Controlling mosquito-borne infections: challenges and opportunities

Neil Ferguson

MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, Norfolk Place, London, W2 1PG, UK
e-mail: neil.ferguson@imperial.ac.uk

Preface

Mosquito-borne diseases remain a major cause of morbidity and mortality across the tropics. Despite much progress in control, malaria remains the major such killer, but arboviruses – most notably dengue – are responsible for a rising burden of disease, even in middle-income countries which have all but eliminated malaria. I discuss how new interventions offer the promise of future dramatic reductions in disease burden, but emphasise that intervention programmes need to be underpinned by rigorous trials and quantitative epidemiological analysis. Such analysis suggests that the long-term goal of elimination is more feasible for dengue than malaria, even if malaria elimination would offer greater overall public health benefit.

Deaths from malaria have almost halved since 2000[1-3], despite rapidly growing populations in many endemic regions. Improvements in vector control and (to a lesser extent) treatment are the principal drivers behind this decline[4,5], but development – leading to improved housing and increased urbanisation across the tropics – has also been a significant contributory factor[6]. The declines have been particularly marked outside sub-Saharan Africa, with only 10% of malaria deaths now occurring outside this region[7]. Over the same period, the burden of disease from dengue has risen dramatically, often in the countries seeing the largest reductions in malaria disease[8,9] (Figure 1). Part of the increase in burden reflects population growth and urbanisation in the tropics, but greater connectivity of human populations[10] (leading to all four dengue serotypes now regularly being detected in all endemic countries[11]), entomology (*Aedes aegypti*, the principal dengue vector, being more highly adapted to urban environments[12]) and climate change (increasing the geographic limits of endemic transmission[13]) have also played a role.

Global malaria deaths remain over 30-fold larger than those from dengue (Figure 1), with this ratio being somewhat less extreme if one solely considers disease burden outside Africa. Furthermore, given the availability of highly effective artemisinin-based malaria treatment, a large proportion of remaining malaria mortality reflects gaps in access to treatment or suboptimal diagnosis[4,5]. Conversely, dengue affects urban populations with better (though often not perfect) access to healthcare. No effective dengue antiviral drugs or monoclonals are yet available for dengue treatment, though improvements in case management have led to substantial reductions in case fatality ratios in situations where the current best standard of care is available[14]. The unpredictability and explosive nature of dengue epidemics also imposes substantial stresses on healthcare systems, and can cause much public anxiety, particularly in contexts where the burden of disease from most other infections has been dramatically reduced in recent decades through vaccination and access to treatment.

Emerging arboviral infections have also caused significant public concern in recent years[15]. Chikungunya emerged in Latin America and the Caribbean in 2013[16,17], followed by Zika in 2015[18].

Both caused large-scale epidemics over an approximately 2-year period, before the accumulation of herd-immunity in populations across the region led to dramatic falls in incidence[19-21]. Despite availability of a highly effective vaccine, Yellow Fever has also caused unpredicted relatively large epidemics in Angola and Brazil in the last two years, necessitating rapid large-scale immunisation campaigns[22]. However, the true burden of disease caused by both Chikungunya and Zika is highly uncertain, in large part due to a lack of systematic surveillance across much of the world and, for Zika, the very mildly symptomatic nature of most infections. The health consequences of infection with both viruses remains poorly characterised and it is unclear the extent to which either virus can be considered truly endemic in the human population globally, or, like Yellow Fever, dependent on a sylvatic cycle of transmission. These knowledge gaps[18] make assessing the public health need for effective interventions highly challenging.

The perceived increasing threat (and disease burden) posed by arboviral infections and the recent global emphasis on reducing malarial disease burden has led to increasing investment in the development of new interventions and the intensification of current vector control in many endemic low and middle-income countries (LMICs). The first vaccines for both malaria and dengue offer some promise for disease reduction but their imperfect and complex efficacy profiles mean neither represents a panacea and their uptake has therefore been slow[23-27]. However, the accelerated roll-out of long lived insecticide treated nets (LLINs) across sub-Saharan Africa over the last decade has led to major declines in malaria incidence, with improved treatment further reducing disease burden[4]. This is not to imply these gains can be taken for granted – insecticide resistance[28] and/or failure to sustain intervention coverage pose risks of rapid bounce-back. However, in contrast, the evidence that current vector control measures for dengue are having significant impact is limited at best[29-32]. While differences in the ecology of the principal vectors (e.g. in landing periodicity[33]) for the two classes of infections clearly affect the effectiveness of different interventions, here I will argue that the failure of dengue control to date is principally a consequence of intrinsic differences in the epidemiology of arboviral and malaria infections. These differences necessitate fundamentally different goals for control policy planning for these two classes of infections. I will then review how new vector control technologies currently under development offer the potential to deliver dramatic reductions in disease burden and even elimination in the coming 10-20 years.

Goals of vector control

For all infections, the goals of control are the reduction of disease incidence and, preferably, transmission. Elimination requires reducing transmission to levels which are less than self-sustaining: in the parlance of mathematical epidemiology, reducing the basic reproduction number (the number of secondary infections caused by a typical index infection in a naïve population), R_0, to below 1. Given the lack of high efficacy vaccines for all mosquito-borne infections other than yellow fever and Japanese encephalitis, the main goal of public health interventions for these infections has been reducing human exposure via vector control. The rationale for malaria is clear: in high transmission settings, a child might be infected multiple times in a year, with each new infection posing a risk of disease. Reducing exposure by a certain proportion then leads to an immediate and comparable reduction in the incidence of disease – a reduction that can be further cemented by improving access to effective antimalarial therapy. Clinical immunity somewhat nuances this picture but doesn't fundamentally change the broad conclusion – while later lifetime exposures have a lower risk of disease (severe disease particularly), this risk declines gradually, with both age and exposure playing a role[34].

The same rationale does not hold true for arboviral infections. Unlike malaria (though controversy remains about the extent to which that pathogen can be viewed as a collection of semi-independent antigenically diverse strains [35]), all arboviruses are thought to generate neutralising homotypic

immunity following infection, meaning individuals can experience only one infection with each virus in their lives. Dengue is composed of four distinct (but immunologically cross-reactive) viral serotypes, meaning four infections are possible. However, secondary dengue infections are responsible for the great majority of severe disease[36-38], with tertiary and quaternary infections thought to be largely inapparent[39]. The immunising nature of arboviral infections has profound consequences for vector control. Completely preventing an individual being exposed in one year has no impact on lifetime disease risk if high level exposure resumes the following year – the only effect of such transient interventions is to postpone infection. The same reasoning applies to partially effective controls. Consider a high transmission setting where individuals have a 20% risk of dengue infection each year. On average, children will be 5 years old when they experience their first infection, and about 12 years old when they experience their second. Imagine a vector control intervention which reduces exposure by 50% - thus reducing the infection risk to 10% per year. The net long-term effect of this intervention is solely to increase the age at which individuals experience their first and second infections – to 10 and 23 years, respectively, for this example. This may paradoxically increase overall disease burden, if dengue disease severity increases with age[40].

This argument can be formalised; Figure 2A shows the relationship between disease risk and the effectiveness of vector controls at reducing exposure predicted by previously validated mathematical models of dengue and malaria transmission. The malaria model used has been used extensively to inform control planning, and was validated against historical prevalence and incidence data both in the absence and presence of control measures[41-43]. The dengue model was previously fitted to the Sanofi dengue vaccine trial data and used to explore the potential impact of largescale use of the Sanofi vaccine and Wolbachia [23,44]. For malaria, reductions in disease near linearly increase with coverage. For dengue, the response curve is highly non-linear, with marginal reductions in lifetime disease risk until the level of exposure reduction is sufficient to reduce R_0 close to 1 (~70% effectiveness, for this example). I conclude that for vector controls against dengue (or other arboviruses) to have a major long-term impact, they must come close to stopping sustained transmission – *i.e.* achieving elimination. Figure 2A also highlights that elimination, in theory, should require considerably less effort for dengue than for malaria – in high transmission settings, R_0 for dengue is around 4, while for malaria it is over 100 (with a large degree of local geographic heterogeneity for both infections [4,45,46]). Hence vector control for dengue needs to reduce exposure by 80% to achieve elimination, but for malaria the reduction required is >99%.

However, focussing solely on the long-term effects of interventions neglects transient temporal effects the large-scale introduction of an intervention may have on transmission (simulated in Figure 2B using the models used to generate Figure 2A). Short- and long-term impacts differ less for malaria than dengue due to the more limited impact of host immunity in modulating transmission. The loss of clinical immunity largely explains the rebound in malaria in Figure 2B. But herd-immunity is fundamental to dengue transmission dynamics; in endemic areas, at any point in time much of the population is immune to any one serotype, so when a new epidemic occurs, it only affects the minority of the population (typically children) who have not yet acquired immunity. Over time, a dynamical equilibrium is reached between viral transmission rates and the level of population immunity, leading to the effective reproduction number (the average number of secondary infections caused by a typical index case in the presence of population immunity), R, to hover around one. An exception to this is marginally endemic areas which have not yet been affected by all serotypes, where the initial epidemic following invasion with a novel serotype can be much larger than typical [47]; however, following such an initial epidemic, the resulting immunity also causes R for the invading serotype to fall below one.

In this context, suddenly introducing a new intervention population-wide disrupts this equilibrium, even if the reduction in transmission achieved is insufficient to cause long-term elimination. An

intervention which achieved a sustained 20% reduction in exposure would initially reduce *R* from 1 to 0.8 – leading to a temporary cessation of transmission. New births into the population would then gradually reduce population immunity, increasing *R*, and sustained transmission would resume once *R* once again reached 1. With an annual birth cohort size of, say, 2% of the total population, it would take up to 10 years for *R* to increase from 0.8 back to 1. Stopping dengue epidemics such a time clearly sounds like an impressive outcome, but it is important to note that it would not necessarily lead to a reduction in lifetime disease risk for individuals in the affected population unless more effective interventions could be introduced before the 10-year 'honeymoon' period finished.

Transient impacts on transmission also need to be taken account of when interpreting data from cluster randomized trials of vector control interventions. The effect size observed in trials of transmission-reduction interventions (such as community-mobilisation[48]) over timescales of 1-2 years will implicitly include the large transient effect on incidence described above, and thus short-term measured effectiveness (e.g. reduction in infection rates over 1 year) would be expected to be considerably greater than the underlying long-term effectiveness of the intervention (as quantified by the fractional reduction in R_0 achieved).

Most of the above argument around the goals and likely impact of interventions against dengue also hold for Chikungunya and Zika, albeit the period between epidemics is much longer and more unpredictable than for dengue[18]. There is one exception; protecting vulnerable populations for a short period. Congenital Zika syndrome is principally associated with maternal exposure to Zika in the first trimester of pregnancy[49,50]. Hence an individually-targeted intervention (e.g. spatial repellents) which reduces exposure for a three-month period might achieve a substantial reduction in the burden of disease caused by a Zika epidemic, even if that intervention has a minimal effect on community levels of transmission. However, just as with vector controls targeting community transmission, interventions aiming to reduce personal exposure require rigorous assessment in randomised trials.

The high level of geographic, environmentally driven heterogeneity in the R_0 of mosquito borne infections nuances but does not invalidate these arguments. However, such heterogeneity – and the existence of high transmission 'hotspots' increases the challenges involved in achieving elimination, albeit with the upside that control in lower-transmission areas may be easier than expected from geographically coarse estimates of transmission intensity.

Vector control measures: assessing effectiveness

Why then has there been so little recent success in controlling dengue (especially in LMICs), yet major reductions in disease for malaria? Singapore (not a LMIC) is perhaps the only formerly hyper-endemic country in recent decades to have achieved high levels of dengue control (though Cuba achieved similar success in the 1970s) [51]. However, even Singapore has experienced increases in dengue incidence in recent years associated with declining levels of population immunity[52]. Yet substantial reductions in malaria transmission have been achieved in some of the poorest countries of the world in the last decade[4,5].

Part of the answer lies in differences in vector ecology. *Anopheles gambiae*, the primary vector of Plasmodium falciparum in sub-Saharan Africa, principally bites at night (and therefore inside houses), meaning LLINs[53,54] (and indoor residual spraying[55,56]) are highly effective at reducing human exposure. *Aedes aegypti* bites during the day (with peaks of activity in the morning and afternoon), both inside and outside houses[33]. Furthermore, *Aedes aegypti* mating patterns and breeding site

preferences are better adapted to urban landscapes[57] than most anopheline species (though there is evidence of urban adaptation of the latter[58]).

Yet while the ecology of *Aedes aegypti* limits the effectiveness of 'simple' interventions such as bednets[30], vector control for arboviruses has also suffered from a profound lack of rigorous evidence to support the effectiveness of the individual measures currently used[29-32,51]. In contrast to malaria – where large cluster-randomised trials with human infection endpoints generated the evidence base supporting scale-up of LLIN and IRS use – randomised trials of vector control approaches for dengue are largely absent, or have typically been underpowered and only measured entomological rather than epidemiological (i.e. human disease) endpoints[32]. 'Integrated Vector Management' is the recommended approach to vector control for both malaria and dengue, defined as "a rational decision-making process for the optimal use of resources for vector control"[59]. Ironically, the evidence doesn't currently exist to make rational decisions for dengue vector control, due to the lack of trial data supporting the effectiveness of current control measures at reducing dengue disease.

Much of current vector control activities against dengue across the tropics is therefore more driven by the understandable hope that reducing mosquito numbers can only give public health benefit than a quantitative evidence base which allows investments in vector control to be directed towards intervention policies which will result in a substantial public health impact. Furthermore, any impact that such interventions might have is often lessened by a tendency for vector control to be undertaken largely in response to ongoing dengue epidemics, rather than sustained consistently all year round. For the reasons outlined in the previous section, reactive short-lived interventions at best protect individuals transiently, but leave them susceptible to infection in the next epidemic. Again, Singapore is perhaps the exception – both in terms of the intensity of vector control activities (and resources put into them) and the largely consistent, sustained nature of their implementation[52].

In recent years, these shortcomings have been increasingly recognised, culminating in the World Health Organization's (WHO) Vector Control Advisory Group (VCAG) issuing new guidance indicating data from randomised trials with epidemiological endpoints will be required for WHO to recommend new interventions in future[60]. Furthermore, a number of studies have provided improved guidance on appropriate trial design for dengue vector control trials[32,61], highlighting the need for trials to be of sufficient size to be powered to allow for the high degree of spatiotemporal heterogeneity in vector-borne disease incidence, to utilise clusters of sufficient size and spacing to minimise contamination or boundary effects, to have a sufficiently long period of follow-up and to measure epidemiological outcomes. Meeting these requirements is undoubtedly challenging, necessitating trials to be considerably larger (and consequently more expensive) than comparable trials for malaria – where higher and more stable infection rates mean trials can be smaller-scale.

Indeed, only one dengue vector control intervention study – of the 'Camino Verde' approach to community mobilisation[48] – has approached best practice in trial design. However, even in that case, extrapolation of the study results to predict likely long-term, large-scale effectiveness of the intervention is challenging. The small scale of individual clusters (140 households) means that the measured effectiveness may have been affected by individuals living in intervention areas being exposed to infection outside those areas. This 'contamination' issue would imply the 25-30% reduction in incidence seen in the trial may underestimate the true effect size that would be seen were the intervention implemented at larger scale. Conversely, for the reasons outlined in the previous section, the effect size measured in that trial (and all other short-term trials) over the approximately 1-year period of follow-up would be expected to incorporate a short-term perturbative effect of the intervention on dengue transmission, and thus over-estimate long-term effectiveness.

Assessing the likely long-term impact of interventions from relatively short-term trial data is therefore challenging – both to adjust for contamination and the typically short-term period of follow-up, but also because the transmission intensity (R_0) of all mosquito borne infections show high levels of spatiotemporal variation[4,45,62]. Hence the effect size seen in one context may over-estimate the effectiveness of the same intervention applied in a higher transmission intensity context, or under-estimate impact in a lower transmission intensity setting. Repeating studies in a range of contexts can mitigate this issue, but is costly. Mathematical modelling of each trial incorporating details of the transmission context, period of follow-up and cluster size is therefore required to derive estimates of effectiveness that can be used to predict the likely long-term impact of large-scale use of novel interventions across a variety of transmission contexts. Such analyses are not straightforward (and are not a substitute for long-term follow-up data on effectiveness), but have been undertaken for LLINs and IRS for malaria[41,43], and for both the CYD-TDV (tradename: Dengvaxia) dengue[23,24] and RTS,S (tradename: Mosquirix)[26,63,64] malaria vaccines, and have been planned for the analysis of trials of *Wolbachia* as a dengue control measure[44,61].

Intervention trials for Zika and Chikungunya – whether of vector controls, vaccines or treatment – are even more challenging than for dengue[65], due to the longer inter-epidemic period and the highly unpredictable nature of epidemic timing. The traditional trial design of recruiting cohorts of participants, randomising to intervention or control and monitoring outcomes is therefore likely to be prohibitively expensive – due to the very large numbers of participants and sites needing to be included. While model-based analysis of available surveillance data can improve the efficiency of site selection[66], reactive designs may be more efficient long-term[67]. Such a trial might involve gaining ethical and regulatory approval to proceed in advance from a large number of potential trial sites, but only triggering recruitment of participants and intervention implementation at a site once transmission was detected there. That said, given their shared vectors and similar transmissibility, vector control interventions which show high efficacy against dengue are likely to also show comparable efficacy against Zika and Chikungunya.

The promise of new interventions

While the large-scale roll-out of LLINs (together with targeted use of IRS) across sub-Saharan Africa in the last decade has had a major effect on both malaria transmission and disease, even very high coverage levels of these interventions and effective treatment are predicted to be insufficient to eliminate malaria from the highest transmission settings[41,43]. Insecticide resistance also poses a growing threat [28]. Mass drug administration (MDA) can have a very large short-term impact on malaria prevalence[68] (by reducing the human parasite reservoir), but unless administration at high coverage levels is repeated indefinitely, such impacts are transient, since transmission quickly restarts once infection is reimported from untreated areas[69]. Similarly, seasonal malaria chemoprevention (SMC) can be highly effective at reducing disease incidence[70] but is only appropriate for moderate to high transmission settings with highly seasonal transmission. Furthermore, both MDA and SMC pose the risk of accelerating the development of widescale artemisinin drug resistance in the parasite population.

For dengue, the situation is worse. As described above, there are currently no interventions in large scale use in LMICs which are likely to be having any significant impact on dengue transmission or disease burden [51]. The intensive vector control interventions adopted largely successfully by Singapore (and high-income settings such as Florida and Queensland) are not easily translated to most LMICs and are likely to be unaffordable by those countries.

In addition to further evaluation and scale-up of current interventions, new intervention technologies are therefore needed to make elimination a feasible policy goal for either infection.

Over the last two decades, major investment and effort has been committed to the development of both vaccines and novel vector controls, with varying degrees of success.

Vaccines

The Sanofi-Pasteur CYD-TDV dengue and GSK RTS,S malaria vaccines, the first to be licensed for either infection, are both the result of over twenty years of development effort. Past development efforts have been hindered by the antigenic/immunological complexity of the pathogens and the lack of an obvious commercial market sufficient to justify development costs.

In the phase III trial, over 2 years of follow-up RTS,S showed 28% (95% C.I.: 22%-33%) efficacy against clinical malaria in children who received 3 doses over a 3 month period, and 36% (95% C.I.: 31%-41%) efficacy in children who additionally received a month 18 booster dose[27]. Efficacy was somewhat lower in infants and against severe malaria. Data from phase II and III studies and associated mathematical modelling of these data demonstrated waning of efficacy over time[25,27], which was correlated with decline of anti-circumsporozoite (anti-CSP) antibody titres[64]. This modelling also showed that anti-CSP antibody titres were a correlate of vaccine-induced protection[63,64]. The model of vaccine action proposed by these analyses also explained the observed negative correlation between vaccine efficacy and the transmission intensity seen at trial sites, and the faster decay of efficacy seen in higher transmission settings.

For CYD-TDV, two large phase III studies (in Asia and Latin America) both showed approximately 60% efficacy against virologically confirmed clinical dengue disease in the one year following completion of a 3-dose vaccine schedule[71,72]. Efficacy varied by serotype, increased with age and was higher for severe dengue. In the immunological subset of trial participants where dengue serological status was measured prior to the first dose, vaccine efficacy was approximately 75% in dengue seropositive individuals, but much lower (and non-significant) in dengue seronegatives. However, in the first year of LTFU, a statistically significant excess risk of hospitalised dengue disease was observed in vaccine recipients in the youngest age group (2-5 years). Since no evidence of excess risk was seen in children over 9 in either trial, Sanofi-Pasteur proceeded with submitting the vaccine for regulatory approval with an age indication of use only in children over 9. The most parsimonious and plausible hypothesis explaining these results is that the vaccine acts akin to a silent natural dengue infection[23]. Seronegative recipients of the vaccine are immunologically primed (akin to natural primary infection), so that their first breakthrough natural infection had the higher severity associated with natural secondary infection in unvaccinated individuals. Conversely, seropositive vaccine recipients see antibody titres against all four serotypes boosted to the high levels seen after secondary infection in unvaccinated individuals – leading to the first breakthrough infection having the low severity associated with natural tertiary infection.

Mathematical modelling was key to extrapolating from the trial results to assess the likely public health impact of large scale use of both vaccines, and these analyses played a key role in informing World Health Organization (WHO) recommendations. For RTS,S, modelling predicted that the vaccine could prevent 1 malaria death per 200 vaccine recipients in moderate to high endemicity settings, making it highly cost-effective compared with many other vaccines[26], albeit less cost-effective than LLINs[73]. WHO recognised the significant potential public health benefit offered by the vaccine, but in light of the potential difficulty of delivering a 4-dose vaccine schedule and in light of the meningitis safety signal, recommended large-scale pilot implementation programmes be conducted[74], which are now due to start this year in Ghana, Kenya and Malawi.

For CYD-TDV, modelling indicated that large-scale vaccination might reduce the incidence of symptomatic and hospitalised dengue disease by up to 25% in high transmission intensity settings.

However, vaccination was predicted to potentially increase the incidence of hospitalised dengue in low-transmission intensity (and hence low seroprevalence) settings[23,24]. WHO recommendations reflected this risk, suggesting that population seroprevalence surveys be undertaken to assess transmission intensity prior to vaccination roll-out, and that the vaccine only be used in settings where over 70% of vaccine recipients were likely to be seropositive[75]. These recommendations have now changed to recommend vaccination only in individuals who test seropositive in light of recent data collected by Sanofi-Pasteur which has conclusively demonstrated that seronegative recipients of all ages experienced a higher risk of hospitalised dengue disease throughout the LTFU of the trials[76].

A number of next-generation dengue and malaria vaccines are currently in development. Two other tetravalent live-attenuated dengue vaccines are currently in phase III trials, with initial results due in the next 12 months. It is unclear whether either will also pose risks of use in seronegative recipients similar to CYD-TDV, but similarities in the immunogenicity profiles of all three vaccines makes this a possibility[77]. A variety of next-generation pre-erythrocytic, blood-stage and transmission-blocking malaria vaccines are in clinical development[78], but none have yet entered phase III studies. For both infections, it is therefore arguably unlikely that vaccines will become available in the next decade which can on their own offer the promise of disease elimination. However, that is not to say that vaccines will not have an impact in that time frame: both current vaccines and next generation late-stage candidates may make a significant contribution to reducing disease burden, combinations of vaccines targeting different parasite life stages may offer synergistic levels of protection for malaria, and some potential exists for the development of 'universal' dengue vaccines [79].

Novel vector control technologies

New insecticides and delivery systems continue to be developed, with perhaps the most interesting and potentially transformative being those which target obligate life-cycle stages such as sugar or blood feeding. While not a new idea, attractive toxic sugar bait technology[80] – which targets sugar-feeding and therefore potentially increases mortality in both male and female mosquitoes – has been advancing rapidly in recent years, with very promising results (at least in anopheline species) seen in recent small-scale trials[81]. Similarly, ivermectin (and newer longer-lived mosquitocidal drug candidates) could cause substantial suppression of mosquito populations and thus malaria transmission if used as part of a mass treatment intervention[82]. However, the approaches to vector control which offer the potential of transformative impacts are those that may give long-term (or even permanent) reductions in disease transmission after only a single implementation period, either by reducing mosquito density or reducing vector competence. Two such technologies are under active development: *Wolbachia* and gene-drive approaches to genetic modification of mosquito species (Figure 3).

Wolbachia is a genus of bacteria which naturally infects many insects[83], strains of which have been deliberately transfected into *Aedes aegypti* mosquitoes. *Wolbachia* typically transmits vertically by achieving high densities in insect eggs. It confers a frequency-dependent fitness advantage relative to uninfected insects via the mechanism of cytoplasmic incompatibility, which results in crosses between *Wolbachia*-infected male insects and wild-type females (which would otherwise result in uninfected progeny) being unviable (Figure 3A). As a biological vector control measure, this offers the advantage that following initial releases of *Wolbachia* infected mosquitoes into a wild-type population, the frequency of *Wolbachia* infection will rise to very high levels as the released mosquitoes interbreed with wild-type insects (Figure 3C). Initially, *Wolbachia* was envisaged as a means to reduce mosquito density, by using a strain – wMelPop – which imposed life-shortening fitness costs on mosquito hosts. However, *Wolbachia*-transfected *Aedes aegypti* were also found to have substantially lower vector competence for a broad range of arboviruses[84], including dengue[85]. It

is this phenotype which is being exploited – via the less pathogenic wMel strain – by the World Mosquito Program[86], the leading development project for *Wolbachia* technology in *Aedes aegypti*. Mathematical modelling of data from experimental dengue infection studies in wMel-infected and wild-type *Aedes aegypti* suggests that successful large-scale release and establishment of wMel-infected mosquitoes could reduce dengue transmission intensity (R_0) by 75%[87] - sufficient to achieve elimination of dengue transmission for decades in even high transmission settings, and permanent elimination in low to moderate transmission settings[44]. Following an extensive programme of small-scale releases, a cluster randomised trial with epidemiological endpoints is now underway in Yogyakarta, Indonesia, with larger non-randomised pilot release studies ongoing in Medellin, Colombia and Rio de Janeiro, Brazil[86]. While at a much earlier stage, Wolbachia may also have some potential as a malaria control measure [88].

Gene-drive systems for genetically modified mosquitoes[89,90] offer similar advantages to *Wolbachia* in potentially allowing finite releases of modified mosquitoes to invade wild-type populations and rise to high frequencies. A variety of gene drive systems have been explored experimentally and theoretically[91,92], but the two most developed technologies are homing endonuclease genes and CRISPR/Cas9. Both rely on homology-dependent repair to be copied from one chromosome to its homologous chromosome during mitosis of germline cells or meiosis[89,90]. In the vector control context, most attention to date has been given to engineering constructs which supress mosquito populations. Biasing the sex ratio toward males is one approach to achieving this. So-called X-shredder constructs achieve this by expressing endonucleases that are only expressed during spermatogenesis and which cleave (and render non-functional) the X-chromosome[93]. Inserting such constructs into the Y-chromosome would generate a highly invasive genetically modified mosquito which in theory could be introduced into a wild-type population once and would eventually drive that population to extinction (Figure 3B,C)[94,95]. In *Aedes aegpti*, targeting male-determining factors using germline Cas9 expression could give similar results[91,96], though research is at an earlier stage compared with Anopheline systems. Development of constructs which reduce vector competence is another area of active research[89], with a variety of potential targets having been identified for both malaria[97,98] and arboviruses[99].

Both *Wolbachia* and gene-drive technologies face several challenges. Gaining public acceptance and regulatory approval requires a rigorous risk assessment/management process and intensive stakeholder engagement. Such barriers are clearly higher for genetically modified organisms than purely biological control measures such as *Wolbachia*. Second, use of these interventions will impose intense selection pressures which are likely to drive the evolution of resistance in either the target pathogen (in the case of *Wolbachia* or vector competence gene drive constructs) or the vector (for population suppression genetic constructs, and perhaps for *Wolbachia*), and the long-term phenotypic stability of *Wolbachia* in *Aedes aegypti* is yet to be determined. While much modelling has been undertaken, knowledge gaps in vector ecology (e.g. regarding the intensity of density-dependent regulation of larval populations, the extent and nature of over-wintering mechanisms) make prediction of the impact of these interventions uncertain, especially for gene-drive systems.

Towards elimination

While current interventions have proved insufficient thus far, the novel vector control technologies described above may make elimination of dengue or malaria and feasible goal, even in the highest transmission settings. However, despite the greater progress in controlling malaria than dengue in recent decades, the scale of the challenge eliminate malaria from the highest transmission hyperendemic settings is larger. The R_0 of dengue likely rarely exceeds 6, meaning reducing transmission by approximately 85% should be sufficient for permanent elimination in nearly all settings. Plus, for the reasons outlined above, even interventions achieving a (sustained) 30%

reduction in R_0 should cause dramatic reductions in dengue incidence for decades if applied at sufficient scale – buying time for more effective interventions to be developed. Conversely, R_0 for Plasmodium falciparum is in the hundreds in the highest transmission settings, requiring a >99% reduction in transmission intensity to achieve elimination. In addition, there are multiple Plasmodium species capable of causing human disease, and multiple competent vector species even outside the *Anopheles gambiae* complex. Nevertheless, even if malaria elimination (and eventual eradication) remains a more distant goal, the vector tools currently under development offer the promise of delivering order-of-magnitude reductions in transmission and disease.

While elimination may be the long-term goal of control programmes, disease reduction must remain the priority in the short- to medium-term. In this context, a wider range of current and near-to-market interventions are relevant – both vector control measures and vaccines. One of the greatest challenges will be making optimal use of limited resources (especially in low-income settings) to deliver the greatest public health impact. Rigorous epidemiological analysis and mathematical modelling will be key to ensuring such optimal deployment – in extrapolating from clinical trial data to predict population impact of each intervention in a wider range of settings and in combination with other control measures. Rigorous monitoring and evaluation is also essential to evaluate the real-world effectiveness of interventions. The epidemiology, vector ecology and transmission intensity of both arboviruses and malaria is highly geographically variable, requiring intervention policies to be tailored to the local environment. Modelling has been pivotal in facilitating the characterisation of this heterogeneity[4,45].

There is unlikely to be a single 'silver bullet' intervention sufficient to control either class of infections, so policy formulation will require setting-specific selection of interventions from the overall portfolio of available tools which have good evidence supporting their effectiveness. Such optimisation should account for the potential synergistic benefits of combining interventions with different mechanisms of action (e.g. vector control and vaccines). Intervention effectiveness is only one of the criteria relevant to making that selection – cost, ease of delivery and public acceptability (and thus achievable coverage) are equally important. Such optimisation is now possible via integrated disease transmission and health economic models[43,73], though reliable surveillance and intervention effectiveness data is essential to calibrate such models. Last, data analytics (spanning dynamical modelling, statistical analysis and machine learning) will become increasingly critical to cope with the ever-growing volumes of surveillance, genomic, remote sensing and other (e.g. mobile phone[100]) data becoming available – to synthesise multiple data streams and derive actionable insights to inform public health policy-making.

Acknowledgements

I thank the Medical Research Council, the National Institute of Health Research Health Protection Research Unit programme, the National Institute of General Medical Sciences 'MIDAS' programme and the Bill and Melinda Gates Foundation for research funding. Among many others, Azra Ghani, Austin Burt and Scott O'Neill have informed my understanding of this topic during many illuminating discussions.

Bibliography

1 Gething, P. W. *et al.* Mapping Plasmodium falciparum Mortality in Africa between 1990 and 2015. *New Engl J Med* **375**, 2435-2445, (2016).

2 Murray, C. J. L. *et al.* Global malaria mortality between 1980 and 2010: a systematic analysis. *Lancet* **379**, 413-431, (2012).

3 World Health Organization. *Estimated malaria deaths by region*, <http://www.who.int/gho/malaria/epidemic/deaths/en/> (2016).

4 Bhatt, S. *et al.* The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. *Nature* **526**, 207-+, (2015).

This study estimates the impact of different malaria interventions and treatment on infection prevalence and disease incidence.

5 Cibulskis, R. E. *et al.* Malaria: Global progress 2000-2015 and future challenges. *Infect Dis Poverty* **5**, (2016).

6 Tatem, A. J., Gething, P. W., Smith, D. L. & Hay, S. I. Urbanization and the global malaria recession. *Malaria Journal* **12**, 133, (2013).

7 World Health Organization. (2017).

8 Naghavi, M. *et al.* Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* **390**, 1151-1210, (2017).

9 Stanaway, J. D. *et al.* The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *The Lancet Infectious Diseases* **16**, 712-723, (2016).

10 Tian, H. *et al.* Increasing airline travel may facilitate co-circulation of multiple dengue virus serotypes in Asia. *PLOS Neglected Tropical Diseases* **11**, e0005694, (2017).

11 Messina, J. P. *et al.* Global spread of dengue virus types: mapping the 70 year history. *Trends in Microbiology* **22**, 138-146, (2014).

12 Jansen, C. C. & Beebe, N. W. The dengue vector Aedes aegypti: what comes next. *Microbes and Infection* **12**, 272-279, (2010).

13 Campbell, L. P. *et al.* Climate change influences on global distributions of dengue and chikungunya virus vectors. *Philosophical Transactions of the Royal Society B: Biological Sciences* **370**, (2015).

14 Kalayanarooj, S., Rothman, A. L. & Srikiatkhachorn, A. Case Management of Dengue: Lessons Learned. *The Journal of Infectious Diseases* **215**, S79-S88, (2017).

15 Weaver, S. C., Charlier, C., Vasilakis, N. & Lecuit, M. Zika, Chikungunya, and Other Emerging Vector-Borne Viral Diseases. *Annual Review of Medicine* **69**, 395-408, (2018).

16 Leparc-Goffart, I., Nougairede, A., Cassadou, S., Prat, C. & de Lamballerie, X. Chikungunya in the Americas. *The Lancet* **383**, 514, (2014).

17 Pialoux, G., Gaüzère, B.-A., Jauréguiberry, S. & Strobel, M. Chikungunya, an epidemic arbovirosis. *The Lancet Infectious Diseases* **7**, 319-327, (2007).

18 Lessler, J. *et al.* Assessing the global threat from Zika virus. *Science*, (2016).

A comprehensive review of the epidemiology of Zika, the public health threat posed and current uncertainties.

19 Cohen, J. Where has all the Zika gone? *Science* **357**, 631-632, (2017).

20 Ferguson, N. M. *et al.* Countering Zika in Latin America. *Science*, (2016).

21 Netto, E. M. *et al.* High Zika Virus Seroprevalence in Salvador, Northeastern Brazil Limits the Potential for Further Outbreaks. *Mbio* **8**, (2017).

22 Shearer, F. M. *et al.* Existing and potential infection risk zones of yellow fever worldwide: a modelling analysis. *The Lancet Global Health* **6**, e270-e278, (2018).

23 Ferguson, N. M. *et al.* Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment. *Science* **353**, 1033-1036, (2016).

24 Flasche, S. *et al.* The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. *PLOS Medicine* **13**, e1002181, (2016).

This study presents the model comparison exercise that informed initial WHO recommendations on use of the Sanofi dengue vaccine.

25 Olotu, A. *et al.* Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. *New Engl J Med* **374**, 2519-2529, (2016).

26 Penny, M. A. *et al.* Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet (London, England)* **387**, 367-375, (2016).

This study presents the model comparison exercise that informed WHO recommendations on use of the RTS, S malaria vaccine.

27 RTS S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *The Lancet* **386**, 31-45, (2015).

28 Hemingway, J. *et al.* Averting a malaria disaster: will insecticide resistance derail malaria control? *The Lancet* **387**, 1785-1788, (2016).

29 Achee, N. L. *et al.* A Critical Assessment of Vector Control for Dengue Prevention. *PLOS Neglected Tropical Diseases* **9**, e0003655, (2015).

30 Bowman, L. R., Donegan, S. & McCall, P. J. Is Dengue Vector Control Deficient in Effectiveness or Evidence?: Systematic Review and Meta-analysis. *Plos Neglected Tropical Diseases* **10**, (2016).

31 Heintze, C., Garrido, M. V. & Kroeger, A. What do community-based dengue control programmes achieve? A systematic review of published evaluations. *T Roy Soc Trop Med H* **101**, 317-325, (2007).

32 Wilson, A. L. *et al.* Evidence-based vector control? Improving the quality of vector control trials. *Trends in Parasitology* **31**, 380-390, (2015).

This paper outlines good practice for the design of field trials of vector control interventions.

33 Barrozo, R. B., Schilman, P. E., Minoli, S. A. & Lazzari, C. R. Daily Rhythms in Disease-Vector Insects. *Biological Rhythm Research* **35**, 79-92, (2004).

34 Griffin, J. T. *et al.* Gradual acquisition of immunity to severe malaria with increasing exposure. *Proc Biol Sci* **282**, 20142657, (2015).

35 Gupta, S., Trenholme, K., Anderson, R. & Day, K. Antigenic diversity and the transmission dynamics of Plasmodium falciparum. *Science* **263**, 961-963, (1994).

36 Clapham, H. E., Cummings, D. A. T. & Johansson, M. A. Immune status alters the probability of apparent illness due to dengue virus infection: Evidence from a pooled analysis across multiple cohort and cluster studies. *PLOS Neglected Tropical Diseases* **11**, e0005926, (2017).

37 Guzman, M. G., Alvarez, M. & Halstead, S. B. Secondary infection as a risk factor for dengue hemorrhagic fever/dengue shock syndrome: an historical perspective and role of antibody-dependent enhancement of infection. *Archives of Virology* **158**, 1445-1459, (2013).

38 Katzelnick, L. C. *et al.* Antibody-dependent enhancement of severe dengue disease in humans. *Science*, (2017).

39 Gibbons, R. V. *et al.* Analysis of Repeat Hospital Admissions for Dengue to Estimate the Frequency of Third or Fourth Dengue Infections Resulting in Admissions and Dengue Hemorrhagic Fever, and Serotype Sequences. *The American Journal of Tropical Medicine and Hygiene* **77**, 910-913, (2007).

40 Thai, K. T. D. *et al.* Age-Specificity of Clinical Dengue during Primary and Secondary Infections. *PLOS Neglected Tropical Diseases* **5**, e1180, (2011).

41 Griffin, J. T. *et al.* Potential for reduction of burden and local elimination of malaria by reducing Plasmodium falciparum malaria transmission: a mathematical modelling study. *The Lancet Infectious Diseases* **16**, 465-472, (2016).

42 Griffin, J. T. *et al.* Reducing Plasmodium falciparum Malaria Transmission in Africa: A Model-Based Evaluation of Intervention Strategies. *PLOS Medicine* **7**, e1000324, (2010).
43 Walker, P. G. T., Griffin, J. T., Ferguson, N. M. & Ghani, A. C. Estimating the most efficient allocation of interventions to achieve reductions in Plasmodium falciparum malaria burden and transmission in Africa: a modelling study. *The Lancet Global Health* **4**, e474-e484, (2016).
This study uses mathematical modelling to assess optimal allocation of different malaria interventions in different transmission settings across Africa.
44 Dorigatti, I., McCormack, C., Nedjati-Gilani, G. & Ferguson, N. M. Using Wolbachia for Dengue Control: Insights from Modelling. *Trends Parasitol* **34**, 102-113, (2018).
45 Bhatt, S. *et al.* The global distribution and burden of dengue. *Nature* **496**, 504, (2013).
46 Salje, H. *et al.* Dengue diversity across spatial and temporal scales: Local structure and the effect of host population size. *Science* **355**, 1302-1306, (2017).
This study uses genetic and epidemiological data to quantitatively characterise the spatial range and local population drivers of dengue virus transmission.
47 Reiner, R. C. *et al.* Time-varying, serotype-specific force of infection of dengue virus. *Proceedings of the National Academy of Sciences* **111**, E2694-E2702, (2014).
48 Andersson, N. *et al.* Evidence based community mobilization for dengue prevention in Nicaragua and Mexico (Camino Verde, the Green Way): cluster randomized controlled trial. *BMJ : British Medical Journal* **351**, (2015).
49 Cauchemez, S. *et al.* Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *The Lancet* **387**, 2125-2132, (2016).
50 Johansson, M. A., Mier-y-Teran-Romero, L., Reefhuis, J., Gilboa, S. M. & Hills, S. L. Zika and the Risk of Microcephaly. *New Engl J Med* **375**, 1-4, (2016).
51 Reiner, R. C., Jr. *et al.* Quantifying the Epidemiological Impact of Vector Control on Dengue. *PLOS Neglected Tropical Diseases* **10**, e0004588, (2016).
52 Ooi, E.-E., Goh, K.-T. & Gubler, D. J. Dengue Prevention and 35 Years of Vector Control in Singapore. *Emerging Infectious Diseases* **12**, 887-893, (2006).
53 Fullman, N., Burstein, R., Lim, S. S., Medlin, C. & Gakidou, E. Nets, spray or both? The effectiveness of insecticide-treated nets and indoor residual spraying in reducing malaria morbidity and child mortality in sub-Saharan Africa. *Malaria Journal* **12**, 62, (2013).
54 Lengeler, C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database of Systematic Reviews*, (2004).
55 Pluess, B., Tanser, F. C., Lengeler, C. & Sharp, B. L. Indoor residual spraying for preventing malaria. *Cochrane Database of Systematic Reviews*, (2010).
56 West, P. A. *et al.* Indoor Residual Spraying in Combination with Insecticide-Treated Nets Compared to Insecticide-Treated Nets Alone for Protection against Malaria: A Cluster Randomised Trial in Tanzania. *PLOS Medicine* **11**, e1001630, (2014).
57 Powell, J. R. & Tabachnick, W. J. History of domestication and spread of Aedes aegypti - A Review. *Memórias do Instituto Oswaldo Cruz* **108**, 11-17, (2013).
58 De Silva, P. M. & Marshall, J. M. Factors Contributing to Urban Malaria Transmission in Sub-Saharan Africa: A Systematic Review. *Journal of Tropical Medicine* **2012**, 10, (2012).
59 World Health Organization. *Integrated Vector Management*, <http://www.who.int/neglected_diseases/vector_ecology/ivm_concept/en/> (
60 World Health Organization. How to design vector control efficacy trials. Guidance on phase III vector control field trial design. (2017). <http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/>.
61 Wolbers, M., Kleinschmidt, I., Simmons, C. P. & Donnelly, C. A. Considerations in the Design of Clinical Trials to Test Novel Entomological Approaches to Dengue Control. *PLOS Neglected Tropical Diseases* **6**, e1937, (2012).

62 Snow, R. W., Guerra, C. A., Noor, A. M., Myint, H. Y. & Hay, S. I. The global distribution of clinical episodes of Plasmodium falciparum malaria. *Nature* **434**, 214, (2005).
63 White, M. T. *et al.* A combined analysis of immunogenicity, antibody kinetics and vaccine efficacy from phase 2 trials of the RTS,S malaria vaccine. *BMC Medicine* **12**, 117, (2014).
64 White, M. T. *et al.* Immunogenicity of the RTS,S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. *The Lancet Infectious Diseases* **15**, 1450-1458, (2015).

This study analyses the data from the phase I trials of the RTS,S malaria vaccine to derive a mechanistic model of vaccine action and propose a predictive correlate of protection.

65 Blackman, M. A., Kim, I.-J., Lin, J.-S. & Thomas, S. J. Challenges of Vaccine Development for Zika Virus. *Viral Immunology*, (2017).
66 Asher, J. *et al.* Preliminary results of models to predict areas in the Americas with increased likelihood of Zika virus transmission in 2017. *bioRxiv*, (2017).
67 World Health Organization. Efficacy trials of ZIKV Vaccines: endpoints, trial design, site selection. (2017). <http://www.who.int/blueprint/what/norms-standards/ZIKV_final_report_public_version.pdf>.
68 Eisele, T. P. *et al.* Short-term Impact of Mass Drug Administration With Dihydroartemisinin Plus Piperaquine on Malaria in Southern Province Zambia: A Cluster-Randomized Controlled Trial. *The Journal of Infectious Diseases* **214**, 1831-1839, (2016).
69 Brady, O. J. *et al.* Role of mass drug administration in elimination of Plasmodium falciparum malaria: a consensus modelling study. *The Lancet Global Health* **5**, e680-e687, (2017).
70 Bigira, V. *et al.* Protective Efficacy and Safety of Three Antimalarial Regimens for the Prevention of Malaria in Young Ugandan Children: A Randomized Controlled Trial. *PLOS Medicine* **11**, e1001689, (2014).
71 Capeding, M. R. *et al.* Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *The Lancet* **384**, 1358-1365, (2014).
72 Villar, L. *et al.* Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America. *New Engl J Med* **372**, 113-123, (2014).
73 Winskill, P., Walker, P. G., Griffin, J. T. & Ghani, A. C. Modelling the cost-effectiveness of introducing the RTS,S malaria vaccine relative to scaling up other malaria interventions in sub-Saharan Africa. *BMJ Global Health* **2**, (2017).
74 World Health Organization. Malaria vaccine: WHO position paper-January 2016. *Weekly Epidemiological Record* **91**, 33-51, (2016).
75 World Health Organization. Dengue vaccine: WHO position paper - July 2016. *Weekly Epidemiological Record* **91**, 349-364, (2016).
76 World Health Organization. *Updated Questions and Answers related to information presented in the Sanofi Pasteur press release on 30 November 2017 with regards to the dengue vaccine Dengvaxia*, <http://www.who.int/immunization/diseases/dengue/q_and_a_dengue_vaccine_dengvaxia/en/> (2017).
77 Screaton, G. & Mongkolsapaya, J. Which Dengue Vaccine Approach Is the Most Promising, and Should We Be Concerned about Enhanced Disease after Vaccination?: The Challenges of a Dengue Vaccine. *Cold Spring Harbor Perspectives in Biology*, (2017).
78 World Health Organization. *Tables of malaria vaccine projects globally*, <http://www.who.int/immunization/research/development/Rainbow_tables/en/> (2017).
79 Barba-Spaeth, G. *et al.* Structural basis of potent Zika–dengue virus antibody cross-neutralization. *Nature* **536**, 48, (2016).
80 Fiorenzano, J. M., Koehler, P. G. & Xue, R.-D. Attractive Toxic Sugar Bait (ATSB) For Control of Mosquitoes and Its Impact on Non-Target Organisms: A Review. *International Journal of Environmental Research and Public Health* **14**, 398, (2017).

81 Qualls, W. A. *et al.* Indoor use of attractive toxic sugar bait (ATSB) to effectively control malaria vectors in Mali, West Africa. *Malaria Journal* **14**, 301, (2015).
82 Slater, H. C., Walker, P. G. T., Bousema, T., Okell, L. C. & Ghani, A. C. The Potential Impact of Adding Ivermectin to a Mass Treatment Intervention to Reduce Malaria Transmission: A Modelling Study. *The Journal of Infectious Diseases* **210**, 1972-1980, (2014).
83 Werren, J. H., Baldo, L. & Clark, M. E. Wolbachia: master manipulators of invertebrate biology. *Nature reviews. Microbiology* **6**, 741-751, (2008).
84 Moreira, L. A. *et al.* A Wolbachia symbiont in Aedes aegypti limits infection with dengue, Chikungunya, and Plasmodium. *Cell* **139**, 1268-1278, (2009).
85 Walker, T. *et al.* The wMel Wolbachia strain blocks dengue and invades caged Aedes aegypti populations. *Nature* **476**, 450-453, (2011).
86 World Mosquito Program. <https://www.worldmosquitoprogram.org/ > (2018).
87 Ferguson, N. M. *et al.* Modeling the impact on virus transmission of Wolbachia-mediated blocking of dengue virus infection of Aedes aegypti. *Science Translational Medicine* **7**, 279ra237-279ra237, (2015).
This study combines experiemental work and modelling to estimate the likely impact on dengue disease transmission of replacing wild type *Aedes aegypti* with *Wolbachia*-infected mosquitoes.
88 Bian, G. *et al.* Wolbachia Invades Anopheles stephensi Populations and Induces Refractoriness to Plasmodium Infection. *Science* **340**, 748-751, (2013).
89 Adelman, Z. N. (Academic Press, 2015).
90 Gabrieli, P., Smidler, A. & Catteruccia, F. Engineering the control of mosquito-borne infectious diseases. *Genome Biology* **15**, 535, (2014).
91 Adelman, Z. N. & Tu, Z. Control of Mosquito-Borne Infectious Diseases: Sex and Gene Drive. *Trends in Parasitology* **32**, 219-229, (2016).
92 Marshall, J. M. & Taylor, C. E. Malaria Control with Transgenic Mosquitoes. *PLOS Medicine* **6**, e1000020, (2009).
93 Galizi, R. *et al.* A synthetic sex ratio distortion system for the control of the human malaria mosquito. *Nature Communications* **5**, 3977, (2014).
94 Burt, A. Site-specific selfish genes as tools for the control and genetic engineering of natural populations. *Proceedings of the Royal Society B: Biological Sciences* **270**, 921-928, (2003).
This study was one of the first to provide a rigorous population genetic assessment of the potential of using homing endonuclease genes to drive genetic modification of vector populations for disease control purposes.
95 Deredec, A., Godfray, H. C. J. & Burt, A. Requirements for effective malaria control with homing endonuclease genes. *Proceedings of the National Academy of Sciences* **108**, E874-E880, (2011).
96 Li, M. *et al.* Germline Cas9 expression yields highly efficient genome engineering in a major worldwide disease vector, Aedes aegypti. *Proceedings of the National Academy of Sciences* **114**, E10540-E10549, (2017).
97 Gantz, V. M. *et al.* Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi. *Proceedings of the National Academy of Sciences* **112**, E6736-E6743, (2015).
98 Wang, S. & Jacobs-Lorena, M. Genetic approaches to interfere with malaria transmission by vector mosquitoes. *Trends in Biotechnology* **31**, 185-193, (2013).
99 Severson, D. W. & Behura, S. K. Genome Investigations of Vector Competence in Aedes aegypti to Inform Novel Arbovirus Disease Control Approaches. *Insects* **7**, 58, (2016).
100 Wesolowski, A. *et al.* Quantifying the impact of human mobility on malaria. *Science* **338**, 267-270, (2012).

Figure Legends

Figure 1. Mortality trends 2000-2016 for malaria and dengue. WHO estimates shown for malaria, combining estimates from the 2015 and 2017 World Malaria Reports[3,7]; other estimates[1,8] are substantially higher but show the same overall trends. In the absence of WHO estimates, dengue mortality estimates from the 2016 Global Burden of Disease study are shown[8]. Note that malaria deaths in Africa are shown on the left axis, dengue deaths and malaria deaths outside Africa on the right.

Figure 2. Comparative effect of vector controls on incidence of clinical malaria and hospitalised dengue in high transmission intensity settings. A. Published mathematical transmission dynamic models of each disease[23,41] are used to show the long-term effect of varying (i) coverage levels of LLINs for malaria in a sub-Saharan African hyperendemic setting with an (assumed constant) entomological inoculation rate (EIR) in the absence of controls of 500 (R_0 of approximately 700); (ii) the proportion of dengue exposure blocked by a hypothetical dengue vector control measure (100% coverage assumed) in a setting where seroprevalence in 9-year olds is 80% on average prior to the introduction of controls (R_0 of approximately 4). B. The temporal impact of controls on annual disease incidence. Controls are introduced in year 20 (50% LLIN coverage assumed for malaria, 50% effective controls for dengue). Inter-annual climate variation is not included in either model, so malaria incidence is constant over time prior to interventions. Dengue incidence varies markedly year-to-year due to semi-chaotic serotype cycling.

Figure 3. Action of *Wolbachia* and Y-linked 'X-shredder' homing-endonuclease gene (HEG) based gene drive control measures. A. *Wolbachia*-infected mosquitoes are refractory to arboviruses and are able to invade wild-type populations due to cytoplasmic incompatibility, which leads to crosses between wild-type females and *Wolbachia* infected males being non-viable. B. Y-linked X-shredder HEG carrying male-mosquitoes bias the sex ratio, since a high proportion (here shown as all) of progeny in their crosses with wild-type females are male and inherit the HEG. C. Illustrative invasion dynamics (releases occurring at day 50). *Wolbachia* exhibits frequency dependent invasion dynamics, with a threshold frequency determined by fitness costs of infection (here assumed to be 30%). Hence invasion can occur when the release size equals 50% of the resident wild-type population, but not at 20%. Y-linked X-shredder HEG carrying mosquitoes can invade at any frequency (here assumed to be 5% of resident population size) and cause the adult mosquito population to crash.

Figure 1

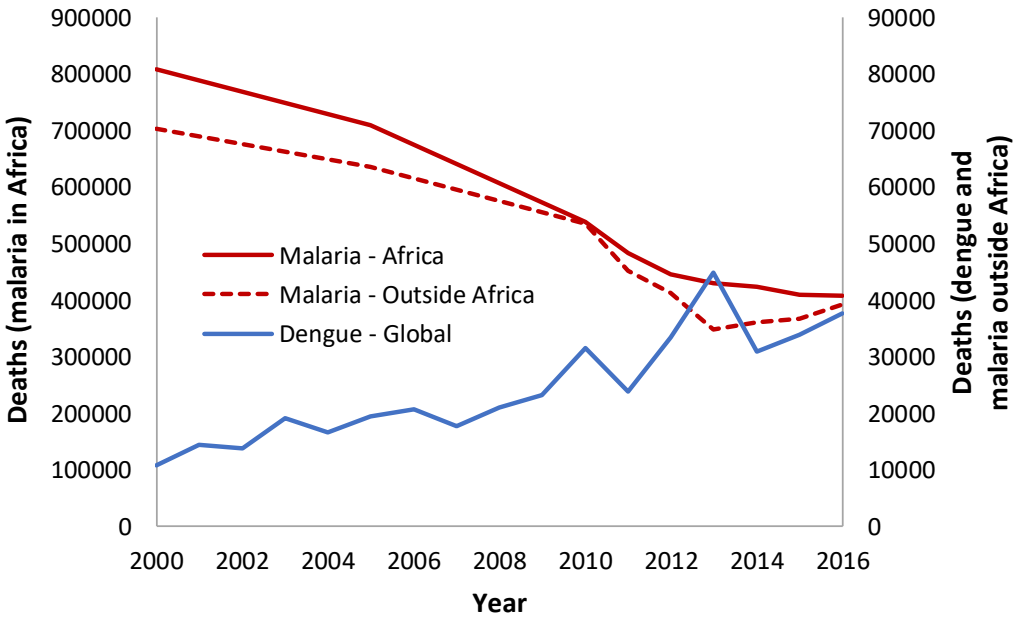

900000
800000
700000
600000
500000
400000
300000
200000
100000
0
Deaths (malaria in Africa)
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
Deaths (dengue and malaria outside Africa)
Malaria - Africa
Malaria - Outside Africa
Dengue - Global
2000
2002
2004
2006
2008
2010
2012
2014
2016
Year

Figure 2

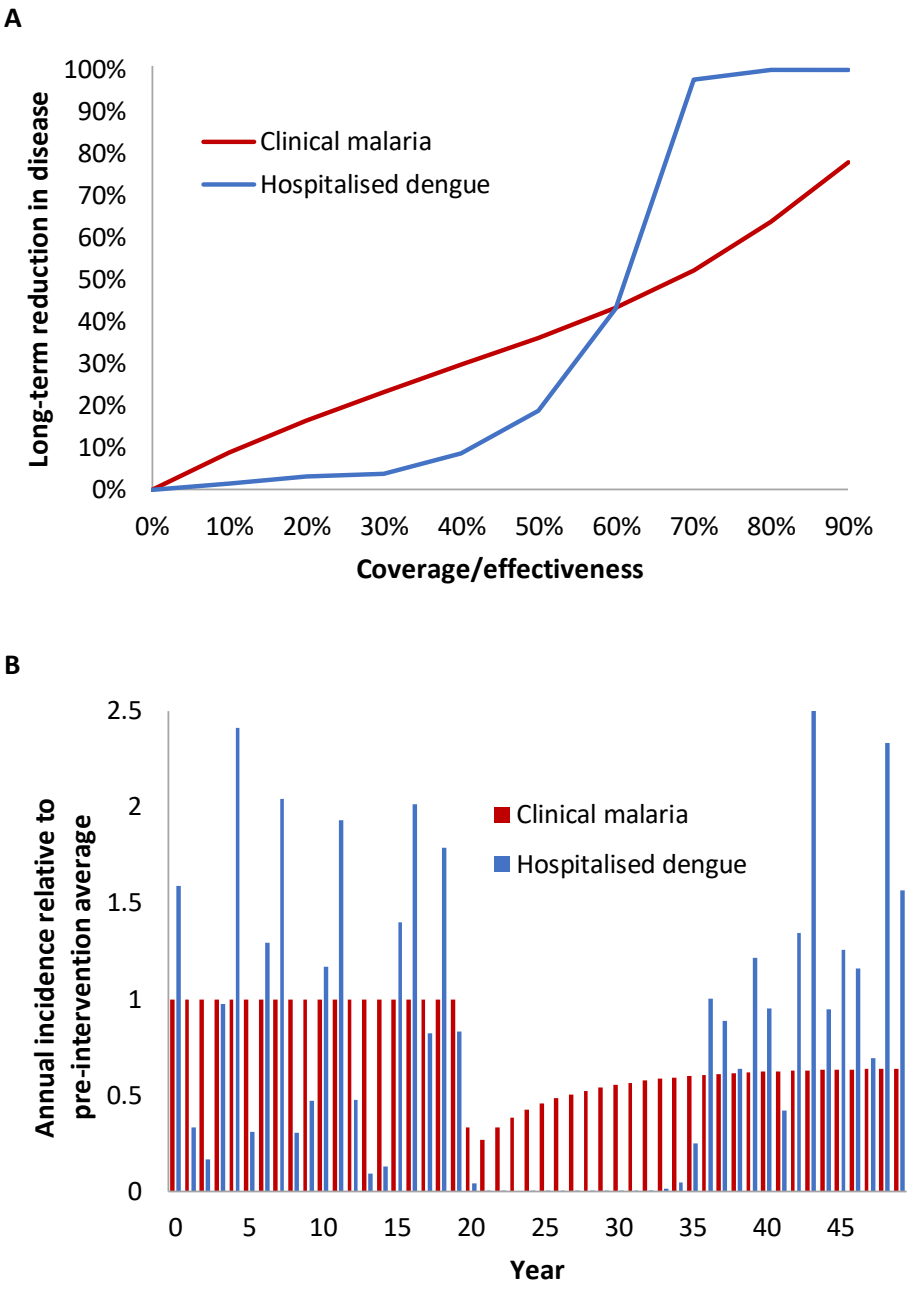
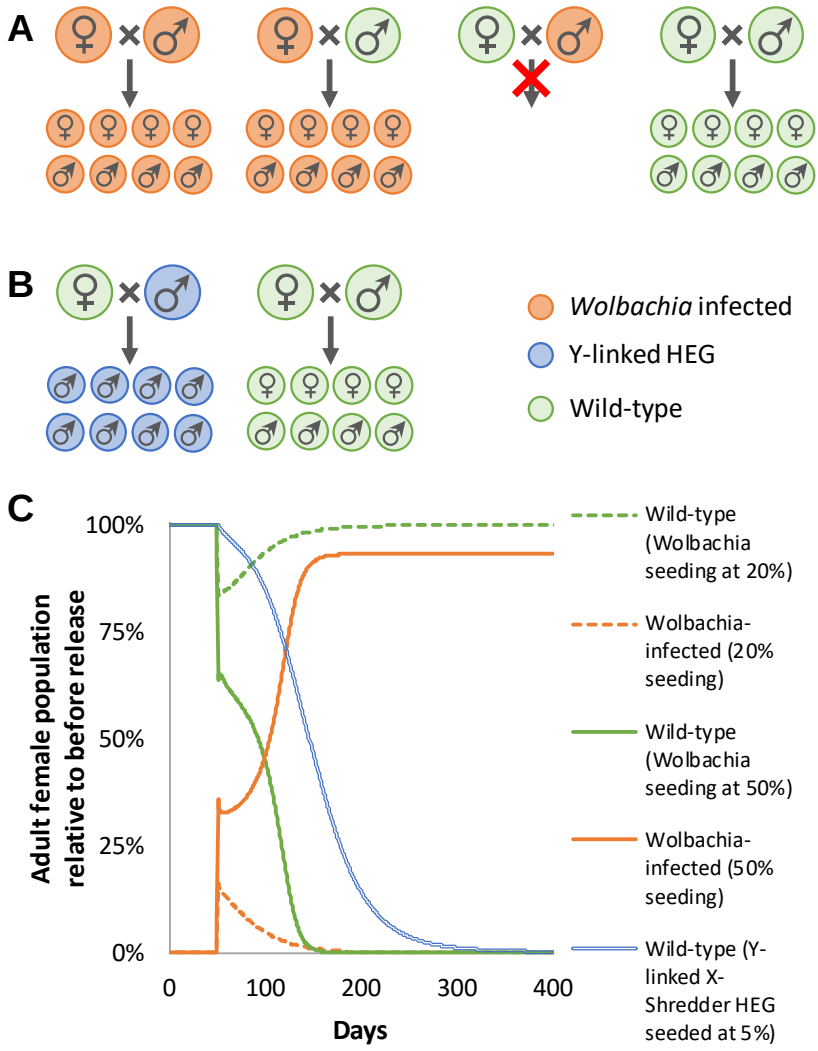

A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Long-term reduction in disease
Clinical malaria
Hospitalised dengue
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Coverage/effectiveness
B
2.5
2
1.5
1
0.5
0
Annual incidence relative to pre-intervention average
Clinical malaria
Hospitalised dengue
0
5
10
15
20
25
30
35
40
45
Year

Figure 3


A
B
Wolbachia infected
Y-linked HEG
Wild-type
C
100%
75%
50%
25%
0%
Adult female population relative to before release
0
100
200
300
400
Days
Wild-type (Wolbachia seeding at 20%)
Wolbachia-infected (20% seeding)
Wild-type (Wolbachia seeding at 50%)
Wolbachia-infected (50% seeding)
Wild-type (Y-linked X-Shredder HEG seeded at 5%)