

Genetic control of vector-borne diseases

The tempo and mode of the evolution of mosquito transposable elements as revealed by molecular phylogenies

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Players

Players

Vector

Gene Drive

Coalescence

What we did

Results 1

Genetic Complexities

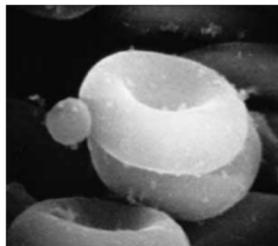
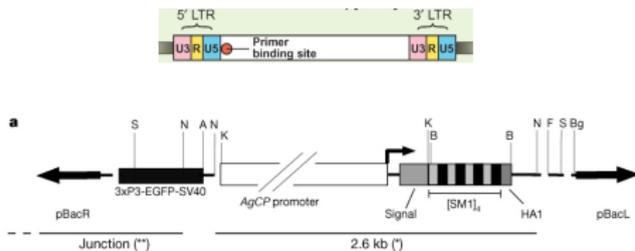


Figure: Main players

Immune Responses

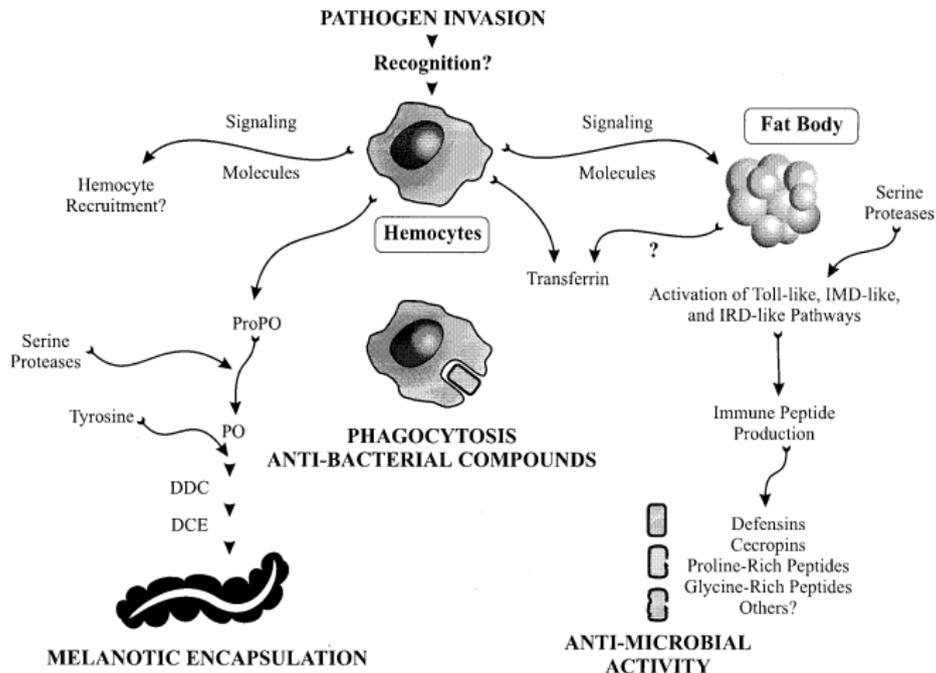


Figure: Mosquito immune responses to pathogens include melanotic encapsulation, phagocytosis, and production of antibacterial compounds and immune peptides (Beerntsen et al., 2000)

Migratory Routes and Development Sites

Players

Vector

Immune Responses

Action Sites

Transgenesis

Gene Drive

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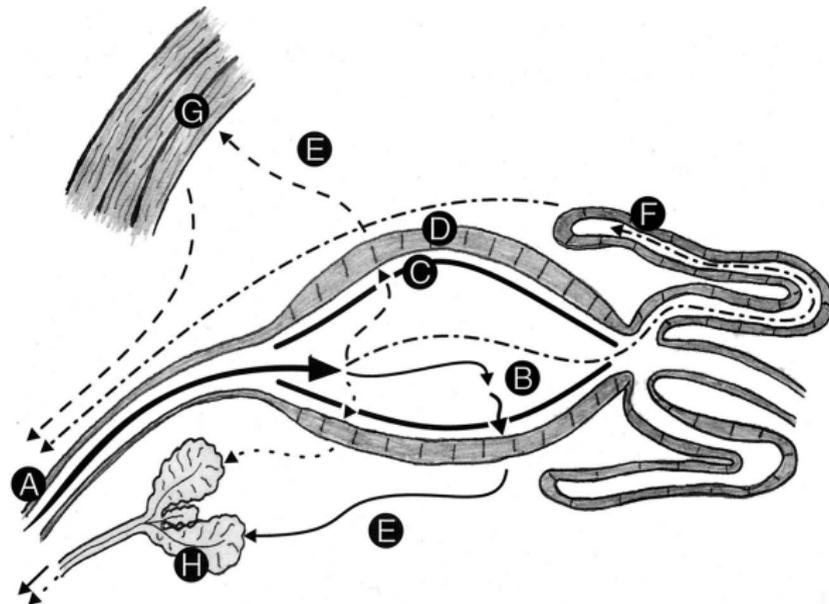


Figure: Developmental sites and migratory routes within the mosquito. Blood meal (A), midgut (B), peritrophic matrix (C), midgut epithelial cells (D), hemolymph-filled hemocoel (E), Malpighian tubules (F), thoracic musculature (G), salivary glands (H). Viruses (—), malaria parasites (---), filarial worms of humans (· · ·) and dog heartworm (-·-·) (Beerntsen et al., 2000)

Transgene Expression

Players

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Figure: Transformation of the kh^W (white-eye) strain of *Aedes aegypti* with a Hermes transposon carrying a wild-type copy of the *D. melanogaster* cinnabar gene (encoding kynurenine hydroxylase) restores eye color. Counterclockwise from the top left: head of a wild-type mosquito showing deep purple eyes; head of a kh^W/kh^W mosquito showing white eyes; three heads of transformed mosquitoes from independent Hermes insertions showing different eye colors (Beerntsen et al., 2000).

Transgene Expression

Players

Vector

Immune Responses

Action Sites

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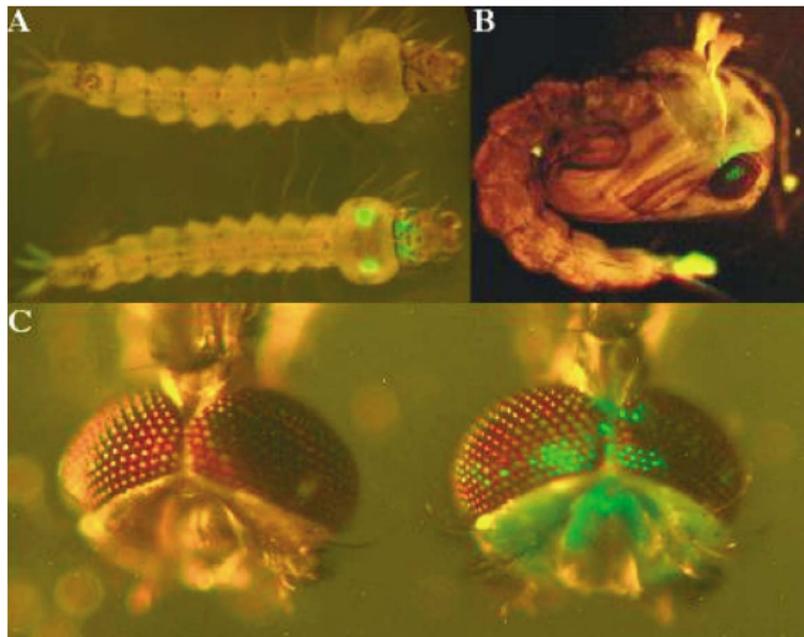
Genetic
Complexities

Figure: Pattern of green fluorescent protein (GFP) expression in transgenic *Anopheles stephensi* mosquitoes transformed with a piggyBac vector (Horn et al., 2000). The GFP gene was under the control of the eye-specific 3XP3 promoter. (A) Two larvae: transgenic (bottom) and non-transgenic (top). GFP is visible in the ocelli and salivary glands of the transgenic larva. (B) Transgenic pupa. Note GFP fluorescence in some of the eye ommatidia. (C) Eyes of a non-transgenic (left) and transgenic (right) mosquito. Note that while all eye ommatidia of the transgenic mosquito express GFP, the pattern of fluorescence depends on the angle of incident light (Moreira et al., 2002).

Transposable Element

Players

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Gene Drive

Cheating

TE cheating

Invasion Dynamics

TE in drosophila

Cages

Coalescence

What we did

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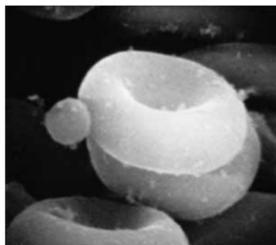
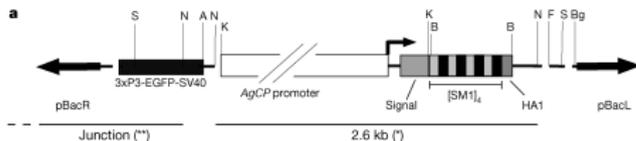


Figure: Main players

Cheating Mendelian Inheritance: gene drives

Players

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Table 1 | Comparative characteristics of potential drive systems*

Characteristic	Classes of potential drive systems				
	Transposable elements	Natural meiotic drive	Engineered meiotic drive or HEG	Engineered underdominance	<i>Wolbachia</i>
Is a release threshold required before population spread begins?	No	No	No	Comparatively high	Usually low
Is efficiency of drive dependent on insert size?	Yes	No	No; unknown for HEGs	No	No
Is there a mechanism for repeated spread?	Different transposable elements might be required	No	Redesign of target sequence	Different promoters and suppressors	Incompatible strains
Can insect tissue-specific promoters be used?	Yes	Yes	Yes	Yes	No
Is there a mechanism for transgene removal from the population?	No	No	Redesign of target sequence	Large-scale release of wild-type insects	Incompatible strains
Is there a risk of spread to non-target species?	Low	Close to zero	Close to zero	Close to zero	Low
Is the system known to function in important pest species?	Yes	Yes, but insensitivity alleles occur	No	No	Yes
Is there a potential use for the same system in secondary vectors?	Yes	Unlikely	Yes	Yes	Yes

Figure: Comparative characteristics of potential drive systems (Sinkins and Gould 2006)

Subverting Mendelian Segregation

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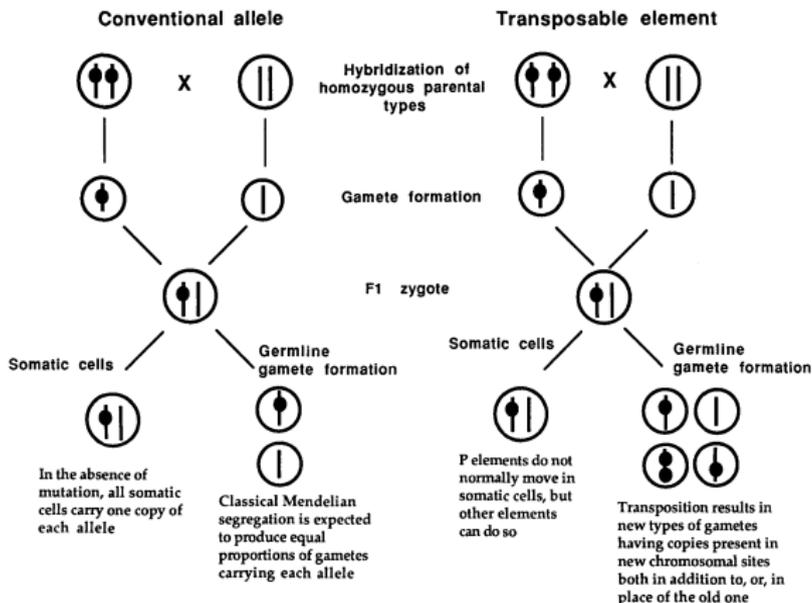


Figure: Transmission of a conventional allele compared with that of an active transposable element such as the P element. Note that, in the case shown, 75% of the gametes contain transposable elements, and thus this element could afford to kill up to 25% of its offspring and still become fixed in the population (Kidwell and Ribeiro, 1992).

Complex Invasion Dynamics

Players

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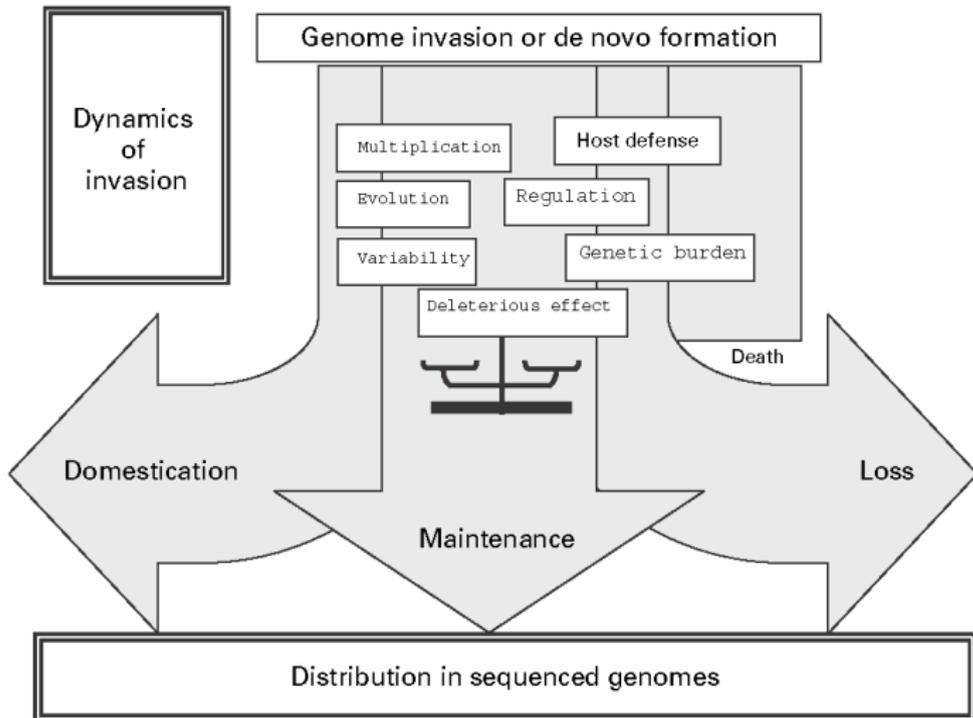


Figure: Gene drive dynamics (Hua-van et al. 2005).

At Least It Worked in Drosophila

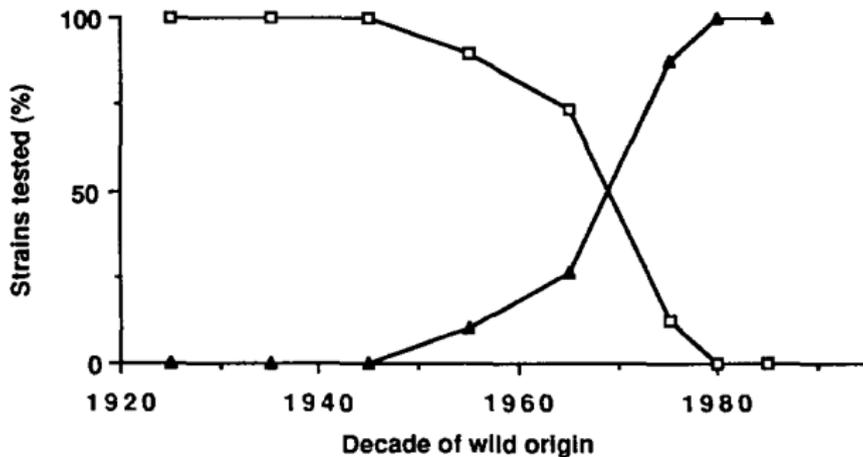


Figure: Graph showing the rapid spread of P elements in populations of *Drosophila melanogaster* worldwide during the past 70 years. P element-bearing strains are represented by closed triangles. Strains lacking P elements are represented by open squares. (Kidwell and Ribeiro, 1992)

Invasion Pattern (absolute numbers)

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TE in drosophila

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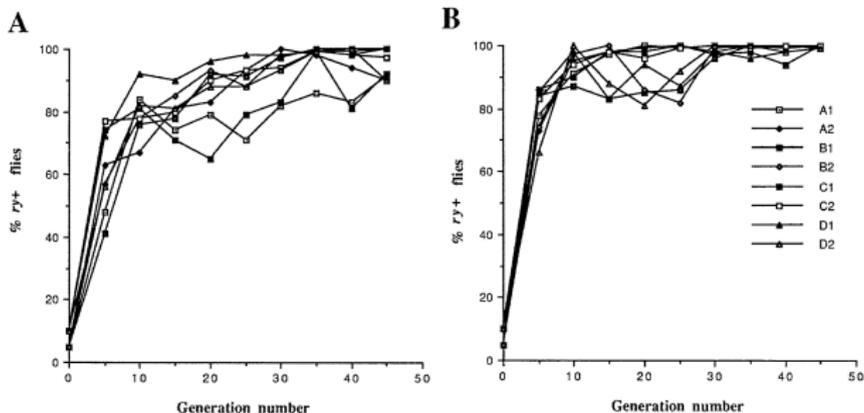
Genetic
Complexities

Figure: Summary of the results of phenotypic assays Experiment I. (A) Mean frequencies of flies carrying at least one P-rosy gene construct in eight populations seeded with individuals carrying the autonomous construct. (B) Mean frequencies of flies carrying at least one P-rosy gene construct in eight populations seeded with individuals carrying the nonautonomous (Carareto, 1997).

Summary of Attrition Forces

Players

Vector

Gene Drive

Coalescence

Chronograms

Demography

What we did

Results 1

Genetic Complexities

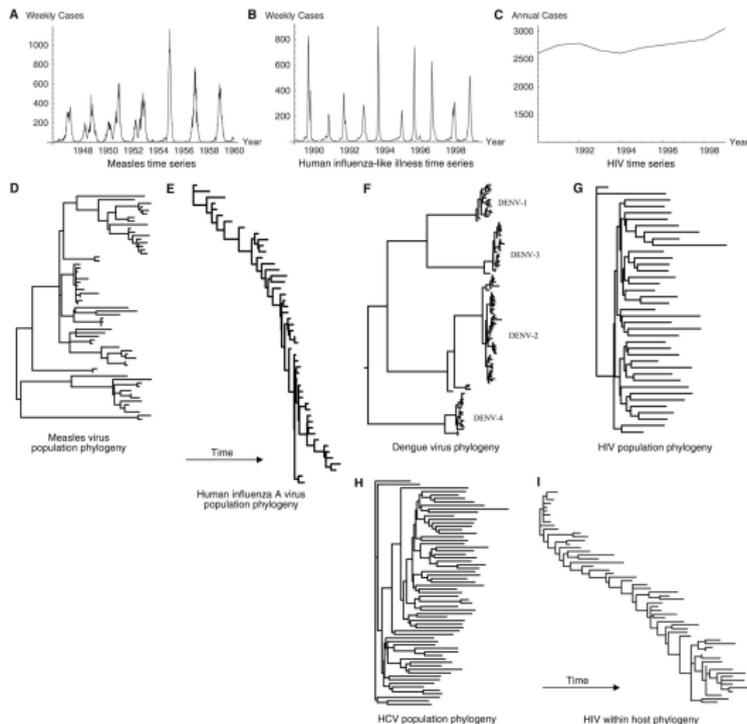


Figure: **Cladogram:** branch lengths have no meaning; **Phylogram:** branch lengths correspond to numbers of substitutions along branches (or numbers of substitutions per site along that branch); **Chronogram:** branch lengths correspond to time durations along branches; **Ratogram** branch lengths correspond to absolute rates of substitution along branches (Grenfell et al., 2004; Sanderson, 2004 (R8S User's Guide))

Types of trees: Birth, Death and Inactivation

Players

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What we did

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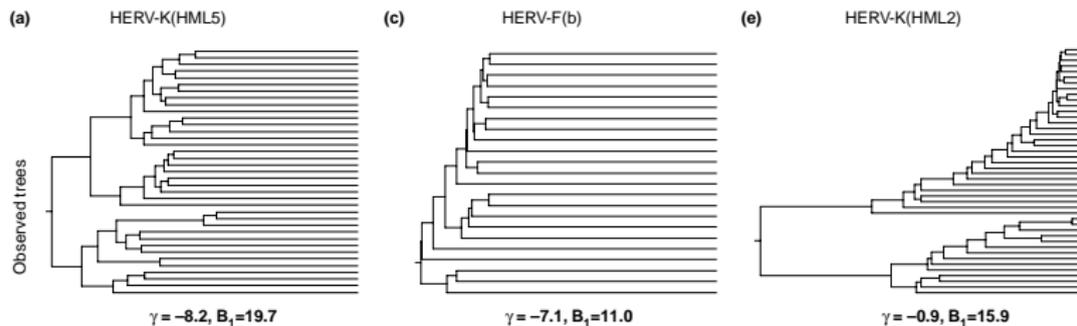
Genetic
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Figure: Phylogenies of the human endogeneous retrovirus HERV-K(HML5), HERV-F(b) and HERV-K(HML2) families, reconstructed from real data (Katzourakis et al., 2005).

Phylogeny and Demography

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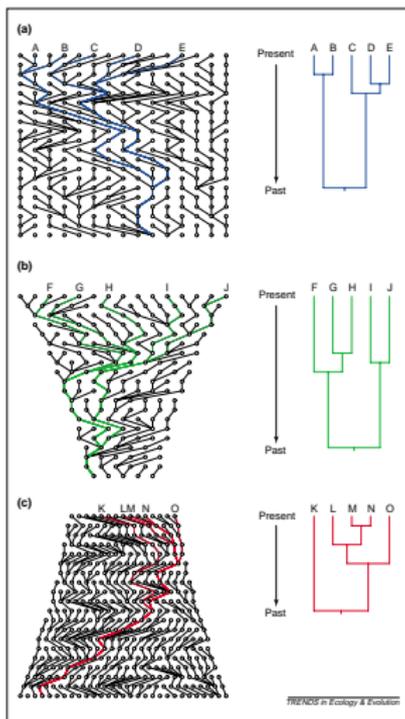


Figure: A fundamental result of coalescent theory in population genetics is the finding of a relationship between COALESCENT TIME and population size. For any two sequences drawn from a population, the probability that they coalesce at a given point in history is a function of population size (Emerson et al., 2001).

Steps

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What we did

Steps

Pipeline

Mining for TEs

Branching

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1. mining the two mosquito genomes currently available in search of TE families;
2. fitting, to selected families found in (1), a phylogeny tree under the general time-reversible (GTR) nucleotide substitution model with an uncorrelated lognormal relaxed clock (UCLN) and a non-parametric demographic model;
3. fitting a non-parametric coalescent model to the tree generated in (2);
4. fitting parametric models motivated by ecological theories to the curve generated in (3).

Pipeline

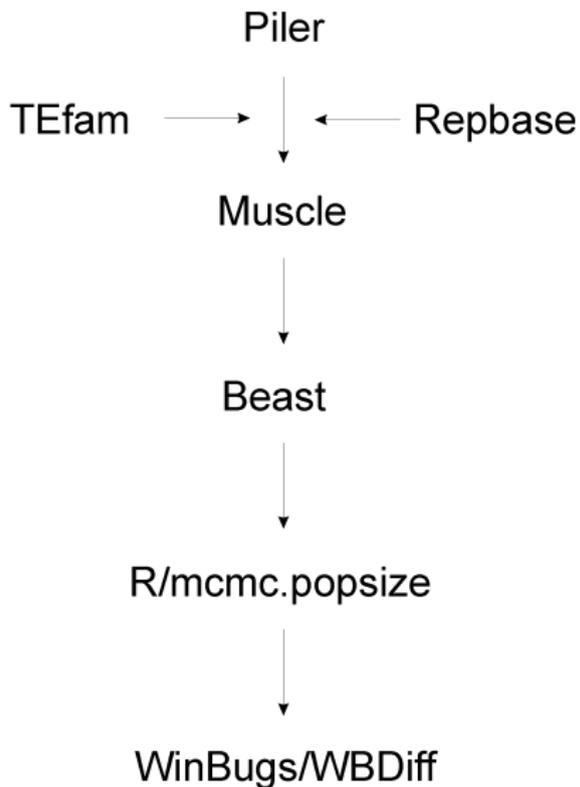


Figure: Pipeline

Like a Virus

Players

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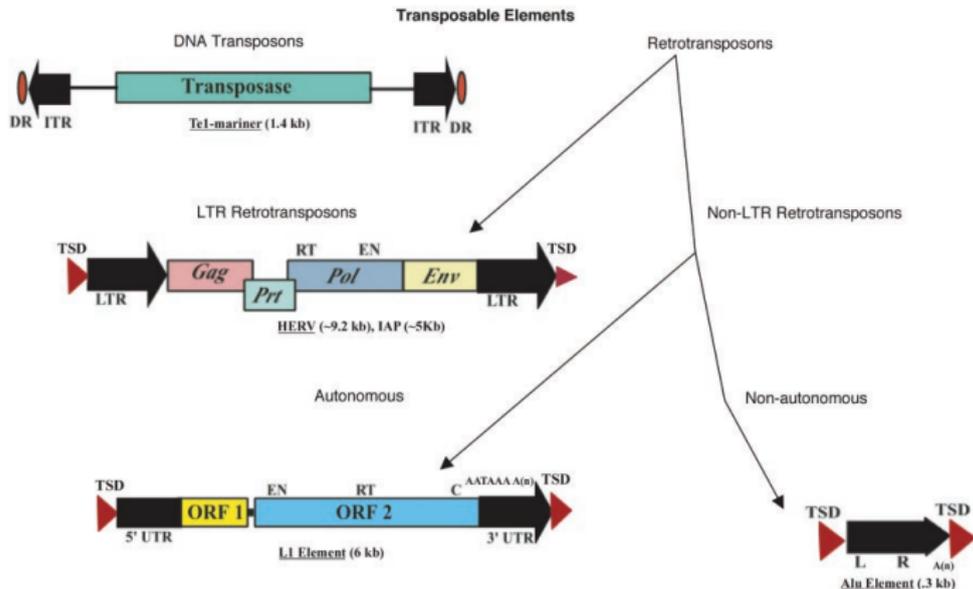


Figure: Classes of mobile elements: inverted terminal inverted repeats (ITRs); open reading frame (ORF); short direct repeats (DRs); human endogeneous retrovirus (HERV); target site duplications (TSDs); reverse transcriptase (RT); endonuclease (EN); intracisternal A-particles (IAPs); early transposons (Etns); mammalian LTR-retrotransposons (MaLRs); 5-untranslated region (5UTR); poly(A) tail (Aⁿ); target site duplications (TSDs). Approximate full-length element sizes are given in parentheses (Kazazian, 1994).

Empirical data: screening the genome for TEs

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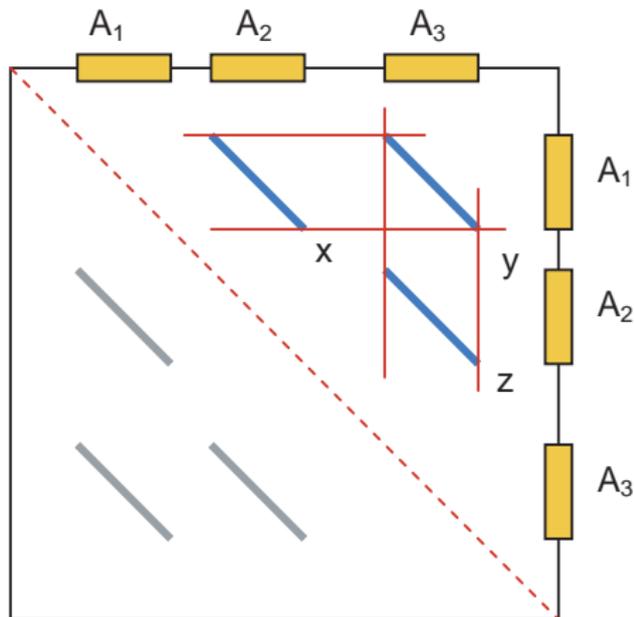


Figure: Characteristic patterns of local alignments induced by certain classes of repeats (Edgar and Myers, 2005)

Empirical data: mining the genome for TEs (Cont)

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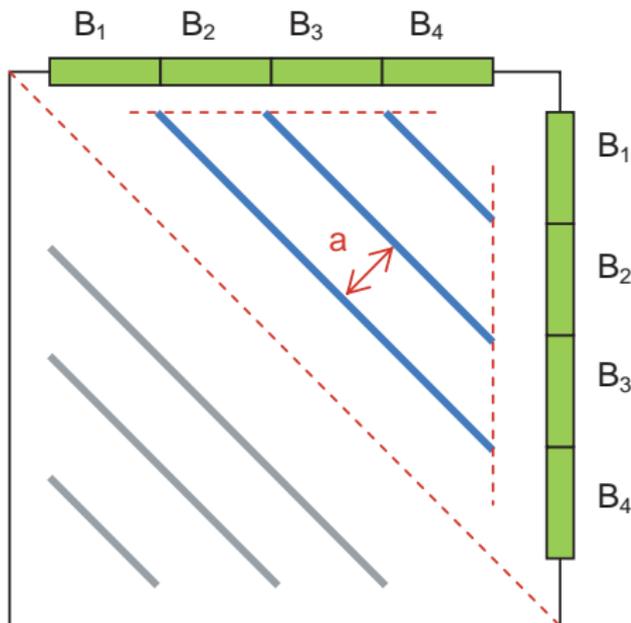


Figure: Characteristic patterns of local alignments induced by certain classes of repeats (Edgar and Myers, 2005)

Empirical data: mining the genome for TEs (Cont)

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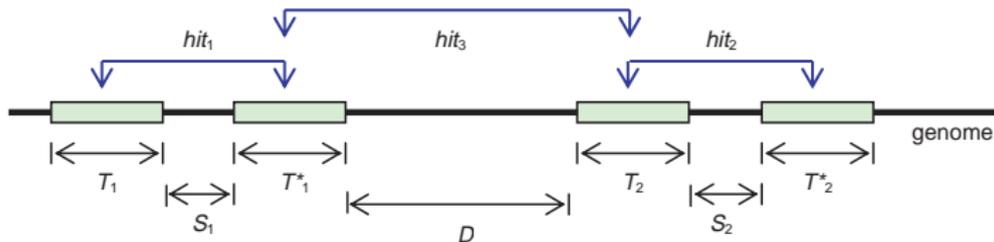


Figure: Characteristic patterns of local alignments induced by certain classes of repeats (Edgar and Myers, 2005)

“Ecological Dynamics”

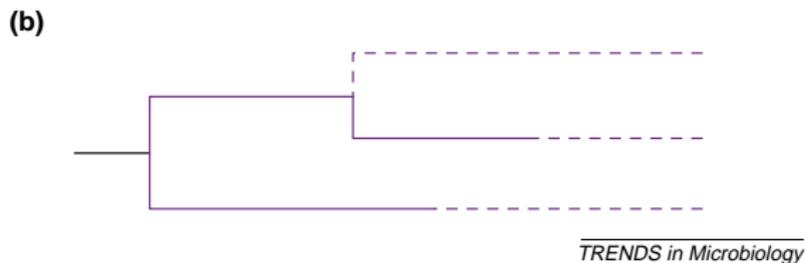
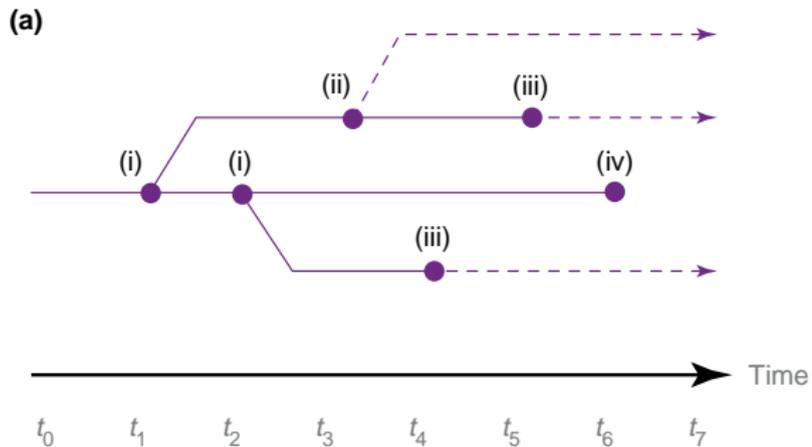


Figure: Katzourakis et al., 2005

Empirical data: Demography

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Demography

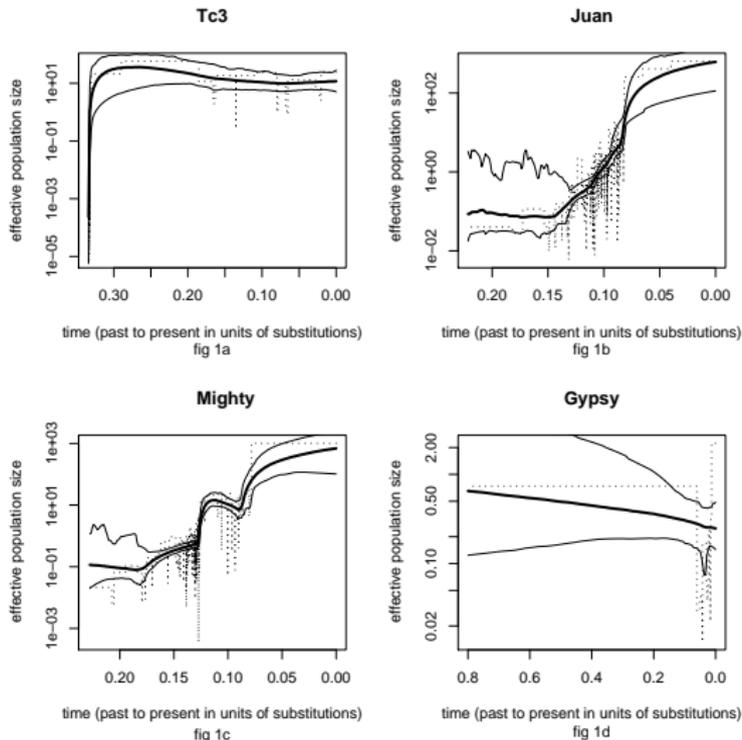
Genetic
Complexities

Figure: Non-parametric demographic history inferred from the phylogeny tree reconstructed by BEAST (see supplemental material) for each of the TE families studied. Thick lines indicate central estimates (median) and were used to fit the models given by systems (1) and (2). Thin lines indicate 95% limits sampled from the posterior distribution by the rjMCMC procedure. The classic skyline plots are

Genomes Compared

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Genomes Compared

Evolutionary Dynamics

Heterogeneity

Artificial Selection

Virulence

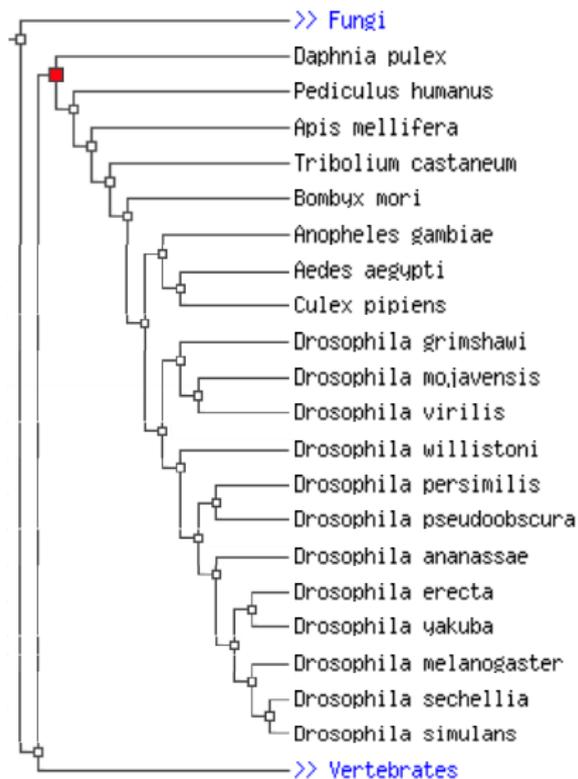


Figure: Insects tree

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Divergence of Orthologous Trios

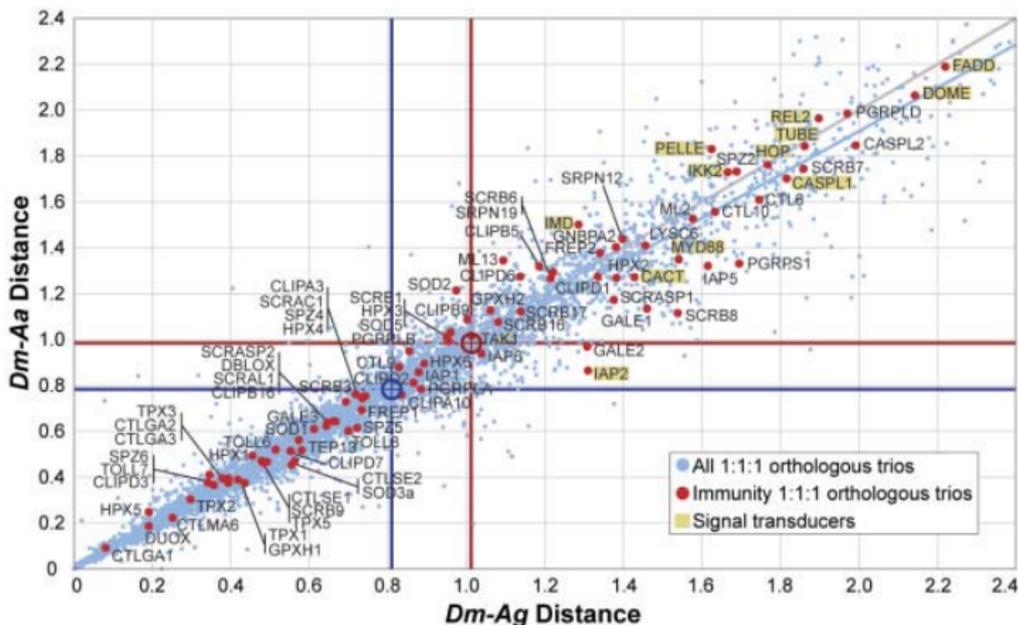


Figure: Divergence of orthologous trios (Waterhouse et al., 2007).

Immune Response Evolves by Convergence

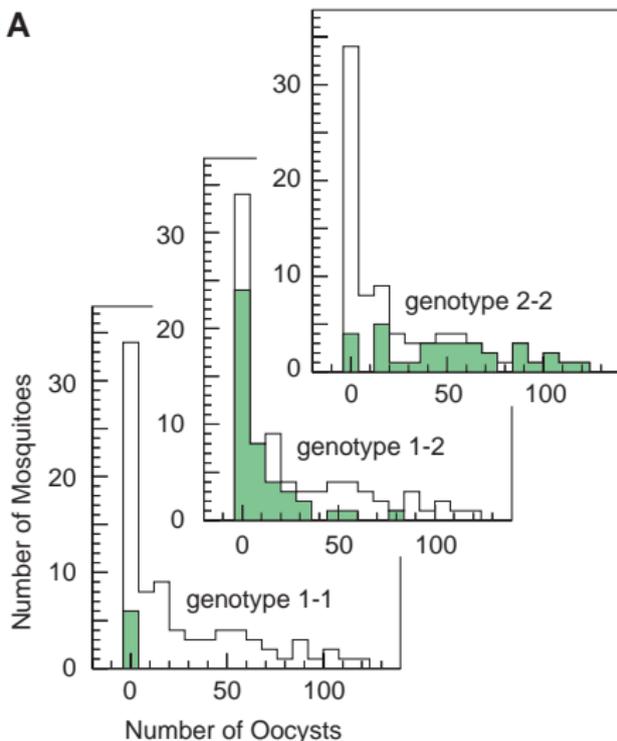


Figure: Infection phenotype of wild *A. gambiae* pedigrees with natural *P. falciparum*. (Niaré et al., 2002)

Sustained Response to Artificial Selection

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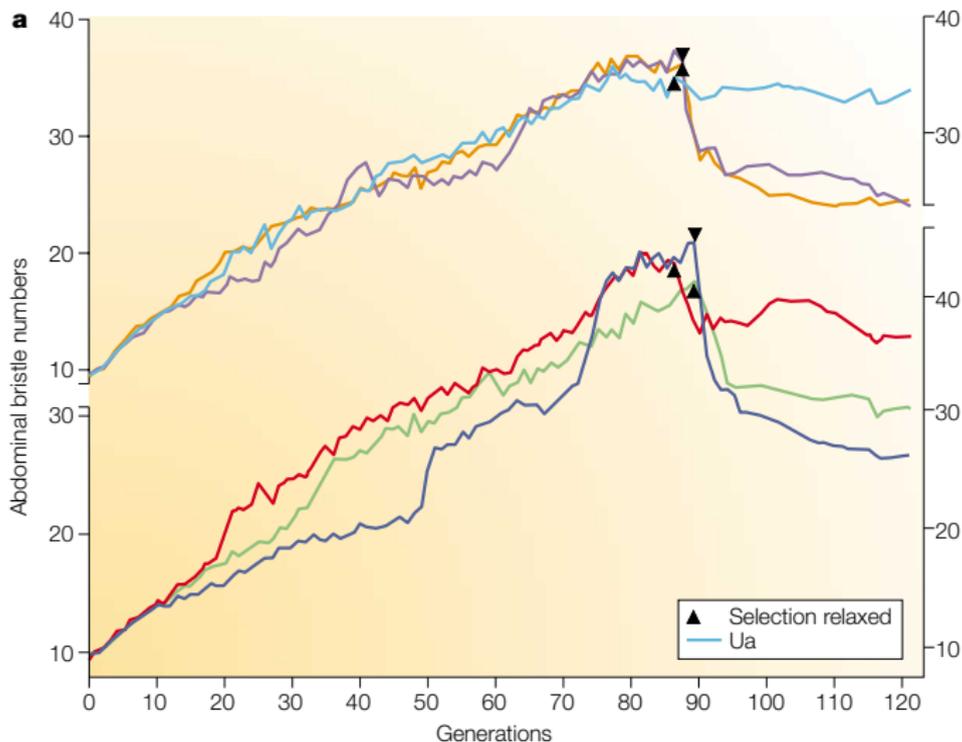


Figure: Top 20% was selected every generation for increased numbers of abdominal bristles; Line Ua carried none recessive lethals (Barton and Keightley, 2002).

Sustained Response to Artificial Selection

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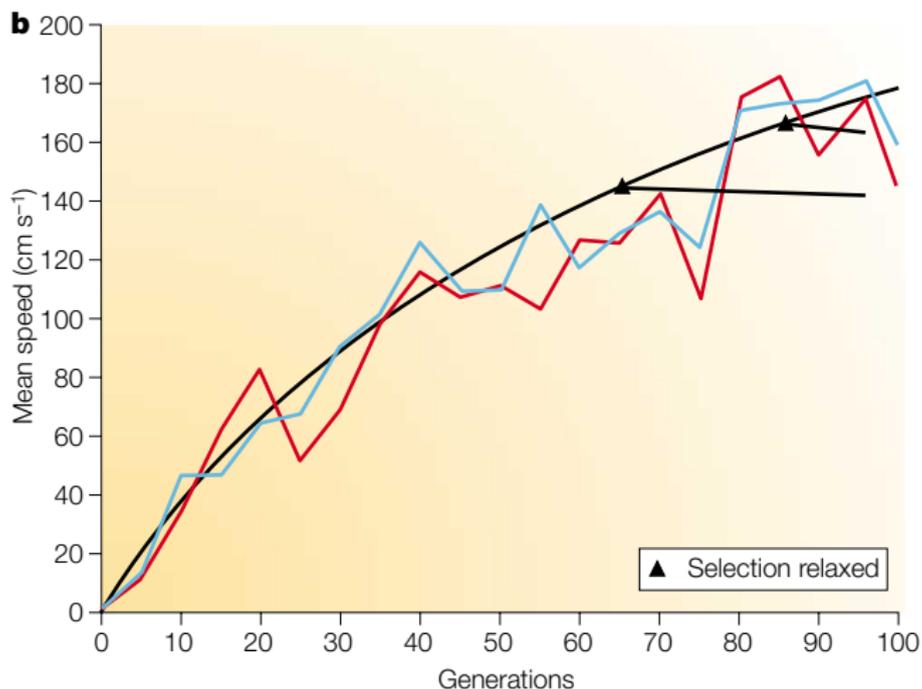


Figure: ability to fly upwind in a wind tunnel. the 4.5% strongest fliers were selected (Barton and Keightley, 2002).

Time and Place are Everything

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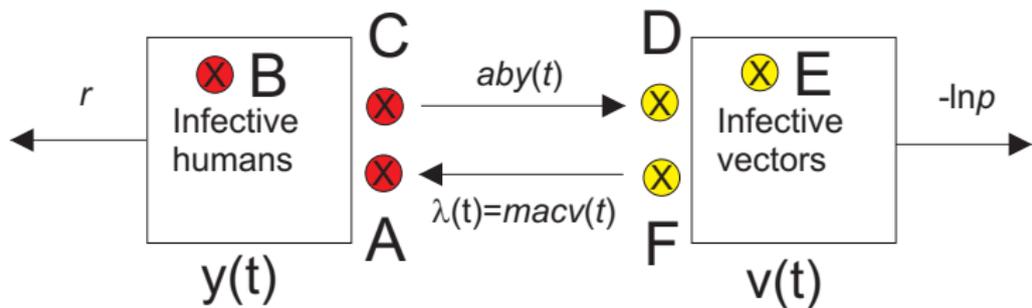


Figure: Time and Place

Trade-offs

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Virulence

Table: Possible evolutionary trade-offs between epidemiological parameters and virulence: β transmission probability; a biting rate of mosquitoes; τ incubation rate (Medlock et al., submitted).

	Virulence to mosquitoes, ν_V	Virulence to humans, ν_H
Transmission	β increases with ν_V	β increases with ν_H
Mosquito biting	a increases with ν_V	a increases with ν_H
Incubation	τ_V increases with ν_V	τ_H increases with ν_H
Recovery	—	γ_H is a function of ν_H

Summary

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Table: Summary of selective pressures due to transgenic strategies and trade-offs (Medlock et al., Submitted).

		Transgenic strategy			
		Blocking transmission	Reducing mosquito biting	Increasing mosquito background mortality	Increasing mosquito infection-induced mortality
Trade-off	β vs. ν_V	$\nu_V \uparrow\downarrow, \beta \uparrow\downarrow$	—	$\nu_V \uparrow, \beta \uparrow$	$\nu_V \uparrow\downarrow, \beta \uparrow\downarrow$
	β vs. ν_H	$\nu_H \uparrow\downarrow, \beta \uparrow\downarrow$	—	—	—
	a vs. ν_V	—	$\nu_V \uparrow\downarrow, a \uparrow\downarrow$	$\nu_V \uparrow, a \uparrow$	$\nu_V \uparrow\downarrow, a \uparrow\downarrow$
	a vs. ν_H	—	$\nu_H \uparrow\downarrow, a \uparrow\downarrow$	—	—
	τ_V vs. ν_V	—	—	$\nu_V \uparrow, \tau_V \uparrow$	$\nu_V \uparrow\downarrow, \tau_V \uparrow\downarrow$
	τ_H vs. ν_H	—	—	—	—
	γ_H vs. ν_H	—	—	—	—

—: no selection. \uparrow : selection for increasing the parameter. \downarrow : selection for decreasing the parameter. $\uparrow\downarrow$: selection for either increasing or decreasing the parameter depending on quantitative features of the effect of the transgene on the trade-off between virulence and the other epidemiological trait.