vectors, such as *A. aegypti*, are genetically modified to carry a late-acting, dominantly expressed, lethal mutation (Phuc et al., 2007). Offspring of the resulting crosses do hatch from their egg stage, but later die after the larval density-dependent mortality has removed some individuals from the population. Thus the effect of this form of SIT vector control is not masked by natural density-dependent mortality and significant reductions in adult mosquito population sizes are expected to occur. This in turn means that there are fewer biting vectors and so ultimately, fewer humans should contract dengue. Development of this approach could yield a useful tool to complement established integrated vector management strategies employed to tackle dengue outbreaks.

Given that there are multiple serotypes of dengue virus in circulation, it is essential that detailed attention is given to how hosts are spatially distributed amongst these virus and vector populations. For example, in developing nations the rise in urbanisation and the growth of city population densities is set to favour dengue transmission (Bhatt et al., 2013) and intensive single control programmes may then be less viable in these urban environments. So rather than inhabiting one large homogeneous space, host populations are grouped into distinct patches to represent living in cities and towns that are connected by commuter behaviour. This adds additional realism to understanding dengue epidemiology (Kyle and Harris, 2008) and is particularly important as dengue has been observed to spread primarily through host movements (Tizzoni et al., 2014) rather than mosquito dispersal (Reiner et al., 2014).

The inclusion of vector dynamics results in a system with feedbacks from vector–host and host–vector that make for complex transmission dynamics. We begin by describing, in some detail, the mathematical model before deriving expressions for R0 in a simple landscape. We investigate how disease and/or vector control methods may be synergistically employed across networks of host populations, with a coupled mosquito population and epidemiological model playing out over this landscape. Additionally, we explore the case of imperfectly efficacious controls, with the intention of providing more realistic predictions for seasonal outbreak suppression and whether imperfections in one technology may be tolerated through using a combination of approaches.

2. Mathematical model

2.1. Epidemiology

We construct a vector–host model as a set of differential equations, where hosts and mosquito dynamics are characterised by the flow of individuals through compartments over time. Here, we give an overview of the model details.

Dengue is a vector-borne disease with viral transmission place between human hosts and infected vector mosquitoes, X, during biting events, occurring with rate a per mosquito per day, at which point b_1 represents the conversion rate of susceptible individuals, S, into infected hosts, I. Hence the rate of change of infections follows:

$$\frac{dI}{dt} = \frac{Sab_1X}{N}.$$