Académie de Montpellier
Université de Perpignan Via Domitia

THÈSE

en vue de l'obtention du grade de

Docteur de l'Université de Perpignan Via Domitia

Discipline et spécialité
Écologie, Évolution – Biologie théorique

Guilhem Rascalou

Écologie, évolution et contrôle des maladies tropicales négligées

---

École doctorale
Énergie et Environnement

Unité de recherche
UMR 5244 CNRS-UPVD Écologie et Évolution des Interactions

Directeur de thèse
Sébastien Gourbière

Remerciements

Je tiens tout d'abord à remercier mon directeur de thèse, Sébastien Gourbière. Pour la qualité de sa direction, mais aussi pour la valeur qu'il accorde tous les jours aux relations humaines. Je retiens de ce doctorat un exemple professionnel et humain dont j'espère être digne dans ma vie future.

Un immense merci à mes parents et à mes frères et sœurs. Pour leur soutien convaincu, depuis le début, et pour leur incessante volonté de s'associer à la réalisation de mes projets.

Ce doctorat a aussi été l'occasion de faire de très belles rencontres. Alors un grand merci à toute l'équipe 'LTS', dont je n'oublierai jamais le souci quotidien d'entretenir une ambiance de travail joviale et chaleureuse. Un grand merci aussi aux membres du laboratoire '2EI', en particulier pour leur disponibilité. Malgré mes heures d'office souvent inféodées à l'écran de mon ordinateur, vos portes me sont toujours restées ouvertes. Et puis un grand merci au 'JMS-5th' de Brighton: merci à Adam pour l'accueil exemplaire et si spontané, merci à David, Pierre, Romain et Toni pour la richesse de leurs conseils, et la valeur qu'ils ont su donner aux pauses cafés et autres after-works. Je tiens aussi à adresser mes remerciements et exprimer ma plus grande gratitude à Corentin Barbu, dont les conseils et l'expertise technique ont été déterminants dans l'avancement de mes travaux.

Je tiens enfin à remercier tous les membres de ma - très - grande famille. Puissent-ils réaliser à quel point leur présence et leur soutien ont été précieux. Un merci tout particulier à Anna, Aude, Bunaken, Deborah, Fannie, Fran, Guillaume, Julie, Lucie, Marco, Marion, Nabil, Théo, Vasilica et Xiao-Ming. Grâce à vous le 50°N ne fut jamais une contrainte mais bel et bien une chance quant au déroulement de ce doctorat. Enfin, un merci très spécial à Amélie, Anaïs, Charles, Jonathan, Mathieu, Nico et Thibault, parce que votre inspiration est sans égal…

Table des matières

Introduction générale **1**

Positionnement général et contribution spécifique de cette thèse 2

1 Les maladies tropicales négligées : mises en perspectives de leur impact sanitaire avec la production scientifique et théorique **4**

1. Les maladies tropicales négligées (« NTD ») 4

1.1 Diversité et similitudes 4

1.2 Risques et impact sanitaires 4

1.3 Contrôle des maladies tropicales négligées 6

2. Production scientifique sur les maladies tropicales négligées 9

2.1 Publications scientifiques 9

2.2 Travaux théoriques sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées 14

3. Principales problématiques abordées sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées 17

4. Conclusion générale 22

2 Émergence et prévalence des maladies vectorielles humaines transmises dans des populations de vecteurs puits **23**

2.1 Introduction 23

2.2 Article publié 24

3 Compétition et diversification intra-hôte des macro-parasites **58**

3.1 Introduction 58

3.2 Article accepté pour publication 59

4 Diversification compétitive des macro-parasites : virulence, distribution et taux évolutifs **79**

4.1 Introduction 79

4.2 Article en préparation 80

5 Discussion **117**
5.1 Transmission des maladies vectorielles dans des populations puits 117
5.1.1 La transmission dans des populations puits suit-elle
les mêmes lois générales pour toutes les maladies vectorielles ? 118
5.1.2 Quelques cas d'études auxquels le chapitre 2
apporte des résultats supplémentaires 119
5.1.3 Que sait-on des capacités migratoires des vecteurs
et des éventuels liens entre migration, biologie
et statut épidémiologiques des individus migrants ? 121
5.2 Diversification compétitive des macro-parasites 122
5.2.1 Quel modèle biologique pour étudier
la diversification compétitive chez les macro-parasites ? 123
5.2.2 Quel lien entre diversification compétitive
et contrôle des macro-parasites ? 124

Conclusion générale **126**

Références bibliographiques **127**

Introduction Générale

En dépit des succès de la lutte contre les maladies infectieuses au cours du XX^{ème} siècle (May, *2007*), il n'est probablement aucune population humaine qui ne soit affectée par au moins un agent pathogène (World Health Statistics, *2011*) Les conséquences de ces infections continuent de représenter un lourd fardeau pour l'humanité. En 2008, le nombre de morts dues aux maladies infectieuses était estimé à plus de 8,7 millions par l'Organisation Mondiale de la Santé (OMS), soit plus d'un sixième de la mortalité mondiale.

L'impact de ces maladies est bien entendu distribué de manière très inégale au sein de la population mondiale. Pour la majorité des maladies infectieuses, les plus forts taux de morbidité et de mortalité sont observés dans les pays émergents, plus particulièrement ceux situés dans les zones tropicales (OMS). Parmi les facteurs expliquant cette hétérogénéité, les différences de statuts socio-économiques entre populations sont depuis longtemps mises en avant (Winslow, *1951*). En effet, non seulement les maladies infectieuses touchent les populations les plus pauvres, mais bien souvent elles contribuent à renforcer leur pauvreté (Hotez, *2008*), et se placent ainsi comme des obstacles supplémentaires au développement de pays qui sont déjà les moins riches (Conteh et al., *2010*). Malgré tout, la vulnérabilité de l'homme face aux maladies infectieuses semble vouée à demeurer un souci d'ordre mondial. L'intensité actuelle des migrations humaines (Arguin et al., *2009*) et animales (Alitzer et al., *2011*), ainsi que celle des échanges commerciaux (Tatem et al., *2006*), participent à la dissémination des agents pathogènes et de leurs hôtes vecteurs à travers le monde. Les prédictions sur l'évolution du climat sont régulièrement associées à une augmentation des populations à risque de rencontrer certains pathogènes (Cooney, *2011*), et l'urbanisation ainsi que les multiples modifications de l'environnement sont souvent associées à des risques accrus de zoonoses (Colwell et al., *2011*). Enfin, le développement de résistances des pathogènes (Goldberg et al., *2012*) ou de leurs vecteurs (Raghavendra et al., *2011*) aux stratégies de contrôle mises en place contribue à la persistance de certaines maladies. Dans un monde connaissant de nombreux et rapides changements globaux, la lutte contre les maladies infectieuses ne se conjugue donc pas seulement au présent, mais constitue bel et bien un des défis majeurs pour le futur de l'ensemble de l'humanité (Varmus et al., *2003* ; May, *2007*).

Si l'impact des maladies infectieuses est distribué de manière inégale entre les populations humaines, il l'est aussi entre maladies. En 2008 le nombre de morts dus aux seuls sida, malaria et tuberculose était estimé à plus de 3,9 millions, soit près de la moitié de la mortalité due aux maladies infectieuses (OMS). Le poids combiné de ces 3 maladies dans les bilans sanitaires est devenu si important qu'il leur a été données le nom de « big three » (Hotez et al., *2006*). Ces « big three » constituent bien entendu la cible prioritaire de nombreuses campagnes de sensibilisation et de programmes de contrôle (Hotez et al., *2006*). Justifiée ou non, la concentration de ces efforts sur ces trois maladies est telle que d'autres maladies infectieuses sont « négligées », tant en termes de fonds investis et de programmes de recherche, que de politiques de santé publique (Payne & Fitchett *2010*). Beaucoup de ces maladies affectent tout particulièrement les populations vivant dans les zones rurales ou les zones urbaines à faibles revenues d'Afrique, d'Asie et d'Amérique latine (First WHO report on neglected tropical diseases, *2010*). Depuis le milieu des années 2000, ces maladies sont communément regroupées sous le terme de « maladies tropicales négligées » - ou « NTD » pour « Neglected Tropical Diseases ». Ceci a probablement contribué à une prise de conscience de l'importance de ces maladies et de la nécessitée d'y apporter des réponses scientifiques et politiques. Ceci a notamment conduit à la création d'un département « Maladies Tropicales Négligées » au sein de l'Organisation Mondiale de la Santé (OMS), et à la naissance d'un journal scientifique, « The Public Library of Science - Neglected Tropical

Diseases» (PLoS NTD), entièrement dédié à ces maladies.

Positionnement général et contribution spécifique de cette thèse

Les travaux effectués au cours de ce doctorat portent sur l'écologie, l'évolution et le contrôle des maladies infectieuses, et pour l'essentiel, des maladies tropicales négligées. L'approche adoptée est celle de la biologie théorique, et repose sur la modélisation par les systèmes dynamiques. Il existe une littérature théorique, relativement riche qui met en relation l'écologie, l'évolution et le contrôle des 3 principales maladies infectieuses évoquées ci-dessus. C'est le cas notamment pour la malaria dont l'étude est depuis longtemps associée à des développements théoriques (Smith et al., *2012*), ou encore le sida (Pinkerton *2011*), dont la première épidémie n'a pourtant été identifiée que dans les années 1980. L'usage de la modélisation pour comprendre la transmission des maladies tropicales négligées est lui considérablement plus réduit (Kealey & Smith *2010*) et ceci constitue un paradoxe. En effet, dans des contextes économiques et éthiques contraignant les approches expérimentales tant en laboratoire qu'en milieu naturel, l'approche théorique offre la possibilité, à des coûts excessivement modestes, de mettre à l'épreuve quantitative des hypothèses sur les processus naturels. Elle permet en effet d'intégrer des données empiriques accumulées au cours du temps par des suivis épidémiologiques et/ou entomologiques réalisés par différentes équipes de recherche ou par les services de surveillance entomologique et de santé publique (Lord *2007*; Luz et al., *2010*). Elle permet également de tester *in silico* des stratégies de contrôle qui ne pourraient tout simplement pas l'être *in situ* pour des raisons purement matérielles et/ou éthiques (Cohen *2004*). Elle permet finalement d'étudier, de façon plus abstraite, et dans une certaine mesure de façon plus indépendante des données, l'influence de processus naturels et de leur interactions sur l'écologie, l'évolution et le contrôle des pathogènes, et de leurs hôtes et vecteurs (Diekmann & Heesterbeek, *2000*; Dieckmann et al., *2002*).

Au cours des 5 chapitres de cette thèse je vais m'efforcer d'illustrer quel peut être l'intérêt d'une approche de modélisation pour mener des recherches fondamentales servant à mieux comprendre et lutter contre la transmission des maladies tropicales négligées. Dans le premier chapitre, je présente une revue de la littérature concernant les maladies tropicales négligées afin de déterminer si celles-ci ont été véritablement négligées d'une façon générale et sur le plan théorique, et de recenser les travaux théoriques existants sur l'écologie, évolution et le contrôle de ces maladies. Dans les chapitres 2, 3 et 4, je présente les trois contributions théoriques que j'ai apportées à l'étude de ces maladies. La première permet d'identifier les facteurs clés de la transmission des principales maladies vectorielles affectant l'homme dans des zones où les populations de vecteurs sont des populations « puits », c'est a dire des populations incapables de se maintenir de façon autonome et donc soutenues par des processus d'immigration depuis des populations « sources » (Pulliam *1988* ; Dias *1996*). Il s'agit d'une extension de la littérature théorique en épidémiologie qui ce concentre pour l'essentiel sur les populations sources de vecteurs que l'on en rencontre classiquement dans les zones à fort endémisme. Ce travail permet de mieux comprendre la transmission en périphérie des niches écologiques des vecteurs, et dans des zones où le contrôle des vecteurs ne permet pas d'éliminer complètement les populations de vecteurs. Les chapitres 2 et 3 traitent de l'évolution adaptative de macro-parasites induite par les interactions intra-hôtes qui s'établissent avec les parasites co-infectants soit directement, au travers de mécanismes de compétition, soit indirectement, au travers des effets sur l'hôte. L'approche est ici beaucoup plus abstraite et prospective. Il s'agit de déterminer les conditions dans lesquelles les interactions intra-hôte pourraient conduire à la diversification de ces parasites, qui sont entre

autres responsables de maladies tropicales négligées très répandues, telles que la schistosomiase ou les helminthiases intestinales. Il s'agit d'une extension de la théorie de la spéciation compétitive qui est développée depuis plus de 30 ans pour les espèces non-parasites, et qui n'avait jusque la jamais été adaptée pour tenir compte des spécificités du mode de vie parasitaire. Elle permet de commencer à analyser quantitativement les processus de duplication intra-hôte, dont la détection dans les co-phylogénies hôte-parasite semble de plus en plus fréquente. Le dernier chapitre discute de l'intérêt des approches comparatives (chapitre 2) ou généraliste (chapitre 3 et 4) présentées dans cette thèse pour une meilleure compréhension et un meilleur contrôle des maladies tropicales négligées, et plus largement, des maladies infectieuses en général.

Chapitre 1

Les maladies tropicales négligées : mises perspectives de leur impact sanitaire avec la production scientifique et théorique

1. Les maladies tropicales négligées (« NTD »)

1.1 Diversité et similitudes

Les maladies tropicales négligées (NTD) peuvent être définies comme un groupe de maladies infectieuses que l'on rencontre surtout dans les zones rurales ou dans les zones urbaines et pauvres des pays à revenu faible et intermédiaire (Frew et al., *2009*), et qui constituent elles-mêmes des facteurs aggravant de pauvreté. A ce jour, le département Maladies Tropicales Négligées de l'OMS a constitué une liste de 20 conditions dont 18 maladies infectieuses qui répondent à cette définition. Au sein de cette liste 9 maladies sont dues à l'infection par un organisme viral, bactérien ou protozaire: la dengue, la rage, la lèpre, le pian, le trachome, l'ulcère de Buruli, la maladie de Chagas (souvent appelée trypanosomiase américaine), la leishmaniose et la trypanosomiase humaine africaine (souvent appelée maladie du sommeil); et 9 maladies sont dues à l'infection par un ver, appelées aussi « helminthiases » : la cysticercose, la dracunculose (ou ver de Guinée), l'échinococcose, la fasciolase, la filariose lymphatique, l'onchocercose, la schistosomiase (aussi appelée bilharziose), les helminthiases intestinales (l'ascaridiose, la trichocéphalose et l'ankylostomose) et la strongyloïdose (aussi appelée anguillulose).

Outre le fait qu'elles touchent surtout les populations les plus défavorisées des zones tropicales, les maladies tropicales négligées ont en commun de nombreux effets sur la santé et l'histoire de vie des individus qui les contractent. Celles-ci ont tendance à se manifester sous diverses formes d'infirmité et de séquelles perdurant à long terme (défigurement, cécité), à affaiblir le développement infantile et détériorer le déroulement des grossesses, et à réduire la productivité des travailleurs malades, tous ces stigmates contribuant eux-mêmes à renforcer la pauvreté des populations touchées (Hotez et al., *2007* ; First WHO report on neglected tropical diseases, *2010*).

1.2 Risques et impact sanitaires

Impact sanitaire des maladies tropicales négligées. Selon la maladie considérée, le nombre de personnes à risque de contracter une NTD dans le monde va de plusieurs dizaines de millions, par exemples pour la maladie de Chagas et la maladie du sommeil, à plusieurs milliards pour les helminthiases intestinales (Hotez et al., *2007*). Malgré l'existence d'interventions à la fois peu coûteuses et économiquement rentables pour la filariose lymphatique, l'onchocerciase ou encore les helminthiases intestinales (First WHO report on neglected tropical diseases, *2010*), leurs prévalences peuvent encore s'élever jusqu'à plusieurs dizaines voire centaines de millions de personnes, comme c'est le cas pour la schistosomiase (tableau 1). La mortalité causée par les NTD à l'échelle mondiale est grande elle aussi. D'après les statistiques de l'OMS, en 2008 celle-ci dépassait les 250.000 morts, un chiffre

comparable voire supérieur aux nombres de morts dues aux maladies sexuellement transmissibles hors-sida, ou encore à des conditions non transmissibles telles que la guerre et les conflits civils, et nombreuses formes de cancers. L'OMS estime généralement l'impact d'une maladie par un indice tenant compte de la réduction de l'espérance de vie et du nombre d'années de vie passées en bonne santé qui sont imputables à la maladie. Cet indice mesure la perte de DALYs, pour « Disease-Adjusted Life Years » (Gold et al., *2002*). Le fardeau que représentent les maladies tropicales négligées apparaît alors de façon très évidente. Le nombre de DALYs perdus annuellement place les NTD en 6ème position parmi les maladies transmissibles, devant les méningites ou encore les maladies sexuellement transmissibles hors-sida (OMS). En outre, à l'échelle locale, certaines NTD peuvent parfois être les maladies ayant le plus fort impact sur les populations. En Amérique latine plusieurs NTD, et notamment la maladie de Chagas, causent bien plus de mortalité que la malaria (OMS). Au Proche et Moyen Orient, la schistosomiase causait en 2008 davantage de morts que le sida (OMS). En Asie du sud-est, les pertes de DALYs causées par l'ensemble des NTD en 2004 étaient supérieures à celles causées par le sida ou la malaria, avec une forte part due à la filariose lymphatique et à la leishmaniose (OMS).

Interactions entre maladies tropicales négligées et autres maladies infectieuses. Nombreuses maladies tropicales négligées ont des aires de distribution qui se recouvrent et qui correspondent également à celles des trois principales maladies infectieuses affectant l'homme. Ainsi dans certaines régions une forte proportion des populations doit faire face au poly-parasitisme, en particulier aux co-infections par des helminthes et un certain nombre de micro-parasites, incluant les agents pathogènes responsables de la malaria ou du sida (Hotez et al., *2006*). Si les effets de ces infections mixtes sont encore mal connus, ils semblent néanmoins pouvoir amplifier la morbidité de certaines NTD, et celles des trois principales maladies infectieuses. En Afrique par exemple, on a observé des degrés d'anémie plus sévères chez les personnes souffrant simultanément de la malaria, d'helminthiases intestinales et/ou de la schistosomiase, que chez les personnes atteintes par une seule de ces maladies. (Midzi et al., *2010*). De part la capacité de certains pathogènes à affecter le système immunitaire humain, ces infections mixtes peuvent aussi renforcer la susceptibilité des malades envers d'autres pathogènes (Pedersen & Fenton, *2006*). Les personnes atteintes d'helminthiases auraient ainsi plus de risques d'être par la suite co-infectées par la malaria (Mwangi et al., *2006*) ou le virus du sida (Fincham et al., *2003*). Il semblerait donc que, à une échelle locale tout du moins, les NTD puissent jouer un rôle significatif dans la dynamique épidémiologique et la lutte contre des maladies qui sont, par contre, « non-négligées ».

Globalisation des maladies tropicales négligées. Bien que la plupart des maladies tropicales négligées se contractent dans des zones tropicales, les globalisations diverses et les changements climatiques en font également une menace croissante pour la santé publique des pays tempérés. Plusieurs épidémies ou risques d'épidémies de maladies qui étaient jusque là confinées à des zones tropicales sont ainsi attribués à l'introduction de pathogènes par des touristes, migrants (Vazeille et al., *2007* ; Norman et al., *2010*) ou animaux (Altizer et al., *2011*) issues des zones endémiques, ainsi qu'à l'introduction (Derraik *2006*) et l'extension jusque dans les milieux tempérés des niches écologiques (González et al., *2010*) des vecteurs.

Les maladies tropicales négligées constituent donc un enjeu scientifique et de santé publique essentiel, non seulement parce que le fardeau qu'elles font peser directement sur les populations des pays tropicaux est très importants, mais également parce qu'elles interagissent avec les autres principales maladies affectant ces populations, et enfin car leur impact tend à dépasser substantiellement le contexte tropical.

Tableau 1. Impact sanitaire des maladies du Big three et des maladies tropicales négligées : estimations récentes et distribution géographique. Tous les chiffres du tableau sont exprimés en « milliers ». Les données présentées correspondent aux estimations données par l'OMS pour la période 2004 – 2011, complétées par d'autres travaux (Hotez et al., *2006, 2007*).

	Mortalité annuelle	**DALYs perdus/an**	**Prévalence** ou *nombre de nouveaux cas par an*
Sida	1.776	58.513	31.395
Tuberculose	1.342	34.217	*11.100*
Malaria	827	33.976	*241.340*
Rage	55	1.740	*382*
Dengue	16	670	*8.951*
Lèpre	12	194	192
Trachome	0,08	1.334	6.246
Pian	0	-	2.500
Ulcère de Buruli	-	-	*5*
Maladie du sommeil	54	1.673	30
Leishmaniose	26	1.974	12.000
Maladie de Chagas	10	430	6.508
Cysticercose	50	-	-
Schistosomiase	44	1.707	261.054
Helminthiases intestinales	3	3.955	150.942
Strongyloïdose	1,4	58	65.000
Echinococcose	0,25	3.600	1.200
Filariose lymphatique	0,19	5.941	65.458
Onchocerciase	0,08	389	907
Fasciolase	-	-	2.400
Dracunculose	-	100	10
Big three	**3.945**	**126.706**	
NTD	**272**	**23.764**	

1.3 Contrôle des maladies tropicales négligées

Les stratégies de contrôle employées contre les maladies tropicales négligées varient d'une maladie à l'autre, et sont détaillées dans le tableau 2. Parmi les 18 NTD considérées ici, seule la lutte contre la strongyloïdose n'a toujours pas bénéficiée du développement de stratégies de santé publique spécifiques (OMS).

Le contrôle des NTD commence souvent par une meilleure éducation et une meilleure information sur les comportements à adopter pour limiter la transmission des pathogènes. De telles stratégies reposent typiquement sur des indications relatives à l'hygiène de vie et l'aménagement de l'habitat humain. Par leur comportement, les populations informées peuvent ainsi réduire le risque d'exposition aux pathogènes (maladie de Chagas, cysticercose, échinococcose, dracunculose, trachome) et/ou aux vecteurs (dengue, maladie de Chagas, trachome).

Tableau 2. Maladies tropicales négligées : principales stratégies de contrôle, zones où elles ne représentent plus un problème de santé publique, et tendances épidémiologiques à court et moyen terme (Feasey et al., *2009*, First WHO report on neglected tropical diseases).

	Stratégies de contrôle	**Zones assainies**	**Tendances**
Rage	Contrôle ou traitement des hôtes animaux, médication thérapeutique, vaccin	Europe de l'ouest, et la plupart des zones urbaines d'Amérique latine	Risque d'augmentation du fardeau économique
Dengue	Aménagement de l'habitat, contrôle des vecteurs		Augmentation globale de l'incidence et de la distribution géographique
Lèpre	Détection, médication thérapeutique	119 pays des 122 pays considérés comme endémiques	Incidence annuelle réduite à un niveau stable depuis 2005
Trachome	Stratégie « SAFE » : chirurgie, médication thérapeutique, hygiène faciale et aménagement de l'habitat	Iran, Maroc, Oman	Elimination globale en tant que cause de cécité d'ici 2020
Pian	Médication thérapeutique	Nombreux pays à travers le monde	Manque d'information. Ré-émergences locales
Ulcère de Buruli	Détection, médication thérapeutique		Manque d'information
Mal. du sommeil	Détection, médication thérapeutique, contrôle des vecteurs, contrôle ou traitement des hôtes animaux	Plusieurs pays d'Afrique sub-saharienne	Risques de ré-émergences
Leishmaniose	Détection, médication thérapeutique, contrôle des vecteurs et des hôtes animaux		Augmentation globale de l'incidence et de la distribution géographique. Emergence des co-infections avec le sida. Risque de résistance du pathogène aux médications thérapeutiques.
Mal. de Chagas	Contrôle des vecteurs, aménagement de l'habitat, hygiène de vie, surveillance des dons de sang ou d'organes, contrôle ou traitement des hôtes animaux		En déclin, mais risques de ré-émergences et d'expansion géographique
Cysticercose	Détection, contrôle ou traitement des hôtes animaux, hygiène de vie, aménagement de l'habitat		Manque d'informations globales. Risque d'augmentation de l'incidence dans les pays endémiques.
Schistosomiase	Médication thérapeutique, assainissement des eaux, contrôle des vecteurs, aménagement de l'habitat	A confirmer pour plusieurs pays à travers le monde	En voie d'élimination dans plusieurs pays, mais risque d'augmentation global de la transmission
Helm. intestin.	Médication thérapeutique		Risque de résistance du pathogène aux médications thérapeutiques
Strongyloïdose	Aucune stratégie de santé publique développée à ce jour		Manque d'information
Echinococcose	Contrôle ou traitement des hôtes animaux, campagne d'information, hygiène alimentaire		Problème de santé publique ré-émergent dans plusieurs pays
Filariose lymph.	Médication préventive et thérapeutique, contrôle des vecteurs, aménagement de l'habitat	Plusieurs pays d'Afrique, d'Amérique, d'Asie et du Pacifique	En déclin dans nombreux pays
Onchocerciase	Médication thérapeutique, contrôle des vecteurs		Risques de ré-émergences et de résistance du pathogène aux médications thérapeutiques
Fasciolase	Médication préventive et thérapeutique		Risque d'augmentation de l'incidence et du fardeau économique
Dracunculose	Détection, confinement des individus infectés, assainissement des eaux, contrôle des vecteurs, campagne d'information	Plusieurs pays d'Afrique et d'Asie	En voie d'éradication

Le contrôle des NTD fait aussi appel à une meilleure surveillance épidémiologique, et donc à la détection des individus infectés, afin de pouvoir les traiter mais aussi de réduire leur chance de transmettre le pathogène (lèpre, ulcère de Buruli, maladie du sommeil, leishmaniose, maladie de Chagas, cysticercose, dracunculose). Dans le cas de la dracunculose, la détection d'individus infectés est souvent suivie d'une mise en confinement, toujours afin de réduire leur chance de transmettre le pathogène.

Sans surprise, les stratégies de santé publique développées pour contrôler la grande majorité des NTD impliquent l'administration de soins thérapeutiques aux individus infectés: rage (pour laquelle il existe même un vaccin), lèpre, trachome, pian, ulcère de Buruli, maladie du sommeil. leishmaniose, schistosomiase, helminthiases intestinales, filariose lymphatique, onchocerciase, fasciolase.

Nombreuses NTD sont transmises par des insectes vecteurs. La lutte contre ces maladies passe donc souvent par le contrôle de ces mêmes vecteurs, comme c'est le cas pour la dengue, la maladie du sommeil, la leishmaniose, la maladie de Chagas, la schistosomiase, la filariose lymphatique, l'onchocerciase et la dracunculose.

Nombreuses NTD persistent également grâce à l'existence d'hôtes animaux. Une stratégie de lutte contre ces maladies consiste donc à contrôler la démographie de ces animaux (abattage, stérilisation) et/ou à traiter les animaux infectés. Dans la grande majorité des cas, les animaux visés sont domestiques et/ou à forte valeur économique, comme les chiens (rage, leishmaniose, maladie de Chagas, échinococcose) et le bétail (rage, maladie du sommeil, cysticercose, échinococcose).

La lutte contre les maladies tropicales négligées a déjà remporté des succès notoires. Il existe notamment des traitements ou médications particulièrement efficaces, comme par exemples l'utilisation d'anitibiotiques (rifampicine, streptomycine, benzathine penicilline, dapsone et clofazimine) contre l'ulcère de Buruli, le pian et la lèpre, ou de fermifuges (ivermectine, albendazole, diéthylcarbamazine) contre la filariose lymphatique, et même un vaccin contre la rage (First WHO report on neglected tropical diseases).

Certaines maladies tropicales négligées font depuis longtemps l'objet de programmes de lutte spécifiques, et il existe également des possibilités de lutte simultanée contre plusieurs de ces maladies (First WHO report on neglected tropical diseases). L'administration d'ivermectine agit par exemple contre plusieurs helminthiases, comme l'onchocerciase, la filariose lymphatique ou les helminthiases intestinales. Finalement, la lutte contre les maladies du Big three pourrait elle-même bénéficier d'un meilleur contrôle des NTD, c'est pourquoi de plus en plus d'auteurs appellent à intégrer les efforts de lutte contre ces 2 groupes de maladies (Hotez et al., *2006* ; Emerson et al., *2008*).

Grâce à l'amélioration et/ou la combinaison de ces multiples stratégies de lutte, la transmission de nombreuses maladies tropicales négligées est en déclin, comme la maladie de Chagas ou la filariose lymphatique (tableau 2). De même, certaines NTD ne représentent plus un problème de santé publique dans nombreux pays à travers le monde, comme la lèpre ou le pian, et sont même en voie d'éradication globale, comme la dracunculose (tableau 2).

Si l'impact sanitaire des maladies tropicales négligées est en diminution globale, certaines d'entre elles sont malheureusement en expansion ou en ré-émergence, comme la dengue et l'échinococcose (tableau 2). Les risques de ré-emergence persistent aussi pour celles dont la surveillance manque de suivi épidémiologique, comme le pian par exemple, et même pour certaines maladies dont de nombreux foyers de transmission sont pourtant sous contrôles, comme la maladie du sommeil ou l'onchocerciase (tableau 2). Qui plus est, des risques de développement de résistance des agents pathogènes aux traitements thérapeutiques sont aussi confirmés ou suggérés pour la leishmaniose (Sundar et al., *2000*), les helminthiases

intestinales et la schistosomiase (Geerts & Gryseels *2000*), ainsi que l'onchocerciase (Osei-Atweneboana et al., *2007*).

L'effort de lutte contre toutes les maladies tropicales négligées nécessite donc d'être maintenu. De nouvelles médications (Frew et al., *2009*) ou stratégies de lutte contre les NTD continuent d'être proposées ou développées, comme par exemples celles permettant une meilleure intégration des efforts de lutte contre les différentes helminthiases (Hotez et al., *2007)* ou contre les différents hôtes vecteurs (van den Berg et al., *2012*). Enfin, nombreux pays se sont engagés dans des plans de lutte contre les NTD dont les objectifs vont parfois jusqu'à l'éradication d'ici la fin de la décennie actuelle (First WHO report on neglected tropical diseases).

2. Production scientifique sur les maladies tropicales négligées

Je propose dans les pages qui suivent un bilan quantitatif des efforts réalisés pour étudier l'écologie, l'évolution et le contrôle des maladies tropicales négligées. Dans un premier temps, je compare la production scientifique globale produite pour les NTD et pour les Big three ainsi que la production scientifique globale au sein du groupe des NTD. Dans un deuxième temps, je compare de la même manière les contributions théoriques traitant des NTD et des Big three, ainsi que la répartition de ces contributions entre les différentes NTD et entre les différents champs que sont l'écologie, l'évolution et le contrôle.

2.1 Publications scientifiques

Les maladies tropicales présentes dans le tableau 1 sont dites négligées. L'objectif de cette première partie est d'établir si ces maladies sont effectivement négligées en termes de production scientifique globale et théorique.

Les maladies tropicales négligées le sont-elles en termes de production scientifique ?

Afin d'apporter des éléments de réponse à cette question j'ai répertorié le nombre de résultats de recherche obtenu sur la base de données bibliographiques Pubmed (National Center for Biotechnology Information), en utilisant comme mots clefs la traduction anglaise du ou des noms communs des 18 NTD (voir Annexe A.1.), et ce pour une période s'étalant du 1er janvier 1800 (date la plus ancienne qu'il soit possible de spécifier dans Pubmed) au 31 décembre 2011.

Sans surprise, le nombre de résultats obtenus pour les Big three (474920) surpasse largement - de plus de 3 fois - celui obtenu pour l'ensemble des NTD (146541) (tableau 3). Néanmoins, cette moindre production scientifique ne signifie pas nécessairement que l'étude de ces maladies est véritablement négligée par les scientifiques. Pour se faire une meilleure idée de ces efforts relatifs, ces données doivent être mises en relation avec l'impact qu'on les maladies sur les populations humaines. J'ai donc calculé le ratio entre le nombre de publications produites et deux des indicateurs les plus classiques de l'impact sanitaire que sont le nombre de morts causées et le nombre de DALYs perdus à travers le monde (tableau 3).

Tableau 3. Big three vs NTD : production scientifique et impact sanitaire récent.

	Période	Résultats Pubmed	Mortalité annuelle		DALYs perdus/an	
			Estimations	Ratio pub./impact (10^{-02})	Estimations	Ratio pub./impact (10^{-04})
Big three	**1800-2011**	474920	3945.10^{03}	12	127.10^{06}	37
	2005-2011	142678		4		11
NTD	**1800-2011**	146541	272.10^{03}	54	24.10^{06}	62
	2005-2011	31126		11		13

Lorsque l'on compare ces productions scientifiques aux estimations de l'impact sanitaire de ces 2 groupes de maladies, le ratio nombre de publications/impact sanitaire est, de façon assez surprenante, en faveur des NTD. Le ratio publications/mortalité des NTD (54.10^{-02}) est ainsi 4,5 fois supérieur à celui des Big three (12.10^{-02}), et la ratio publication/DALYs est lui 1,7 fois supérieur ($62.\ 10^{-04}$ contre 37.10^{-04}). Bien que la production scientifique totale soit largement inférieure à celle concernant les Big three, celle-ci n'est donc pas biaisée au regard du fardeau que représente ce groupe de maladies.

Il est possible que les ratio publications/impact sanitaire calculés pour les maladies tropicales négligées soient surestimés, car certaines données sur l'impact de ces maladies manquent (voir tableau 1), et parce que le handicap qu'elles causent est souvent sous-estimé (Feasey et al., *2009*, Fenwick *2012*). Néanmoins un rapide calcul indique qu'il faudrait que ce biais soit respectivement de l'ordre de 1 pour 14,6 et 1 pour 5,4 pour que la quantité de publications concernant les NTD soit directement proportionnelle, respectivement, à la mortalité et aux pertes de DALYs qu'elles induisent. On pourrait également objecter que sont comparées des estimations récentes des impactes sanitaires, et un nombre cumulé de publications scientifiques sur une large période de temps. Les chiffres du tableau 3 ne tiennent pas compte, par exemple, du fait que certaines maladies – comme la tuberculose, la rage ou la lèpre – existent où ont existé sous la forme d'endémismes pendant de nombreuses années dans certains pays, et sont donc susceptibles d'avoir cumulé au cours du temps davantage de publications scientifiques que des maladies dont l'apparition (le sida par exemple) ou l'intérêt des scientifique (pour la dengue par exemple) a pu augmenter plus récemment. Afin d'évaluer ce possible biais j'ai effectué les mêmes comparaisons que précédemment, mais pour une période allant des années 2005 à 2011 (tableau 3). Là encore, le nombre de publications sur les Big three dépasse largement le nombre de publications concernant les NTD, - d'un facteur 4,6, tandis que les différences de ratios publications/impact demeurent favorables pour les NTD mais à des degrés moindres que sur la plus large période (facteur 2,8 pour la mortalité et 1,2 pour les DALYs). L'augmentation du rapport entre la production pour les Big three et les NTD est due à une croissance du nombre d'études portants sur le sida (depuis les années 1980) qui se fait à une vitesse beaucoup plus grande que l'accumulation des études portants sur les NTD (voir figure A.1 dans l'annexe A). Malgré cela, les ratios publications/impacts des NTD restent supérieurs à ceux des Big three.

La production scientifique concernant les maladies tropicales négligées n'apparait donc pas particulièrement faible lorsqu'elle est comparée à l'impact de ces maladies sur les populations humaines.

Existe-t-il des maladies tropicales effectivement négligées en termes de production scientifique ?

Collectivement, les maladies tropicales négligées n'apparaissent donc pas négligées par la communauté scientifique, mais il est possible qu'il existe une certaine hétérogénéité dans la production entre ces maladies. Comme précédemment, j'ai donc comparé le nombre

de publications parues entre 1800 et 2011, ainsi que des estimations récentes de leurs impacts sanitaires, mais cette fois pour chacune des 18 NTD (tableau 4). Le nombre absolu de publications est effectivement très hétérogène entre les maladies. Le pian ou l'ulcère de Buruli représentent moins de 1% des publications à eux deux, alors que la somme des publications concernant la schistosomiase, la lèpre, la leishmaniose et l'échinoccose représente plus de 57% des publications sur les NTD. On observe aussi une forte hétérogénéité dans les ratios publications/impacts. En comparant ces ratios à ceux des Big three (tableau 3), on peut classer ces maladies selon 3 groupes, définis comme le groupe des maladies « non-négligées », dont les ratios sont supérieurs ou égaux à ceux des Big three, le groupe des maladies « négligées », dont les ratios sont inférieurs à ceux des Big three (signalés par une étoile dans le tableau 4), et parmi celles-ci, des maladies « très négligées » lorsque les ratios ne dépassent la moitié des valeurs observées pour les Big three (signalés par deux étoiles dans le tableau 4). Confirmant les résultats précédent, on peut ainsi montrer que la plupart des NTD pour lesquelles des estimations ont été répertoriées sont « non-négligées » pour la période allant jusqu'à 2011. Seules apparaissent « négligées » la maladie du sommeil, la cysticercose et le trachome si l'on considère leur impact sanitaire en termes de mortalité ou de DALYs, respectivement. Apparaissent par contre comme «très négligées » les helminthiases intestinales et la filariose lymphatique si l'on considère leur impact en terme de DALYs. Enfin, la comparaison n'est pas possible pour certaines maladies du fait de l'absence d'estimations récentes de leur impact sanitaires (voir tableau 1). Comme précédemment, j'ai aussi calculé ces ratios pour la période 2005–2011. Là aussi la plupart des NTD apparaissent comme « non-négligées » par rapport aux Big three. Si l'on se réfère à la mortalité causée, seules la cysticercose et la maladie su sommeil apparaissent comme « très négligées », et si l'on se réfère aux DALYs perdus, l'échinococcose et la maladie du sommeil apparaissent comme « négligées », les helminthiases intestinales, le trachome et la filariose lymphatique comme « très négligées ».

On peut donc conclure qu'en termes de publications scientifiques, certaines maladies tropicales sont bel et bien négligées voire très négligées, mais celles-ci sont en plus petit nombre que ce qui est communément admis, et ces degrés de négligence dépendent beaucoup du type d'impact sanitaire considéré. La seule maladie qui apparaisse négligée ou très négligée par les études scientifiques lorsque l'on considère à la fois la mortalité et les pertes de DALYs est la maladie du sommeil, ce qui ne fait que renforcer l'idée selon laquelle elle fait partie des maladies répondant le plus à la définition des maladies tropicales négligées (Feasey et al., *2010*).

Tableau 4. Maladies tropicales négligées : production scientifique et impact sanitaire récent. Les ratios publications/impact sanitaire sont calculés en utilisant les estimations répertoriées dans les colonnes 2 et 3 du tableau 1.

	Résultats Pubmed (% des NTD)		Ratio publications/impact Mortalité annuelle ($.10^{e-02}$)		DALYs perdus/an ($.10^{e-04}$)	
	1800-2011	**2005-2011**	**1800-2011**	**2005-2011**	**1800-2011**	**2005-2011**
Schistosomiase	26931 (18,4)	4321 (13,3)	61	10	158	25
Lèpre	22448 (15,3)	2817 (8,7)	192	24	1158	145
Leishmaniose	17827 (12,2)	5584 (17,2)	69	21	90	28
Echinococcose	16448 (11,2)	2696 (8,3)	6553	1074	46	7*
Rage	11669 (8,0)	2218 (6,8)	21	4	67	13
Mal. de Chagas	11669 (7,7)	3460 (10,6)	114	35	262	80
Dengue	9290 (6,3)	4563 (14,0)	58	28	139	68
Helm. intestin.	7496 (5,1)	778 (2,4)	270	28	19**	2**
Cysticercose	5295 (3,6)	1150 (3,5)	11*	2**	-	-
Trachome	4085 (2,8)	581 (1,8)	5044	717	31*	4**
Onchocerciase	4032 (2,8)	526 (1,6)	4838	631	104	14
Mal. du sommeil	3913 (2,7)	1345 (4,1)	7*	2**	23*	8*
Fasciolase	3228 (2,2)	676 (2,1)	-	-	-	-
Strongyloïdose	3163 (2,2)	560 (1,7)	220	39	544	96
Filariose lymph.	1855 (1,3)	710 (2,2)	1003	384	3**	1**
Dracunculose	1854 (1,3)	189 (0,6)	-	-	185	19
Pian	868 (0,6)	53 (0,2)	-	-	-	-
Ulcère de Buruli	485 (0,3)	298 (0,9)	-	-	-	-
NTD	**146541**	**32525**	**54**	**11**	**62**	**13**

Quelle est la part des études théoriques dans les publications sur les maladies tropicales négligées ?

Dans le cadre de cette thèse, il était également important de s'intéresser plus spécifiquement aux travaux théoriques concernant les maladies tropicales négligées. J'ai donc répertorié le nombre de publications théoriques sur les Big three et les NTD, toujours sur la base de données bibliographiques collectées dans Pubmed. J'ai pour cela ajouté à la recherche précédente les mots clés « AND((MATHEMATICAL)AND(MODEL*)) ». L'utilisation des approches théoriques en biologie s'étant significativement développée dans les dernières décennies, j'ai à nouveau réalisé ma recherche non seulement entre 1800 et 2011, mais aussi entre 2005 et 2011. (tableau 5).

Tableau 5. Big three vs NTD : production scientifique théorique. Entre parenthèse sont donnés les ratios production théorique/scientifique calculés à partir des données du tableau 3, et exprimés en taux de 1 pour 1000.

	Période	Sida	Tuberculose	Malaria	Big three	NTD
Résultats Pubmed	**1800-2011**	1099 (4,7)	212 (1,1)	283 (4,7)	1538 (3,2)	331 (2,3)
	2005-2011	568 (6,5)	116 (3,4)	157 (8,2)	808 (5,7)	159 (5,1)

Sans surprise, le taux de contribution théorique est supérieur pour la période 2005-2011 pour les Big three comme pour les maladies tropicales négligées. Le nombre de travaux répertoriés est supérieur pour les Big three quelque soit la période considérée; il est 1,4 fois supérieur entre 1800 et 2011, et 1,1 fois supérieur ente 2005 et 2011. On peut d'ailleurs remarquer que la quantité d'articles produits pour les 18 NTD est approximativement la même que pour la seule malaria; 331 vs 283 entre 1800 et 2011, et 159 vs 157 entre 2005 et 2011. Néanmoins les taux de contribution théorique se sont resserrés entre les Big three et les NTD, si bien que la différence entre eux n'est statistiquement significative que sur la période 1800-2011 (test de proportion: p-value<3E-09). Aujourd'hui, la contribution des travaux

théoriques à la production scientifique globale pour les NTD est donc sensiblement la même que pour les Big three (p-value=0.25).

La contribution des travaux théoriques à l'étude des maladies tropicales négligées paraît donc faible, puisqu'elle est systématiquement inférieure à 10‰ des publications scientifiques (tableau 5). Dans un exercice de revue similaire à celui effectué ici, Otto et Day (*2001*) ont estimé que le pourcentage de publications faisant appel à des modèles théoriques non statistiques était de 59% dans *American Naturalist*, 35% dans *Ecology* et 35% dans *Evolution*. Une partie de cette différence est probablement expliquée par la différence entre les méthodes de recherche et la diversité des revues concernées. Comme le faisaient remarquer Otto et Day (*2001*), l'utilisation du mot clé « Math » ne permet pas de répertorier la totalité des modèles théoriques. En outre il est vraisemblable que les 3 revues citées ci-dessus soient particulièrement ouvertes aux travaux de modélisation. Néanmoins, le chiffre de 10‰ reste indéniablement très faible et très vraisemblablement l'approche théorique fait globalement défaut dans l'étude des maladies tropicales négligées.

Tout comme précédemment, à la suite de ces comparaisons globales, se pose la question des hétérogénéités entre maladies tropicales négligées.

Quelles sont les maladies tropicales négligées étudiées par les approches théoriques ?

On observe effectivement une grande hétérogénéité à la fois dans le nombre de publications théoriques concernant les différentes maladies tropicales négligées et ce qu'elles représentent par rapport à l'ensemble de la littérature les concernant. Pour les périodes 1800-2011 et 2005-2011, le nombre de travaux théoriques produits est beaucoup plus grand pour 2 maladies, la schistosomiase et la dengue, que pour les autres NTD. Ce nombre est même très faible pour nombreuses maladies, ne dépassant pas l'unité pour l'ulcère de Buruli et la dracunculose. Là encore, en comparant ces contributions à celles des Big three (tableau 6), on peut classer ces maladies selon 3 groupes définis arbitrairement: des maladies dont les contributions des travaux théoriques sont supérieures ou égales à celles des Big three, des maladies dont les contributions des travaux théoriques sont inférieures à celles des Big three (signalées par une étoile dans le tableau 6), et parmi celles-ci, des maladies dont les contributions des travaux théoriques ne dépassent pas la moitié des valeurs observées pour les Big three (signalées par deux étoiles dans le tableau 6). Pour la période 1800-2011, cette contribution est inférieure à celle des Big three pour toutes les NTD mises à part la schistosomiase, la dengue, la rage, l'onchocerciase, la maladie du sommeil, la filariose lymphatique, et le trachome. La tendance reste similaire pour la période 2005-2011, mis à part pour les helminthiases intestinales dont la contribution théorique devient supérieure à celle des Big three.

Si beaucoup de NTD ne semblent pas négligées par rapport aux Big three en termes de ratio production scientifique/impact sanitaire (voir points précédents), la majorité le sont en terme de contribution des travaux théoriques (tableau 6), ce qui porte à croire que ces niveaux de contribution théorique ne sont pas directement liés aux impact sanitaires des NTD.

Tableau 6. Travaux théoriques pour l'étude des NTD. Entre parenthèses sont donnés les ratios production théorique/scientifique calculés à partir des données du tableau 4, et exprimés en taux de 1 pour 1000.

	Travaux théoriques (contribution à la production scientifique totale, taux pour 1000)	
	1800-2011	**2005-2011**
Schistosmiase	123 (4,6)	49 (11,13)
Dengue	103 (11,1)	71 (15,6)
Rage	52 (4,5)	17 (7,7)
Leishmaniose	30 (1,7) *	11 (2,0) **
Onchocerciase	29 (7,2)	8 (15,2)
Echinococcose	27 (1,6) **	12 (4,5) *
Maladie du sommeil	25 (6,4)	8 (5,9)
Maladie de Chagas	24 (2,1) *	14 (4,0) *
Helminthiases intestinales	19 (2,5) *	9 (11,6)
Filariose lymphatique	17 (9,2)	8 (11,3)
Lèpre	14 (0,6) **	2 (0,7) **
Trachome	14 (3,4)	8 (13,8)
Fasciolase	9 (2,8) *	3 (4,4) *
Cysticercose	4 (0,8) **	2 (1,7) **
Strongyloïdose	4 (1,3) **	1 (1,8) **
Pian	2 (2,3) *	0 **
Ulcère de Buruli	1 (2,1) *	1 (3,4) *
Dracunculose	1 (0,5) **	0 **

2.2 Travaux théoriques sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées

Parmi l'ensemble des travaux théoriques existants, je me suis finalement concentre sur ceux dont l'objet est d'étudier l'écologie, l'évolution et le contrôle des maladies tropicales négligées par le biais de modèles de type systèmes dynamiques, car ceux-ci correspondent directement à l'approche adoptée pendant ma thèse. Ceci exclue donc les modèles à vocation plus descriptive, comme par exemple les modèles statistiques de caractérisation de niches écologiques (ex : González et al., *2010*) ou d'estimation de risque (« risk assessment ») (ex : Sarkar et al., *2010*). Qui plus est, seuls ont été retenus les systèmes modélisés dont la dynamique est décrite à l'échelle populationnelle (densité de pathogène et/ou d'hôtes), ou par des approches centrées sur les individus. J'ai exclu également les modèles qui décrivent la dynamique-intra-hôte des pathogènes à l'échelle d'un seul individu hôte lorsque ceux-ci ne s'intéressent pas directement à l'écologie et/ou l'évolution des pathogènes. Bien que certaines des questions qu'ils posent puissent bien sûr être intéressantes dans un contexte éco-évolutif, ils ne décrivent pas la transmission entre hôtes et leurs résultats sont donc difficilement comparables à ceux présentés dans ma thèse. Au total, les travaux recensés pour les 18 NTD représentent un ensemble de 302 publications (tableau 7, voir l'annexe A.2 pour les références bibliographiques).

Tableau 7. Systèmes dynamiques pour l'étude de l'écologie, l'évolution et le contrôle des maladies tropicales négligées. Entre parenthèses, la contribution de chaque maladie à l'ensemble des travaux retenus pour les NTD. Les maladies dont aucun modèle n'a été répertorié sont absentes du tableau.

	Systèmes dynamiques en écologie, évolution et contrôle des NTD	
	1800-2011	**2005-2011**
Schistosmiase	70 (23,2%)	22 (17,6%)
Dengue	69 (22,9%)	48 (38,4%)
Rage	40 (13,3%)	13 (10,4%)
Echinococcose	22 (7,3%)	7 (5,6%)
Onchocerciase	19 (6,3%)	7 (5,6%)
Helminthiases intestinales	17 (5,6%)	5 (4,0%)
Leishmaniose	15 (5,0%)	3 (2,4%)
Maladie de Chagas	13 (4,3%)	9 (7,2%)
Maladie du sommeil	11 (3,6%)	2 (1,6%)
Trachome	9 (3,0%)	6 (4,8%)
Lèpre	6 (2,0%)	1 (0,8%)
Fasciolase	6 (2,0%)	0 (0%)
Pian	2 (0,7%)	0 (0%)
Filariose lymphatique	1 (0,3%)	0 (0%)
Cysticercose	1 (0,3%)	1 (0,8%)
Strongyloïdose	1 (0,3%)	1 (0,8%)
NTD	**302**	**125**

Comme précédemment, les maladies les plus représentées sont la schistosomiase et la dengue, auxquelles il convient d'ajouter cette-fois ci la rage. Ces trois maladies représentent à elles-seules près de 60% des travaux examinés pour la période 1800-2011, et plus de 66% pour la période 2005-2011, Pour le reste des maladies le nombre de contributions oscille entre 0 et 22 pour la période 1800-2011, et entre 0 et 9 pour la période 2005-2011. Au contraire, la filariose lymphatique, NTD dont l'impact sur les populations humaines est le plus lourd en termes de perte de DALYs (près de 6 millions par an, tableau 1), et dont la prévalence est parmi les plus grandes (65 millions de gens infectés à travers le monde, tableau 1), est celle dont l'étude de l'écologie, l'évolution et le contrôle fait le moins appel aux approches relevant de la théorie des systèmes dynamiques.

Les modèles pour maladies tropicales négligées risquent-ils l'endogamie ?

Je me suis également intéressé à la diversité des auteurs associés aux 302 travaux théoriques examinés. En effet compte tenu du faible nombre de travaux théoriques existant pour la plupart des NTD (en moyenne 17 par maladie pour la période 1800-2011), il existe un risque certain que la diversité des modèles soit encore plus faible que révélée par le seul nombre de publications. Pour évaluer ce risque d'« endogamie » dans les travaux théoriques concernant les NTD, j'ai utilisé un indice statistique très utilisé dans l'étude de la dispersion des données, le ratio variance/moyenne (RVM). Pour chaque maladie, j'ai calculé le RVM de la proportion du nombre de travaux total à laquelle ont participé chaque auteur (tableau 8).

Tableau 8. Modèles pour l'écologie, l'évolution et le contrôle des maladies tropicales négligées: dispersion de la contribution des auteurs à l'ensemble des travaux produits pour une maladie donnée (RVM). Les maladies absentes de ce tableau sont celles dont une seule ou aucune publication n'a été examinée (voir tableau 7).

	RVM	**Nombre de travaux**
Dengue	1,04	69
Rage	1,31	40
Schistosomiase	1,48	70
Echinococcose	3,89	22
Maladie de Chagas	3,97	13
Helminthiases intestinales	4,3	17
Leishmaniose	5,13	15
Lèpre	5,25	6
Trachome	6,55	9
Maladie du sommeil	6,81	11
Onchocerciase	8,42	19
Fasciolase	16,07	6
Pian	4018	2

Seules les trois maladies les plus étudiées (la schistosomiase, la dengue et la rage) ont un RMV proche de 1, ce qui signifie une distribution relativement aléatoire de la contribution des différents auteurs à l'ensemble des travaux produits pour ces maladies. Pour toutes les autres maladies, le RMV est supérieur voire très supérieur à 3. Ceci signifie que seuls quelques auteurs ont participé à la plus grande partie de la production, ce qui n'est pas surprenant compte tenu du petit nombre de ces travaux. Il semble donc que non seulement les NTD font l'objet d'assez peu de travaux théoriques, mais en outre qu'il existe un fort risque d'endogamie dans l'étude de leur écologie, évolution et contrôle.

De quelles thématiques relèvent les contributions théoriques ?

Deux principales observations peuvent être faites lorsque l'on classe les travaux théoriques selon les trois grandes thématiques qui nous intéressent dans le cadre de cette thèse ; l'écologie, l'évolution et le contrôle (tableau 9).

Premièrement, le nombre de travaux s'intéressant à l'évolution des maladies tropicales négligées est très faible. Il ne représente que 5% de l'ensemble des travaux examinés, et une grande part d'entre eux (7 sur 16) concerne uniquement la dengue.

Deuxièmement, le nombre de travaux concernant l'écologie des NTD est souvent proche voire supérieur au nombre de travaux portant sur le contrôle des NTD. Globalement, les efforts faits pour modéliser l'écologie des NTD sont donc loin d'être systématiquement utilisés pour soutenir des évaluations quantitatives de stratégie de contrôle, même si bien sur les résultats de ces modèles sont assez fréquemment discutés en termes de contrôle ou santé publique.

Tableau 9. Thématiques des travaux théoriques pour l'étude des NTD. Aucune publication retenue pour l'ulcère de Buruli et la dracunculose (voir tableau 7).

Maladie	Ecologie (%)	Evolution (%)	Contrôle (%)
Schistosmiase	28 (40%)	4 (6%)	38 (54%)
Dengue	50 (72%)	7 (10%)	12 (17%)
Rage	18 (45%)	0	22 (55%)
Echinococcose	13 (59%)	0	9 (41%)
Onchocerciase	5 (26%)	1 (5%)	13 (68%)
Helminthiases intestinales	7 (41%)	0	10 (58%)
Leishmaniose	7 (47%)	1 (7%)	7 (47%)
Maladie de Chagas	7 (54%)	1 (8%)	5 (38%)
Maladie du sommeil	6 (55%)	1 (9%)	4 (36%)
Trachome	1 (11%)	0	8 (89%)
Lèpre	2 (33%)	0	4 (67%)
Fasciolase	2 (33%)	0	4 (67%)
Pian	0	0	2 (100%)
Filariose lymphatique	1 (100%)	0	0
Cysticercose	0	0	1 (100%)
Strongyloïdose	0	1 (100%)	0
NTD	**147 (49%)**	**16 (5%)**	**139 (46%)**

3. Principales problématiques abordées sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées

Cette dernière partie présente les principales questions sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées pour lesquelles il existe des résultats théoriques. Etant donné l'absence ou le peu de travaux examinés pour la plupart des maladies, je me suis limité a celles pour lesquelles il existait au moins 10 publications (tableau 7), à savoir la schistosmiase, la dengue, la rage, l'échinococcose, l'onchocerciase, les helminthiases intestinales, la leishmaniose, la maladie de Chagas et la maladie du sommeil.

Quelles sont les grandes problématiques abordées par les modèles pour l'étude de l'écologie des maladies tropicales négligées ?

Peu de travaux s'intéressent à la diversité intra-spécifique des agents pathogènes des NTD, sauf pour la dengue (tableau 10). Ceci est sûrement du au fait que la diversité des souches du virus de la dengue (au nombre de 4) a de fortes conséquences sur l'épidémiologie cette maladie. En effet, si l'infection par une souche donnée procure une immunité vis-à-vis de cette même souche, elle tend aussi à accroitre la morbidité de la dengue lorsque l'on est ensuite infecté par une autre souche. Ce phénomène est connu sous le nom de « Antibody-Dependent Enhancement » (Wahala & Silva *2011*), et dans le cas de la dengue il peut avoir des conséquences mortelles. Encore moins de travaux s'intéressent à la diversité inter-spécifique des agents pathogènes responsables d'une même NTD, ce qui est logique puisque la plupart d'entre elles sont causées par une seule espèce. Il existe néanmoins quelques travaux pour les helminthiases intestinales, la maladie de Chagas, l'onchocerciase, la schistosomiase et la maladie du sommeil.

Tableau 10. Ecologie des maladies tropicales négligées : Problématiques abordées par les modèles relevant de la théorie des systèmes dynamiques. Abbréviations: Sc=schistosomiase, De=dengue, Ra=rage, Ec=échinococcose, On=onchocerciase, HI=helminthiases intestinales, Ch=maladie de Chagas, So=maladie du sommeil, Le=leishmaniose. (Voir le tableau A.1 dans l'annexe A pour les références bibliographiques par maladie et par problématique)

Problématiques	**Maladies**
Diversité des agents pathogènes	Ch, De, HI, On, Sc, So
Densité-dépendance de la dynamique intra-hôte	Ec, HI, On, Sc
Agrégation au sein de la population hôte	Ec, HI, On, Sc
Vecteurs ou hôtes intermédiaires	Ch, De, Ec, Le, On, Sc, So
Hôtes définitifs non-humains	Ch, Ec, Le, Ra, Sc, So
Âge des hôtes humains et acquisition d'immunité	Ch, De, HI, Le, On, Sc

Les travaux portant sur la densité-dépendance de la dynamique intra-hôte des pathogènes, ou sur l'agrégation des pathogènes au sein des populations hôtes, ne portent que sur des helminthiases (schistosomiase, échinococcose, onchocerciase et helminthiases intestinales). En effet il s'agit là de deux caractéristiques classiques des systèmes hôtes-macro-parasites en général, et beaucoup moins considérés dans le cas des micro-parasites.

Nombreuses NTD sont causées par des pathogènes dont le cycle de vie inclue des hôtes dits « vecteurs » ou « intermédiaires ». Parmi celles considérées ici, ces hôtes sont des insectes pour la dengue, l'onchocerciase, la leishmaniose, la maladie de Chagas et la maladie du sommeil, des gastéropodes pour la schistosomiase, et des mammifères pour l'échinococcose. Dans la mesure où le contrôle de ces vecteurs ou hôtes intermédiaires fait partie des stratégies de lutte couramment utilisées pour lutter contre ces maladies (tableau 2), il est donc logique de trouver pour chacune d'entre elles plusieurs travaux théoriques s'intéressant à ces mêmes vecteurs ou hôtes intermédiaires. Le plus grands nombre de travaux porte sur la dengue et son vecteur principal, les moustiques du genre *Aedes*. La diversité de ces travaux est sûrement en partie liée au fait qu'il s'agit de moustiques au fort pouvoir de colonisation à travers le monde et d'adaptation au milieu urbain (Enserink *2008*). Qui plus est, ces moustiques sont capables de transmettre plusieurs maladies tropicales en plus de la dengue, et font donc souvent l'objet de publications transversales.

La transmission de nombreuses NTD se maintient aussi grâce à l'existence d'hôtes définitifs non-humains, et c'est d'ailleurs le cas de toutes les maladies considérées ici mises à part la dengue et l'échinococcose. Le contrôle ou le traitement de ces hôtes non-humains fait partie des stratégies de lutte les plus utilisées contre la rage, l'échinococcose, la leishmaniose, la maladie de Chagas et la maladie du sommeil (tableau 2). Il est donc logique de trouver, parmi les études sur l'écologie de ces maladies, plusieurs travaux théoriques qui prennent en compte le rôle de ces hôtes non-humains (tableau 8). Enfin, il est également logique de constater que les 2 maladies dont l'écologie est étudiée par le plus grand nombre de travaux théoriques s'intéressant aux hôtes définitifs non-humains sont la rage et l'échinococcose, c'est-à-dire les deux seules NTD dont les hôtes humains sont très peu susceptibles de contribuer à la transmission, et la seule NTD – l'échinococcose – pour laquelle l'homme n'est pas un hôte définitif mais intermédiaire.

Enfin, une autre thématique écologique très étudiée est celle de la relation entre l'âge des hôtes humains et la morbidité des maladies. C'est notamment le cas pour des maladies dues à l'infection par des vers telles que la schistosmiase ou les helminthiases intestinales, car le nombre d'expositions au cours de la vie peut se traduire par l'acquisition d'une immunité contre ces maladies. C'est aussi le cas pour la dengue, mais cette fois parce que l'exposition

successive à différentes souches du virus peut se traduire par une morbidité accrue voire mortelle, comme expliqué ci-dessus pour les travaux s'intéressant à la diversité des souches de pathogènes.

L'utilisation de modèles relevant de la théorie des systèmes dynamiques pour l'étude de l'écologie des NTD semble donc corrélée aux stratégies de contrôles utilisées, mais aussi au cycle de vie des pathogènes, à leur dynamique intra-hôte, et aux interactions hôtes-parasites. A la vue de la littérature théorique et généraliste pré-existante (Diekmann & Heesterbeek, *2000*), les problématiques les plus récurrentes peuvent être considérées comme des problématiques classiques en parasitologie et épidémiologie des maladies infectieuses.

Quelle contribution des approches évolutives pour la lutte contre les maladies tropicales négligées ?

Comme on peut le voir dans le tableau 7, la part des travaux théoriques pour l'étude de l'évolution des NTD est très faible. Ceci peut paraître surprenant dans la mesure où il existe une riche littérature théorique générale (Kubiak et al., *2010*; Osnas & Dobson *2012*) et spécifique (Koella & Boëte *2003*; Coutinho et al., *1999*) sur l'évolution des pathogènes et des interactions hôtes-pathogènes, et qu'une meilleure compréhension de cette évolution peut contribuer à mieux lutter contre les maladies infectieuses (Dieckmann et al., *2002*). Les références bibliographiques de ces travaux sont répertoriés pour chaque NTD dans l'annexe A.2.

Bien que la plupart de ces travaux s'inscrivent dans travaux ayant un intérêt pour le contrôle des NTD, très peu des modèles utilisés incluent des processus de contrôle. Plusieurs travaux théoriques se sont intéressés à la diversité des souches du virus de la dengue et leurs interactions, car cette diversité a elle-même de fortes implications quant aux interactions hôte-virus (Wahala & Silva *2011*). A ce jour néanmoins, les contributions théoriques à l'étude de l'évolution de la dengue au contrôle de cette même maladie viennent probablement des travaux sur l'introduction d'individus transgéniques au sein des populations de moustiques, afin d'en réduire les capacités vectorielles.

La contribution de ces travaux au contrôle des helminthiases est encore plus faible. Au sein de travaux examinés, elle se limite surtout aux conséquences que pourraient impliquer le développement de phénomènes de résistance contre les chemo-thérapies antihelminthiques utilisées pour lutter contre ces maladies.

Pour quelles stratégies de contrôle des maladies tropicales négligées existe-t-il des résultats théoriques ?

Comme présenté précédemment, il existe plusieurs stratégies de contrôle des NTD (tableau 2), et celles-ci varient d'une maladie à l'autre selon le cycle de vie du pathogène et selon les progrès réalisés dans la recherche et le développement de ces stratégies. Certaines de ces stratégies sont néanmoins davantage étudiées par les travaux théoriques, toujours selon la maladie considérée (tableau 11).

Tableau 11. Stratégies de contrôles des maladies tropicales négligées étudiées à l'aide de modèles de type systèmes dynamiques. Abbréviations: Sc=schistosomiase, De=dengue, Ra=rage, Ec=échinococcose, On=onchocerciase, HI=helminthiases intestinales, Ch=maladie de Chagas, So=maladie du sommeil, Le=leishmaniose. (Voir le tableau A.2 dans l'annexe A pour les références bibliographiques par maladie et par stratégie de contrôle)

Stratégie de contrôle	**Maladies**
Aménagement de l'habitat humain	Ch, De, Sc, So
Traitement ou vaccination des hôtes intermédiaires	Ec
Contrôle des vecteurs ou hôtes intermédiaires	Ch, De, Le, On, Sc, So
Traitement ou vaccin des hôtes définitifs non-humains	Ec, Le, Ra, Sc, So
Contrôle des hôtes définitifs non-humains	Ch, Ec, Le, Ra, So
Education, campagne préventive	De, Ec, De, Sc
Surveillance, traitement des hôtes humains	Ch, HI, Le, On, Sc, So
Vaccin des hôtes humains	De, HI, Le, Sc

Aménagement de l'habitat. Le contrôle par l'aménagement de l'habitat humain est étudié pour quelques maladies seulement. Il s'agit d'une des stratégies les plus étudiées dans la lutte contre la schistosomiase. Dans le cas de cette maladie, cette stratégie correspond souvent à un assainissement des eaux car la transmission à l'homme se fait typiquement par contact avec les larves infectantes aquatiques.

Contrôle des vecteurs ou hôtes intermédiaires. Le contrôle des vecteurs ou hôtes intermédiaires est une stratégie étudiée pour chacune des maladies dont la transmission fait justement appel à des vecteurs ou hôtes intermédiaires, sauf pour l'échinococcose. Il s'agit d'une des stratégies les plus étudiées pour la schistosomiase, où elle correspond le plus souvent à l'usage de molluscicides tuant les gastéropodes seravnt d'hôte intermédiaire à certains stades immatures du pathogène. C'est aussi une stratégies très étudiées pour la dengue, l'onchocerciase, la maladie de Chagas et la maladie du sommeil. Dans le cas des 3 dernières, cette stratégie correspond le plus souvent à l'usage d'insecticides. Dans le cas de la dengue, il peut également s'agir d'insecticide, mais aussi de l'introduction d'individus stériles dans les populations de moustiques. L'échinococcose fait exception au contrôle des hôtes intermédiaires, mais il existe des résultats pour une autre stratégie de lutte ciblant ces hôtes intermédiaires: la vaccination des moutons.

Contrôle et traitement des hôtes animaux. Il existe également des stratégies de lutte ciblant des hôtes définitifs non-humains pour chacune des maladies pouvant persister dans ce type d'hôte, sauf pour les helminthiases intestinales. Le traitement et/ou la vaccination de ces hôtes est une stratégie très étudiées pour la rage et l'échinococcose, ce qui est logique puisque ce sont deux maladies dont l'homme ne contribue pas ou très peu à la transmission, et puisque dans le cas de l'échinococcose l'homme est un hôte intermédiaire. Le contrôle de ces hôtes non-humains est aussi très étudié pour la leishmaniose. Comme pour la rage, il s'agit le plus souvent d'un contrôle des populations de chiens (et de renard pour la rage) par euthanasie massive, ou par euthanasie limitée aux individus infectés. Les helminthiases intestinales font exception ici malgré l'existence d'hôtes définitifs non-humains (chien, chat) pour certains des agents pathogènes. Ceci est néanmoins en accord avec le fait que ces hôtes ne sont pas les cibles des stratégies de contrôle communément utilisées pour lutter contre cette maladie.

Education des populations. Il existe bien sûr des résultats pour les stratégies de contrôle s'appliquant au niveau des hôtes humains pour toutes les maladies sauf la rage. Une de ces stratégies consiste à éduquer les populations à risque afin qu'elles réduisent par elles-mêmes les risques d'exposition aux pathogènes. Cette stratégie est étudiée pour quelques

maladies seulement: la schistosomiase, la dengue et l'échinococcose. Dans le cas de l'échinococcose, il s'agit justement d'une des stratégies de contrôle communément utilisées (tableau 2). Dans le cas de la schistosomiase, c'est une stratégie très étudiée car elle permet notamment de réduire les risques d'exposition des enfants, dont l'attrait pour les jeux aquatiques peut favoriser la mise en contact avec les larves infectantes.

Traitement des hôtes humains. Les effets du traitement des hôtes humains sont étudiés pour la plupart des maladies considérées, ce qui est en accord avec l'usage fréquent de cette stratégie dans la lutte contre les NTD (tableau 2). Il s'agit même de la stratégie la plus étudiée pour la schistosomiase, l'onchocerciase et les helminthiases intestinales. Pour ces 3 helminthiases le mode de traitement considérée est le plus souvent l'administration de médications telles que le praziquantel pour lutter contre la schistosomiase, ou l'ivermectine contre l'onchocerciase et les helminthiases intestinales. Les résultats produits visent souvent à répondre à des questions communes à ces 3 maladies : la distribution des médicaments doit-elle se faire de manière sélective ou massive ? Dans ce cas, quel pourcentage de la population doit-on traiter ? A quelle fréquence ?

Vaccination des hôtes humains. Enfin, il est intéressant de constater que, bien que seule la lutte contre la rage bénéficie de l'utilisation d'un vaccin pour les humains (tableau 2), il existe pourtant des résultats pour la schistosomiase, la dengue, la leishmaniose et les helminthiases intestinales. Ce sont là des travaux très minoritaires mais qui illustrent pour certaines NTD l'existence de résultats théoriques sur l'utilisation éventuelle de stratégies de contrôle qui n'en sont encore qu'à l'état de projet (ex : dengue).

A l'image des problématiques écologiques, les stratégies de contrôle étudiées dépendent donc surtout du cycle de vie des pathogènes et des moyens de lutte existants et utilisés dans la réalité. Néanmoins il existe aussi quelques résultats théoriques pour des stratégies encore peu communes au sein des NTD, comme l'introduction d'insectes stériles comme moyen de contrôle des vecteurs, voire inexistantes pour la plupart de ces maladies, comme l'utilisation de vaccin.

Les résultats se limitent-ils aux zones tropicales ?

Aujourd'hui les maladies tropicales négligées touchent essentiellement des populations habitants les zones tropicales ou sub-tropicales mais certaines d'entre elles, comme la rage ou l'échinococcose, ont existé sous la forme d'endémisme historique dans des zones tempérées (Vitasek *2004* ; Moro & Schantz *2009*), et nombreuses études théoriques décrivent les risques futurs de voir une NTD toucher des pays riches et tempérés (de Wet et al., 2001 ; González et al., *2010*). Dans le cas des travaux théoriques sur l'écologie, l'évolution et le contrôle des NTD on peut donc se demander si les résultats se restreignent à des zones tropicales, ou si certains d'entre eux concernent des pays riches et tempérés ? (tableau 12). Selon une liste de pays choisis arbitrairement (Australie, Canada, Corée du Sud, Etats-Unis, pays européens, Japon et Nouvelle-Zélande), on peut voir d'après le tableau 10 que des résultats s'adressant explicitement à un pays riche et tempéré ont été produits pour 7 NTD, et qu'ils représentent 14% des travaux examinés pour l'ensemble des NTD.

Tableau 12. Travaux théoriques sur l'écologie, l'évolution et le contrôle des NTD : résultats faisant références aux pays riches et tempérés. (Voir le tableau A.3 dans l'annexe A pour les références bibliographiques par maladie et par stratégie de contrôle)

	Rage	**Echinoc.**	**Lèpre**	**Fasciol.**	**Leishm.**	**Mal. de Chagas**	**Dengue**	**NTD**
Pays riches et tempérés	22 (58%)	12 (55%)	2 (33%)	2 (33%)	2 (13%)	1 (8%)	2 (3%)	43 (14%)

Les maladies les plus concernées par ces pays riches sont l'échinococcose (55%) et la rage (62%). Ceci n'est pas surprenant car elles persistent aujourd'hui encore à des niveaux problématiques pour la santé publique de certains de ces pays, notamment à cause de la présence d'hôtes réservoirs domestiques ou sauvages (Vitasek *2004* ; Moro & Schantz *2009*). Ce dernier point est d'ailleurs reflété par le fait que la plupart des modèles retenus pour ces maladies concernent justement des hôtes non-humains. Néanmoins, il peut paraître surprenant que pour ces deux maladies qui sont pourtant parmi les plus étudiées des NTD (voir tableaux 4, 6 et 7), plus de la moitié des modèles font référence à des contextes de pays riches et tempérés, ce qui s'apparente à une forme supplémentaire de la négligence dont pourraient souffrir les populations les plus touchées par les maladies tropicales négligées.

4. Conclusion générale

Si les maladies tropicales négligées font l'objet de beaucoup moins de travaux scientifiques que les Big three, elles n'apparaissent néanmoins pas négligées par les scientifiques lorsque l'on met en perspective la quantité de publications produites avec l'impact sanitaire des maladies en questions. Il existe d'ailleurs une quantité assez importante de résultats théoriques sur l'écologie et le contrôle de certaines d'entre elles, notamment la schistosomiase, la dengue et, à moindre titre, la rage.

Néanmoins plusieurs constats s'imposent à l'issu de ce chapitre 1. Premièrement, la plupart des autres maladies font l'objet de très peu voire aucun travail théorique, alors que le fardeau sanitaire ou économique qu'elles représentent n'en demeure pas moins un problème pour de nombreuses populations à travers le monde. Deuxièmement, il existe très peu de résultats théoriques sur l'évolution des maladies tropicales négligées en général, ce qui pose la question de notre capacité à anticiper les conséquences à long terme des stratégies employées pour lutter contre ces maladies. Nous sommes par exemple aujourd'hui dépourvu de bases théoriques spécifiques aux maladies tropicales négligées sur lesquelles appréhender les risques de développement de résistance des pathogènes ou des vecteurs. Il est tout à fait probable que ceci contraigne fortement l'optimisation de l'utilisation des stratégies existantes, et le développement de stratégies de contrôles alternatives. A l'évidence, ceci invite à développer des approches théoriques éco-évolutives pour l'étude des maladies tropicales négligées.

Chapitre 2

Émergence et prévalence des maladies vectorielles humaines transmises dans des populations de vecteurs puits

2.1 Introduction

Beaucoup de maladies tropicales correspondent à des maladies vectorielles, transmises par une ou plusieurs espèces d'insectes. Parmi les maladies tropicales négligées (NTD), on compte la leishmaniose, la maladie du sommeil, le trachome et l'onchocerciase qui sont transmises par des mouches, la dengue et la filariose lymphatique qui sont transmises par des moustiques, et la maladie de Chagas qui est transmise par des punaises.

Les connaissances expérimentales et théoriques que nous avons sur la transmission de ces maladies vectorielles ont été obtenues principalement pour des populations « sources » (Pulliam *1988* ; Dias *1996*) de vecteurs, c'est à dire des populations capables de persister indépendamment de tout phénomène d'immigration. Pourtant en de nombreuses circonstances, où les populations de vecteurs constituent des « puits » caractérisés par de relativement faibles abondances d'insectes, ces maladies vectorielles sont néanmoins transmises à l'homme dans des proportions tout à fait significatives. C'est le cas par exemple pour la malaria (Baber et al. *2010*), la maladie de Chagas (Gourbière et al., *2008*) ou la maladie du sommeil (Rogers et al., *1984*). Les études de la transmission dans de telles populations sont bien moins nombreuses, notamment car les faibles densités de vecteurs typiquement observées dans ces populations rendent difficile l'obtention de données de terrain (Dumonteil et al., *2009* ; Abad-Franch et al., *2010*). La transmission des maladies vectorielles dans les populations puits demeure donc peu sinon pas étudiée.

Déterminer les facteurs clés affectant la transmission dans ces conditions est essentiel car les parasites sont très vraisemblablement transmis dans des populations puits bien plus souvent que la littérature ne le porte à croire. Ces populations puits se trouvent en effet à l'état naturel aux limites des niches écologiques des vecteurs. Identifier ces facteurs permettrait donc de mieux comprendre la transmission des parasites aux bords des aires de répartition des vecteurs, ce qui est évidement important dans un contexte où ces aires de distributions évoluent avec le réchauffement climatique (Githeko et al., *2000* ; Kovats et al., *2001*). En outre, à l'intérieur même de leurs aires de répartition, les vecteurs se développent généralement dans des habitats hétérogènes constitués des mosaïques de zones sources et de zones puits. Comprendre la dynamique de transmission des parasite nécessite donc de comprendre ses déterminants dans ces deux types d'environnements. Finalement, par essence, le contrôle vectoriel a pour objectif de transformer des populations de vecteurs sources en populations puits. Mieux connaître les dynamiques de transmissions de parasite par des populations puits de vecteurs doit donc également permettre de mieux comprendre les phénomènes de persistance et/ou ré-émergence des pathogènes lorsque le contrôle échoue.

L'objectif de ce travail était donc d'obtenir des résultats théoriques sur les conditions

d'émergence et des niveaux de persistance de maladies vectorielles transmises dans des populations de vecteurs puits. L'idée était d'identifier quels étaient, dans ces conditions entomologiques, les paramètres clés de la transmission des principales maladies vectorielles affectant l'homme, et ainsi d'identifier des objectifs prioritaires pour les travaux empiriques, particulièrement difficiles dans ces situations de faible abondance vectorielle.

La stratégie de modélisation employée dans ce chapitre est celle du développement d' « core model », comme utilisé par Wonham et al. (2006) pour l'étude de la transmission des arbovirus. Cette stratégie consiste à construire un modèle sur la base du plus petit dénominateur commun aux modèles existant pour différentes maladies vectorielles. Elle comporte deux principaux avantages : celui de pouvoir utiliser un modèle commun pour plusieurs maladies et ainsi faciliter les comparaisons entre elles, et celui d'offrir la perspective de développements futurs plus spécifiques à partir d'une référence commune. Le modèle construit est un modèle à compartiments de type SIRS (« Susceptible-Infectious-Recovered-Susceptible »), et considère la transmission à des hôtes humains et non-humains. Le modèle est appliqué à 6 maladies vectorielles : la malaria, quatre NTD (la dengue, la maladie du sommeil, la leishmaniose et la maladie de Chagas), et l'encéphalite japonaise. Le modèle est paramétré à l'aide d'une large revue de la littérature ayant permis de collecter les estimations répertoriées au sein de la littérature.

Les prédictions obtenues pour la probabilité d'émergence et la prévalence au sein des populations humaines confirment que les niveaux de transmission au sein de ces populations peuvent potentiellement être préoccupants pour chacune des 6 maladies puisqu'ils sont typiquement de l'ordre de quelque pourcents pour la dengue, la leishmaniose et l'encéphalite japonaise, et peuvent atteindre des valeurs supérieures à 15% pour des maladies à plus longue durée d'infection telles que la malaria et les trypanosomiases américaine et africaine. Les analyses de sensibilité montrent que la démographie et le comportement des vecteurs sont les facteurs clefs expliquant les probabilités d'émergence et les niveaux de prévalences des 6 maladies. Ces résultats soulignent l'intérêt de prendre en compte les dynamiques de transmission des maladies vectorielles au sein de meta-populations de vecteurs, et par la suite de réfléchir aux interventions de contrôle dans le contexte de dynamiques spatialisées.

2.2 Emergence and Prevalence of Human Vector-Borne Diseases in Sink Vector Populations (article accepté pour publication)

OPEN ACCESS Freely available online

PLoS one

Emergence and Prevalence of Human Vector-Borne Diseases in Sink Vector Populations

Guilhem Rascalou[1], Dominique Pontier[2], Frédéric Menu[2], Sébastien Gourbière[1,3]*

1 UMR 5244 CNRS-UPVD Ecologie et Evolution des Interactions, Université de Perpignan Via Domitia, Perpignan, France, **2** UMR 5558 CNRS-UCBL Laboratoire de Biométrie et Biologie Evolutive, Université de Lyon, Université Lyon 1, Villeurbanne, France, **3** School of Life Sciences, University of Sussex, Brighton, United Kingdom

Abstract

Vector-borne diseases represent a major public health concern in most tropical and subtropical areas, and an emerging threat for more developed countries. Our understanding of the ecology, evolution and control of these diseases relies predominantly on theory and data on pathogen transmission in large self-sustaining 'source' populations of vectors representative of highly endemic areas. However, there are numerous places where environmental conditions are less favourable to vector populations, but where immigration allows them to persist. We built an epidemiological model to investigate the dynamics of six major human vector borne-diseases in such non self-sustaining 'sink' vector populations. The model was parameterized through a review of the literature, and we performed extensive sensitivity analysis to look at the emergence and prevalence of the pathogen that could be encountered in these populations. Despite the low vector abundance in typical sink populations, all six human diseases were able to spread in 15–55% of cases after accidental introduction. The rate of spread was much more strongly influenced by vector longevity, immigration and feeding rates, than by transmission and virulence of the pathogen. Prevalence in humans remained lower than 5% for dengue, leishmaniasis and Japanese encephalitis, but substantially higher for diseases with longer duration of infection; malaria and the American and African trypanosomiasis. Vector-related parameters were again the key factors, although their influence was lower than on pathogen emergence. Our results emphasize the need for ecology and evolution to be thought in the context of metapopulations made of a mosaic of sink and source habitats, and to design vector control program not only targeting areas of high vector density, but working at a larger spatial scale.

Citation: Rascalou G, Pontier D, Menu F, Gourbière S (2012) Emergence and Prevalence of Human Vector-Borne Diseases in Sink Vector Populations. PLoS ONE 7(5): e36858. doi:10.1371/journal.pone.0036858

Editor: Maciej F. Boni, University of Oxford, Viet Nam

Received November 11, 2011; **Accepted** April 16, 2012; **Published** May 18, 2012

Copyright: © 2012 Rascalou et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: This work has been supported by EU-FP7-PEOPLE-Intra-European Fellowship for career development (IEF) grant no. 253483, and by the French National Research Agency (grant reference "ANR-08-MIE-007"). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: gourbiere@univ-perp.fr

Introduction

Vector-borne diseases represent one of the biggest challenges to the current and future human wellbeing [1,2]. Various insects are responsible for the transmission of the well-known malaria, West-Nile virus, yellow fever, Japanese encephalitis, as well as a cluster of so-called 'neglected tropical diseases' such as dengue, leishmaniasis, human American and African trypanosomiasis [3]. All these diseases have severe impacts on many tropical and subtropical countries, where they are responsible for around 10% of human deaths [4–7], and contribute substantially to impoverishment by imposing annually a burden of more than 50 million of disability-adjusted life years (DALYs) [4–9]. Vector-borne diseases are also becoming a serious health-concern for more developed countries [10–13], because of the expansion of vectors geographic distribution in response to climatic changes [14–19], or the accidental introductions of vectors or pathogens through increasing international migration and commercial exchanges [20–23].

A large body of empirical and theoretical studies on human vector-borne diseases has contributed to our understanding of the importance of vectors ecology and evolution in disease transmission (e.g., [24]), pathogen evolution (e.g., [25]) and the design of efficient control strategies [26]. These studies typically focus on highly endemic areas, where pathogens are transmitted by large self-sustaining 'source' populations [27,28] of key vectors of human diseases; mosquitoes (*Anopheles*, [29], *Aedes*, [30], or *Culex*, [31]), flies (*Glossina*, [32], and phlebotomines, [33]), or triatomines (*Triatoma infestans*, [34,35], and *Rhodnius prolixus*, [36]).

However, vector populations can also be 'sink' populations wherever the environment does not provide suitable conditions for reproduction or survival of individual vectors, so that such 'sink' populations cannot sustain themselves and have to be sustained by immigration [27,28]. Sink populations have been described for the vectors of human African trypanosomiasis [37], Chagas disease [38], and malaria [39]. Although much less attention has been paid to such populations, they are likely to play a significant role in the transmission of vector borne diseases. In highly endemic areas, vector control is a key strategy to lower the impact of those diseases on humans [3,40] through chemical [41–43] or biological control [44–46]. However such campaigns are unavoidably restricted in their local efficacy and/or spatial coverage [47,48], so that partially controlled populations effectively constitute 'anthropic' sinks sustained by immigration from wild or non-targeted areas [49–54]. Vector populations can also be 'natural' sinks either in the core of their niche, when the habitat is heterogeneous, or at the

border of the niche [37,55–57]. Such populations will be the typical pathogen environment where vectors spatial distributions are expanding following environmental changes [17–19]. A better knowledge of pathogen transmission in sink vector populations is thus critically needed to address two main challenges to human health associated with vector-borne pathogens: the persistence of transmission in highly endemic areas despite ongoing vector control programs [35,58], and the prediction of the risk of disease emergence in areas where vectors are expanding because of environmental changes [14,59,60].

The spread of vector-borne pathogens is commonly thought to critically rely on vector demography and feeding rates (e.g., [61]). In sink populations, vector immigration and local (negative) growth rate will undoubtedly be two key demographic processes, since species abundance has repeatedly been demonstrated to depend on the balance between them [27,28]. In such populations one can also anticipate that, given the low vector abundance, the number of contacts each individual is able to make with hosts will have a critical impact on transmission. A quantitative assessment of such qualitative predictions requires to tightly link transmission and the two main determinants of vector feeding; the minimal amount of time elapsing between two blood-meals (e.g., [61]), and the host availability and accessibility (e.g., [62]). Clearly, the fate of vector-borne pathogens in sink vector populations will also depend on the ease of the transmission when contacts are established, and on the within-host dynamics of the pathogens. Critically, those last two determinants of disease dynamics show significant variations among human vector-borne diseases (e.g., [24]). Unfortunately, the typically low vector abundances encountered in sinks make it difficult to set up field experiments to look at these different components of vector transmission in such populations [63,64].

In the present work, we aim to produce theoretical insights into key human pathogens' transmission in sink vector populations. Our general objective is to identify the key processes determining the emergence and subsequent prevalence of pathogens in such vector populations to help specifying priority targets for future field studies. We adopted an approach inspired from [65] that consists of developing a unique 'core model' including the main processes described above and involved in the transmission of major human vector-borne diseases, not accounting for the more disease-specific processes, such as seasonal forcing, host or pathogen diversity and heterogeneity, which would divert from drawing general conclusions and limit cross comparisons between diseases [65]. We developed a SIRS model ('Susceptible-Infected-Recovered-Susceptible', e.g., [66] p. 247), which provides a simple description of the key processes of vector demography and feeding that we identified above, as well as of pathogen transmission and virulence. This 'core model' includes human and alternative hosts, thereafter generically referred to as 'non-human hosts', as these non-human hosts can have profound effects on disease dynamics when the pathogen is not specific to humans (e.g., [67]). Since a systematic analysis of the model would be rather cumbersome, and irrelevant in most of the highly dimensional parameter space, we focused on six human diseases that, not only represent major public health concerns, but also show contrasted patterns regarding the existence or absence of non-human hosts, their vector's life-history and feeding rate, and the transmission and within-host dynamics of their causal agents.

Importantly, there are two different ways for vector immigration to influence the pathogen transmission [68]. When immigrating vectors carry on the pathogens, they can have a direct effect not only on vector abundance, but also on pathogen transmission. Such a situation has been documented when tsetse flies [69], sandflies [55] or triatomines [70–72] infest human habitat bringing in the pathogens. Immigration of non-infectious vectors can also contribute to build-up a susceptible vector population, where pathogens can subsequently be introduced by the arrival of, e.g. mammals, hosts from endemic areas. It has indeed been shown that both human [73,74] and non-human hosts [23,75] have been the cause of pathogens' introduction or re-introduction. We thus investigated separately these two epidemiologically very different situations within our 'core model'.

Materials and Methods

Human Vector-borne Diseases

We considered three diseases with only human hosts; malaria (MAL), dengue (DEN), and the Gambian form of human African trypanosomiasis (HAT), which all together affect over 250 millions people and kill around 900,000 humans every year [4,5,7]. We also included three diseases with non-human hosts; Japanese encephalitis (JE), American trypanosomiasis, often called Chagas disease (CD), and visceral leishmaniasis (VL). Those additional diseases are responsible for more than 50,000 human deaths a year, and incapacitate several hundred thousands people [4,7]. Detailed descriptions of these diseases can be found in specialized books (see [76–81] for MAL, DEN, HAT, JE, CD and VL, respectively). Below we provide a brief summary of the main differences in the characteristics of their vectors, non-human hosts and pathogens, which were quantified by reviewing the literature. S1 provides a detailed description of the origin of the data and procedures used to obtain estimates of all parameters appearing in Table 1.

Diseases with only human hosts. MAL and DEN are two diseases transmitted by mosquitoes, while the vectors of HAT are tsetse flies. Mosquitoes and tsetse flies have similar average frequency of feeding (around 3 days), but tsetse flies tend to have longer adult life-expectancy than mosquitoes (around 2 vs. 6 weeks) so that individuals can bite around 15 times vs. 5 for mosquitoes, during the hematophagous stage of their life-cycle. On the contrary, the transmission potential is lower for tsetse flies (around 0.008) than for mosquitoes transmitting MAL (0.003–0.03 depending on the status of human host, see below) and DEN (around 0.3). This transmission potential was defined as the product of the probabilities of transmission from vector to host and from host to vector, and was calculated from the median of the range of parameter values that appear in Table 1. These three diseases also differ in the way pathogens afflict their hosts. For MAL and DEN, individuals first go through an infectious state, which can last from a few days for DEN and up to several months for MAL. Individuals infected with DEN can then recover and acquire a life-long immunity, while hosts infected with MAL enter a state of reduced infectivity [82,83] and eventually return to a susceptible state after a few months or years. The course of HAT is more singular. Infected hosts first enter an asymptomatic state, usually called 'phase 1', followed by a symptomatic state, called 'phase 2', both of which lasting several months. Individuals in phase 1 are infectious, while those in phase 2 are usually considered as non-infectious, all the more as they may be under treatment. Further, phase 2 is eventually fatal for humans not pursuing treatment, and those surviving this phase do not acquire immunity but return to the susceptible pool. Finally, disease-induced mortality is higher for HAT than for MAL and DEN.

Diseases with Non-human Hosts. JE, CD, and VL show significant differences in their vector and pathogen's within-host dynamics. Sandflies have similar feeding frequency (around 3 days) and life-expectancy (around 2 weeks) to mosquitoes, but triatomines are very unusual vectors. Although they feed less

Table 1. Parameters definition and range of values.

Parameter definition	Symbol	Dimension	MAL	DEN	HAT	VL	JE	CD
Vector demography and feeding								
Vector life expectancy [(1)]	$1/\Delta_V$	days	1–15	1–15	1–45	1–15	1–15	1–210
Number of immigrants	i_V	ind.day^{-1}	]0, 67]	]0, 67]	]0, 22]	]0, 67]	]0, 67]	]0, 5]
Fraction of infectious immigrants	i_{I_V}/i_V	–	]0, 0.02]	]0, 0.02]	]0, 0.02]	]0, 0.02]	]0, 0.02]	]0, 0.35]
Minimal delay between blood-meals	T_d	days	]2, 6]	]2, 6]	]2, 6]	]2, 6]	]2, 6]	]7, 28]
Finding rate	a	day^{-1}	]0, 1]	]0, 1]	]0, 1]	]0, 1]	]0, 1]	]0, 1]
Host demography								
Human abundance	N_H	ind.	1000	1000	1000	1000	1000	1000
Non-human hosts abundance	N_h	ind.	–	–	–	1000/6	1000/6	1000/6
Human natural life expectancy [(1)]	$1/d_H$	years	60	60	60	60	60	60
Non-human natural life expectancy [(1)]	$1/d_h$	years	–	–	–	3	1	3
Pathogen transmission								
From vector to human hosts	p_{HI}	–	0.01–0.13	0.50–1	0.50–0.70	0.20–0.40	0.01–0.04	$0.6e^{-3}$–$3.8e^{-3}$
From vector to non-human hosts	p_{hI}	–	–	–	–	0.20–0.40	0.27–0.45	$0.6e^{-3}$–$3.8e^{-3}$
From infectious human to vector	p_{VR_H}	–	0.24–0.64	0.15–0.73	$1.7e^{-3}$–$25e^{-3}$	0.21–0.29	0.14–0.38	0.90–0.99
From 'recovered' human to vector	p_{VI_R}	–	0.024–0.064	0	0	0	0	$4.2e^{-3}$–$6.2e^{-3}$
From infectious non-human hosts to vector	p_{VI_h}	–	–	–	–	0.05–0.28	0.55–1	0.90–0.99
From 'recovered' non-human hosts to vector	p_{VR_h}	–	–	–	–	0	0	0.05–0.31
Pathogen within-host dynamics								
Infectious human death rate [(2)]	d_{I_H}	day^{-1}	$0.4e^{-4}$–$4.9e^{-4}$	$0.4e^{-4}$–$67.8e^{-4}$	$0.4e^{-4}$	$2.7e^{-4}$–$4.3e^{-2}$	$37.1e^{-4}$–0.26	$0.4e^{-4}$–$11.9e^{-4}$
'Recovered' human death rate	d_{R_H}	day^{-1}	$0.4e^{-4}$	$0.4e^{-4}$	$73.3e^{-3}$–$3.8e^{-2}$	$0.4e^{-4}$	$0.4e^{-4}$	$0.4e^{-4}$–$64.0e^{-4}$
Infectious human rate of recovery	r_{I_H}	day^{-1}	$15.9e^{-4}$–$1.7e^{-2}$	$6.6e^{-2}$–0.33	$12.8e^{-4}$–$83.3e^{-4}$	$55.6e^{-4}$–$1.1e^{-2}$	$7.1e^{-2}$–0.50	$1.7e^{-2}$–$2.2e^{-2}$
Human rate of loss of immunity	l_{R_H}	day^{-1}	0–$1.1e^{-2}$	$0.4e^{-4}$	$13.7e^{-4}$–$83.3e^{-4}$	0	0	0
Infectious non-human hosts death rate [(2)]	d_{I_h}	day^{-1}	–	–	–	$51.2e^{-4}$–4.61	$27.4e^{-4}$–4.61	$9.1e^{-4}$–$20.5e^{-4}$
'Recovered' non-human hosts death rate	d_{R_h}	day^{-1}	–	–	–	$9.1e^{-4}$	$27.4e^{-4}$	$9.1e^{-4}$–$12.8e^{-4}$
Infectious non-human hosts rate of recovery	r_{I_h}	day^{-1}	–	–	–	$9.1e^{-4}$–1	0.14–1	$1.3e^{-2}$–$2.2e^{-2}$
Non-human hosts rate of loss of immunity	l_{R_h}	day^{-1}	–	–	–	1	0	0

[(1)]Vector, human and non-human hosts natural death rates were estimated as 1/individual longevity. The range of variation of longevity (i.e. 1/death rate parameter defined in the model), as those are the raw data found in the literature (see sections '*Vector local growth rate*' and '*Human and non-human hosts natural death rates*' in Text S1).

[(2)]Death rates were calculated as the sum of the natural death rate of human (d_H) or non-human (d_h) hosts and additional mortality imposed by the pathogen to infectious and 'recovered' individuals (as calculated in section '*Human and non-human hosts mortality induced by the pathogen*' in Text S1).

doi:10.1371/journal.pone.0036858.t001

frequently (around 1–4 weeks), adults live for several months so that they can bite 10–30 times. The transmission potential between vectors and human hosts is larger for VL (around 0.08) than for JE (around 0.007) and for CD (around 0.002 and 1.10^{-5} for human hosts with acute and chronic infection, respectively). The transmission potential between vector and non-human hosts shows a similar trend, with larger probabilities for JE (around 0.28) than for VL (around 0.05) and for CD (around 0.002 and 4.10^{-4} for non-human hosts with acute and chronic infection, respectively). The course of the disease in hosts also differs between the three diseases. Human hosts affected by VL and JE go through an acute and infectious state that last a few days for JE, or up to several months for VL. Once they have recovered, individuals are immune for the rest of their life. Disease-induced death rate during the infectious state can be very high for both diseases, and humans suffering from VL will eventually die if not treated. JE, CD and VL's pathogens are known to circulate in various non-human hosts, although an understanding of the pathogens' development in those hosts remains limited. Here, we focused on emblematic domestic hosts, dogs for VL and CD and swine for JE, as they are claimed to be key actors regarding transmission, and they are central to control strategies set up to limit the impact of these diseases. The course of VL in dogs or JE in swine is roughly similar, except that infected dogs do not usually recover and remain infectious until death, which can be natural, induced by the disease, or due to euthanasia. The progress of CD in (human or dog) hosts is different from the course of VL and JE (in humans, dogs and swine). An acute phase, lasting several weeks, is followed by a chronic and life-long phase and hosts are infectious in both phases, although parasitemia is significantly lower in the chronic stage of the disease [80].

Modelling

The SIRS model. We developed a SIRS model ([66] p. 247) to study the vector transmission of a pathogen between human and non-human hosts. The complete model was used to investigate diseases with non-human hosts (JE, CD, and VL), and the number of such hosts was set to 0 when considering diseases with only human hosts (MAL, DEN and HAT). In our complete model, human and non-human hosts can be susceptible (S_H,S_h), infectious (I_H,I_h) or belong to a last category (R_H,R_h), whose exact meaning varies with the modelled disease. Human hosts falling in this last category are thought to be *recovered* and immune when considering DEN [84]. When modelling MAL and HAT individuals with status R_H still carry the pathogen, but are *removed* from the infectious category as they become much less able [82,83] or unable to transmit [85]. For JE and VL, human (R_H) and non-human (R_h) individuals are thought to have *recovered* and be immune to new infection [31,86]. Finally, when considering CD, infectious human and non-human hosts are individuals in the acute phase of the disease, while R_H and R_h individuals have entered the chronic phase, where there are fewer circulating pathogens but hosts remain able to transmit [67]. Effectively, for all diseases, individuals thereafter commonly referred to as 'recovered', are thus either not or much less able to transmit the pathogen than when they are infectious.

Human host population size is assumed to be constant, and equal to N_H, so that only the numbers of infectious and 'recovered' are modelled explicitly. Infectious humans die at rate d_{I_H} (which includes natural death, d_H, and disease-induced mortality of infectious human hosts, v_{I_H}), become 'recovered' at rate r_{I_H}, and are gained through contacts of susceptible individuals with infectious vectors (I_V) at rate C_{HV} (see section '*Modelling transmission with respect to vector feeding*' for a formal expression). This leads to a first ordinary differential equation:

$$\frac{dI_H}{dt} = -\left(d_{I_H} + r_{I_H}\right) I_H + C_{HV} S_H I_V \tag{1}$$

'Recovered' humans die at rate d_{R_H} (which includes natural death, d_H, and disease-induced mortality of 'recovered' humans, v_{R_H}), and can re-join the pool of susceptible by losing their immunity (for MAL and DEN) or after treatment (for HAT) at rate l_{R_H}. This leads to a second ordinary differential equation:

$$\frac{dR_H}{dt} = -\left(d_{R_H} + l_{R_H}\right) R_H + r_{I_H} I_H \tag{2}$$

The non-human host population is also assumed to be constant (N_h), and is modelled exactly in the same way as the human host population, although demographic and transmission parameters are allowed to take on specific values. This leads to define two additional ordinary differential equations:

$$\frac{dI_h}{dt} = -\left(d_{I_h} + r_{I_h}\right) I_h + C_{hV} S_h I_V \tag{3}$$

$$\frac{dR_h}{dt} = -\left(d_{R_h} + l_{R_h}\right) R_h + r_{I_h} I_h \tag{4}$$

where d_{I_h} (which includes non-human hosts natural death, d_h, and disease-induced mortality of infectious non-human hosts, v_{I_h}), r_{I_h}, C_{hV}, d_{R_h} (which includes natural death, d_h, and disease-induced mortality of 'recovered' non-human hosts, v_{R_h}), and l_{R_h} are defined as for the human host population.

By contrast to human and non-human hosts, both the number of susceptible and infectious vectors are modelled explicitly. Since we are interested in sink vector populations, the local growth rate of vectors is assumed to be negative ($-\Delta_V$). Such a local growth rate actually represents the net balance between vector's births, deaths and emigration, and $1/\Delta_V$ corresponds to the average time spent in the sink, or vector 'longevity' in the sink. Vector population is sustained by immigration of individuals (i_V), some being susceptible (i_{S_V}), while others are infectious (i_{I_V}). Neglecting vertical transmission, susceptible vectors become infectious only by contact with infectious and recovered human and non-human hosts at rate C_{VI_H}, C_{VR_H} and C_{VI_h}, C_{VR_h}, respectively (see section '*Modelling transmission with respect to vector feeding*'). The two ordinary differential equations describing the temporal variations of the vector population then read:

$$\begin{aligned}\frac{dS_V}{dt} = i_{S_V} - \Delta_V S_V - C_{VI_H} S_V I_H - C_{VR_H} S_V R_H \\ - C_{VI_h} S_V I_h - C_{VR_h} S_V R_h\end{aligned} \tag{5}$$

$$\begin{aligned}\frac{dI_V}{dt} = i_{I_V} - \Delta_V I_V + C_{VI_H} S_V I_H + C_{VR_H} S_V R_H \\ + C_{VI_h} S_V I_h + C_{VR_h} S_V R_h\end{aligned} \tag{6}$$

Altogether equations 1–6, where $S_H = N_H - I_H - R_H$ and $S_h = N_h - I_h - R_h$, define our SIRS model.

Modelling transmission with respect to vector feeding. Key ingredients of any infectious disease model are the rates of transmission of the pathogen (noted C in our model). For vector-borne diseases, they usually are taken to be frequency-dependent, assuming that each vector bites at a constant rate [25,24]. In this contribution, we aim to look at the importance of the vector feeding in determining this biting rate. We took advantage of an original function of transmission [87], which links explicitly the biting rate of the vector to two key ingredients of vector feeding through a couple of parameters. First, the proportion of the host population that has been found by a vector within a given time period, thereafter referred to as 'finding rate' of the vector (a), which accounts for various features of vector feeding behavior and host accessibility and availability. Second, the minimal amount of time between two consecutive blood-meals (T_d). Using this function one can write the rate at which vectors become infected by contact with infectious humans:

$$C_{VI_H} = p_{VI_H} \frac{a}{1 + a T_d N_H} \tag{7}$$

where p_{VI_H} stands for the probability of transmission (per contact) from an infectious human host to a vector. Interestingly, when considering a long delay between blood-meals (T_d) or a high finding rate (a), the Antonovics et al.'s function [87] tends towards a frequency-dependent function of transmission, while in case of a short delay (T_d) or a low finding rate (a), it becomes density-dependent. All the other rates of contact (C_{HV},C_{VR_H}, C_{hV}, C_{VI_h}, C_{VR_h}) can be expressed exactly in the same way, but changing the probability of transmission (p_{VI_H} above) and the number of hosts (N_H above), with respect to the type of human or non-human hosts

being considered. This function of transmission does not account for any host preference. Such preferences have been documented for most vectors of human pathogens, although the pattern of vector feeding plasticity are still hard to measure and there is no general understanding of their ecological and evolutionary determinants [88]. Although host preference can have effects on transmission [89] and control [90] of multi-host pathogens, looking at these effects thus falls far behind the goal of this paper.

Analysis

Dynamical properties of the model. We first investigated the dynamical properties of our model to determine conditions on vector demography and feeding rates as well as on pathogen transmission and virulence that allow for the spread and persistence of vector-borne diseases in sink vector populations. We identified the basic reproduction rate of the parasite, noted R_0 (e.g., [91]), the steady states of the model, and evaluated their properties of local stability. The expression of the equilibrium levels of susceptible/infectious/recovered humans and alternative hosts were derived from basic methods to analyse second order polynomial equations, and Cardan's method to solve cubic equations. The stability properties of these steady states were established using standard Routh-Hurwitz criterion [92].

Quantitative investigations of the spread and persistence of the pathogens. The expressions of the R_0 or the level of prevalence of the pathogens in human populations derived from these analyses were then investigated quantitatively. Because studies on sink vector populations are rare (see introduction), we would not find estimates of all relevant parameters in a given field site (as it can be for well documented source populations, e.g., [30,34]). This precluded us from performing standard sensitivity analysis in the vicinity of a trustable set of parameter values estimated on a specific population (e.g., [93]). Instead we used an approach developed by [94], which consists of generating random combinations of parameter values within the biologically plausible range of these parameters (rather than around specific estimates). In this way, we aimed at reproducing a representative set of biologically sensible conditions that could be encountered by different pathogens in various sink vector populations. We thus used the estimates of the parameters of the model that could be gained from our review of the literature (Text S1) to specify the biologically relevant subset of the parameter space to be looked at (Table 1).

We performed sensitivity analysis to identify which of the parameters most strongly influence the value of R_0, and the prevalence in humans. For each modelled disease, we generated 10,000 sets of parameter values by randomly sampling each parameter within its identified range of plausible values according to a uniform distribution. The assumption that parameters are uniformly distributed has been used to model transmission in other contributions (e.g., [95,96]). Potentially, considering alternative distributions could change the quantitative details of the results, though qualitative trends are likely to be robust as they reflect the basic features of the source-sink situation we modelled (see discussion). A uniform distribution is the simplest non-informative assumption that can be made according to the principle of 'insufficient reason' [96] in the absence of data supporting a specific pattern of variability, We then calculated the value of R_0 and the prevalence in humans for each of the 10,000 sets of parameter values and used this to draw, for each disease, the distribution of the expected values of R_0 and of human prevalence (I_H/N_H and R_H/N_H) in sink vector populations. A great value of this approach is that the effect of a given parameter is quantified, while all other parameters are varied randomly within their range, rather than when they take on given estimated values.

The effect of a given parameter on R_0 can then be quantified by *a posteriori* comparing the subsets of its values that were associated with $R_0>1$ and with $R_0<1$ in the 10,000 virtual populations that we generated by sampling the plausible range of parameter values [94]. If a parameter has a small effect on R_0, one expects this parameter to take on similar values in populations where the pathogen spreads ($R_0>1$) and in populations where it does not ($R_0<1$). In the opposite situation, whereby a parameter has a strong effect on R_0, small changes in its value will be sufficient to switch from a situation where the pathogen spreads to a situation where it gets extinct. Accordingly, the larger the effect of a parameter on R_0, the lower the overlap between the distributions corresponding to the two subsets is expected to be. We thus calculated the proportion p of the two distributions that overlapped, and use $1-p$ as a measure of the effect of the parameter being considered.

The effect of a given parameter on the percentage of human individuals being infectious or recovered cannot be quantified as its effect on R_0. As a matter of fact, in this case, one cannot define two subsets of values corresponding to two qualitatively different dynamical outcomes (such as, in the previous case, 'spread' corresponding to $R_0>1$, vs 'extinction' corresponding to $R_0<1$). Instead, we thus simply correlated the values of these percentages (calculated while sampling in all the range of parameter values) with the sampled values of the parameter being considered. We then used the coefficient of determination of the regression to the mean as a measure of the effect of the parameter on the percentage of infectious or recovered individuals, since it typically gives the proportion of the total variation of the dependent variable that is accounted for by the explanatory variable. The analytical expression of the equilibrium levels of susceptible/infectious/recovered human and non-human hosts were evaluated numerically for any given set of parameter values using Mathematica [97].

Results

Conditions for the Spread of Vector-borne Pathogens in Sink Vector Populations

The stability analysis of our model confirmed that the two epidemiological situations presented in introduction, whereby pathogens are introduced by immigrating vectors, or independently of vector immigration (i.e. via the accidental arrival of infected human or non-human hosts in the sink population), are very different from a dynamical system point of view. The dynamical behaviour of the model in these two situations is briefly summarized below.

Introduction of pathogens via immigrating vectors. Because a fraction of the immigrating vectors is infectious, both vector and pathogen will persist as soon as vector immigration into the sink population is present. As expected, there is then only one stable positive 'endemic equilibrium (thereafter referred to as EE), where the pathogen infects human hosts and, when they are present, non-human hosts. A more formal way to express the conditions for pathogen persistence is to phrase it in term of R_0, where $R_0 = 1+i_V$, which indicates that the vector immigration threshold for the parasite to spread is 0. In this first situation, the spread of the pathogen thus does not depend on the various other parameters of the model.

Independent introduction of vectors and pathogens. In this second situation, there are two equilibria; a disease-free equilibrium (thereafter referred to as DFE) and the endemic equilibrium EE. As for most vector-borne disease models, we found

a transcritical bifurcation, whereby 1) the DFE is unstable when the EE is stable (and vice versa), and 2) the DFE is unstable when the basic reproduction rate of the parasite R_0 is larger than 1 (e.g., [91]). However, as the transmission process is modelled by using the Antonovics et al.'s function [87], an expression of R_0 can be proposed that, according to the minimal amount of time between two blood-meals (T_d) and the vector finding rate (a), will be associated to either a density- or a frequency-dependent function of transmission [87]. The general expression of R_0 in sink vector population then reads:

$$R_0 = \frac{i_{S_V}}{\Delta_V^2}\left[C_{HV}\times N_H \times \frac{\left(d_{R_H}+l_{R_H}\right)C_{VI_H}+r_{I_H}C_{VR_H}}{\left(d_{I_H}+r_{I_H}\right)\left(d_{R_H}+l_{R_H}\right)} + C_{hV}\times N_h \times \frac{\left(d_{R_h}+l_{R_h}\right)C_{VI_h}+r_{I_h}C_{VR_h}}{\left(d_{I_h}+r_{I_h}\right)\left(d_{R_h}+l_{R_h}\right)}\right] \quad (9)$$

Straightforward calculations show that when considering long time between blood-meals or high finding rate (which makes the function of transmission frequency-dependent, as commonly modelled for vector-borne diseases), the R_0 in sink vector population simplifies to:

$$R_0 = \frac{i_{S_V}}{\Delta_V^2 T_d^2}\left[\frac{p_{HV}}{N_H}\times \frac{\left(d_{R_H}+l_{R_H}\right)p_{VI_H}+r_{I_H}p_{VR_H}}{\left(d_{I_H}+r_{I_H}\right)\left(d_{R_H}+l_{R_H}\right)} + \frac{p_{hV}}{N_h}\times \frac{\left(d_{R_h}+l_{R_h}\right)p_{VI_h}+r_{I_h}p_{VR_h}}{\left(d_{I_h}+r_{I_h}\right)\left(d_{R_h}+l_{R_h}\right)}\right] \quad (10)$$

We note that substituting the immigration term (i_{S_V}) with a constant reproduction rate, this expression is similar to those derived for a source vector population (e.g., [25] page 16). From equation 9 (or 10) it is obvious to show that the persistence of a pathogen in a sink population sustained by the arrival of non-infectious vectors requires immigration to exceed a threshold, so that $R_0>1$. This threshold depends on all other parameters describing vector demography and feeding rates, host demography, transmission and within-host dynamics (see Table 1) in various non-linear ways. The sensitivity analysis presented in the next paragraph will allow identifying which of these parameters play a key role in the spread of the 6 diseases considered in this study.

Identification of the Key Processes Determining the Emergence and Prevalence of Vector-borne Pathogens in Sink Vector Populations

Rate of spread of pathogen in disease-free sink vector populations. The previous section has made explicit that, obviously, when some immigrating vectors are infectious, the pathogen will always persist in the sink population. Here, we will only look at the condition for the pathogen to spread when it is not introduced by immigrating vectors but by the incidental arrival of infected hosts (see equation 9). To determine the typical rates of spread in this second case, we generated the distribution of R_0 for the six diseases considered by randomly sampling into each parameter range of plausible values (Table 1).

All the distributions of R_0 look very similar (figure 1). They all are right-skewed distributions with, unsurprisingly, a majority of R_0 values being lower than 1. However, all pathogens remain able to spread ($R_0>1$) in 15–30% (and up to 55% for MAL) of cases following their incidental introduction. In addition, the tails of the distributions include large values of R_0, suggesting a true potential for strong outbreaks for all these diseases. To identify the key processes determining the spread of pathogens in such sink vector populations, we then looked at the effect of the various parameters of the model on R_0.

Our sensitivity analysis showed that vector-related parameters have the largest effects on R_0 (figure 2). Demographic parameters, namely the local growth rate, representing the net balance between births, deaths and emigration ($-\Delta_V$), and the immigration (i_V) rate, are highly influential. Vector local growth rate has the largest effect because it determines both vector population abundance (which is equal to i_V/Δ_V), and the average time spent in the sink (which is equal to $1/\Delta_V$), while immigration only has an effect on vector abundance. Variations in the time spent in the sink have an important impact on transmission, since they obviously influence the number of opportunities for vectors to encounter hosts. Vector feeding is another well-recognized factor in determining the rate of contact between vectors and hosts. Remarkably, by using the Antonovics et al.'s function of transmission [87], we were able to look at relative effect of the time delay between two blood-meals (T_d), and the vectors finding rate (a). An interesting outcome is that the minimal amount of time between two blood-meals has a significant effect, similar to the impact of immigration, or even larger for the two trypanosomiases (HAT and CD). On the other hand, quite surprisingly, the vectors finding rate (a) has virtually no impact on R_0, whatever the disease being considered. This suggests that the spread of the pathogen is more limited by temporal constraints associated to the reproductive biology of the vector, than by its dispersal ability.

Parameters related to pathogen transmission and within-host dynamics typically have smaller and much more disease-specific effects. Still, the spread of DEN and HAT is significantly influenced by the human recovery rate (r_{I_H}). This is because at the typically low abundances encountered in sink vector populations, it is important that human hosts remain infectious for the pathogen to be transmitted back to the vectors. The spread of diseases with non-human hosts tends to be more sensitive to non-human hosts-related parameters, than to human hosts-related parameters. For similar reasons as explained above, the most important parameters are the rate of non-human hosts recovery and the probabilities of transmission between vectors and non-human hosts. Mostly, the non-human hosts recovery rate (r_{I_h}) has a noticeable effect on the spread of JE, and the transmission probability from vectors to non-human hosts (p_{hI_V}) has an effect on CD. Finally, all the remaining parameters have lower effect, or virtually no impact on R_0.

Prevalence of pathogens in sink vector populations. Results of the previous sections have clarified the conditions for the pathogens to spread in sink populations. While such spread relies only on vector immigration when pathogens are introduced via immigrating vectors (since $R_0 = 1+i_V$), it is influenced by vector local growth rate ($-\Delta_V$), and the minimal amount of time between blood-meals (T_d), when pathogens are introduced independently of immigrating vectors. To determine if the same processes were also the key determinants of pathogen's prevalence when it becomes established in the population, we looked at the distribution of the percentage of infectious and recovered humans obtained while randomly sampling into the range of plausible parameter values (Table 1).

Independent introduction of vectors and pathogens in the sink vector population. The distribution of infection in humans shows that, when no immigrating vectors is infectious, the percentage of

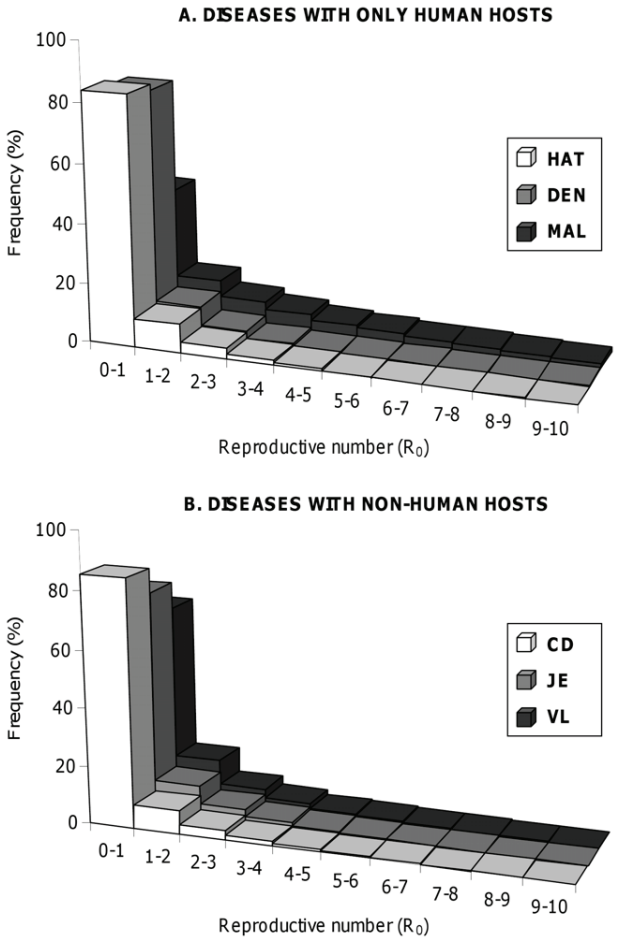


Figure 1. Distribution of the pathogen's basic reproduction number (R_0) for each of the six vector-borne diseases considered. (**A**) Diseases with only human hosts: human African trypanosomiasis (HAT), dengue (DEN) and malaria (MAL). (**B**) Diseases with non-human hosts: Chagas disease (CD), Japanese encephalitis (JE), and visceral leishmaniasis (VL). Distributions were obtained from 10,000 simulations for each disease.
doi:10.1371/journal.pone.0036858.g001

humans being infectious (I_H) or 'recovered' (R_H) are lower than 5% in most conditions obtained from our random sampling (figure 3). For DEN, JE and VL, the percentage of infectious humans is systematically less than 5%, while the percentage of immune 'recovered' individuals can be more than 5% in roughly 20% of cases of pathogen's introduction for each of these diseases. For MAL, the percentage of infectious humans can be significantly higher, since 19% of prevalence values are larger than 5%. Concomitantly, the percentage of immune 'recovered' individuals is also larger, with around 35% of the predicted prevalence larger than 15%. The higher prevalence of humans infectious with MAL is explained by a longer duration of infection (generated by lower rates of death and/or recovery of infected individuals) than for DEN, JE or VL. This, in turn, results in a higher prevalence of 'recovered' (and reduced infectivity) individuals in MAL than in these 3 other diseases. For HAT and CD, infectious and 'recovered' human hosts are both infected with the pathogen since they correspond to the two different phases of the disease. The percentage of infected human hosts (in either one or the other phase of the diseases) can, as for MAL, be larger than 5%. Typically, 10–15% of simulations lead to more than 15% of humans affected by HAT, and around 10% of simulations lead to more than 15% of individuals chronically infected with CD. Again, the higher rates of infection for these two trypanosomiases than for DEN, JE and VL, are mostly due to longer durations of infection, which result in larger accumulations of human cases despite low vector abundances. Overall, although all prevalence values are expectably lower than observed in typical vector source populations, 'anthropic' or naturally occurring sink vector populations can thus represent serious potential threats. If the pathogens is to be accidently introduced in such populations by the arrival of infected hosts, one expects 0–5% of the population to be affected by DEN, JE and VL, and even a larger fraction of the population to be suffering from diseases with longer duration of infection such as MAL, HAT and CD.

Introduction of pathogens via immigrating vectors. The distribution of prevalence in humans is modified when some immigrating vectors are infectious (figure 4). For DEN, JE, and VL, the percentage of infectious humans remains always lower than 5%. However, it is rather clear that the pathogen has infected many more individuals. The percentage of cases with more than 5% of immune 'recovered' individuals is indeed 3–6 times higher than when no immigrant is infectious (figure 3), and there is now more than 90%, more than 70% and 35% of simulations where more than 15% of individuals are immune to DEN, VL and JE, respectively. Similar changes were observed for MAL, though in smaller proportion. The percentage distribution of I_H individuals remains virtually the same as when no immigrant is infectious (figure 3), but the transmission of the pathogen has also increased since the proportion of cases where more than 5% of individuals are 'recovered' raises from 34% to 74%. It is clear that transmission of HAT and CD was also much higher. For HAT, this manifested by a shift of the distribution of prevalence of the two stages of the diseases, with 4–5 more simulations where the prevalence of infectious and 'recovered' individuals were more than 5%. By contrast, for CD, only the prevalence of the second chronic phase of the disease markedly raised with 5–6 more simulations leading to more than 5% of chronically infected individuals. The difference between the two trypanosomiases is consistent with the much longer duration of the chronic stage than the acute phase of CD. Overall, the percentage of people currently suffering from DEN, JE, MAL, and VL, i.e. 'infectious' individuals, is not significantly higher when some immigrants are infectious, although the circulation of the pathogens in human hosts has been increased. This suggests that the within-host dynamics of the pathogen plays a critical role in determining the prevalence of infection for these diseases. On the contrary, the prevalence of individuals affected by HAT or CD, i.e. both 'infectious' and 'recovered' individuals, increased significantly when some immigrants are infectious. Such an increase for CD is clearly due to the high prevalence of infectious triatomines (resulting from their long life expectancy). For HAT, such an increase is rather explained by the very low probability of transmission from infectious humans to vectors, which strongly constrains the circulation of the pathogen. Compensating for this low probability, by introducing already infectious vectors, strongly facilitates the spread of the disease.

To identify the key parameters determining those variations in the level of pathogen prevalence in humans, we performed a sensitivity analysis summarized in figure 5 (and figures S1 and S2). For DEN, JE, and VL we focused on the 'recovered' individuals since the prevalence of infectious individuals remains lower than 5% in all simulated conditions (see figures 3 and 4). Prevalence of 'recovered' provides a better picture of the overall transmission of

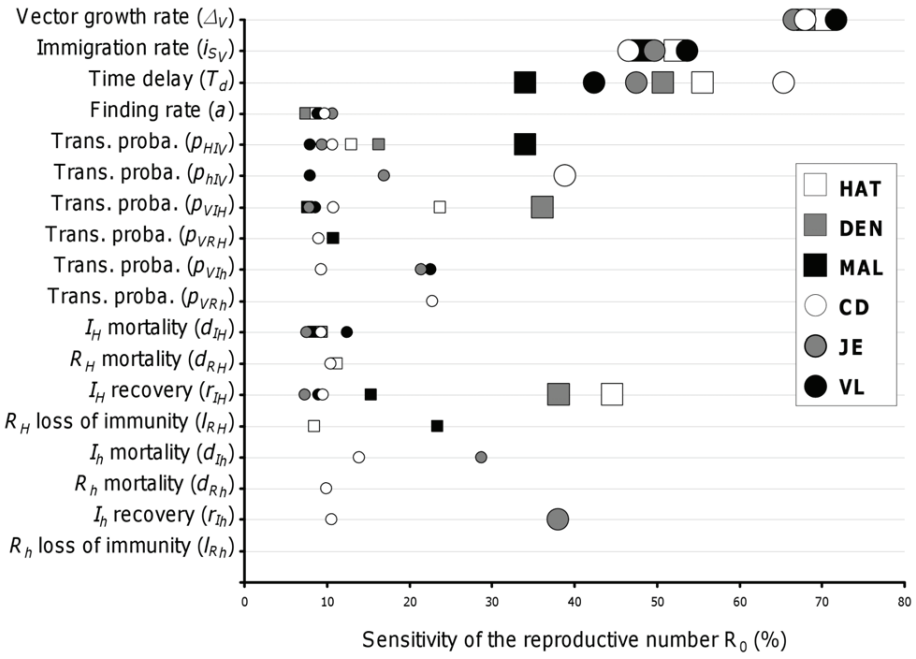


Figure 2. Sensitivity of the basic reproduction number (R_0) to vector's demography and feeding rates, and to pathogen's transmissibility and virulence. All six vector-borne diseases appear on the same graph. Squares correspond to diseases with only human hosts: human African trypanosomiasis (HAT), dengue (DEN) and malaria (MAL). Circles correspond to diseases with non-human hosts: Chagas disease (CD), Japanese encephalitis (JE), and visceral leishmaniasis (VL). Larger symbols correspond to the key determinants of the variations of R_0 (see main text for comments). Sensitivities were calculated from 10,000 simulations for each disease.
doi:10.1371/journal.pone.0036858.g002

pathogens to humans, especially because individuals in this category had long lasting immunity to DEN, JE or VL. We also focused on 'recovered' humans for CD since there are much more individuals in the chronic than in the acute stage of the disease. For MAL and HAT, both percentages of infectious and 'recovered' individuals reached higher levels, and we thus accounted for these two categories.

Sensitivity analysis for the independent introduction of vectors and pathogens. The vector-related parameters are no longer systematically the key parameters in determining the percentages of infectious or 'recovered' individuals (figure 5A and S1), as they were in influencing R_0 (figure 2). The influence of vector- and pathogen-related parameters now varies from one disease to another. For DEN, VL and JE, there is no key parameter. The sensitivities of prevalence to each of the parameters were indeed roughly similar and lower than 10%. On the contrary, for the other three diseases, 2 to 4 parameters had marked effects exceeding 10%. The prevalence of infectious individuals with MAL was critically influenced by two parameters related to the within-host dynamics of the pathogen. First, the rate of recovery from infection (r_{I_H}), which determines how long individuals stay in the pool of highly infectious individuals. Second, the rate of return to a susceptible state (l_{R_H}), which directly influences both the pool of individuals that can be infected and the number of hosts from which the pathogen can be uploaded by vectors. On the contrary, vector-related parameters were the most influential on the percentage of individuals chronically infected with CD. These included, the minimal amount of time between two blood-meals (T_d) and immigration (i_V), as well as the probability of transmission of the disease from vector to humans (p_{HV}), which all together determine the force of infection to humans. Interestingly, the analysis for HAT showed an intermediate pattern as key parameters were both vector- and within-host dynamics-related. Understandably, the human rate of return to the pool of susceptible (l_{R_H}) and the virulence to individuals in the second phase of the disease (d_{R_H}) had a major impact on the loss, and thus on the prevalence of 'recovered' individuals. Similarly, the rate of transition to the second phase of the disease (r_{I_H}) had a direct significant effect on the prevalence of individuals in the first phase of the diseases, i.e. 'infectious'. However, the vector local growth rate ($-\Delta_V$) and the probability of transmission to humans (p_{HV}) also had an impact on the prevalence of both 'recovered' and 'infectious' individuals.

Sensitivity analysis for the introduction of pathogens via immigrating vectors. When some immigrating vectors were infectious (see above), the key factors allowing for disease's emergence and shaping the epidemiological dynamics that follows the initial spread of the pathogen could be identified from the sensitivity analysis of R_0 (figure 2) and prevalence (figure 5A), respectively. The factors influencing the two stages of the dynamics can no longer be disentangled here since the pathogen spreads systematically. Accordingly, the parameters now influencing prevalence values (figure 5B and S2) are a combination of those that were shown to influence the R_0 and prevalence in the previous situation. The most influential parameters are vector-related parameters (previously determining R_0), eventually followed by additional parameters with smaller but noticeable effects. Interestingly, the latter are then the parameters that influenced prevalence when pathogens and immigrating vectors were introduced independently in the sink population. For all diseases, vector demography (Δ_V and i_V) had the most influential effect, although the differences with the effect of other parameters were typically lower than what they were for R_0 (figure 5B to be compared to figure 2). Only for individuals highly infectious with

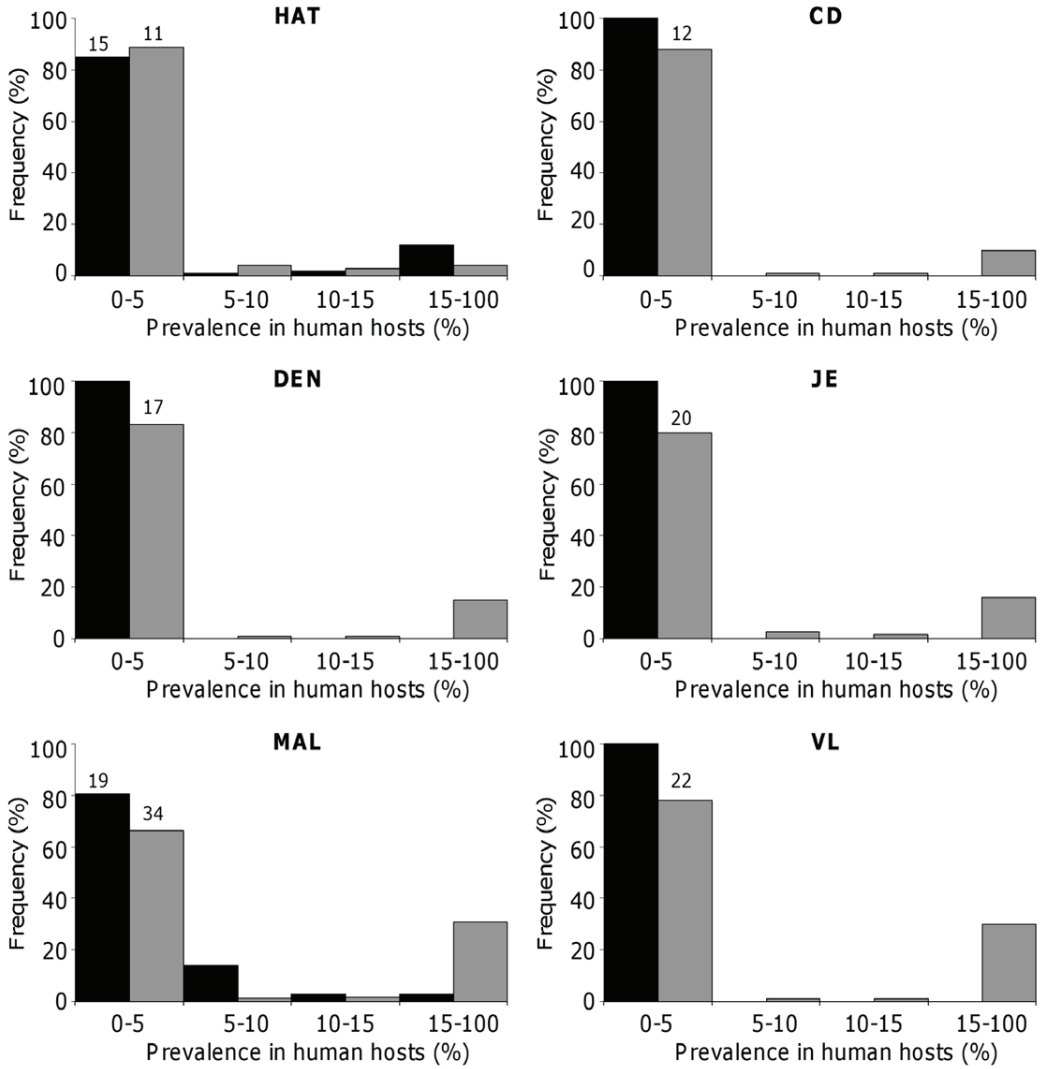


Figure 3. Distribution of the prevalence of infectious and recovered humans when no immigrant vector is infectious ($i_{I_V}=0$). Black and grey bars give the prevalence of infectious (I_H^*) and recovered (R_H^*) humans, respectively. Numbers above bars give (if any) the percentage of simulations leading to prevalence larger than 5%. Distributions were obtained from 10,000 simulations for each disease.
doi:10.1371/journal.pone.0036858.g003

MAL (I_H), the rate of recovery (r_{I_H}) and the rate of return to the pool of susceptible (l_{R_H}) had a similar influence as vector demography (Δ_V and i_V). This is very consistent with the results obtained when no immigrating vector was infectious since the exact same parameters describing the within-host dynamics were already determining the prevalence of infection with MAL (figure 5A). Similarly, the parameters that were shown to influence the prevalence of HAT (i.e., r_{I_H}, l_{R_H} and d_{R_H}) and CD (T_d and i_V) in the previous situation (figure 5A) are still playing a significant role in determining the rate of human infections (figure 5B). Finally, it is worth noting that the percentage of infectious vectors has low influence on human prevalence, except for DEN. This is mostly explained by the very low prevalence of infection in humans (figure 4) combined with the absence of non-human hosts. Opportunities for a susceptible vector to get infected are thus very limited, and can be substantially raised by the arrival of infectious immigrants, which makes the dynamics of the pathogen in the sink sensitive to the prevalence in dispersing vectors.

Discussion

The concepts of 'source' and 'sink' have played a pivotal role in ecology by improving our understanding of species persistence out of their fundamental niche [27,28], coexistence between competitive species (e.g., [98]) and predator-prey relationship (e.g., [99]). Such advances underline many decisions in today's conservation biology (e.g., [100]). Surprisingly, those concepts have not been applied to improve our understanding of the transmission of human vector-borne diseases, and our ability to control such diseases, while many populations of transmitting vectors actually are 'natural' (e.g., [37,70,101,72]) or 'anthropic' (typically generated by partially effective control intervention, [49,50–54,35,58]) 'sinks'. We aimed at identifying the key factors determining the possibility of emergence, and subsequent prevalence of infection, of six major human vector-borne diseases in such 'sink' populations. The approach intended was to design a unique 'strategic model' as a tool for qualitative and quantitative reasoning [102]. Such a 'core' model [65] does not allow

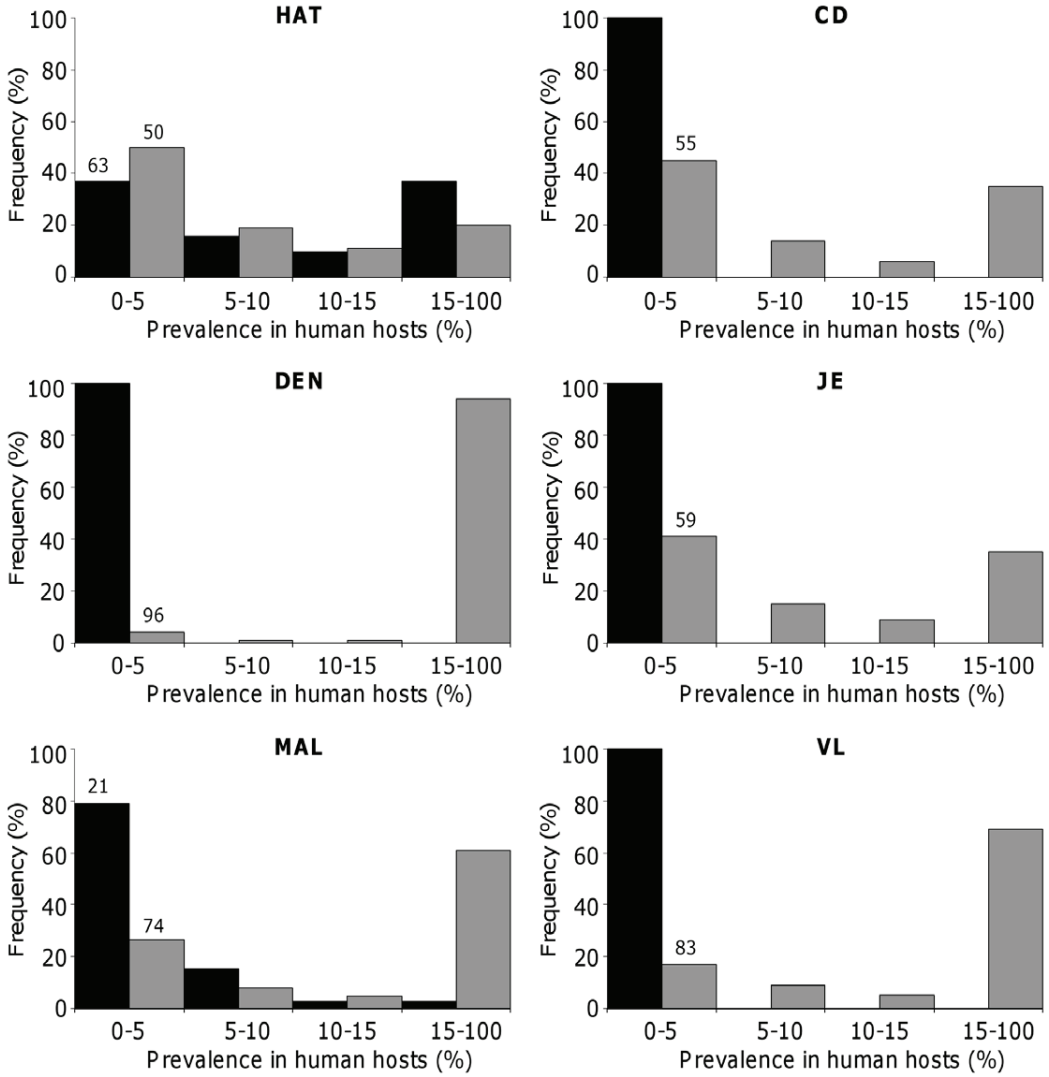


Figure 4. Distribution of the prevalence of infected and recovered humans when some immigrant vectors are infectious ($i_{I_V} > 0$). Black and grey bars give the prevalence of infectious (I_H^*) and recovered (R_H^*) humans, respectively. Numbers above bars give (if any) the percentage of simulations leading to prevalence larger than 5%. Distributions were obtained from 10,000 simulations for each disease.
doi:10.1371/journal.pone.0036858.g004

accounting for disease specific processes, e.g. strong spatio-temporal heterogeneities or host feeding preference [88], which clearly are of fundamental importance to make predictions about the distribution and control of any particular pathogen [103]. The main results discussed below thus provide general insights that should now be contemplated and challenged by disease-specific models relying on detailed quantitative knowledge of particular systems.

Emergence of Vector-borne Diseases in Sink Vector Populations

A first interesting outcome of our analyses is that all six human diseases were able to spread in about 15–30% (and up to 55% for MAL) of cases when pathogens are introduced accidently in a susceptible sink vector population, with potentially high reproductive ratio (R_0) despite low vector abundance. The sensitivity analysis of R_0 to the different parameters of the model showed that vector-related parameters (longevity, immigration, and feeding frequency) had the strongest influence on disease emergence. This pattern was very consistent across all six diseases, which suggests that it is a robust conclusion regardless of the existence of non-human hosts, and of the specificity of the transmission and within-host dynamics of the pathogens. More specifically, vector longevity is the key parameter in determining whether or not a pathogen would spread, and it has a larger effect on R_0 than immigration and feeding frequency. Interestingly, while vector immigration (i_V) and longevity ($1/\Delta_V$) play a symmetrical role in determining vector abundance in a sink population since the latter is formally given by their product (i_V/Δ_V), these two components bring different contributions to the emergence of pathogens in such populations. The rationale behind this differential sensitivity is quite simple and consistent with our understanding of factors influencing emergence in vector source populations (e.g., [61]). While different combinations of vector longevity and immigration can lead to identical vector abundance, the larger the longevity the smaller the turnover of the population. This, in turn, favours

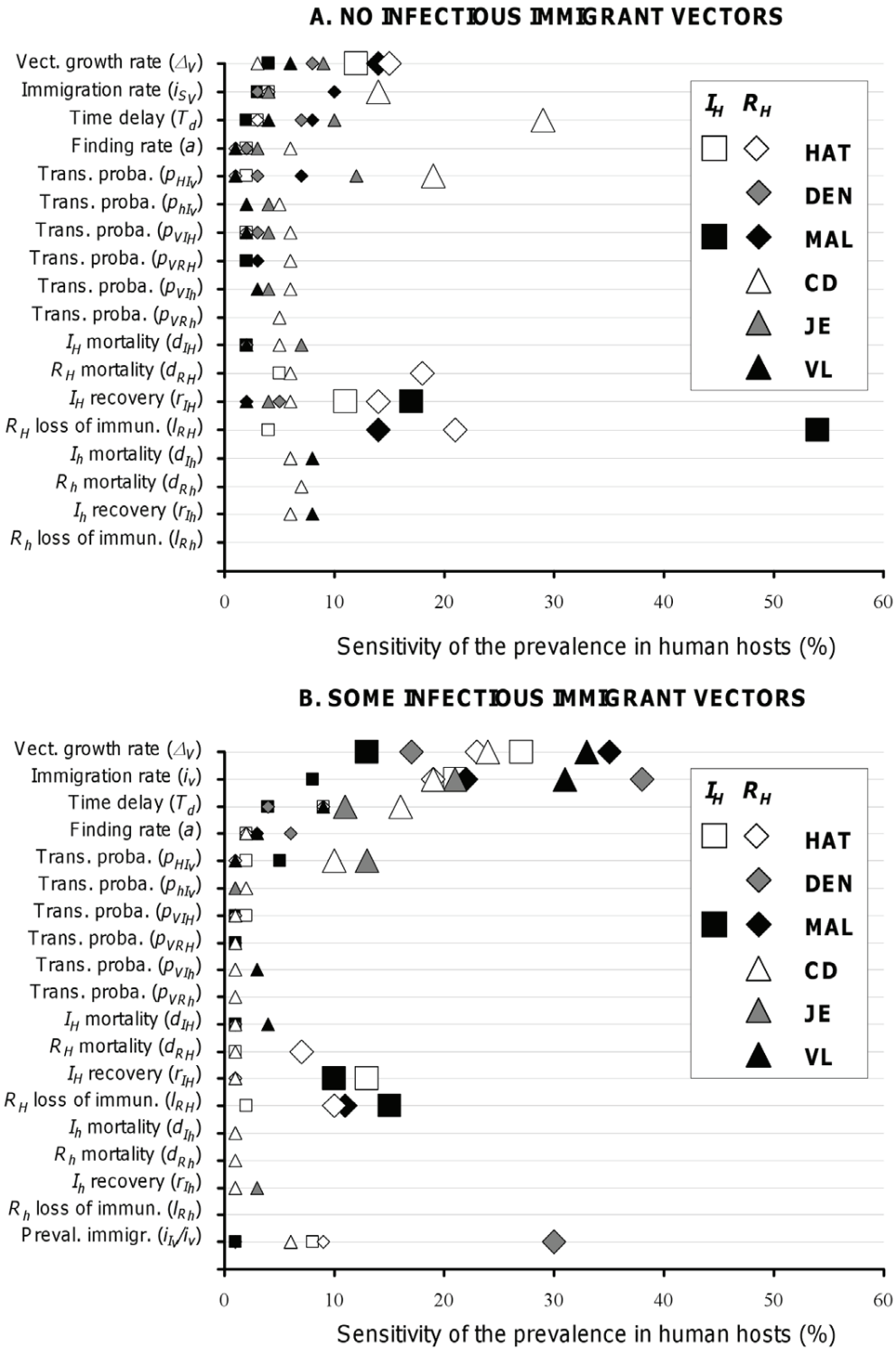


Figure 5. Sensitivity of the prevalence of infectious (I_H^*) and 'recovered' (R_H^*) humans to vector's demography and feeding rates, and to the pathogen's transmission and within-host dynamics. (**A**) No immigrant vector is infectious ($i_{I_V}=0$). (**B**) Some immigrant vectors are infectious ($i_{I_V}>0$). All six vector-borne diseases appear on each of the two graphs. Squares and diamonds correspond to the prevalence of infectious and recovered humans, respectively, for diseases with only human hosts: human African trypanosomiasis (HAT), dengue (DEN) and malaria (MAL). Circles and triangles correspond to the prevalence of infectious and recovered humans, respectively, for diseases with non-human hosts: Chagas disease (CD), Japanese encephalitis (JE), and visceral leishmaniasis (VL). Larger symbols correspond to the key determinants of the variations of prevalence in humans (see main text for comments). Sensitivities were calculated from 10,000 simulations for each disease.
doi:10.1371/journal.pone.0036858.g005

disease emergence since it requires vector individuals to live long enough to get infected and to infect a host back. To reinforce this conclusion, it is worth noting that the importance of vector longevity in the sink is undoubtedly underestimated here since we did not account for any development time of pathogen within the vector. Such delay would reduce the number of potentially infective contacts, and thus make the time spent in the sink population even more critical, especially for the emergence of diseases transmitted by short-lived vector such as DEN, MAL and JE. Similar effects of the interaction between the extrinsic incubation period and the survival rate of the vector have been demonstrated on the ground of general models [104], and more specific modelling of dengue [105] and malaria [106]. One must also point out that outbreak cycles of dengue are known to be influenced by the epidemiological status of the populations [107], so that, along with the above parameters, the transmission history in a given place is expected to have a strong influence on the spread of pathogens. The asymmetrical role of immigration and vector longevity has implications for pathogen transmission in a mosaic of vector habitats. One can indeed assume that as the distances or the 'impermeability' of the matrix between sources and sinks (e.g., [108]) increases, individuals reaching sinks will not only be fewer but also older, which will contribute (even more than the reduction in the number of individuals) to prevent the spread of the pathogen. Although this could be mitigated by the increase in the prevalence of infection with the age of the vector, the level of fragmentation of the landscape (i.e., many small and nearby patches instead of a few large and distant patches) is thus expected to favour disease emergence, not only because it increases the number of dispersers [109,110], but also because it changes the age-structure of the immigrants. The differential effect of longevity and immigration may also be relevant in the context of 'anthropic' sinks if control had an impact on the age-structure of the immigrants. Indoor insecticide spraying is indeed known to induce dispersal of individuals receiving sub-lethal doses [111], or to select for exophilic individuals at the population scale [50]. If such effects were biased towards the youngest individuals, either because of an age-dependent behavioural response to chemicals, or because genotypes dispersing earlier in life would be selected for, the spread of the pathogen in surrounding sinks could then be favoured. Finally, given the importance of vector longevity, one would have expected HAT and CD to spread more easily than other diseases, since tsetse flies and triatomines have longer life-expectancy. On the contrary, the values of R_0 were found very similar for all diseases. This implies that other disease specificities are balancing against the risk factors associated to vector life-history. Indeed, HAT and CD are both characterized by very low transmission probabilities between vectors and humans, which undoubtedly lowered the rates of spread of these two trypanosomiases. Thus, although vector life-history and feeding were critical to explain variations in pathogen's reproductive rate for each of the diseases considered, they did not induce significant in-between diseases differences in the risk of emergence. Thus one cannot point out human vector-borne pathogens that would be more prone to emerge in vector sink populations. Vector sink populations appear to be a real threat of emergence or re-emergence of all six human vector-borne diseases considered here. As expected, vector control in the source will have an important effect on the rate of spread of the pathogen in the connected sink populations. Interestingly, control interventions in the source that would reduce vector longevity in the sink appear to be as relevant as interventions that would directly reduce the number of vector individuals migrating from the source into the sinks.

Prevalence of Vector-borne Diseases in Sink Vector Populations

Our analyses show that even in a disease-free sink vector population (sustained by the immigration of non-infectious vectors), the spread of the pathogen (when introduced accidentally by infected hosts) can potentially represent significant health concern. Prevalence of infection larger than 5% is observed in up to 11–34% of cases for diseases with long duration of infection such as MAL, CD and HAT. In addition, when the prevalence of infection remains lower than 5%, such as for DEN, VL and JE, the pathogens actually spread through a more substantial part of the population since the percentage of 'recovered' individuals is larger than 5% in about 20% of cases. When pathogens are regularly introduced by immigrating vectors, the spread of the pathogens was expectably facilitated. However for DEN, VL and JE the prevalence did not significantly increase. This is mostly because vectors have a short life expectancy, so that the prevalence of infection hardly exceeds 2% among immigrants. In any case, the percentage of humans afflicted by any of the six diseases typically remains lower than 15%. These figures are consistent with the few estimates available from areas where vector populations are known or expected to be sinks. In the Yucatán peninsula, Mexico, sink populations of non-domiciliated triatomines [38,112,113] are responsible for human sero-prevalence rates of 5–18% [71]. Similarly, wild sandflies species are responsible for 2–3% prevalence of leishmaniasis (calculated from incidence in [114]), and transmission by sylvatic species of glossines leads to less than 5% of the Gambian form of sleeping sickness in West and Central Africa [115]. Finally, the prevalence of highly infectious individuals with MAL is consistent with the less than 10% of infection typically observed in areas where the transmission of the pathogen is associated with vector dispersal. Examples include dispersal in urban areas representing a fragmented habitat for *Anopheles*, or dispersal from sites located at lower or most suitable altitudes [116–118].

Prevalence values that could be reached if a pathogen was to be introduced in a sink population of susceptible vectors are overall influenced in a much more comparable way by vector's (demography and feeding) and pathogen's (transmission and within-host dynamics) parameters, than R_0 was in the same epidemiological situation (see first part of the discussion). No important parameter could be identified for the transmission of DEN, VL and JE, and key parameters were disease specific for CD, HAT and MAL. For CD, prevalence was mostly determined by vector-related parameters, which is best explained by the strikingly low probability of 'stercorarian' transmission of the pathogen to mammals [101,119]. On the contrary, the prevalence of humans suffering from MAL and HAT was mostly influenced by parameters related to the pathogen-humans interaction; rate of recovery, loss of immunity and disease-induced mortality, as it is usually the case when there are only human hosts for the pathogen [24]. However, when pathogens were introduced through vector immigration, the importance of vector longevity and immigration was again prominent, although the transmission and within-host parameters mentioned above still had some influence on prevalence. Overall, this confirms that vector demography and feeding rates are the key determinants of disease dynamics, apart for HAT and MAL for which variations in pathogen's interaction with its human host also is influencing its prevalence.

Such a conclusion reinforces the idea that the key determinants of epidemiological dynamics are roughly similar for all the pathogens that we considered in sink vector populations. The primacy of vector-related parameters has implications for the control of transmission to humans. Essentially, reducing vector

presence in human habitat could readily be efficient even if vector abundance is already typically low. In such situations, public health policies promoting drug administration should thus not undermine vector control programs. Clearly, control intervention in source populations are expected to have an impact on prevalence in the connected sink populations. Another implication of our results is that, even if human transmission is reduced through vector control programs in source populations, small residual level of infection in vectors can still be responsible for the spread of the pathogen in surrounding sink populations. This corroborates the previous conclusion that, when implementing control strategies, interruption of transmission should be targeted at larger scale rather than in areas of high transmission [120].

Conclusion and Potential Guidelines for Field Studies

Our analyses indicate that sink vector populations can represent serious threats to human health, with 1–15% prevalence of key vector borne diseases. Such 'residual' transmission is expected to be especially noticeable for diseases with long duration of infection, such as the African and American trypanosomiasis, but also appears relevant to other diseases. Our results thus have potential implications for future theoretical and field studies of vector-borne diseases.

First, to understand pathogen transmission and evolution will require to account for sink vector populations (within a typical mosaic of vector habitats), and then to properly disentangle local growth from immigration since these two processes have different effects on the R_0 and prevalence of the pathogens. Estimates of local vector abundance provided by population or genetic studies, which represent the combined outcome of local growth and immigration, will thus only be worth collecting if they provide enough information on spatial structures that allow inferring about local adaptation and immigration, possibly through an approach of model selection [113,121]. Second, incomplete interruption of transmission in areas of high vector abundance will still allow for the pathogen to spread in surrounding sink populations, which implies that vector control programs should be considered a meta-population context [122], and implemented at larger scale than areas of high vector densities. Third, as pathogen transmission and within-host dynamics have low influence on disease dynamics, different strains are expected to spread similarly in sink vector populations and, accordingly, selection on virulence is expected to be weak in such habitat. Although evolution in a mosaic of source-sink habitats has been investigated for non-pathogenic species (e.g., [123]), it has been widely overlooked in studies of vector-borne pathogens. Our results suggest that considering a realistic source-sink dynamics for vector populations, may alter our conclusion on pathogen transmission by promoting strain diversity and affecting the evolution of virulence. A similar conclusion was recently reached about the plausible effect of temporal dispersal, arising from vector developmental delays, on the spread and prevalence of vector-borne pathogens [124].

Much theoretical and field study is needed on the ecological and evolutionary potential of sink vector populations if one is to frame more substantially the control of infectious diseases in the context of meta-population, as it has already been proved successful for conservation biology [125].

Supporting Information

Figure S1 Sensitivity analysis for the prevalence in humans when no immigrant vector is infectious. The widths of arrows are set up according to the value of sensitivity appearing in figure 5A. Symbols correspond to the key-parameters identified in the main text, and are set next to processes (arrows) in which they are involved. For each disease, the compartments of interest are represented as in figure 5A (e.g., black square and diamond for MAL I_H and R_H individuals, respectively), while all other compartments are round-shaped (e.g., MAL susceptible individuals). For MAL and HAT, full and dashed arrows refer to the influence of parameters on the prevalence of 'recovered' and infectious human hosts, respectively.
(TIF)

Figure S2 Sensitivity analysis for the prevalence in humans when some immigrant vectors are infectious. The legend is the same as for figure S1, though values of sensitivity and key parameters now appear as identified in figure 5B rather than figure 5A.
(TIF)

Text S1 Estimates of parameters.
(DOC)

Author Contributions

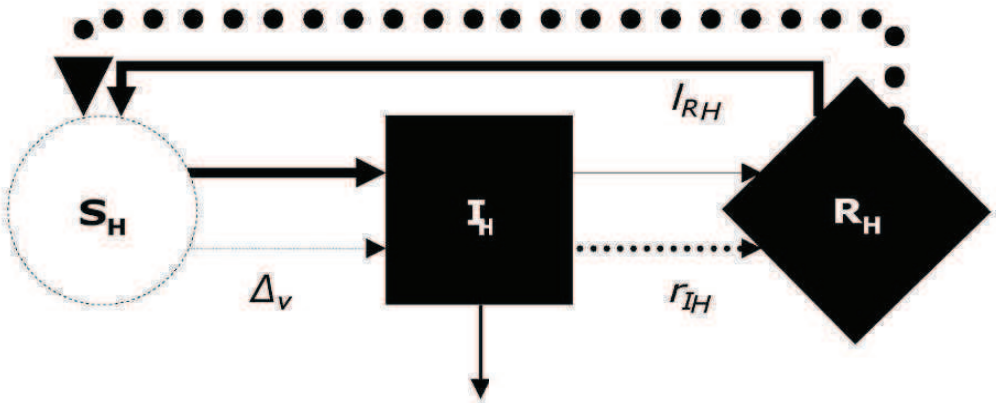
Conceived and designed the experiments: GR SG. Performed the experiments: GR. Analyzed the data: GR SG. Contributed reagents/materials/analysis tools: GR DP FM SG. Wrote the paper: GR SG.

References

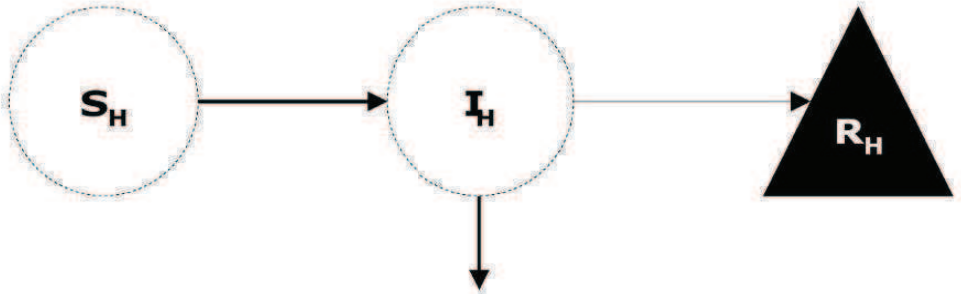
1. Varmus H, Klausner R, Zerhouni E, Acharva T, Daar AS, et al. (2003) Public health. Grand challenges in global health. Science 302: 398–399.
2. Hill CA, Kafatos FC, Stansfield Sk, Collins FH (2005) Arthropod-borne diseases: vector control in the genomics era. Nat Rev Microbiol 3: 262–268.
3. Hotez PJ, Molyneux DH, fenwick A, Kumaresan J, Ehrlich Sachs S, et al. (2007) Control of neglected tropical diseases. N Engl J Med 357: 1018–1027.
4. World Health Organisation. Available: http://apps.who.int/ghodata/?vid = 10012. Accessed 3 November 2011.
5. World Health Organisation (2011) World malaria report. Geneva, Switzerland: World Health Organisation. Available: http://www.who.int/malaria/world_malaria_report_2011/en/. Accessed 25 April 2012.
6. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, et al. (2011) Estimated global incidence of Japanese encephalitis: a systemic review. Bull World Health Organisation 89: 766–774.
7. World Health Organisation (2010) First WHO report on neglected tropical diseases 2010: working to overcome the global impact of neglected tropical diseases. Geneva, Switzerland: World Health Organisation. Available: http://www.who.int/neglected-diseases/2010report/en/index.html. Accessed 25 April 2012.
8. Gold MR, Stevenson D, Fryback DG (2002) HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Annu Rev Public Health 23: 115–134.
9. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S, et al. (2006) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. PLoS Med 3: e102.
10. The Vector-borne human infection of Europe: their distribution and burden on public health. World Health Organisation,.
11. Gratz NG (2006) Vector- and rodent-borne diseases in Europe and North America. Distribution, public health burden, and control. World Health Organisation, Geneva. Cambridge University Press. 410 p.
12. Takken W, Knols BGJ (2007) Emerging pests and vector-borne diseases in Europe. Wageningen Academics Publishers, Wageningen. 500 p.
13. Hotez PJ (2008) Neglected infections of poverty in the United States of America. PLoS Negl Trop Dis 2: e256.
14. Martens WJ, Niessen LW, Rotmans J, Jetten TH, McMichael AJ (1995) Potential impact of global climate change on malaria risk. Env Health Perspect 103: 458–464.
15. Githeko AK, Lindsay SW, Confalonieri UE, Patz JA (2000) Changement climatique et maladies à transmission vectorielle: une analyse régionale. Bull World Health Org 78: 1136–1147.
16. Rogers DJ, Randolph SE (2000) The global spread of malaria in a future, warmer world. Science 289: 1763–1766.
17. Kovats RS, Campbell-Lendrum DH, McMichael AJ, Woodward A, Cox JS (2001) Early effects of climate change: do they include changes in vector-borne diseases ? Philos Trans R Soc Lond B Biol Sci 356: 1057–1068.

18. Carbajo AE, Schweigmann N, Curto SI, de Garín A, Befarán R (2001) Dengue transmission risk maps of Argentina. Trop Med Int Health 6: 170–183.
19. González C, Wang O, Strutz SE, González-Salazar C, Sánchez-Cordero V, et al. (2010) Climate change and risk of leishmaniasis in North America: Predictions from ecological niche models of vector and reservoir species. PLoS Negl Trop Dis 4: e585.
20. Tatem AJ, Rogers DJ, Hay SI (2006) Global transport networks and infectious disease spread. Adv Parasitol 62: 293–343.
21. Enserink M (2008) A mosquito goes global. Science 320: 864–866.
22. Norman FF, Pérez de Ayala A, Pérez-Molina J-A, Monge-Maillo B, Zamarrón P, et al. (2010) Neglected Tropical Diseases outside the Tropics. PLoS Negl Trop Dis 4: e762.
23. Altizer S, Bartel R, Han BA (2011) Animal migration and infectious disease risk. Science 331: 296–302.
24. Keeling MJ, Rohani P (2007) Modeling Infectious Diseases in Humans and Animals. Princeton University Press, Princeton. 408 p.
25. Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K (2002) Adaptive dynamics of infectious diseases: in pursuit of virulence management (Cambridge studies in adaptive dynamics). Cambridge University Press, Cambridge. 463 p.
26. Rivero A, Vézilier J, Weill M, Read AF, Gandon S (2010) Insecticide control of vector-borne diseases: when is insecticide resistance a problem ? PLoS Pathog 6: e1001000.
27. Pulliam HR (1988) Sources, sinks, and population regulation. American Naturalist 132: 652–661.
28. Dias PC (1996) Sources and sinks in population biology. Trends Ecol Evol 11: 326–330.
29. Ruiz D, Poveda G, Vélez ID, Quiñones ML, Rúa GL, et al. (2006) Modelling entomological-climatic interactions of *Plasmodium falciparum* malaria transmission in two Colombian endemic-regions: contributions to a National Malaria Early Warning System. Malar J 5: 66.
30. Focks DA, Daniels E, Haile DG, Keesling JE (1995) A simulation model of epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am J Trop Med Hyg 53: 489–506.
31. Tapaswi PK, Ghosh AK, Muhkhopadhyay BB (1995) Transmission of Japanese encephalitis in a 3-population model. Ecological Modelling 83: 295–309.
32. Artzrouni M, Gouteux J-P (1996) A compartmental model of sleeping sickness in central Africa. J Biol Syst 4: 459–477.
33. Rabinovich JE, Feliciangeli MD (2004) Parameters of *Leishmania braziliensis* transmission by indoor *Lutzomyia ovallesi* in Venezuela. Am J Trop Med Hyg 70: 373–382.
34. Cohen JE, Gürtler RE (2001) Modeling household transmission of American trypanosomiasis. Science 293: 694–698.
35. Gürtler RE, Kitron U, Cecere MC, Segura EL, Cohen JE (2007) Sustainable vector control and management of Chagas disease in the Gran Chaco, Argentina. Proc Natl Acad Sci USA 104: 16194–16199.
36. Paz-Bailey G, Monroy C, Rodas A, Rosales R, Tabaru R, et al. (2002) Incidence of *Trypanosoma cruzi* infection in two Guatemalan communities. Trans R Soc Trop Med Hyg 96: 48–52.
37. Rogers DJ, Randolph SE, Kuzoe FA (1984) Local variation in the population dynamics of *Glossina palpalis palpalis* (Robineau-Desvoidy) (Diptera: Glossinidae). I. Natural population regulation. Bull Entomol Res 74: 403–423.
38. Gourbière S, Dumonteil E, Rabinovich JE, Minkoue R, Menu F (2008) Demographic and dispersal constraints for domestic infestation by non-domiciliated Chagas disease vectors in the Yucatán peninsula, Mexico. Am J Trop Med Hyg 78: 133–139.
39. Baber I, Keita M, Sogoba N, Konate M, Diallo M, et al. (2010) Population size and migration of *Anopheles gambiae* in the Bancoumana Region of Mali and their significance for efficient vector control. PLoS One 21: e10270.
40. Lambrechts L, Knox TB, Wong J, Liebman KA, Albright RG, et al. (2009) Shifting priorities in vector biology to improve control of vector-borne disease. Trop Med Int Health 14: 1505–1514.
41. World Malaria Report (2005) World Health Organisation and UNICEF.
42. van den Berg H (2009) Global status of DDT and its alternatives for use in vector control to prevent disease. Env Health Perspect 117: 1656–1663.
43. van den Berg H (2011) Global status of DDT and its alternatives for use in vector control to prevent disease. Cien Saude Colet 16: 575–590.
44. Scholte EJ, Ng'habi K, Kihonda J, Takken W, Paaijmans K, et al. (2005) An entomopathogenic fungus for control of adult African malaria mosquitoes. Science 308: 1641–1642.
45. Thomas MB, Read AF (2007) Can fungal biopesticices control malaria ? Nat Rev Microbiol 5: 377–383.
46. Pedrini MR, Reid S, Nielsen LK, Chan LC (2011) Kinetic characterization of the group II *Helicoverpa armigera* nucleopolyhedrovirus propagated in suspension cell cultures: implications for development of a biopesticides production process. Biotechnol Prog 27: 614–624.
47. Carter R, Mendis KN, Roberts D (2000) Spatial targeting of interventions against malaria. Bull World Health Org 78: 1401–1411.
48. Gürtler RE, Garelli FM, Coto HD (2009) Effects of a five-year citywide intervention program to control *Aedes aegypti* and prevent dengue outbreaks in northern Argentina, PLoS Negl Trop Dis 3: e427.
49. Hargrove JW (2003) Tsetse eradication: sufficiency, necessity and desirability. UK Centre for Tropical Veterinary Medicine, University of Edinburgh. 148 p.
50. Pates H, Curtis C (2005) Mosquito behaviour and vector control. Annu Rev Entomol 50: 53–70.
51. Sanchez-Martin MJ, Feliciangeli MD, Campbell-Lendrum D, Davies CR (2006) Could the Chagas disease elimination programme in Venezuela be compromised by reinvasion of houses by sylvatic *Rhodnius prolixus* bug populations ? Trop Med Int Health 11: 1585–1593.
52. Cecere MC, Vasquez-Prokopec GM, Gürtler RE, Kitron U (2006) Reinfestation sources for Chagas disease vector, *Triatoma infestans*, Argentina. Emerg Infect Dis 12: 1096–1102.
53. Vreysen MJB, Robinson AS, Hendrichs J (2007) Area-wide control of insect pests: from research to field implementation. Publisher: Springer. 792 p.
54. Guhl F, Pinto N, Aguilera G (2009) Sylvatic triatominae: a new challenge in vector control transmission. Mem Inst Oswaldo Cruz 104 Suppl 1: 71–75.
55. Gomes Ade C, Santos JL, Galati Ea (1986) Ecological aspects of American cutaneous leishmaniasis. 4. Observations on the endophilic behavior of the sandfly and the vectorial role of *Psychodopygus intermedius* in the Ribeira Valley region of the S. Paulo State, Brazil. Rev Saude Publica 20: 280–287.
56. Vazquez-Prokopec GM, Cecere MC, Canale DM, Gürtler RE, Kitron U (2005) Spatiotemporal patterns of reinfestation by *Triatoma guasayana* (Hemiptera: Reduviidae) in a rural community of northwestern Argentina. J Med Entomol 42: 571–581.
57. Sogoba N, Doumbia S, Vounatsou P, Baber I, Keita M, et al. (2007) Monitoring of larval habitats and mosquito densities in the Sudan savanna of Mali: implications for malaria vector control. Am J Trop Med Hyg 77: 82–88.
58. Stratton L, O'Neill MS, Kruk ME, Bell ML (2008) The persistent problem of malaria addressing the fundamental causes of a global killer. Soc Sci Med 67: 854–862.
59. Peterson AT, Shaw J (2003) *Lutzomiya* vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. Int J Parasitol 33: 919–931.
60. Rosenthal J (2009) Climate change and the geographic distribution of infectious diseases. Ecohealth 6: 489–495.
61. Cohuet A, Harris C, Robert V, Fontenille D (2010) Evolutionary forces on Anopheles: what makes a malaria vector ? Trends Parasitol 26: 130–136.
62. Killen GF, Fillinger U, Knols BG (2002) Advantages of larval control for African malaria vectors: low mobility and behavioural responsiveness of immature mosquito stages allow high effective coverage. Malar J 1: 8.
63. Dumonteil E, Ramirez-Sierra MJ, Ferral J, Euan-Garcia M, et al. (2009) Usefulness of community participation for the fine temporal monitoring of house infestation by non-domiciliated triatomines. J Parasitol 95: 469–471.
64. Abad-Franch F, Ferraz G, Campos C, Palomeque FS, Grijalva MJ, et al. (2010) Modeling disease vector occurrence when detection is imperfect: infestation of Amazonian palm trees by triatomine bugs at three spatial scales. PLoS Negl Trop Dis 4: e620.
65. Wonham MJ, Lewis MA, Renclawowicz J, van den Driessche P (2006) Transmission assumptions generate conflicting predictions in host-vector disease models: a case study in West Nile virus. Ecol Lett 9: 706–725.
66. Edelstein-Keshet LN (1998) Mathematical models in biology. Random House, New York. 586 p.
67. Devilliers H, Lobry JR, Menu F (2008) An agent-based model for predicting the prevalence of *Trypanosoma cruzi* I and II in their host and vector populations. J Theor Biol 255: 307–315.
68. Juliano SA, Lounibos LP (2005) Ecology of invasive mosquitoes: effects on resident species and on human health. Ecol Lett 8: 558–574.
69. Molyneux DH, Baldry DA, Fairhurst C (1979) Tsetse movement in wind fields: possible epidemiological and entomological implications for trypanosomiasis and its control. Acta Trop 36: 53–65.
70. Dumonteil E, Gourbière S, Barrera-Pérez M, Rodriguez-Félix E, Ruiz-Piña H, et al. (2002) Geographic distribution of *Triatoma dimidiata* and transmission dynamics of *Trypanosoma cruzi* in the Yucatán peninsula of Mexico. Am J Trop Med Hyg 67: 176–183.
71. Dumonteil E, Gourbière S (2004) Predicting *Triatoma dimidiate* abundance and infection rate: a risk map for natural transmission of Chagas disease in the Yucatán peninsula of Mexico. Am J Trop Med Hyg 70: 514–519.
72. Nouvellet P, Ramirez-Sierra MJ, Dumonteil E, Gourbière S (2011) Effects of genetic factors and infection status on wing morphology of *Triatoma dimidiata* species complex in the Yucatán peninsula, Mexico. Infect Genet Evol 11: 1243–1249.
73. Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, et al. (2007) Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 370: 1840–1846.
74. Stoddard ST, Morrison AC, Vazquez-Prokopec GM, Paz Soldan V, Kochel TJ, et al. (2009) The role of human movement in the transmission of vector-borne pathogens. PLoS Negl Trop Dis 3: e481.
75. Gubler DJ (2007) The continuing spread of West Nile virus in the western hemisphere. Clin Infect Dis 45: 1039–1046.
76. Peterson AM, Calamandrei GE (2011) Malaria, etiology, pathogenesis and treatments. Nova Science Publishers Inc. 70 p.
77. Gubler DJ, Kuno G (1997) Dengue and dengue hemorrhagic fever. Centre for Agricultural Bioscience International. 478 p.
78. Black SJ, Seed JR (2001) The African trypanosomes. Kluwer Academic Publishers. 192 p.
79. Mackenzie JS, Barrett ADT, Deubel V (2002) Japanese encephalitis and West Nile virus. Springer-Verlag Berlin and Heidelberg GmbH & Co. K. 425 p.

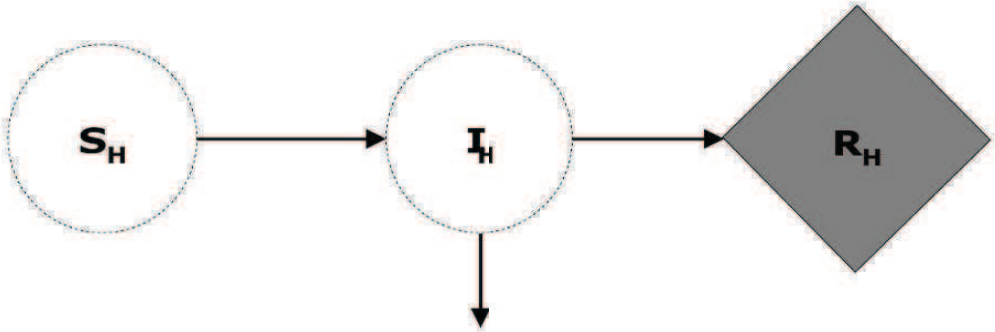
80. Tibayrenc M, Telleria J (2010) American trypanosomiasis: Chagas disease one hundred years of research. Elsevier Science Publishing Co Inc. 870 p.
81. Farrell JP (2002) Leishmania. Kluwer Academic Publisher. 208 p.
82. Killeen GF, Ross A, Smith TA (2006) Infectiousness of malaria-endemic human populations to vector mosquitoes. Am J Trop Med Hyg 76(Suppl. 2): 38–45.
83. Ross A, Killeen GF, Smith TA (2006) Relationships of host infectivity to mosquitoes and asexual parasite density in *Plasmodium falciparum*. Am J Trop Med Hyg 75(Suppl. 2): 32–37.
84. Esteva L, Vargas C (1998) Analysis of a dengue disease transmission model. Math Biosci 150: 131–151.
85. Artzrouni M, Gouteux J-P (2001) A model of Gambian sleeping sickness with open vector populations. IMA J Math Appl Med Biol 8: 99–117.
86. Mubayi A, Castillo-Chavez C, Chowell G, Kribs-Zaleta C, Ali Siddiqui N, et al. (2010) Transmission dynamics and underreporting of kala-azar in the Indian state of Bihar. J Theor Biol 262: 177–185.
87. Antonovics J, Iwasa Y, Hassell MP (1995) A generalized model of parasitoid, venereal, and vector-based transmission processes. Am Nat 145: 661–675.
88. Ferguson HM, Dornhaus A, Beeche A, Borgemeister C, Gottlieb M, et al. (2010) Ecology: a prerequisite for malaria elimination and eradication. PLoS Med 7: e1000303.
89. Simpson JE, Hurtado PJ, Medlock J, Molaei G, Andreadis TG, et al. (2011) Vector host-feeding preferences drive transmission of multi-host pathogens : West Nile virus as a model system. Proc Biol Sci 279: 925–933.
90. Saul A (2003) Zooprophylaxis or zoopotentiation: the outcome of introducing animals on vector transmission is highly dependent on the mosquito mortality while searching. Malar J 2: Epub 2003.
91. Ewald PW, De Leo G (2002) Alternative transmission modes and the evolution of virulence In: Dieckmann U, Metz JA, Sabelis MW, Sigmund K, eds. Adaptive dynamics of infectious diseases: in pursuit of virulence management (Cambridge Studies in Adaptive Dynamics) Cambridge University Press. pp 10–25.
92. Otto SP, Day T (2007) A biologist's guide to mathematical modelling in ecology and evolution. Princeton University Press, Princeton. 752 p.
93. Caswell H (2006) Matrix population models: construction, analysis, and interpretation. Sinauer Associates, Inc., U.S.722 p.
94. Coelho FC, Codeco CT, Struchiner CJ (2008) Complete treatment of uncertainties in a model for dengue R_0 estimation. Cad Saude Publica 24: 853–861.
95. Luz PM, Codeço CT, Massad E, Struchiner CJ (2003) Uncertainties regarding dengue modeling in Rio de Janeiro, Brazil. Mem Inst Oswaldo Cruz 98: 871–878.
96. Coelho FC, Codeço CT, Struchiner CJ (2008) Complete treatment of uncertainties in a model for dengue R0 estimation. Cad Saude Publica 24: 853–861.
97. Wolfram Research, Inc (2008) Mathematica, Version 7.0, Champaign, Illinois.
98. Fox JW (2007) Testing the mechanisms by which source-sink dynamics alter competitive outcomes in a model system. Am Nat 170: 396–408.
99. Sepulveda AJ, Lowe WH (2011) Coexistence in streams: do source-sink dynamics allow salamanders to persist with fish predators ? Oecologia 166: 1043–1054.
100. Tittler R, Fahrig L, Villard MA (2006) Evidence of large-scale source-sink dynamics and long-distance dispersal among wood thrush populations. Ecology 87: 3029–3036.
101. Gourbière S, Dorn P, Tripet F, Dumonteil E (2011) Genetics and evolution of triatomines from phylogeny to vector control. Heredity 108: 190–202.
102. Smith TA, Maire N, Dietz K, Killeen GF, Vounatsou P, et al. (2006) Relationship between entomologic inoculation rate and the force of infection for *Plasmodium falciparum* malaria. Am J Trop Med Hyg. 75 (Supplement 2): 11–18.
103. Gu W, Novak RJ (2009) Predicting the impact of insecticide-treated bednets on malaria transmission: the devil is in the detail. Malar J. 8: 256.
104. Bellan SE (2010) The importance of age dependent mortality and the extrinsic incubation period in models of mosquito-borne disease transmission and control. PLoS One 5: e10165.
105. Pongsumpun P, Garcia Lopez D, Favier C, Torres L, Llosa J, et al. (2008) Dynamics of dengue epidemics in urban contexts. Trop Med Int Health 13: 1180–1187.
106. Paaijmans KP, Read AF, Thomas MB (2009) Understanding the link between malaria risk and climate. Proc Natl Acad Sci USA 106: 13844–13849.
107. Grenfell BT, Pybus OG, Gog JR, Wood JL, Daly JM, et al. (2004) Unifying the epidemiological and evolutionary dynamics of pathogens. Science 303: 327–332.
108. Castellon TD, Sieving KE (2006) An experimental test of matrix permeability and corridor use by an endemic understory bird. Conservation Biology 20: 135–145.
109. Bowman J, Cappuccino N, Fahrig L (2002) Patch size and population density: the effect of immigration behaviour. Conservation Ecology 6: 9.
110. Fahrig L (2003) Effects of habitat fragmentation on biodiversity. Annu Rev Ecol, Evol, Syst 34: 487–515.
111. Rawlings P, Davidson G (1982) The dispersal and survival of *Anopheles culicifaces* Giles (Diptera: Culicidae) in a Sri Lankan village under malathion spraying. Bull Entomol Res 72: 139–144.
112. Barbu C, Dumonteil E, Gourbière S (2009) Optimization of control strategies for non-domiciliated *Triatoma dimidiata*, Chagas disease vector in the Yucatán peninsula, Mexico. PLoS Negl Trop Dis 3: e416.
113. Barbu C, Dumonteil E, Gourbière S (2010) Characterization of the dispersal of non-domiciliated *Triatoma dimidiata* through the selection of spatially explicit models. PLoS Negl Trop Dis 4: e777.
114. Kumar V, Kesari S, Kumar AJ, Dinesh DS, Ranjan A, et al. (2009) Vector density and the control of kala-azar in Bihar, India. Mem Inst Oswaldo Cruz 104: 1019–1022.
115. Gouteux JP, Kounda Gboumbi JC, Noutoua L, D'Amico E, Bailly C, et al. (1993) Man-fly contact in the Gambian trypanosomiasis focus of Nola-Bilolo (Central African Republic). Trop Med Parasitol 44: 213–218.
116. Akhwale WS, Lum JK, Kaneko A, Eto H, Obonyo C, et al. (2004) Anemia and malaria at different altitudes in the western highlands of Kenya. Acta Trop 91: 167–175.
117. Rutar T, Baldomar Salgueiro EJ, Maguire JH (2004) Introduced *Plasmodium vivax* malaria in a Bolivian community at an elevation of 2,300 meters. Am J Trop Med Hyg 70: 15–19.
118. Graves PM, Richards FO, Ngondi J, Emerson PM, Shargie EB, et al. (2009) Individual, household and environmental risk factors for malaria infection in Amhara, Oromia and SNNP regions of Ethiopia. Trans R Soc Trop Med Hyg 103: 1211–1220.
119. Nouvellet P, Dumonteil E, Gourbière S (2011) Estimating the unobservable: the 'milli-transmission' of Chagas disease to human. *In preparation.*
120. Killeen GF, Knols BCJ, Gu W (2003) Taking malaria transmission out of the bottle: implications of mosquito dispersal for vector control interventions. The Lancet Infect Dis 3: 297–303.
121. Barbu C, Dumonteil E, Gourbière S (2011) Evaluation of spatially targeted strategies to control non-domiciliated *Triatoma dimidiate* vector of Chagas disease. PLoS Negl Trop Dis 5: e1045.
122. Gourbière S, Gourbière F (2002) Competition between unit-restricted fungi: a metapopulation model. J Theor Biol 217: 351–368.
123. Gomulkiewicz R, Holt RD, Barfiels M (1999) The effects of density dependence and immigration on local adaptation and niche evolution in a black-hole sink environment. Theor Pop Biol 55: 283–296.
124. Menu F, Ginoux M, Rajon E, Lazzari CR, Rabinovich JE (2010) Adaptive developmental delay in Chagas disease vectors : an evolutionary ecology approach. PLoS Negl Trop Dis 4: e691.
125. Hanski I (1999) Metapopulation ecology. Oxford University Press, USA. 328 p.


I_{RH}
S_H
I_H
R_H
Δ_v
r_{IH}

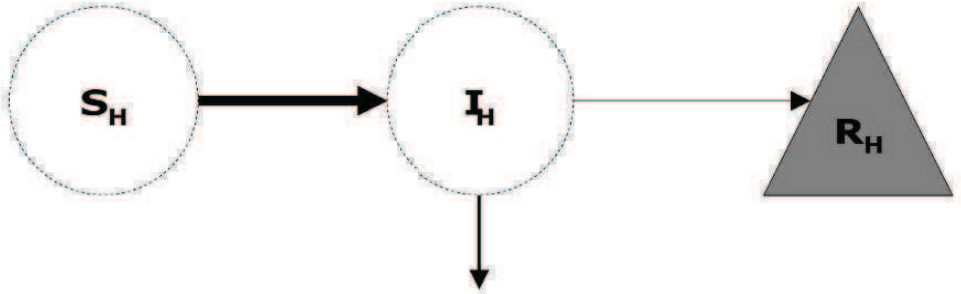
DEN


S_H
I_H
R_H

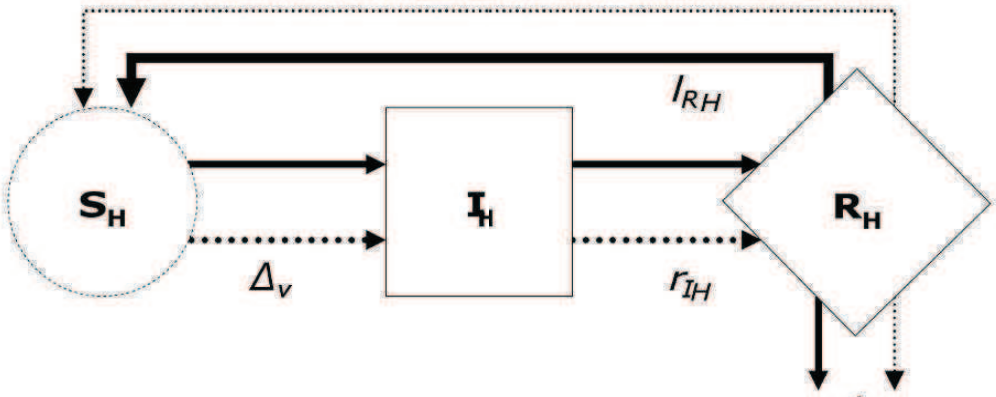
JE

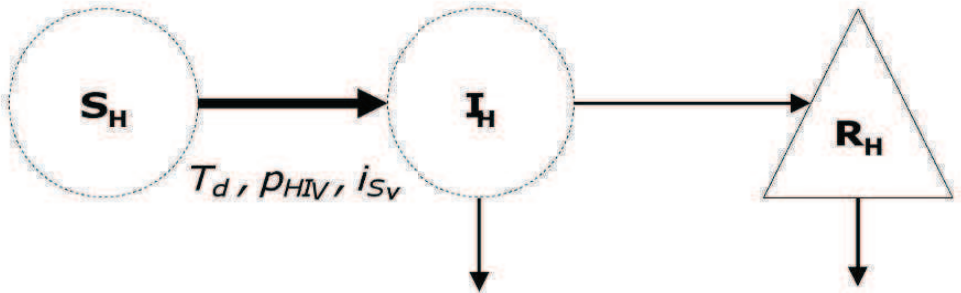

S_H
I_H
R_H

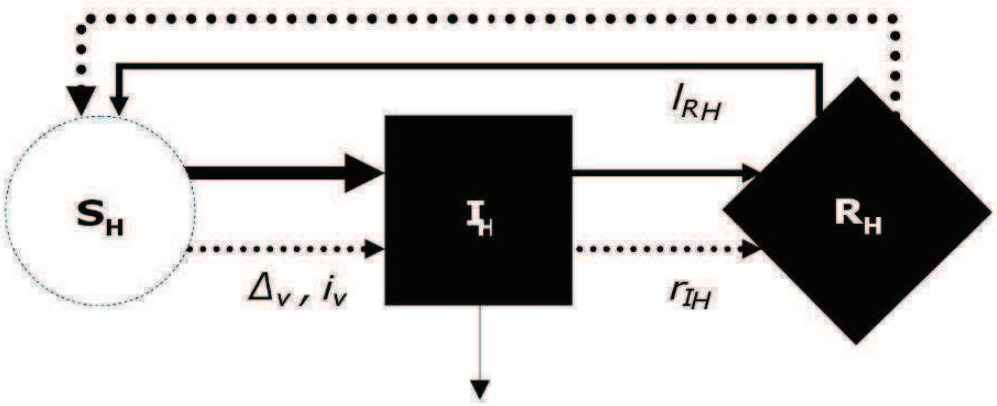
HAT


S_H
I_H
R_H

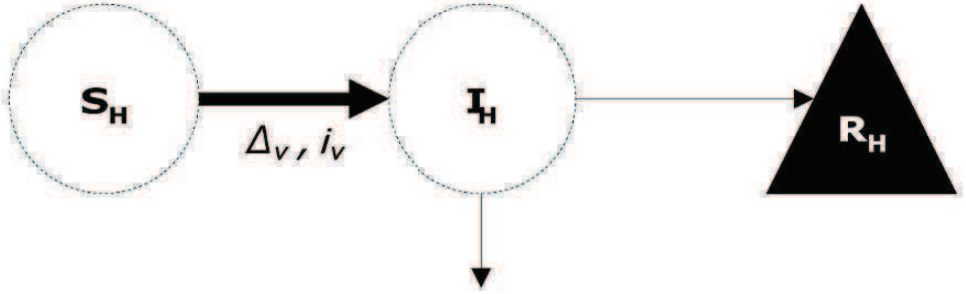
CD


I_{RH}
S_H
I_H
R_H
Δ_v
r_{IH}

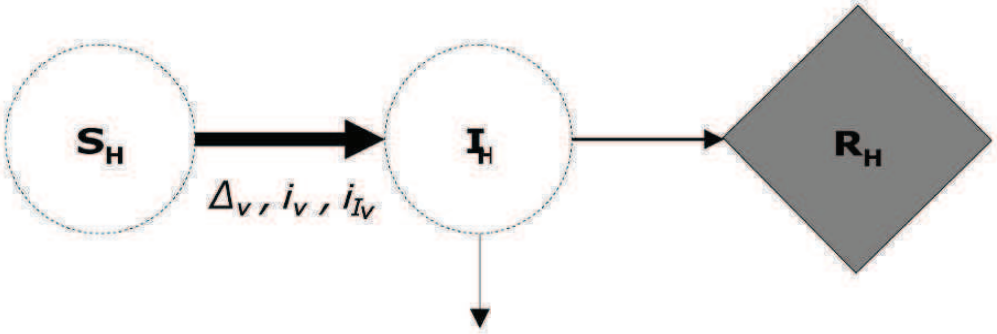

S_H
I_H
R_H
T_d , p_{HIV} , i_{Sv}


S_H
I_H
R_H
l_{RH}
Δ_v , i_v
r_{IH}

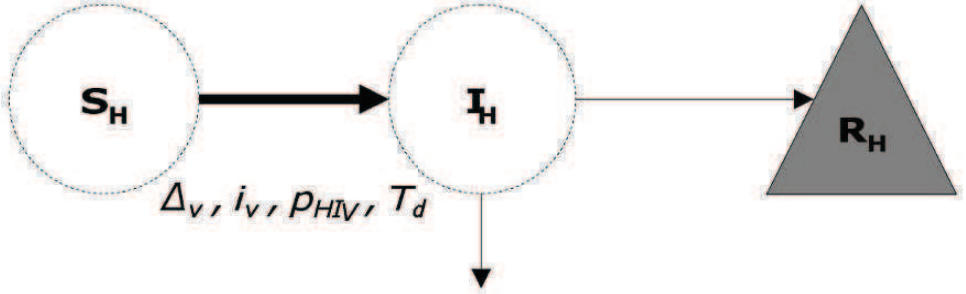
DEN


S_H
I_H
R_H
Δ_v , i_v

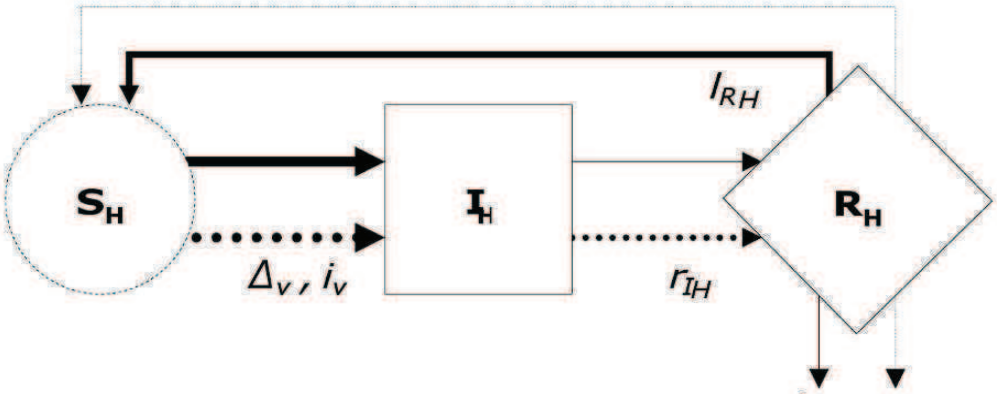
JE

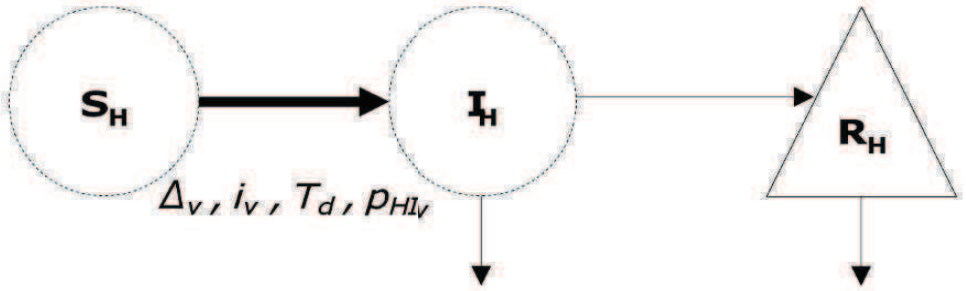

S_H
I_H
R_H
Δ_v , i_v , i_{Iv}

HAT


S_H
I_H
R_H
Δ_v , i_v , p_{HIV} , T_d

CD


S_H
I_H
R_H
l_{RH}
Δ_v , i_v
r_{IH}


S_H
I_H
R_H
Δ_v , i_v , T_d , p_{HIv}

Text S1: Estimates of Parameters

This appendix provides a review of the estimates of the parameters defined in table 1, that we have been able to gather from the literature. Most papers we are referring to are empirical research papers with data from experimental lab work or field studies.

Demography and feeding rates of the vectors

Vector local growth rate (Δ_V). The range of variation in vector growth rate was determined according to variations in vector longevity, neglecting the typically low reproduction of maladapted vectors in sink populations (see, e.g., [1]). Since the modelled vectors are thought to live shorter in sink populations, we used the values of longevity typically estimated in source populations (Table S1), as a clue of the maximum vector life expectancy in the sink. The minimal value of vector life expectancy in the village was set to one day. The range of Δ_V values to be used was then calculated assuming Δ_V =1/vector life expectancy.

Table S1. Vectors adult longevity.

Vector (Disease)	Estimates (days)	Reference
Mosquitoes (MAL – DEN)	5.8 - 20	[2]
Mosquitoes (JE)	2 - 29	[3]
Sandflies (VL)	6 - 27	[4]
Tsetse flies (HAT)	45 (20 - 60)	[5]
Triatomines (CD)	210 (102 - 338)	[6,7]

Because the estimates found in the literature for mosquitoes (transmitting MAL, DEN and JE) and sandflies (transmitting VL), were roughly similar, they were given the same standard value of 15 days corresponding to the median of their ranges. According to the other estimates collected, tsetse flies (transmitting HAT) were considered to live up to 45 days (the median of the observed values), while the longevity of triatomines (transmitting CD) was fixed to 210 days (the median of the observed values).

Vector immigration ($i_V = i_{S_V} + i_{I_V}$). The maximal rate of vector immigration was set for the ratio of vector to human densities N_V^*/N_H to be ≤ 1. Since the total number of vectors at equilibrium equals $N_V^* = i_V/\Delta_V$, the maximal immigration rate was given by $\Delta_V N_V^*$ with $N_V^*/N_H = 1$, that is $\Delta_V N_H$. Using the maximal values of Δ_V specified above and the estimate of the number of human hosts N_H (see below), the maximal daily rate of immigration was found to be approximately 67 individuals for mosquitoes (transmitting MAL, DEN and JE) and sandflies (transmitting VL), 22 individuals for tsetse flies (transmitting HAT), and 5 for triatomines (transmitting CD). The minimal rate of immigration was set to 0 immigrants per day for all vectors.

Prevalence of infection in immigrant vectors (i_{I_V}/i_V). Prevalence of infection is typically low in mosquitoes (e.g., 2.1% in *Anopheles* - MAL, [8], 0.097% in *Aedes* - DEN, [9], and 1.67% in *Culex* - JE, [10] and flies (0.18% in *Glossina* - HAT, [11], and 1.56% in phlebotomines - VL, [12]). We thus let the prevalence in immigrant vectors of MAL, DEN, JE, VL, and HAT takes on small values within a common range: 0 to 2%. Levels of prevalence of *Trypanosoma cruzi* found in triatomines are much higher, typically of the order of 20-50% (e.g., [13-17]), and we thus used an upper limit of 35% that corresponds to the median of the observed values.

Minimal amount of time between two blood-meals (T_d). The length of the gonotrophic cycle is commonly thought to be the main determinant of the time elapsed between 2 consecutive contacts made by a vector individual with its host. For dipterous species, such as of mosquitoes or flies, blood-feeding on vertebrate/human hosts, this time interval is on average 3-4 days (see e.g., [2] for *Anopheles*, [18] for *Glossina*, [19] for phlebotomines). We thus let parameter T_d vary in a typical range of 2 to 6 days for the five diseases transmitted by dipterous insects: MAL, DEN, JE, VL, and HAT. However, for the triatomines vectors of CD, this amount of time is significantly larger and have been shown to last from 6 days [20] to 13-26 days [21]. Accordingly, the minimal amount of time between two blood-meals for CD transmitting bugs was varied between 1 and 4 weeks.

Vector finding rate (a). There is virtually no estimate of vector finding rate in the literature (but see [22]). We thus choose to set up the limits of parameter a to allow for a daily rate ranging from 0 to 100% of the modelled human population.

Demography of human and non-human hosts

Human and non-human hosts population size (N_H, N_h). Human population size (N_H) was set up to 1000 individuals to model a standard village or a small town. Key domestic non-human hosts of the diseases considered in this study are dogs (for CD and VL) and swine (for JE). [23] recently reviewed dog populations in 23 locations over 14 developing countries. The number of dogs per hundred inhabitants in rural areas typically ranged from 9 to 33.6, with an average of 16.9. A similar estimate could be derived from a study of domestic swine in rural provinces of Lao [24]; the number of swine per hundred inhabitants there varied from 9.5 to 197.3. The corresponding ratio of dogs or swine to humans equals 5.9 (95% IC: 4.9-7.5) and 5.2 (95% IC: 4.0-6.3), respectively. In our model, this ratio was then set up to 1/6, and the number of non-human hosts (N_h) calculated accordingly, $N_h = 1000/6 \approx 167$.

Human and non-human hosts natural death rates (d_H, d_h). Natural mortality rates were calculated as 1/longevity. They constitute the mortality rate of susceptible human and non-human hosts, and the baseline to which a disease-induced mortality (see '*Human and non-human mortality induced by the pathogen*') was added to obtain the mortality rate of infectious and recovered human and non-human hosts. Human hosts natural life expectancy was set to 60 years. The longevity of domestic swine (transmitting JE) was set to 12 months, considering that animals are raised for humans meat-consumption and slaughtered at that age. The life expectancy of dogs, non-human hosts of VL and CD, was set to 3 years, in agreement with [23] and [25] who found that dogs' longevity ranges from around 2.5 to 4 years.

Probabilities of transmission of the pathogens

Transmission probability from an infectious vector to a human host (p_{HI_V}). Estimates of those probabilities appear in table S2. As we could not find any estimate of the probability of transmission from an infectious sandfly to a human host, we used the estimate of the probability of transmission from a sandfly to a dog (see '*Transmission probability from an infectious vector to a non-human host'*).

Table S2. Probability of transmission from vector to human host.

Vector (Disease)	Range	Reference
Mosquitoes (MAL)	0.01 - 0.13	[2]
Mosquitoes (DEN)	0.5 - 1.0	[26,27]
Mosquitoes (JE)	0.01 - 0.04	[28]
Sandflies (VL)	0.2 - 0.4	same values as for dogs (see text)
Tsetse flies (HAT)	0.5 – 0.7	[29]
Triatomines (CD)	$0.6e^{-3}$ - $3.8e^{-3}$	[30, 31]

Transmission probability from an infectious vector to a non-human host (p_{hI_V}). The only value of the probability of transmission of VL from vector to non-human hosts that we found came from an earlier model of VL in dogs [32]. This probability was equal to 0.32 per bite, and we thus considered values in the range 0.2 to 0.4 per bite. For JE, we used estimates of the ability of mosquitoes (*Aedes albopictus*) to transmit the virus to susceptible mice, which ranged from 0.27 to 0.45 per bite [33]. Finally, we assumed vector transmission of CD to dogs to be equivalent to vector transmission to humans (see Table S2.).

Probability of transmission from infectious or recovered humans to vector (p_{VI_H} , p_{VR_H}). Values of the probability of transmission from infectious humans to vector we used appear in table S3. While estimates of this probability were available for MAL and DEN, we used estimates obtained from other mammals, that is hamster, mice and dog, for JE, VL, and CD, respectively (see '*Probability of transmission from infectious or recovered non-human hosts to vector*'). *Glossina*

female flies (transmitting HAT) are considered to be susceptible only while taking their first blood-meal. The susceptibility of such 'teneral' females to *Trypanosoma brucei gambiense* ranges from 0.05 to 0.14 per bite [34,35]. We did not explicitly model this age-dependent susceptibility in tsetse (as, e.g., in [36]), but weighted the infectiousness of humans in early phase of HAT by the probability for a biting tsetse fly to be a 'teneral' individual. Such probability was estimated by considering that 'teneral' individuals have their first blood meal on their first day of life. Assuming a constant natural death rate of 1/45 per day (see table S1), and considering a stable age-structure, this probability (that equals the fraction of 1-day old individual in the population) was found to be equal to 0.034.

Table S3. Probability of transmission from infectious humans to vector.

Vector (Disease)	Range	Reference
Mosquitoes (MAL)	0.24 - 0.64	[2]
Mosquitoes (DEN)	0.15 - 0.73	[37]
Mosquitoes (JE)	0.14 - 0.38	[38]
Sandflies (VL)	0.21 - 0.29	[39]
Tsetse flies (HAT)	[0.05 - 0.14] * 0.034	to limit susceptibility to teneral flies (see text)
Triatomines (CD)	0.90 - 0.94 (0.99)	same values as for dogs (see text)

Recovered humans were assumed to have cleared the pathogen for DEN, JE and VL (see section 'Modelling' in the main text), so that their ability to transmit to vector was set to 0. While modelling HAT, 'recovered' individuals are in the second stage of the disease. Though circulating pathogens could potentially be transmitted to vectors, it is commonly assumed to be unlikely because of the typically low pathogen concentration in the blood [40]. We thus set the probability of transmission from humans in the second stage of the disease to vector to 0. On the contrary, infectiousness of MAL 'recovered' individuals (which are thought to be able to transmit but with reduced infectiousness), and CD 'recovered' individuals (which are thought to be in the chronic phase of the disease), was considered positive. This infectiousness p_{VR_H} was considered to range from 0.024 to 0.064 for MAL, that is, a probability ten times as small as p_{VI_H}, following [41], and from $4.2e^{-3}$ to $6.2e^{-3}$ for CD, following [42].

Probability of transmission from infectious or recovered non-human hosts to vector (p_{VI_h} , p_{VR_h}). Estimates of the probability of transmission from infectious non-human hosts to vector appear in table S4. Since estimates for CD were obtained on bugs' larvae, and because adults are thought to be even more susceptible [42], the maximal transmission probability was increased from 0.94 to 0.99.

Table S4. Probability of transmission from infectious non-human hosts to vector.

Vector (Disease)	Range	Reference
Mosquitoes (JE)	0.55 - 1.00	[43]
Sandflies (VL)	0.05 - 0.28	[44]
Triatomines (CD)	0.90 - 0.94 (0.99)	[45]

Because we assumed that no dog recovered from VL, and that swine recovered from JE have cleared the pathogen (see section 'Modelling' in the main text), the only 'recovered' non-human individuals able to transmit pathogens to susceptible vectors were dogs chronically infected with CD. We then considered probabilities of transmission ranging from 0.05 [45] to 0.31 [42].

Within-host dynamics of the pathogens

Human and non-human mortality induced by the pathogen (v_{I_H} , d_{I_H} , v_{R_H} , d_{R_H} , v_{I_h} , d_{I_h} , v_{R_h} , d_{R_h}). The virulence of the different pathogens to infectious or 'recovered' human hosts was calculated from fatality rates collected in the literature (Table S5). The additional mortality induced by the pathogen was calculated as $-\frac{1}{T}\log\left(\frac{100-\textit{fatality rate}}{100}\right)$, where T stands for the period of time over which the fatality rate was reported. T was 365 days for MAL, since this disease fatality rate was evaluated on an annual basis. T was set to the duration of the infectious stage (i.e., $1/r_{I_H}$) for all other diseases, since their fatality rates were evaluated per case.

Table S5. Rate of fatality for infectious humans and pathogen-induced mortality.

Disease	Fatality rate	Reference	Pathogen-induced mortality (v_{I_H})
MAL	0% - 15% per year	[2]	$0 – 4.5e^{-4}$ per day
DEN	0% - 2% per case	[46]	$0 – 6.7e^{-4}$ per day
JE	5% to 40% per case	[47]	$3.7e^{-3} – 0.26$ per day
VL	4% - 98% per case	[48,49]	$2.3e^{-4} – 4.4e^{-2}$ per day
HAT	0% per case	[50]	0
CD	0% - 5% per case	[51]	$0 – 1.1e^{-3}$ per day

We further considered an additional mortality for 'recovered' humans. Individuals in 'recovered' stage of the African and American trypanosomiasis, though they are no longer in the pool of infectious, are still at risk of death because they are in a second phase of the disease. For HAT, the fatality rate in the late phase of the disease can drop down to 2% if people are given drugs [52], while it can potentially reach 100% in absence of such treatment. Accordingly, the range of pathogen-induced mortality was set to $2.7e^{-5}$ - $3.8e^{-2}$ per day. For CD, up to one third of individuals in the chronic phase of the disease can die [51]. We thus varied the fatality rate from 0% to 33%, and the pathogen induced mortality from 0 to $1.8e^{-5}$ per day.

The virulence of JE, VL, and CD's pathogens to infectious or 'recovered' non-human hosts were calculated from fatality rates in the same way as for virulence to human hosts. Fatality rates of infected swine that are non-human hosts of JE, can vary from 0 in adults to 100% in new-borns [53,54]. We considered this whole range of variation so that the additional mortality due to the diseases was varied from 0 to 4.61. Infected dogs that are non-human hosts of VL are typically killed through culling program. The fatality rate of infectious dogs was set to 99%, assuming that a small fraction of infected dogs was not killed because of inefficient detection, failed diagnosis, or non-participation of dog-owners [55,56]. The additional mortality due to the pathogen was then varied from $4.2e^{-3}$ to 4.61 per day. We could not find estimates of the fatality rate for infected dogs hosts of CD. We then assumed the fatality rates in both the acute (I_h) and chronic (R_h) stage of CD to be the same as in humans. Dog is indeed viewed as the best experimental model for studying CD pathology, because the course of the disease is very similar to what is observed in human hosts [57]. Accordingly, additional mortality induced by the pathogen was

varied from 0 – $1.1e^{-3}$ per day in the acute stage, and from 0 – $3.6e^{-4}$ per day in the chronic stage of the disease.

Human recovery and loss of immunity (r_{I_H}, l_{R_H}). The rates of human recovery and loss of immunity were calculated as the inverse of the duration of infectious and 'recovered' stages, i.e. $1/r_{I_H}$ and $1/l_{R_H}$, respectively. Duration of the infectious state in human hosts used for the calculation of the recovery rates are reported in table S6.

Table S6. Duration of the infectious state in human hosts $1/r_{I_H}$.

Disease	$1/r_{I_H}$ **(days)**	**Reference**
MAL	60 – 630	[2]
DEN	3 - 15	[58,59]
JE	2 - 14	[60]
VL	90 - 180	[61]
HAT	120 – 780	[36,62]
CD	45 - 60	[63]

For MAL, the rate of return to a susceptible and non-infectious state was calculated for the duration of reduced infectivity to range from 3 months to life-long, following [2]. For HAT, the rate at which individuals leave the pool of 'recovered' was calculated from the average duration of the late phase of the disease (state R_H), which ranges from 4 [36] to 24 months [62]. We assumed long-life immunity for JE, and VL, and considered that CD chronic infection also lasts for life.

Non-human recovery and loss of immunity (r_{I_h}, l_{R_h}). As for human hosts, the rates of recovery and loss of immunity of non-human hosts were calculated as the 1/duration of the I_h and R_h stages, respectively. We varied the duration of infection in swine hosts of JE from 1 day [64] to 7 days [65], and assumed long-life immunity for 'recovered' individuals. For VL, we considered a dog population where infection can be cleared by natural death or by cull-and-replacement program, as typically done in other modelling attempts, [55,66]. We let the possibility for the

infection to be life-long in absence of control program, and reduced it to a unique day to mimic extremely timely interventions. Additionally, the rate of return to the susceptible stage was assumed to be infinitely large since in both cases, natural death or cull-and-replacement, dogs die (rather than recover) and are then typically replaced by a susceptible individual. In agreement with [57], we varied the duration of the acute phase of CD in dogs from 45 to 75 days, and assumed a life-long chronic stage of the disease, i.e. no return to the susceptible stage.

211 **REFERENCES**

212 1. Gourbière S, Dumonteil E, Rabinovich JE, Minkoue R, Menu F (2008) Demographic and
213 dispersal constraints for domestic infestation by non-domiciliated Chagas disease vectors in the
214 Yucatán peninsula, Mexico. Am J Trop Med Hyg 78: 133-139.

215 2. Chitnis N, Hyman JM, Cushing JM (2008) Determining important parameters in the spread of
216 malaria through the sensitivity analysis of a mathematical model. Bull Math Biol 70: 1272-1296.

217 3. Fouque F, Carinci R, Gaborit P, Issaly J, Bicout DJ, et al. (2006) *Aedes aegypti* survival and
218 dengue transmission patterns in French Guiana. J Vector Ecol 31: 390-399.

219 4. Srinivasan R, Panicker KN (1993) Laboratory observations on the biology of the phlebotomid
220 sandfly, *Phlebotomus papatasi* (Scopoli, 1786). Southeast Asian J Trop Med Public Health 24:
221 536-539.

222 5. Gouteux JP, Laveissiere C (1982) Ecologie des glossines en secteur pré-forestier de Côte
223 d'Ivoire 4. Dynamique de l'écodistribution en terroir villageois (1) Cah ORSTOM, sér Ent Med
224 Parasitol 20: 199-229.

225 6. Rabinovich JE (1972) Vital statistics of Triatominae (Hemiptera: Reduviidae) under laboratory
226 conditions. I. *Triatoma infestans* Klug. J Med Entomol 9: 351-370.

227 7. Zeledón R, Cordero M, Marroquín R, Lorosa ES (2010) Life cycle of *Triatoma ryckmani*
228 (Hemiptera: Reduviidae) in the laboratory, feeding patterns in nature and experimental infection
229 with *Trypanosoma cruzi*, Mem Inst Oswaldo Cruz 105: 99-102.

230 8. Atangana J, Bigoga JD, Patchoké S, Ndjemaï MN, Tabue RN, et al. (2010) Anopheline fauna
231 and malaria transmission in four ecologically distinct zones in Cameroon. Acta Trop 115: 131-
232 136.

233 9. Chen CF, Shu PY, Teng HJ, Su CL, Wu JW, et al. (2010) Screening of dengue virus in field-
234 caught *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) by one-step SYBR green-based

235 reverse transcriptase-polymerase chain reaction assay during 2004-2007 in Southern Taiwan.
236 Vector Borne Zoonotic Dis 10: 1017-1025.

237 10. Jeong YE, Jeon MJ, Cho JE, Han MG, Choi HJ, et al. (2010) Development and field
238 evaluation of a nested RT-PCR kit for detecting Japanese encephalitis virus in mosquitoes. J
239 Virol Methods 171: 248-252.

240 11. Dagnogo M, Traoré G, Souleymane F (2004) Determination of sleeping sickness
241 transmission risk areas from trypanosome infection rates of tsetse flies in Daloa, Côte d'Ivoire.
242 Int J Trop Insect Science 24: 170-176.

243 12. Felipe IM, de Aquino DM, Kuppinger O, Santos MD, Rangel ME, et al. (2011) Leishmania
244 infection in humans, dogs and sandflies in a visceral leishmaniasis endemic area in Maranhão,
245 Brazil. Mem Inst Osw Cruz 106: 207-211.

246 13. Gürtler RE, Cohen JE, Cecere MC, Lauricella MA, Chuit R, et al. (1998) Influence of
247 humans and domestic animals on the household prevalence of *Trypanosoma cruzi* in *Triatoma*
248 *infestans* populations in northwest Argentina. Am J Trop Med Hyg 58: 748-758.

249 14. Dumonteil E, Gourbière S, Barrera-Pérez M, Rodriguez-Félix E, Ruiz-Piña H, et al. (2002)
250 Geographic distribution of *Triatoma dimidiata* and transmission dynamics of *Trypanosoma cruzi*
251 in the Yucatán peninsula of Mexico. Am J Trop Med Hyg 67: 176-183.

252 15. Dumonteil E, Gourbière S (2004) Predicting *Triatoma dimidiata* abundance and infection
253 rate: a risk map for natural transmission of Chagas disease in the Yucatán peninsula of Mexico.
254 Am J Trop Med Hyg 70: 514-519.

255 16. Ramirez-Sierra MJ, Herrera-Aguilar M, Gourbière S, Dumonteil E (2010) Patterns of house
256 infestation dynamics by non-domiciliated *Triatoma dimidiata* reveal a spatial gradient of
257 infestation in rural villages and potential insect manipulation by *Trypanosoma cruzi*. Trop Med
258 Health 15: 77-86.

17. Nouvellet P, Ramirez-Sierra MJ, Dumonteil E, Gourbière S (2011) Effects of genetic factors and infection status on wing morphology of *Triatoma dimidiata* species complex in the Yucatán peninsula, Mexico. Infect Genet Evol 11: 1243-1249.

18. Rogers D (1977) Study of a natural population of *Glossina fuscipes fuscipes* Newstead and a model of fly movement. J Anim Ecol 46: 309-330.

19. Dye C, Davies CR, Lainson R (1991) Communication among phlebotomine sandflies: a field study of domesticated *Lutzomyia longipalpis* populations in Amazonian Brazil. Animal Behaviour 42: 183-192.

20. Rabinovich JE, Leal JA, Feliciangeli de Piñero D (1979) Domiciliary biting frequency and blood ingestion of the Chagas's disease vector *Rhodnius prolixus* Ståhl (Hemiptera: Reduviidae), in Venezuela. Trans R Soc Trop Med Hyg 73: 272-283.

21. Schilman PE, Lazzari CR (2004) Temperature preference in *Rhodnius prolixus*, effects and possible consequences. Acta Trop 90: 115-122.

22. Botto-Mahan C, Cattan PE, Canals M, Acuña M (2005) Seasonal variation in the home range and host availability of the blood-sucking insect *Mepraia spinolai* in wild environment. Acta trop 95: 160-163.

23. Jackman J, Rowan A (2007) Free-roaming dogs in developing countries: the public health and animal welfare benefits of capture, neuter, and return programs. In: State of the animals. Salem D, Rowan A, editors. Human Society Press, Washington, DC. pp. 55-78.

24. Stür W, Gray D, Bastin G (2002) Review of the livestock sector in the Lao People's Democratic Republic. International Livestock Research Institute. 57 p.

25. Reece JF, Chawla SK, Hiby EF, Hiby LR (2008) Fecundity and longevity of roaming dogs in Jaipur, India. BMC Vet Res 4:6.

26. Bartley LM, Donnelly CA, Garnett GP (2002) The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Trans R Soc Trop Med Hyg 96: 387-397.

27. Focks DA, Daniels E, Haile DG, Keesling JE (1995) A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am J Trop Med Hyg 53: 489-506.

28. Grossman RA, Edelman R, Chiewanich P, Voodhikul P, Siriwan C (1973) Study of Japanese encephalitis virus in Chiangmai valley, Thailand. II. Human clinical infections. Am J Epidemiol 98: 1211-1232.

29. Rogers DJ (1988) A general model for the African trypanosomiases. Parasitology 97: 193-212.

30. Rabinovich JE, Wisnivesky-Colli C, Solarz ND, Gürtler RE (1990) Probability of transmission of Chagas disease by *Triatoma infestans* (Hemiptera: Reduviidae) in an endemic area of Santiago del Estero, Argentina. Bull World Health Org 68: 737-746.

31. Nouvellet P, Dumonteil E, Gourbière S (2011) Estimating the unobservable: the 'milli-transmission' of Chagas disease to human. *In preparation*

32. Reithinger R, Colemen PG, Alexander B, Vieira EP, Assis G, et al. (2004) Are insecticide-impregnated dog collars a feasible alternative to dog cullings as a strategy for controlling canine visceral leishmaniasis in Brazil ? Int J Parasitol 34: 55-62.

33. Weng MH, Lien JC, Wang YM, Wu HL, Chin C (1997) Susceptibility of three laboratory strains of *Aedes albopictus* (Diptera: Culicidae) to Japanese encephalitis virus from Taiwan. J Med Entomol 34: 745-747.

34. Le Ray D (1989) Vector susceptibility to African trypanosomes. Ann Soc Belg Med Trop 69 Suppl 1: 165-171; discussion 212-214.

35. Artzrouni M, Gouteux J-P (1996) A compartmental model of sleeping sickness in central Africa. J Biol Syst 4: 459-477.

36. Artzrouni M, Gouteux J-P (2001) A model of Gambian sleeping sickness with open vector populations. IMA J Math Appl Med Biol 8: 99-117.

309 37. Hanley KA, Nelson JT, Schirtzinger EE, Whitehead SS, Hanson CT (2008) Superior
310 infectivity for mosquito vectors contributes to competitive displacement among strains of dengue
311 virus. BMC Ecol 8:1.

312 38. Doi R, Shirasaka A, Sasa M, Ova A (1977) Studies on the susceptibility of three species of
313 mosquitoes to Japanese encephalitis virus. J Med Entomol 13: 591-594.

314 39. Vivenes A, Oviedo M, Márquez JC, Montoya-Lerma J (2001) Effects of a second bloodmeal
315 on the oesophagus colonization by *Leishmania Mexicana* complex in *Lutzomyia evansi* (Diptera:
316 Psychodidae). Mem Inst Oswaldo Cruz 96: 281-283.

317 40. Kennedy PGE (2004) Human African trypanosomiasis of the CNS: current issues and
318 challenges. J Clin Invest 113: 496-504.

319 41. Ngwa GA, Shu WS (2000) A mathematical model for endemic malaria with variable human
320 and mosquito populations. Math Comput Model 32: 747-763.

321 42. Gürtler RE, Cecere MC, Castanera MB, Canale D, Lauricella MA, et al. (1996) Probability of
322 infection with *Trypanosoma cruzi* of the vector *Triatoma infestans* fed on infected humans and
323 dogs in northwest Argentina. Am J Trop Med Hyg 55: 24-31.

324 43. Michalsky EM, Rocha MF, da Rocha Lima AC, França-Silva JC, Pires MQ, et al. (2007)
325 Infectivity of seropositive dogs, showing different clinical forms of leishmaniasis, to *Lutzomyia*
326 *longipalpis* phlebotomines sand flies. Vet Parasitol 147: 67-76.

327 44. van den Hurk AF, Nisbet DJ, Hall RA, Kay BH, MacKenzie JS, et al. (2003) Vector
328 competence of Australian mosquitoes (Diptera: Culicidae) for Japanese encephalitis virus. J Med
329 Entomol 40: 82-90.

330 45. Machado EM, Fernandes AJ, Murta SM, Vitor RW, Camilo DJ Jr, et al. (2001) A study of
331 experimental reinfection by *Trypanosoma cruzi* in dogs. Am J Trop Med Hyg 65: 958-965.

332 46. World Health Organisation. Available: http:/www.who.int/mediacentre/factsheets/fs117/en.
333 Accessed 3 November 2011.

334 47. Gould EA (2001) Flavivirus infections in humans. Encyclopedia of Life Sciences.

335 48. Bora D (1999) Epidemiology of visceral leishmaniasis in India. Natl Med J India 12: 62-68.

336 49. Ministério de Saúde (1999) Enfermedades Infecciosas y Parasitarias: guía de bolso. Brasília,
337 Brazil. 332 p.

338 50. Brun R, Blum J, Chappuis F, Burri C (2010) Human African trypanosomiasis. The Lancet
339 375: 148-159.

340 51. Teixeira AR, Nitz N, Guimaro MC, Gomes C, Santos-Buch CA (2006) Chagas disease.
341 Postgrad Med J 82: 788-798.

342 52. Pépin J, Milord F, Khonde AN, Niyonsenga T, Loko L, et al. (1995) Risk factors for
343 encephalopathy and mortality during melarsoprol treatment of *Trypanosoma brucei gambiense*
344 sleeping sickness. Trans R Soc Trop Med Hyg 89: 92-97.

345 53. The Center for Food Security and Public Health (2007). JAPE_A2007. Ames, Iowa: The
346 Center for Food Security and Public Health. Available:
347 http://www.cfsph.iastate.edu/Factsheets/pdfs/japanese_encephalitis.pdf. Accessed 3 November
348 2011.

349 54. Centre de Coopération Internationale en Recherche Agronomique pour le Développement
350 (2011). Japanese Encephalitis. Available: http://pigtrop.cirad.fr/content/pdf.984. Accessed 3
351 November 2011.

352 55. Courtenay O, Quinnell RJ, Garcez LM, Shaw JJ, Dye C (2002) Infectiousness in a cohort of
353 Brazilian dogs: why culling fails to control visceral leishmaniasis in areas of high transmission. J
354 Infect Dis 186: 1314-1320.

355 56. Nunes CM, Lima VM, Paula HB, Perri SH, Andrade AM, et al. (2008) Dog culling and
356 replacement in an area endemic for visceral leishmaniasis in Brazil. Vet Parasitol 153: 19-23.

357 57. Eloy LJ, Lucheis SB (2009) Canine trypanosomiasis: etiology of infection and implications
358 for public health. J Venom Anim Toxins incl Trop Dis 15: 589-611.

359 58. Nuraini N, Soewono E, Sidarto KA (2007) Mathematical model of dengue disease
360 transmission with severe DHF Compartment. Bull Malays Math Sci 30: 143-157.

361 59. Otero M, Solari HG (2010) Stochastic eco-epidemiological model of dengue disease
362 transmission by *Aedes aegypti* mosquito. Math Biosci 223: 32-46.

363 60. Watt G, Jongsakul K (2003) Acute undifferentiated fever caused by infection with Japanese
364 encephalitis virus. Am J Trop Med Hyg 68: 704-706.

365 61. Alvar J, Bashave S, Argaw D, Cruz I, Aparicio P, et al. (2007) Kala-azar outbreak in Libo
366 Kemkem, Ethiopa: epidemiologic and parasitologic assessment. Am J Trop Med Hyg 77: 275-
367 282.

368 62. Checchi F, Filipe JA, Haydon DT, Chandramohan D, Chappuis F (2008) estimates of the
369 duration of the early and late stage of gambiense sleeping sickness. BMC Infect Dis 8:16.

370 63. Rassi A, Marcondes de Rezende J, Luquetti AO, Rassi A Jr (2010) Clinical phases and forms
371 of Chagas disease. In: American trypanosomiasis: Chagas disease one hundred years of research.
372 Tibayrenc M, Tellería J, editors. Elsevier. pp. 711-715.

373 64. Ueba N, Kimura T, Nakajima S, Kurimura T, Kitaura T (1978) Field experiments on live
374 attenuated Japanese encephalitis virus vaccine for swine. Biken J 21: 95-103.

375 65. Scherer WF, Moyer JT, Izumi T (1959) Immunologic studies of Japanese encephalitis virus
376 in Japan. V. Maternal antibodies, antibody responses and viremia following infection of swine. J
377 Immunol 83: 620-626.

378 66. Palatnik-de-Sousa CB, Batista-de-Melo LM, Borja-Cabrera GP, Palatnik M, Lavor CC (2004)
379 Improving methods for epidemiological control of canine visceral leishmaniasis based on a
380 mathematical model. Impact on the incidence of the canine and human disease. Anais da
381 Academia Brasileira de Ciências 76: 583-593.

Chapitre 3

Compétition et diversification intra-hôte des macro-parasites

3.1 Introduction

Les espèces parasites sont d'une très grande diversité et représentent entre 30 et 50% de la biodiversité actuelle (Poulin & Morand *2004*). Depuis 30 ans de nombreux auteurs ont tenté d'expliquer les origines de cette diversité (Price, *1980*). Une des hypothèses couramment proposées est que les espèces parasites seraient dotées d'un fort potentiel adaptatif (de Meeûs et al., *1998* ; Giraud, *2006*). Ceci expliquerait notamment de plus grands taux de spéciation sympatrique que pour les espèces non-parasites.

Jusqu'à présent cette hypothèse s'appuie sur un certain nombre de résultats empiriques étayés par des modèles verbaux. C'est le cas par exemple lorsque la diversité des espèces hôtes, la taille des hôtes, ou encore l'hétérogénéité de l'environnement intra-hôte, sont présentés comme autant de facteurs favorisant la diversification des niches écologiques des parasites (Emelianov, *2007*). A l'opposé, il n'existe toujours pas de travaux théoriques fournissant des prédictions quantitatives sur l'influence de ces caractéristiques du mode de vie parasite sur les taux de spéciation sympatrique et les niveaux de diversité en résultant. Ceci est d'autant plus surprenant que la théorie de la spéciation adaptative, qui analyse la façon dont les interactions biotiques peuvent induire des processus de diversification et d'isolement reproducteur, a connu d'importants développements au cours des dernières décennies chez les espèces non-parasites (Coyne & Orr, *2004* ; Dieckmann et al., *2004* ; Gavrilets, *2004* ; Weissing et al., *2011*). Ces travaux théoriques ont partiellement remis en cause l'idée selon laquelle la spéciation sympatrique serait très improbable, et ont ainsi stimulé de nombreuses études empiriques permettant de mieux comprendre l'évolution d'organismes aussi variés que des plantes (Savolainen et al., *2006* ; Gavrilets & Vose, *2007*), champignons (Giraud et al., *2010* ; Giraud & Gourbière, *2011*), algues (Jancek et al., *2008*), poissons (Barluenga et al., *2006* ; Gavrilets et al., *2007*), et d'autres encore (Gourbière & Mallet, *2010*).

L'objectif du chapitre 3 est donc d'adapter la théorie de la spéciation adaptative développée dans un premier temps pour les espèces non-parasites, afin d'apporter les premiers éléments de réponses théoriques à la question « le mode de vie des espèces parasites influence-t-il leurs probabilités de spéciation adaptative et leur diversité ? ». Le type d'interaction le plus étudié dans le cadre de la théorie de la spéciation adaptative chez les espèces non-parasites est la compétition intra-spécifique. Celle-ci conduit à un type particulier de spéciation adaptative: la spéciation compétitive (Dieckmann et al., *2004*, pages 8-9). Or il a été suggéré que la compétition intra spécifique puisse expliquer l'évolution de la diversité de plusieurs espèces de parasites sympatriques, notamment parmi des groupes de macro-parasites tels que les monogènes parasites des branchies de poissons (Lo & Morand, 2000 ; Šimková et al., *2004*), et les nematodes parasites des intestins de vertébrés (Poulin, *1999*). Dans ce chapitre, je me focalise donc sur la spéciation compétitive chez les macro-parasites, et je me limite au plus simple des scénarios envisagés dans le contexte de la théorie de la spéciation adaptative; le scénario dit « pléiotropique » (Dieckmann & Doebeli, *1999*). Dans

ce scénario, le caractère écologique qui se diversifie sous l'effet de la sélection naturelle engendrée par les interactions compétitives est aussi celui qui guide le choix du partenaire sexuel. La divergence écologique conduit donc instantanément (pléiotropiquement) à l'isolement reproducteur. L'étude de ce scénario est une étape indispensable avant d'étudier des scénarios plus complexes impliquant la coévolution d'un trait écologique et de règles d'appariements.

L'approche adoptée consiste a construire un modèle décrivant la dynamique de population de macro-parasites à cycle directe au sein d'une population hôte, en tenant compte des spécificités de ces parasites, et notamment du caractère agrégé de leur distribution parmi les individus hôtes. La population modélisée est polymorphe pour un trait quantitatif dont les valeurs déterminent le type de ressource utilisée, et par suite l'intensité de la compétition entre individus au sein des hôtes. Ce modèle de compétition intra-hôte permet de dériver une expression générale de la fitness d'invasion d'un individu de phénotype mutant (pour le trait écologique considéré), au sein d'une population de résidents. L'analyse évolutive réalisée à partir de cette fonction de fitness permet de définir les conditions de branchement évolutif en faisant appel aux méthodes de « dynamique adaptative » utilisées précédemment pour développer la théorie de la spéciation compétitive chez les espèces non-parasites (Dieckmann & Doebeli, *1999* ; Doebeli & Dieckmann, *2000*).

Lorsque mutant et résidents infectent les mêmes individus hôtes, la fitness invasive obtenue pour les macro-parasites est de la même forme que celle classiquement obtenue pour les espèces non-parasites, et ne dépend pas du degré d'agrégation des parasites. L'expression de cette fitness diffère par contre lorsque mutant et résidents sont distribués de manière indépendante ou que le mutant tend à éviter les hôtes au sein de la population hôte, et dépend alors du degré d'agrégation des parasites. De façon inattendue, malgré ces différences dans la forme des fonctions de fitness, leur analyse évolutive prédit que les conditions de spéciation compétitive sont elles identiques à celles des espèces non-parasites quelle que soit l'hypothèse faite sur la co-distribution des mutant et résidents ou le degré d'agrégation des parasites. Cette prédiction est testée à l'aide de données sur la phylogénie et l'agrégation d'espèces con-génériques de monogènes parasitant les branchies de poissons d'eau douce. Les taux de spéciation intra-hôte sont dans ces groupes effectivement indépendants des degrés d'agrégation observés.

Ce chapitre 3 pose donc les premiers fondements d'une théorie permettant de faire des prédictions testables sur l'influence du mode de vie des macro-parasites sur leur probabilité de diversification adaptative et de spéciation sympatrique. Cette théorie sera complexifiée dans le chapitre 4, ou l'on tiendra compte de l'éventuelle virulence des macro-parasites et des ses effets sur leur diversification intra-hôtes.

3.2 Within-host competition and diversification of macro-parasites (article accepté pour publication)

JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2012) **00**, 1–11
doi:10.1098/rsif.2012.0358
Published online 00 Month 0000

Within-host competition and diversification of macro-parasites

Rascalou Guilhem[1], Andrea Šimková[2], Serge Morand[3] and Sébastien Gourbière[1,4,*]

[1]*UMR 5244 CNRS-UPVD 'Ecologie et Evolution des Interactions', Université de Perpignan Via Domitia, Perpignan 66100, France*
[2]*Department of Botany and Zoology, Faculty of Science, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic*
[3]*Institut des Sciences de l'Evolution—CNRS, Département Génétique Environnement, CC065, Université Montpellier 2, 34095 Montpellier cedex 05, France*
[4]*School of Life Sciences, Centre for the Study of Evolution, University of Sussex, Brighton BN1 9QG, UK*

Although competitive speciation is more and more regarded as a plausible mechanism for sympatric speciation of non-parasite species, virtually no empirical or theoretical study has considered this evolutionary process to explain intra-host diversification of parasites. We expanded the theory of competitive speciation to parasite species looking at the effect of macro-parasites' life history on the conditions for sympatric speciation under the so-called pleiotropic scenario. We included within-host competition in the classical Anderson and May's framework assuming that individuals exploit within-host resources according to a quantitative trait. We derived the invasion fitness function of mutants considering different distributions of individuals among hosts. Although the mutant fitness depends on parameters describing the key features of macro-parasites life history, and on the relative distributions of mutant and residents in hosts, the conditions for competitive speciation of macro-parasites are exactly the same as those previously established for free-living species. As an interesting by-product, within-host competitive speciation is expected not to depend on the aggregation level of the parasites. This theoretical pattern is confirmed by comparing the speciation rate of weakly and strongly aggregated monogenean parasites.

Keywords: sympatric speciation; competitive speciation; parasite duplication; aggregation; adaptive dynamics; monogenean parasites

1. INTRODUCTION

Parasites are regarded as good biological models for evolutionary studies, mainly because of their high species diversity [1], adaptive potential [2] and because most of their biotope—the host—is also a living and an evolving entity [3]. The different modes of parasites' speciation are defined with respect to the level of interaction between parasite evolution and host diversification. While 'host-switch' implicitly requires previous host diversification, and 'co-speciation' literally emphasizes the contemporaneous diversification of a host and its parasite, 'duplication' that is speciation of parasites within a single host species, does not require host to diversify. Literature on parasites' diversification is overwhelmingly dominated by studies of host-switch and co-speciation events, which are believed to be the main modes of evolution of parasites species diversity [4,5].

Events of duplication have yet been shown to contribute to enhance parasites diversity of monogenean flatworms colonizing fish gills [6], *Plasmodium* species responsible for avian malaria [4] to *Trypanosoma cruzi*, the causal agent of the human American trypanosomiasis [7]. There are also more and more studies revealing the importance and variety of ecological interactions between parasites at the scale of the host body [8,9], including competition [10], facilitation by immuno-suppression [11] and inhibition by the elicitation of non-specific immune response [12]. With the concurrent theoretical and empirical realization that biotic interactions can lead to adaptive diversification in plants [13], fungi [14], algae [15], fishes [16] and various other taxa [17], one expects more adaptive duplication events to be reported as more attention would be given to this overlooked source of parasite diversity.

An important mechanism that could cause adaptive duplication is within-host competition for resources, as it can potentially lead to 'competitive speciation' [18]. Under such a scenario, competitive interactions at the host individual scale, i.e. within a parasite 'infra-population', lead to parasite diversification inside a population of con-specifics and sympatric host

*Author for correspondence (gourbiere@univ-perp.fr).

Electronic supplementary material is available at http://dx.doi.org/10.1098/rsif.2012.0358 or via http://rsif.royalsocietypublishing.org.

Received 3 May 2012
Accepted 16 May 2012

This journal is © 2012 The Royal Society

rsif20120358—23/5/12—18:36–Copy Edited by: Shalom Kumar Sigworth

individuals. Several lines of evidences point at the potential significance of such adaptive speciation in macro-parasites: within-host intraspecific competition has an impact on parasite life history [19], infra-populations are often genetically diverse [20], several congeneric species can live on the same host individual [21] and within-host competition influences the patterns of associations between such species [10]. Hypothetically, within-host competition could also contribute to micro-parasites diversity because infra-populations also are genetically diverse [7,22], and competition between strains is an important force-driving parasite life-history evolution [23].

The theory of competitive speciation has been broadly extended in the last 10 years, using a wide range of models typically assuming that a quantitative trait is under disruptive selection generated by frequency and density-dependent intraspecific competition [24,25]. Some models consider that the ecological trait pleiotropically affects mate choice [26–28], while others explicitly describe the evolution of mating preferences according to the ecological trait under natural selection [26–30] or an additional neutral trait [26,31]. Despite criticisms [32], these studies have contributed to attract attention on the potential of intraspecific competition to induce adaptive diversification of non-parasite species. Surprisingly, no attempt has been made to account for the specific features of the parasite lifestyle, while parasites may represent 30 to 50 per cent of species diversity [1].

The main goal of this study was to investigate how conditions for competitive speciation depend on the typical features of macro-parasite life history by identifying when within-host competitive interactions can induce adaptive duplication. In this first attempt to expand the theory of competitive speciation to macro-parasites, we focused on the simplest case, the 'pleiotropic scenario' [33], whereby a 'magic trait' [24] under disruptive natural selection also contributes to non-random mating. Such 'magic traits' have been shown to be produced by a great variety of mechanisms in non-parasite species [34] and have been suggested to contribute to several events of within-host macro-parasites speciation [35]. We considered the exploitation of a gradient of resource, as the theory of competitive speciation is deeply rooted in the ecological literature on character displacement along such a gradient [28]. Examples of gradient of resource at the host body scale include fishes gill arches exploited by monogeneans [36], or nutrients exploited by gut helminths [37]. The scenario of speciation considered assumes that macro-parasites with different morphological or physiological phenotypes can exploit different parts of the gradient and that local competitive interactions contribute to shape the phenotypic distribution. According to the theoretical results developed for non-parasite species, one then expects the phenotypic distribution to become bimodal if local competition is strong enough [26]. We shall here identify whether or not considering key features of macro-parasites life history influences the conditions for such competitive processes to induce adaptive duplication, by comparing the theoretical results existing for non-parasite species [26,27] with the conditions identified from a general model that we shall design to include a description of the typical macro-parasite life history.

2. THE THEORY OF WITHIN-HOST COMPETITION AND ADAPTIVE DIVERSIFICATION OF MACRO-PARASITES

2.1. General approach

We expanded the theory of competitive speciation to macro-parasites using the model of Anderson & May [38,39]. To bridge the gap between this influential model and the theoretical literature on competitive speciation, we included within-host competition by assuming that individual competitive abilities depend on a quantitative trait, such as body mass or size [26–28]. We first established the population dynamic equations for the change in the number of individuals of two competing phenotypes. Considering these two phenotypes as mutant and resident, we then derived the fitness function of a mutant individual competing with residents already established in the host population. We finally performed an evolutionary analysis to reveal the condition for adaptive duplication of parasites, using the 'adaptive dynamics' approach previously applied to look at adaptive diversification of non-parasite species [26,27]. Importantly, we considered three hypotheses about the distributions of mutant and resident individuals among hosts, as such distributions were obviously anticipated to affect the fitness of the mutants. We assumed that mutant individuals tend to (i) colonize hosts at random, (ii) colonize the same hosts as the residents, or (iii) colonize hosts that are not already infected by the residents. These distributions are three simple alternatives to explore the role of spatial segregation in competitive interactions. They can potentially describe the distribution resulting from heterogeneities in host exposure/susceptibility to parasites or in pathological effects. For instance, heterogeneity in the spatial or temporal distribution of infective stages can determine the aggregated distribution of parasites in hosts ([40], p. 98), which would lead to a positive correlation between mutant and resident distributions. Alternatively, infection by resident individuals can lead to a pathological reduction of host mobility, and thus a lower susceptibility to infection by mutants, which would generate a negative correlation between mutant and resident distributions.

2.2. The extension of the Anderson and May's model to a polymorphic parasite population

We denoted $H_{n_i,n_j}(t)$ the number of hosts at time t that harbour n_i and n_j parasites with phenotype i and j. We also let $\mu(i)$, $\mu(j)$ be the natural mortality rates of the two phenotypes, and $\beta(i)$, $\beta(j)$ their colonization rates. We described competition using two additional parameters; $\alpha(i,j) = \alpha(j,i)$, the strength of within-host symmetrical competition between two individuals with phenotype i and j, and $K(i)$, $K(j)$, the carrying capacities for individuals with phenotype i and j.

For simplicity, we disregarded host demography and described transmission as a parasite pure immigration

death-process using standard modelling methods ([41], p. 140). Keeping n_j as a constant, variations in the number of hosts with n_i parasites are given by

$$\begin{aligned}\left.\frac{\mathrm{d}H_{n_i,n_j}}{\mathrm{d}t}\right|_{n_j} &= -\mu(i)((n_i)H_{n_i,n_j}(t)-(n_i+1)H_{n_i+1,n_j}(t))\\ &\quad+\beta(i)(H_{n_i-1,n_j}(t)-H_{n_i,n_j}(t))\\ &\quad-\alpha(i,i)\left(\frac{n_i^2}{K(i)}H_{n_i,n_j}(t)-\frac{(n_i+1)^2}{K(i)}H_{n_i+1,n_j}(t)\right)\\ &\quad-\alpha(i,j)\left(\frac{n_in_j}{K(i)}H_{n_i,n_j}(t)-\frac{(n_i+1)n_j}{K(i)}H_{n_i+1,n_j}(t)\right).\end{aligned} \tag{2.1a}$$

Competition is described here as in the existing theory of competitive speciation; its effects are assumed to reduce parasite within-host mortality and we did not consider alternative impacts that competition may have in reducing the rate of parasite establishment or reproduction.

A similar equation can be derived for the variations in the number of hosts with n_j parasites while keeping n_i as a constant

$$\begin{aligned}\left.\frac{\mathrm{d}H_{n_i,n_j}}{\mathrm{d}t}\right|_{n_i} &= -\mu(j)((n_j)H_{n_i,n_j}(t)-(n_j+1)H_{n_i,n_j+1}(t))\\ &\quad+\beta(j)(H_{n_i,n_j-1}(t)-H_{n_i,n_j}(t))\\ &\quad-\alpha(j,j)\left(\frac{n_j^2}{K(j)}H_{n_i,n_j}(t)-\frac{(n_j+1)^2}{K(j)}H_{n_i,n_j+1}(t)\right)\\ &\quad-\alpha(j,i)\left(\frac{n_in_j}{K(j)}H_{n_i,n_j}(t)-\frac{n_i(n_j+1)}{K(j)}H_{n_i,n_j+1}(t)\right).\end{aligned} \tag{2.1b}$$

Summing over n_i and n_j, one can derive two equations for the change in the number of parasites with phenotype i and j

$$\begin{aligned}\frac{\mathrm{d}P(i)}{\mathrm{d}t} &= \sum_{n_i,n_j} n_i\left.\frac{\mathrm{d}H_{n_i,n_j}}{\mathrm{d}t}\right|_{n_j} = -\mu(i)P(i)+\beta(i)H\\ &\quad-\alpha(i,i)\sum_{n_i,n_j}\frac{n_i^2}{K(i)}H_{n_i,n_j}(t)\\ &\quad-\alpha(i,j)\sum_{n_i,n_j}\frac{n_in_j}{K(i)}H_{n_i,n_j}(t)\end{aligned} \tag{2.2a}$$

and

$$\begin{aligned}\frac{\mathrm{d}P(j)}{\mathrm{d}t} &= \sum_{n_i,n_j} n_j\left.\frac{\mathrm{d}H_{n_i,n_j}}{\mathrm{d}t}\right|_{n_i} = -\mu(j)P(j)+\beta(j)H\\ &\quad-\alpha(j,j)\sum_{n_i,n_j}\frac{n_j^2}{K(j)}H_{n_i,n_j}(t)\\ &\quad-\alpha(j,i)\sum_{n_i,n_j}\frac{n_in_j}{K(j)}H_{n_i,n_j}(t),\end{aligned} \tag{2.2b}$$

where $P(i)$ and $P(j)$ are the numbers of parasites with phenotype i and j, and H is the number of hosts. Under the usual assumption of a fast equilibrium in the free-larval stage dynamics [41]: $\beta(i)H = \lambda\theta P(i)H/(\theta H+v)$ and $\beta(j)H = \lambda\theta P(j)H/(\theta H+v)$, where λ, v and θ stand for the rates of production of larvae by adults, death of larvae and of host infection, respectively.

To further describe the competition between individuals $\alpha(i,j)$ and $K(i)$, $K(j)$ have to be specified. We used standard assumptions of the theory of niche competition and competitive speciation [26–28]. A Gaussian distribution allows describing that competition is more intense between individuals with similar phenotypes

$$\alpha(i,j) = \mathrm{e}^{-((i-j)^2)/(2\sigma_\alpha^2)}, \tag{2.3}$$

where σ_α^2 quantifies the intensity of competition: the lower σ_α^2, the stronger the competition for any given pair of phenotypes. A Gaussian distribution describes the carrying capacity of individuals with phenotype i

$$K(i) = K(s_0)\mathrm{e}^{-((i-s_0)^2)/(2\sigma_K^2)}, \tag{2.4}$$

where s_0 is the intermediate trait value associated with the maximal phenotypic carrying capacity $K(s_0)$, and σ_K^2 specify the width of the carrying capacity distribution according to individual phenotypes.

2.3. The invasive fitness function of competing mutant macro-parasites

To analyse the evolution of the quantitative trait determining the use of resources by competing macro-parasites, we searched for the fitness function of a mutant with phenotype (m) invading a population of residents with phenotype (r). Such fitness function can be derived from equations describing the ecological interactions between mutant and resident individuals [26–28]. We used equations (2.2*a*) and (2.2*b*) to describe the dynamics of such interactions, assuming that mutant individuals are rare, and that residents are at their population dynamics equilibrium. The first assumption allows neglecting competition between mutants and simplifying the description of competition between mutant and resident individuals. Indeed, the number n_m of mutants in any given host can only be 0 or 1, and further considering that, at all time, $H_{n_\mathrm{r}}(t) = H^*_{n_\mathrm{r}}$, the sum $S(m,r)$ in equation (2.2*a*) becomes

$$\begin{aligned}S(m,r) &= \sum_{n_\mathrm{m},n_\mathrm{r}} n_\mathrm{m}n_\mathrm{r}H_{n_\mathrm{m},n_\mathrm{r}}\\ &\approx P(m)\sum_{n_\mathrm{r}} n_\mathrm{r}H^*_{n_\mathrm{r}}p(n_\mathrm{r}),\end{aligned} \tag{2.5}$$

where $p(n_\mathrm{r})$ is the probability for a mutant parasite to enter a host already infected with n_r resident parasites. This approximation involves that the number of hosts harbouring n_m and n_r mutant and resident parasites is proportional to the number of mutants, because this number is the limiting factor in the co-occurrence of both types within a host.

Using equation (2.2*a*) and the earlier-mentioned assumptions, one can derive a general expression of

Table 1. Fitness functions under different assumptions of distribution of mutant and resident individuals. $p_d(n_r)$ is the probability for a mutant individual to parasite, an host already harbouring n_r resident individuals. $S_d(m,r)$ is the sum describing interaction between resident and mutant individuals as defined by equation (2.5). $F_d(r)$ is defined as in equation (2.10). $p_d(n_r)$, $S_d(m,r)$ and $F_d(r)$are given for three distributions of mutant individuals: a random distribution ($d=1$), a co-aggregated distribution ($d=2$) and an inversely aggregated distribution ($d=3$). The standard theoretical result for non-parasite species [26,27] appears in the last row of the table.

mutant distribution	$p_d(n_r)$	$S_d(m,r)$	$F_d(r)$
random ($d=1$)	$\frac{1}{H}$	$P(m)\left(\frac{P(r)^*}{H}\right)$	$\frac{k}{k+1}(cK(r)-1)$
co-aggregation ($d=2$)	$\frac{n_r}{P(r)^*}$	$P(m)\left(\frac{P(r)^*}{H}\left(\frac{k+1}{k}\right)+1\right)$	$cK(r)$
inverse-aggregation ($d=3$)	$\frac{1-(n_r/P(r)^*)}{H-1}$	$\frac{P(m)}{H-1}\left(P(r)^*-\frac{P(r)^*}{H}\left(\frac{k+1}{k}\right)-1\right)$	$\frac{H((k/k+1))(cK(r)-1)-cK(r)}{H-1}$
non-parasite ($d=4$)	—	—	$cK(r)$

the invasion fitness of a mutant m in a population of residents r

$$f(m,r)=\frac{\mathrm{d}P(m)}{P(m)\mathrm{d}t}=-\mu(m)+\frac{\lambda\theta H}{\theta H+v}-\frac{\alpha(m,r)}{K(m)}\frac{S(m,r)}{P(m)}. \tag{2.6}$$

Specifying the probabilities $p(n_r)$ appearing in $S(m,r)$ would thus allows us to complete the definition of the fitness function.

We used the traditional assumption that the aggregated distribution of residents is described by a Negative Binomial Distribution [38]. We then worked out three expressions of $p(n_r)$, noted $p_d(n_r)$, whereby mutant and residents distributions are either independent ($d=1$), positively ($d=2$) or negatively ($d=3$) correlated. When $d=1$, the probability for a mutant to enter a host harbouring n_r resident parasites is proportional to the frequency of hosts carrying n_r residents. When $d=2$, this probability is proportional to the number n_r of residents. When $d=3$, the probability is inversely proportional to the number n_r of residents. Normalizing these probabilities, we found the expressions $p_d(n_r)$ appearing in table 1. Since residents are assumed to be distributed in hosts according to a Negative Binomial Distribution

$$\sum_{n_r} n_r^2 H_{n_r}(t)=\frac{P(r)^2}{H}\left(\frac{k+1}{k}\right)+P(r), \tag{2.7}$$

where k is the usual aggregation parameter [38]. One can then express $S(m,r)$ with respect to $P(r)^*$, the number of resident parasites at their population dynamic equilibrium in absence of mutant (table 1). This equilibrium level, $P(r)^*$, can be derived from equation (2.2a), which now reads

$$\frac{\mathrm{d}P(r)}{\mathrm{d}t}=-\mu(r)P(r)+\frac{\lambda\theta H}{\theta H+v}P(r)-\frac{\alpha(r,r)}{K(r)}\left(\frac{P(r)^2}{H}\left(\frac{k+1}{k}\right)+P(r)\right), \tag{2.8}$$

and is given by

$$P(r)^*=H\left(\frac{k}{k+1}\right)(c(r)K(r)-1) \tag{2.9}$$

with $c(r)=-\mu(r)+(\lambda\theta H)/(\theta H+v)$.

Substituting $P(r)^*$ into $S(m,r)$, the fitness functions defined for the three mutant distributions, can be re-written (from equation (2.6)) in the general form:

$$f_d(m,r)=c(r)-\frac{\alpha(m,r)}{K(m)}F_d(r), \tag{2.10}$$

where $F_d(r)$ are as defined in table 1.

Interestingly, the mutant fitness function derived for non-parasite species [26,27] can also be written in that form:

$$f_4(m,r)=c-\frac{\alpha(m,r)}{K(m)}[cK(r)], \tag{2.11}$$

where c is usually thought not to depend on the individual phenotype. We thus assumed that c is a constant for the three fitness functions defined for parasite species, to ease the comparison with non-parasite species.

A first conclusion (from equation (2.10) and definitions of $F_d(r)$ in table 1) is that, when the mutant and residents distributions are positively correlated ($d=2$), the fitness functions for parasite and non-parasite species are equivalent. The only difference between them lies in the definition of c, which is related to parameters reflecting parasite or non-parasite life histories. On the contrary, when mutant distribution is random ($d=1$) or negatively correlated ($d=3$) with the distribution of residents, the mutant parasite fitness functions depend on the aggregation level of the residents. It can also be shown that $F_2(r)=F_4(r)>F_1(r)>F_3(r)$ so that $f_2(r)=f_4(r)<f_1(r)<f_3(r)$, which means that, as expected, the more segregated the mutant and resident are, the fittest the mutant since it suffers less competition from resident.

2.4. Evolutionary dynamics and adaptive duplication of macro-parasites

The 'adaptive dynamics' approach [42] allows identifying evolutionary singularities; that is trait values where the selection gradient vanishes. Four evolutionary properties of these singularities are usually assessed: evolutionary stability, convergence stability, invasion potential and mutual invadibility. These properties are assessed using rules on the derivatives of the fitness function with respect to m and r. We thus worked out these derivatives and properties using the general form of the fitness function equation (2.10), assuming that c does not depend on the individual phenotype (as usually done for non-parasite species [26]), and describing competition according to equations (2.3) and (2.4). Later, we report the conditions for the evolutionary singularity of the four fitness functions to have the different properties evocated earlier. Details of the mathematical derivation of these results as well as numerical illustrations of the analytical results are given in the electronic supplementary material.

Evolutionary singularities can be identified by solving

$$\left.\frac{\delta f_d(m,r)}{\delta m}\right|_{m=r=s^*} = -\frac{F_d(s^*)}{K(s^*)}\left(\frac{s^*-s_0}{\sigma_K^2}\right) = 0. \qquad (2.12)$$

Since $F_d(s^*) \neq 0$ ($\forall$ d $\in [1;\ 4]$) (see the electronic supplementary material), there is only one evolutionary singularity: $s^* = s_0$, which is exactly the same for all macro-parasite fitness functions ($d = 1,2,3$), and for the non-parasite species ($d = 4$ and [26,27]). It simply corresponds to the value of the trait providing the maximal amount of resource ($K(s_0)$), and it is worth mentioning that this evolutionary singularity does not depend on the distribution of the mutants nor on the level of aggregation of the residents.

Such an evolutionary singularity is evolutionary stable if

$$\left.\frac{\delta^2 f_d(m,r)}{\delta^2 m}\right|_{m=r=s^*} = \frac{F_d(s^*)}{K(s^*)}\left(\frac{1}{\sigma_\alpha^2}-\frac{1}{\sigma_K^2}\right) < 0. \qquad (2.13)$$

Since $F_d(s^*) > 0$ ($\forall$ d $\in [1;\ 4]$) (see the electronic supplementary material), whatever the fitness function, the condition for the evolutionary singularity $s^* = s_0$ to be an evolutionary stable strategy is $\sigma_\alpha^2 > \sigma_K^2$. This condition is biologically meaningful as large σ_α^2 means that residents $s^* = s_0$ compete with (mutant) individuals having different phenotypic values, which can prevent invasion. Instead, if σ_α^2 is small, residents do not exert any competition pressure on mutants, which can then invade. Again, the results we obtained for macro-parasites ($d = 1,2,3$) are similar to the one obtained for non-parasite species ($d = 4$ and [26,27]).

The evolutionary singularity is a convergent stable strategy (CSS) if

$$\left.\frac{\partial^2 f_d(m,r)}{\partial^2 r}\right|_{m=r=s*} - \left.\frac{\partial^2 f_d(m,r)}{\partial^2 m}\right|_{m=r=s^*} = \frac{1}{K(s^*)}\left(\frac{F_d(s^*)}{\sigma_K^2} - \left.\frac{\partial^2 F_d(r)}{\partial^2 r}\right|_{m=r=s^*}\right) > 0. \qquad (2.14)$$

Evaluating this inequality according to the different function F_d and their second derivative with respect to r, we obtained the conditions for the evolutionary singularity to be a CSS for each of the four fitness functions (see the electronic supplementary material). When the mutant distribution is positively correlated with the resident distribution ($d = 2$), the expression of this condition is exactly the same as for non-parasite species ($d = 4$) and, remarkably, it does not depend on the aggregation parameter. On the contrary, for the other two types of mutant distribution, these expressions depend on the details of the parasite life history and, especially, on the aggregation level. Despite these differences, s^* remains always an evolutionary convergent strategy (see the electronic supplementary material), which means that s^* can be gradually reached through a sequence of adaptive mutations with small phenotypic effects.

The evolutionary singularity is an invasive strategy if

$$\left.\frac{\partial^2 f_d(m,r)}{\partial^2 r}\right|_{m=r=s*} = \frac{1}{K(s^*)}\left\{\frac{F_d(s^*)}{\sigma_\alpha^2} - \left.\frac{\partial^2 F_d(r)}{\partial^2 r}\right|_{m=r=s^*}\right\} > 0. \qquad (2.15)$$

Evaluating this inequality for the different functions $F_d(r)$, one obtains the conditions for the evolutionary singularity s^* to be able to invade in a non-gradual way (see the electronic supplementary material). Again, those conditions are exactly the same when the mutant distribution is positively correlated with the resident distribution ($d = 2$) and for non-parasite species ($d = 4$). When mutant and residents distributions are different ($d = 1$ and 3), the conditions depend on the parameter related to macro-parasite life history (see the electronic supplementary material). These conditions are analogous to the conditions for s^* to be convergent stable, except that, in the first term, σ_K^2 is replaced by σ_α^2. Again, those conditions are always verified (see the electronic supplementary material). Evolution can thus lead to the establishment of s^* in a non-gradual way, typically by the fixation of a mutation of a large effect.

Finally, a protected polymorphism (PP) could appear in the vicinity of the singular strategy if

$$\left.\frac{\partial^2 f_i(m,r)}{\partial^2 r}\right|_{m=r=s^*} + \left.\frac{\partial^2 f_i(m,r)}{\partial^2 m}\right|_{m=r=s^*} = \frac{1}{K(s^*)}\left(\frac{2F_j(s^*)}{\sigma_\alpha^2} - \left.\frac{\partial^2 F_j(r)}{\partial^2 r}\right|_{m=r=s^*} - \frac{F_j(s^*)}{\sigma_K^2}\right) > 0. \qquad (2.16)$$

Not surprisingly, these conditions are exactly the same when the mutant distribution is positively correlated with the resident distribution ($d = 2$) and for non-parasite species ($d = 4$), and they are always satisfied (see the electronic supplementary material). When mutant and resident distributions are different ($d = 1$ and 3), the condition also always holds (see the electronic supplementary material). A pair of mutations

with larger and smaller trait values than s^* can then invade each other, so that a PP can potentially gets established, leading to two sets of individuals exploiting two opposite parts of the resource gradient.

2.5. Branching point

Branching points are paradigmatic features of the adaptive dynamics background, especially when looking at adaptive diversification and speciation. They are points around which a monomorphic population can become polymorphic because frequency- and density-dependent ecological interactions generate a disruptive selection pressure. In addition, when the ecological trait under disruptive selection pleiotropically affects pre-zygotic isolation, adaptive ecological diversification almost systematically leads to adaptive speciation [26,27]. Conditions for adaptive diversification under such scenario are thus identified by identifying the range of parameter values where s^* is a 'branching point'. For s^* to be a 'branching point', it has to be CSS with the potential to invade (IP) in a non-gradual way, and to be a non-evolutionary stable strategy (non-ESS) around which a PP can appear. The first two properties (CSS and IP) ensure that evolution can lead to s^*. The last two properties (non-ESS and PP) allows for diversification around this strategy after it has been reached.

Whatever the assumption about the mutant distribution among hosts, the conditions for the singular strategy to be convergent stable, to be able to invade and for a PP to appear always hold. Thus, the only requirement for s^* to be a branching point is not to be an evolutionary stable strategy, which, as previously stated for non-parasite species, requires $\sigma_\alpha^2 < \sigma_K^2$ [26,27].

The conditions for adaptive duplication owing to within-host competitive interactions are thus the same as the conditions for competitive speciation of non-parasite species. An important by-product of this conclusion is that, despite the variations of the fitness function with the mutant distribution and the aggregation level of the residents (see the definition of parameter c and function $F_d(r)$, and numerical results in the electronic supplementary material), these changes do not affect the properties of the evolutionary singularity. Accordingly, the conditions for adaptive diversification around a branching point do not depend on the level of aggregation of the parasites. This is a key prediction since aggregation has been shown to have a strong influence on many features of macro-parasite ecology [1,38,43,44], which we decided to test.

3. TEST OF THE 'AGGREGATION-FREE' ADAPTIVE DUPLICATION HYPOTHESIS

Monogeans are good candidates to test our theoretical prediction that within-host adaptive diversification does not depend on the level of aggregation of macro-parasites. The monogenean genus *Dactylogyrus* indeed represents a group of fish gills ecto-parasites highly diversified (a high number of species often live on the same cyprinid species) and highly host-specific, which fits the assumption of our model. In addition, parasite duplication is a major mode of speciation in this group [6] and has been proposed as a case of the 'pleiotropic scenario' [24,33] we investigated. Phylogenetic reconstruction indeed showed that speciation event is linked with change of at least one parameter of the parasite niche, i.e. the micro-habitat position of the parasites on the fish gills. The most important adaptation of those gills ecto-parasites is a special attachment organ called haptor, and monogeneans living on the same micro-habitat (position on the gills) show similar haptor morphology. Because individuals reproduce within their micro-habitat, mating tends to be assortative with respect to the morphological trait under natural selection [45]. The morphology of attachment organ is considered being related to parasite speciation and host specificity [46] and typically is a quantitative trait involved in both the evolution of pre- and post-zygotic isolations between incipient species as considered in the modelling of the pleiotropic scenario of competitive speciation [26–28] and in this contribution.

We investigated the effect of aggregation on diversification across the *Dactylogyrus* species (Monogenea) parasitizing six fish species of Cyprinidae using field data collected from July to August 2000 and from May to September 2001 from the selected localities belonging to Morava river basin (Czech Republic). On the basis of the phylogenetic study of Šimková *et al.* [6], we separated 20 species of intra-host speciation's origin and six species originated from other types of speciation (figure 1). Intra-host speciation or duplication events were depicted using host-parasite tangle tree representation, and the robustness of the intra-host speciation (duplication events) was tested by bootstrap percentage on randomized parasite and host phylogenies (see Šimková *et al.* [6] for details). We then used MacroCAIC program [47], derived from CAIC [48] to test our prediction of independence between the aggregation level and speciation of parasites. MacroCAIC is designed specifically for studies of diversification and uses a basic approach based on phylogenetically independent contrasts. MacroCAIC allows using species richness as a variable in a comparative analysis to estimate whether a trait (here aggregation) is associated with high speciation rates [49]. We used a widely acknowledged measure of the aggregation level of parasites [50]; the ratio of the variance of abundance [$V(M)$] of a parasite's distribution to its mean abundance (M). We used this measure instead of the parameter k of the negative binomial as the latter can be biased when estimated on different species with obvious different sample sizes [51].

We regressed the natural log of the CladeBigX/CladeSmallX ratio where CladeBigX is the species richness of the sister clade with larger aggregation, for each node of the phylogeny, and CladeSmallX is the species richness of its sister clade with lower aggregation. The ln(CladeBigX/CladeSmallX) was regressed against standardized contrasts for $\mathrm{Var}(M)/M$, and we found no significant correlation between monogenean aggregation and diversification ($p = 0.40$, $n = 16$; figure 2). In other words, clades with higher species richness are not characterized by smaller or larger aggregation than their sister clades. Despite the potential bias

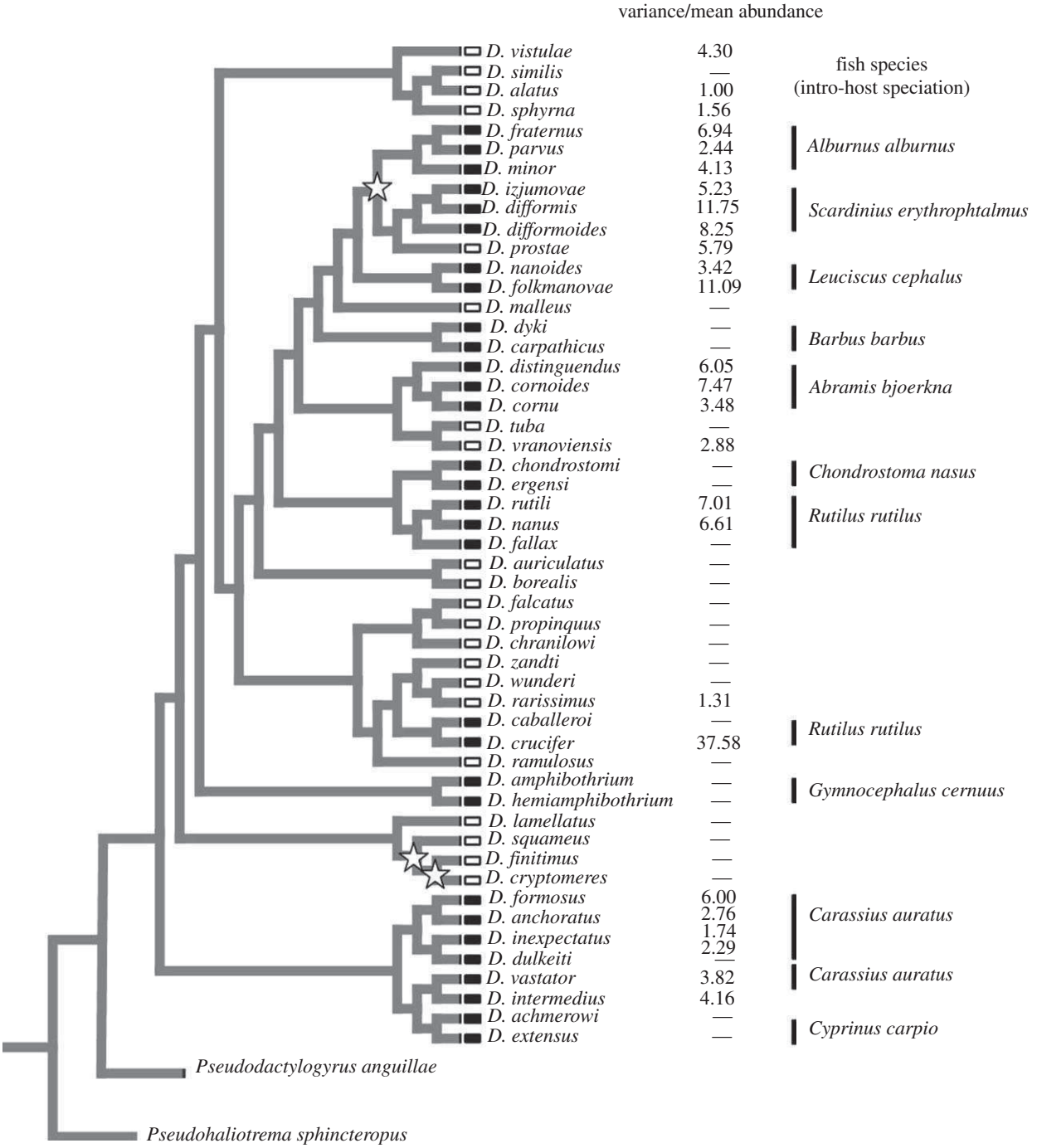


Figure 1. Phylogeny of the *Dactylogyrus* species (Monogenea), with indications of cospeciation and intra-host speciation events, and with the name of fish hosts. Intra-host speciation or duplication events were obtained using host–parasite tangle trees and were tested by bootstrap procedure (see Šimková *et al.* [6] for details). Tree rooting was done using phylogenetic information and taxonomic knowledge on the family Ancerocephalidae [6]. Open rectangles, speciation by host switch; filled rectangles, intra-host speciation; stars, co-speciation.

when using parameter k, we performed the same comparative analysis on k estimates and found a similar pattern, suggesting that this conclusion is robust.

4. DISCUSSION

We investigated the conditions for within-host adaptive diversification by expanding the theory of competitive speciation to macro-parasites species, and by confronting our theory to a comparative analysis of speciation rates in monogenean parasites.

Although the invasion fitness depends on parameters describing key features of the macro-parasites life history, we showed that it is typologically equivalent to those previously derived for non-parasite species as long as the mutants tend to colonize the same hosts as the residents. On the contrary, when mutants randomly colonize host individuals, or when they tend to colonize less infected hosts, the fitness function of parasites and non-parasites are no longer similar. As expected, differences between the distribution of mutants and residents promote mutants' invasion. This

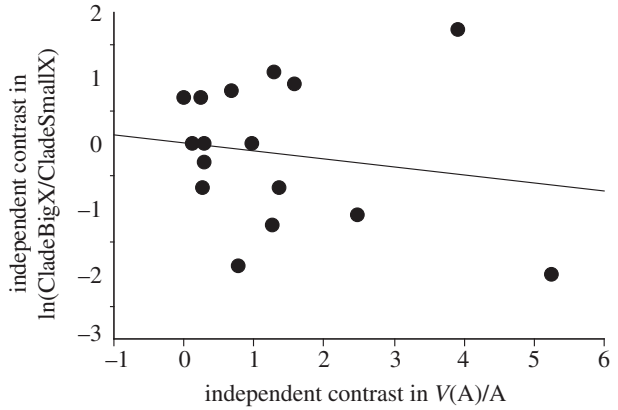


Figure 2. Lack of relationship between aggregation, estimated by the ratio of the variance of the mean parasite abundance $V(M)$ to the mean parasite abundance M, and the rate of species diversification, estimated by ratio of the most diversified sister clade (CladeBigX) to the less diversified (CladeSmallX) (in Ln).

is consistent with the well-known effect of spatial heterogeneity to promote coexistence between competitive species of mammals [52], birds [53], plants [54], fungi [55] as well as macro-parasites [56].

Regardless of differences in fitness functions obtained for various distributions of the mutant among hosts, the conditions for within-host adaptive diversification remain the same and are exactly the same as for competitive diversification of non-parasite species [25]. This suggests that previous results on the influence of intraspecific competition on non-parasite species diversity are robust to the life history of the organisms being considered. This leads to the unanticipated conclusion that within-host adaptive diversification of macro-parasites does not depend on the level of aggregation among hosts. Such a conclusion contrasts with the recognized effects of aggregation on population dynamics [38,44] interspecific competition [43,57], and the evolution of both host and parasite [40]. Interestingly, the comparison of speciation rates between clades of monogeneans with low and high level of aggregation was consistent with this theoretical prediction. Although the failure of detecting an effect of aggregation may entail a lack of statistical power, this finding is consistent with those of Šimková *et al.* [58] and suggests that intra and interspecific aggregation affect the strength of population regulation of monogeneans, but with no incidence on their diversification through competitive speciation.

We used a simple strategic 'core' model [59] that allows accounting for general features of macro-parasite lifestyle to specify the conditions for within-host competition to cause adaptive diversification. Although the description of the parasite life history was consistent with the lifestyle of the monogeneans used to confront our theory to existing phylogenetic studies, there are several lines along which to improve our theory and our understanding of the role of within-host competition in parasite diversity.

Our evolutionary analysis relied on a phenotypic approach, which does not account for sexual reproduction. The conditions for the population to split into subpopulations of different phenotypes might thus not strictly correspond to the conditions for within-host duplication [28]. However, when considering a 'magic' trait, whereby assortative mating between phenotypically similar individuals appears as a by-product of ecological specialization, the conditions for competitive speciation established by individual-based models (including sexual reproduction and the genetic underlying the ecological trait) do match the conditions for the ecological phenotype diversification [26,27]. Because the size of the haptors used by monogeneans to attach on gills is thought to be such a magic trait [35], our results indeed inform on duplication events. For parasites developing within the host body, such as intestinal nematodes, chemical communication can influence encounters between con-specific individuals as well as encounters between individuals of different species [60,61]. Such chemical communication has also been observed for non-parasite [62] and plant parasite [63] species closely related to nematodes. Potentially, such communication could thus evolve to limit hybridization between incipient species of intestinal nematodes, as observed in the plant–parasite nematode *Radopholus similis* [64]. According to the general theory of reinforcement [24], the conditions for parasite duplication involving the evolution of assortative mating based on such chemical communication are likely to be more limited, even if the post-zygotic isolation owing to intraspecific competitive interactions provides the required selective pressure [26]. It would thus be worth expanding the theory to account for the evolution of such 'mating trait' as previously done for non-parasite organisms [26]. Identifying the condition for such mating clue to evolve would undoubtedly provide new insights into the idea that the present chemical signalisation between con-specific individuals represents the ghost of a past competition.

The theory we developed does not consider any effect of macro-parasites on their hosts. Such an assumption is consistent with the common view that macro-parasites are less virulent than many micro-parasites, such as bacteria [65], virus [66] or protozoan [67]. Nevertheless, macro-parasites can affect their host survival and reproductive rates either on their own [68] or through co-infection with micro-parasites [69]. To expand the theory to account for parasite virulence is likely to produce further stimulating results, especially about the role of aggregation. Indeed, as the most heavily infected hosts are where the intraspecific competition is the highest, they also are where disruptive selection is the strongest. If such hosts were to die because of their heavy rate of infection, aggregation would have an adverse effect on adaptive diversification. Potentially, the virulence of the resident population could thus freeze further evolution. Such a possibility of 'frozen evolution' has been widely overlooked, while it could be relevant to the evolution of any other life-history trait of macro-parasites. We thus anticipate that accounting for virulence would limit adaptive diversification and duplication induced by within-host competition, a conclusion that is likely to depend on the level of co-distribution between mutants and residents.

The model we used provides a proper theoretical background to better understand the origin and evolution of 'species flocks' observed in single host species,

such as fish gills monogeneans [70,71] or gastrointestinal helminths [21,70] that interact along a gradient of resource. However, some macro-parasites show much stronger spatial segregation as they colonize different locations within the host body. For instance, adult flatworms such as *Schistosoma* settle in various parts of the blood vessels network [72], while adults of the filarial roundworms *Onchocerca* are found in tissues such as the skin, muscles, joints or blood vessels [73]. Here again, expanding the theory of competitive speciation to macro-parasite could stimulate research on parasite evolution. In a recent attempt, Thibert-Plante & Hendry [74] have explored adaptive diversification when individuals compete for a bimodal resource distribution. They looked at how competition and mate choice interact with the discreteness of the environment to allow for sympatric speciation. Although the initial phenotypic distribution used mimicked the colonization of a new host with different potential locations and no initial adaptation to any of them (rather than the adaptation to a new location within the host body), this framework could allow questioning how within-host interactions can promote or impede adaptive diversification. This would imply to account for the specificity of macro-parasites, and could lead to an original scenario of competitive speciation as parasites using one of the peaks (or locations) are undoubtedly eliciting an immune response. Such a response to macro-parasites typically involves the TH2 immune response [75] and is likely to be non-specific [76]. It would then impose a negative density-dependent effect on mutants trying to colonize a new location, and therefore increase selection against mutants that are already likely to suffer from rare phenotype mating disadvantage [28,77]. The indirect interactions owing to the non-specific immune response may then impose an additional form of stabilizing selection opposing within-host adaptive diversification.

In conclusion, this study is the first attempt to expand the theory of competitive speciation to macro-parasites and to better understand duplication as an adaptive response to within-host competition for resource. We have enlightened how expanding the existing theory to macro-parasites can enhance the general theory of adaptive speciation and provide new conceptual insights into our nascent understanding of the origin of macro-parasites' diversity [71]. Hopefully, this will help parasitologists to overcome difficulties in looking at the variability of life-history traits and interactions at the intraspecific level, where the selective pressures explaining parasite diversification can be identified. To improve predictions about the adaptive evolution of macro-parasites require developing more specific models corroborated by a fine understanding of their life-history and interactions with the host. Importantly, most theoretical contributions about the ecology, evolution and control of macro-parasites infecting wild animals, livestock or human, were obtained using Anderson & May's model [39]. The theory we developed, and the improvements we discussed, thus provide the natural framework to understand the influence of within-host competitive interaction on life-history evolution and speciation of macro-parasites, as well as to design evolutionary-proof control to reduce their impact on livestock and human populations [78].

This work has been supported by the GDR 'COMEVOL' project 'Dynamics of parasite community' (2008–2009); and by the EU-FP7-PEOPLE-Intra-European Fellowship for career development (IEF) grant no. 253483.

REFERENCES

1 Poulin, R. & Morand, S. 2004 *Parasite biodiversity.* Washington: Smithsonian Books.
2 de Meeûs, T., Michalakis, Y. & Renaud, F. 1998 Santa Rosalia revisited: or why are there so many kinds of parasites in the garden of earthly delights? *Parasitol. Today* **14**, 10–13. (doi:10.1016/S0169-4758(97)01163-0)
3 Renaud, F., Clayton, D. & de Meuûs, T. 1996 Biodiversity and evolution in host-parasite associations. *Biodiv. Conserv.* **5**, 963–974. (doi:10.1007/BF00054414)
4 Ricklefs, R. E., Fallon, S. M. & Bermingham, E. 2004 Evolutionary relationships, cospeciation, and host switching in avian malaria parasites. *Syst. Biol.* **53**, 111–119. (doi:10.1080/10635150490264987)
5 Emelianov, I. 2007 How adaptive is parasite species diversity? *Int. J. Parasitol.* **37**, 851–860. (doi:10.1016/j.ijpara.2007.04.010)
6 Šimková, A., Morand, S., Jobet, E., Gelnar, M. & Verneau, O. 2004 Molecular phylogeny of congeneric monogenean parasites (*Dactylogyrus*): a case of intrahost speciation. *Evolution* **58**, 1001–1018. (doi:10.1554/03-606)
7 Llewellyn, M. S., Rivett-Carnac, J. B., Fitzpatrick, S., Lewis, M. D., Yeo, M., Gaunt, M. W. & Miles, M. A. 2011 Extraordinary *Trypanosoma cruzi* diversity within single mammalian reservoir hosts implies a mechanism of diversifying selection. *Int. J. Parasitol.* **41**, 609–614. (doi:10.1016/j.ijpara.2010.12.004)
8 Pedersen, A. B. & Fenton, A. 2006 Emphasizing the ecology in parasite community ecology. *Trends Ecol. Evol.* **22**, 133–139. (doi:10.1016/j.tree.2006.11.005)
9 Gourbière, S., Dorn, P., Tripet, F. & Dumonteil, E. 2011 Genetics and evolution of triatomines: from phylogeny to vector control. *Heredity* **108**, 190–202. (doi:10.1038/hdy.2011.71)
10 Lo, C. M. & Morand, S. 2000 Spatial distribution and coexistence of monogenean gill parasites inhabiting two damselfishes from Moorea island in French Polynesia. *J. Helminthol.* **74**, 329–336. (doi:10.1017/S0022149X00000482)
11 Su, Z., Segura, M., Morgan, K., Loredo-Osti, J. C. & Stevenson, M. M. 2005 Impairment of protective immunity to blood-stage malaria by concurrent nematode infection. *Infect. Immun.* **73**, 3531–3539. (doi:10.1128/IAI.73.6.3531-3539.2005)
12 Jackson, J. A., Pleass, R. J., Cable, J., Bradley, J. E. & Tinsley, R. C. 2006 Heterogeneous interspecific interactions in a host-parasite system. *Int. J. Parasitol.* **36**, 1341–1349. (doi:10.1016/j.ijpara.2006.07.003)
13 Savolainen, V. *et al.* 2006 Sympatric speciation in palms on an oceanic island. *Nature* **441**, 210–213. (doi:10.1038/nature04566)
14 Giraud, T. & Gourbière, S. 2012 The tempo and modes of evolution of reproductive isolation in fungi. *Heredity.* **Q3**
15 Jancek, S., Gourbière, S., Moreau, H. & Piganeau, G. 2008 Clues about the genetic basis of adaptation emerge from comparing the proteomes of two *Ostreococcus* ecotypes (Chlorophyta, Prasinophyceae). *Mol. Biol. Evol.* **25**, 2293–2300. (doi:10.1093/molbev/msn168)

16 Barluenga, M., Stölting, K. N., Salzburger, W., Muschick, M. & Meyer, A. 2006 Sympatric speciation in Nicaraguan crater lake cichlid fish. *Nature* **439**, 719–723. (doi:10.1038/nature04325)

17 Gourbière, S. & Mallet, J. 2010 Are species real? The shape of the species boundary with exponential failure, reinforcement, and the 'missing snowball'. *Evolution* **64**, 1–42. (doi:10.1111/j.1558-5646.2009.00844.x)

18 Rosenzweig, M. L. 1978 Competitive speciation. *Biol. J. Linn. Soc.* **10**, 275–289. (doi:10.1111/j.1095-8312.1978.tb00016.x)

19 Valero, M. A., De Renzi, M., Panova, M., Garcia-Bodelon, M. A., Periago, M. V., Ordoñez, D. & Mas-Coma, S. 2006 Crowding effect on adult growth, pre-patent period and egg shedding of *Fasciola hepatica*. *Parasitology* **133**, 453–463. (doi:10.1017/S003118200600059X)

20 Agola, L. E., Steinauer, M. L., Mburu, D. N., Mungai, B. N., Mwangi, I. N., Magoma, G. N., Loker, E. S. & Mkoji, G. M. 2009 Genetic diversity and population structure of *Schistosoma mansoni* within human infrapopulations in Mwea, central Kenya assessed by microsatellite markers. *Acta Trop.* **111**, 219–225. (doi:10.1016/j.actatropica.2009.04.012)

21 Poulin, R. 1999 Speciation and diversification of parasite lineages: an analysis of congeneric parasite species in vertebrates. *Evol. Ecol.* **13**, 455–467. (doi:10.1023/A:1006703927711)

22 Bharaj, P., Chahar, H. S., Pandey, A., Diddi, K., Dar, L., Guleria, R., Kabra, S. K. & Broor, S. 2008 Concurrent infections by all four dengue virus serotypes during an outbreak of dengue in 2006 in Delhi, India. *Virol. J.* **5**, 1. (doi:10.1186/1743-422X-5-1)

23 Mideo, N. 2009 Parasite adaptations to within-host competition. *Trends Parasitol.* **25**, 261–268. (doi:10.1016/j.pt.2009.03.001)

24 Gavrilets, S. 2004 *Fitness landscapes and the origin of species* (*Monographs in Population Biology*). Princeton, NJ: Princeton University Press.

25 Weissing, F. J., Edelaar, P. & van Doorn, G. S. 2011 Adaptive speciation theory: a conceptual review. *Behav. Ecol. Sociobiol.* **65**, 461–480. (doi:10.1007/s00265-010-1125-7)

26 Dieckmann, U. & Doebeli, M. 1999 On the origin of species by sympatric speciation. *Nature* **400**, 354–367. (doi:10.1038/22521)

27 Doebeli, M. & Dieckmann, U. 2000 Evolutionary branching and sympatric speciation caused by different types of ecological interactions. *Am. Nat.* **156**, S77–S101. (doi:10.1086/303417)

28 Gourbière, S. 2004 How do natural and sexual selection contribute to sympatric speciation? *J. Evol. Biol.* **17**, 1207–1309. (doi:10.1111/j.1420-9101.2004.00776.x)

29 Schneider, K. A. 2005 Competitive divergence in non-random mating populations. *Theor. Popul. Biol.* **68**, 105–118. (doi:10.1016/j.tpb.2005.05.001)

30 Bolnick, D. I. 2006 Multi-species outcomes in a common model of sympatric speciation. *J. Theor. Biol.* **24**, 734–744. (doi:10.1016/j.jtbi.2006.01.009)

31 Ribeiro, F. & Caticha, N. 2009 Emergence and loss of assortative mating in sympatric speciation. *J. Theor. Biol.* **258**, 465–477. (doi:10.1016/j.jtbi.2008.11.027)

32 Gavrilets, S. 2005 'Adaptive speciation'—it is not that simple: a reply to Doebeli *et al. Evolution* **59**, 696–699. (doi:10.1111/j.0014-3820.2005.tb0129.x)

33 Maynard-Smith, J. 1966 Sympatric speciation. *Am. Nat.* **100**, 637–650. (doi:10.1086/282457)

34 Servedio, M. R., Van Doom, G. S., Kopp, M., Frame, A. M. & Nosil, P. 2011 Magic traits in speciation: 'magic' but not rare? *Trends Ecol. Evol.* **26**, 389–397. (doi:10.1016/j.tree.2011.04.005)

35 Šimková, A., Ondračková, M., Gelnar, M. & Morand, S. 2002 Morphology and coexistence of congeneric ectoparasite species: reinforcement of reproductive isolation? *Biol. J. Linn. Soc.* **76**, 125–135. (doi:10.1111/j.1095-8312.2002.tb01719.x)

36 Kadlec, D., Šimková, A. & Gelnar, M. 2003 The microhabitat distribution of two *Dactylogyrus* species parasitizing the gills of the barbell, *Barbus barbus*. *J. Helminthol.* **77**, 317–325. (doi:10.1079/JOH2003183)

37 Richardson, D. J. & Nickol, B. B. 2000 Experimental investigation of physiological factors that may influence microhabitat specificity exhibited by *Leptorhynchoides thecatus* (Acanthocephala) in green sunfish (*Lepomis cyanellus*). *J. Parasitol.* **86**, 685–690. (doi:10.1645/0022-3395(2000)086[0685:EIOPFT]2.0.CO;2)

38 Anderson, R. M. & May, R. M. 1978 Regulation and stability of host-parasite population interactions. I. Regulatory process. *J. Anim. Ecol.* **47**, 219–247. (doi:10.2307/3933)

39 Anderson, R. M. & May, R. M. 1992 *Infectious diseases of humans: dynamics and control*. Oxford, UK: Oxford University Press.

40 Poulin, R. 1998 *Evolutionary ecology of parasites*. New York, NY: Chapman and Hall.

41 Diekmann, O. & Heesterbeek, J. A. P. 2000 *Mathematical epidemiology of infectious diseases*. New York, NY: Wiley-Blackwell.

42 Metz, J. A. J., Geritz, S. A. H., Meszéna, G., Jacobs, F. J. A. & van Heerwaarden, J. S. 1996 Adaptive dynamics, a geometrical study of the consequences of nearly faithful reproduction. In *Stochastic and spatial structures of dynamical systems* (eds S. J. van Strien & S. M. Verduyn Lunel), pp. 183–231. Amsterdam, The Netherlands: North Holland.

43 Dobson, A. 1985 The population dynamics of competition between parasites. *Parasitology* **92**, 675–682. (doi:10.1017/S0031182000057401)

44 Gaba, S. & Gourbière, S. 2008 To delay once or twice: the effect of hypobiosis and free-living stages on the stability of host-parasite interactions. *J. R. Soc. Interface* **5**, 919–928. (doi:10.1098/rsif.2007.1282)

45 Rohde, K., Hayward, C. & Heap, M. 1995 Aspects of the ecology of metazoan ectoparasites of marine fishes. *Int. J. Parasitol.* **25**, 945–970. (doi:10.1016/0020-7519(95)00015-T)

46 Šimková, A., Verneau, O., Gelnar, M. & Morand, S. 2006 Specificity and specialization of congeneric monogeneans parasitizing cyprinid fish. *Evolution* **60**, 1023–1037. (doi:10.1554/05-521.1)

47 Agapow, P. M. & Isaac, N. J. B. 2002 MacroCAIC: revealing correlates of species richness by comparative analysis. *Div. Distrib.* **8**, 41–43. (doi:10.1046/j.1366-9516.2001.00121.x)

48 Purvis, A. & Rambaut, A. 1995 Comparative analysis by independent contrasts (CAIC): an Apple Macintosh application for analysing comparative data. *Comput. Appl. Biosci.* **11**, 247–251. (doi:10.1093/bioinformatics/11.3.247)

49 Morand, S. & Poulin, R. 2003 Phylogenies, the comparative method and parasite evolutionary ecology. *Adv. Parasitol.* **54**, 281–302. (doi:10.1016/SOO65-308X(03)54006-4)

50 Scott, M. E. 1987 Temporal changes in aggregation: a laboratory study. *Parasitology* **94**, 583–595. (doi:10.1017/S0031182000055918)

51 Morand, S. & Deter, J. 2009 Parasitism and regulation of the host population. In *Ecology and evolution of parasitism* (eds F. Thomas, J.-F. Guégan & F. Renaud), pp. 83–106. Oxford, UK: Oxford University Press.

52 Apps, C. D., McLellan, B. N. & Woods, J. G. 2006 Landscape partitioning and spatial inferences of

competition between black and grizzly bears. *Ecography* **29**, 561–572. (doi:10.1111/j.0906-7590.2006.04564.x)

53 Qvarnström, A., Wiley, C., Svedin, N. & Vallin, N. 2009 Life history divergence facilitates regional coexistence of competing *Ficedula* flycatchers. *Ecology* **90**, 1948–1957. (doi:10.1890/08-0494.1)

54 Snyder, R. E. & Chesson, P. 2004 How the spatial scales of dispersal, competition, and environmental heterogeneity interact to affect coexistence. *Am. Nat.* **164**, 633–650. (doi:10.1086/424969)

55 Gourbière, S. & Gourbière, F. 2002 Competition between unit-restricted fungi: a metapopulation model. *J. Theor. Biol.* **217**, 351–368. (doi:10.1006/jtbi.2002.3033)

56 Bottomley, C., Isham, V. & Basáñez, M. G. 2007 Population biology of multispecies helminth infection: competition and coexistence. *J. Theor. Biol.* **244**, 81–95. (doi:10.1016/j.tbi.2006.07.002)

57 Morand, S., Poulin, R., Rohde, K. & Hayward, C. 1999 Aggregation and species coexistence of ectoparasites of marine fishes. *Int. J. Parasitol.* **29**, 663–672. (doi:10.1016/S0020-7519(99)00029-6)

58 Šimková, A., Desdevises, Y., Gelnar, M. & Morand, S. 2000 Co-existence of nine gill ectoparasites (*Dactylogyrus*: Monogenea) parasitising the roach (*Rutilus rutilus* L.): history and present ecology. *Int. J. Parasitol.* **30**, 1077–1088. (doi:10.1016/S0020-7519(00)00098-9)

59 Rascalou, G., Pontier, D., Menu, F. & Gourbière, S. 2012 Emergence and prevalence of human vector-borne diseases in sink vector populations. *PLoS ONE* **7**, e36858. (doi:10.1371/journal.pone.0036858)

60 Roberts, T. M. & Thorson, R. E. 1977 Pairing between adults of *Nippostrongylus brasiliensis* and other species of nematodes *in vitro*. *J. Parasitol.* **63**, 764–766. (doi:10.2307/3279595)

61 Boag, P. R., Newton, S. E. & Gasser, R. B. 2001 Molecular aspects of sexual development and reproduction in nematodes and schistosomes. *Adv. Parasitol.* **50**, 153–198. (doi:10.1016/S0065-308X(01)50031-7)

62 Bone, L. W. & Shorey, H. H. 1978 Nematode sex pheromones. *J. Chem. Ecol.* **4**, 595–612. (doi:10.1007/BF00988923)

63 Green, C. D. & Plumb, S. C. 1970 The interrelationships of some *Heterodera* spp. indicated by the specificity of the male attractants emitted by their females. *Nematologica* **16**, 39–46. (doi:10.1163/187529270X00441)

64 Huettel, R. N., Dickson, D. W. & Kaplan, D. T. 1982 Sex attractants and behavior in the two races of *Radopholus similis*. *Nematologica* **28**, 360–369. (doi:10.1163/187529282X00411)

65 Frans, I., Michiels, C. W., Bossier, P., Willems, K. A., Lievens, B. & Rediers, H. 2011 Vibrio anguillarum as a fish pathogen: virulence factors, diagnosis and prevention. *J. Fish. Dis.* **34**, 643–661. (doi:10.1111/j.1365-2761.2011.01279.x)

66 MacNeil, A. *et al.* 2010 Proportion of deaths and clinical features in Bundibugyo virus infection, Uganda. *Emerg. Infect. Dis.* **16**, 1969–1972. (doi:10.3201/eid1612.100627)

67 Kim, J. H., Kang, K. I., Kang, W. C., Sohn, H. J., Jean, Y. H., Park, B. K., Kim, Y. & Kim, D. Y. 2009 Porcine abortion outbreak associated with *Toxoplasma gondii* in Jeju Island, Korea. *J. Vet. Sci.* **10**, 147–151. (doi:10.4142/jvs.2009.10.2.147)

68 Knudsen, R., Amundsen, P. A. & Klementsen, A. 2002 Parasite-induced host mortality: indirect evidence from a long-term study. *Environ. Biol. Fishes* **64**, 257–265. (doi:10.1023/A:1016058304762)

69 Karp, C. L., Auwaerter, P. G. & Mayer, K. H. 2007 Coinfection with HIV and tropical infectious diseases. II. Helminthic, fungal, bacterial, and viral pathogens. *Clin. Infect. Dis.* **45**, 1214–1220. (doi:10.1086/522180)

70 Kennedy, C. R. & Bush, A. O. 1992 Species richness in helminth communities: the importance of multiple congeners. *Parasitology* **104**, 189–197. (doi:10.1017/S0031182000060935)

71 Poulin, R. 2002 The evolution of monogenean diversity. *Int. J. Parasitol.* **32**, 245–254. (doi:10.1016/S0020-7519(01)00329-0)

72 Garba, A. *et al.* 2010 Schistosomiasis in infants and preschool-aged children: infection in a single *Schistosoma haematobium* and a mixed *S. haematobium-S. mansoni* foci of Niger. *Acta Tropica* **115**, 212–219. (doi:10.1016/j.actatropica.2010.03.005)

73 Seidenfaden, R., Fischer, A., Bonow, I., Ekale, D., Tanya, V. & Renz, A. 2001 Combined benefits of annual mass treatment with ivermectin and cattle zooprophylaxis on the severity of human onchocerciasis in northern Cameroon. *Trop. Med. Int. Health* **6**, 715–725. (doi:10.1046/j.1365-3156.2001.00771.x)

74 Thibert-Plante, X. & Hendry, A. P. 2011 Factors influencing progress toward sympatric speciation. *J. Evol. Biol.* **24**, 2186–2196. (doi:10.1111/j.1420-9101.2011.02348.x)

75 Allen, J. E. & Maizels, R. M. 2011 Diversity and dialogue in immunity to helminths. *Nature* **11**, 375–388. (doi:10.1038/nri2992)

76 Koyasu, S. & Moro, K. 2011 Type 2 innate immune responses and the natural helper cell. *Immunology* **132**, 475–481. (doi:10.1111/j.1365-2567.2011.03413.x)

77 Gourbière, S. & Mallet, J. 2005 Has adaptive dynamics contributed to the understanding of adaptive and sympatric speciation? *J. Evol. Biol.* **18**, 1201–1204. (doi:10.1111/j.1420-9101.2004.00865.x)

78 Read, A. F., Lynch, P. A. & Thomas, M. B. 2009 How to make evolution-proof insecticides for malaria control. *PLoS Biol.* **7**, e1000058. (doi:10.1371/journal.pbio.1000058)

79 Brooker, S. 2010 Estimating the global distribution and disease burden of intestinal nematode infections: adding up the numbers—a review. *Int. J. Parasitol.* **40**, 1137–1144. (doi:10.1016/j.ijpara.2010.04.004)

Within-host competition and diversification of macro-parasites - supplement

Rascalou Guilhem[1], Andrea Šimková[2], Serge Morand[3] and Sébastien Gourbière[1,4*]

[1] Université de Perpignan Via Domitia, UMR 5244 CNRS-UPVD 'Ecologie et Evolution des Interactions', Perpignan 66100, France.

[2] Department of Botany and Zoology, Faculty of Science, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic.

[3] Institut des Sciences de l'Evolution - CNRS, Département Génétique Environnement, CC065, Université Montpellier 2, 34095, Montpellier cedex 05, France.

[4] University of Sussex, School of Life Sciences, Centre for the Study of Evolution, Brighton BN1 9QG, United Kingdom.

* corresponding author: Sébastien Gourbière [1,2]

[1] Univ. Perpignan Via Domitia, Ecologie et Evolution des Interactions, UMR 5244, F-66860 , Perpignan, France.

[2] CNRS, Ecologie et Evolution des Interactions, UMR 5244, F-66860 , Perpignan, France.

Tel: 33 (0)4 68 66 21 83. Fax: 33 (0)4 68 50 36 86. Email: gourbiere@univ-perp.fr

The differences between our four fitness functions are encapsulated in function $F_d(r)$ provided in table 1 (main document). In this supplementary material, we first summarize simple mathematical results about these $F_d(r)$ functions (section 1), which are needed to produce the evolutionary analysis. We then proceed to the evolutionary analysis (section 2) through the usual derivations of the adaptive dynamics background [1].

1. Sign of functions $F_d(r)$

$F_2(r) = F_4(r) = cK(r) > 0$ since both c and $K(r)$ must be positive; and clearly, $F_1(r) = \frac{P(r)^*}{H} > 0$. To show that $F_3(r) > 0$, it is convenient to define $A = H\left(\frac{k}{k+1}\right)$ so that $P(r)^* = A\left(cK(r) - 1\right)$ and $F_3(r) = \frac{(A-1)cK(r) - A}{H-1}$. According to the expected order of magnitude for k and H, then A must be much larger than 1. In the same time, $cK(r)$ is also likely to be much larger than 1. These two conditions ensure that $F_3(r) > 0$.

We can then conclude that $F_d(r) > 0$ ($\forall$ d $\in$ [1;4]).

2. Evolutionary analysis

The evolutionary analysis allowed by the adaptive dynamics background relies on the first and second derivatives of the fitness function with respect to the mutant phenotype, and on its second derivative with respect to the residents phenotype. These three derivatives allow identifying evolutionary singularities (the so-called 'evolutionary fixed points') and their evolutionary properties [2,3]. We first performed these derivations on the general form of the fitness function (equation 10 in the main text), which does not specify the function $F_d(r)$. Accordingly, the derivatives we obtained are themselves functions of the derivatives of $F_d(r)$. We then evaluated the derivatives of the four different fitness functions by specifying the function $F_d(r)$.

The three derivatives of the general form of the fitness function (as required evaluated at a singular strategy s*) are:

$$\left.\frac{\partial f_d(m,r)}{\partial m}\right|_{m=r=s^*} = -\frac{F_d(s^*)}{K(s^*)}\left(\frac{(s^*-s_0)}{\sigma_K^2}\right),$$

$$\left.\frac{\partial^2 f_d(m,r)}{\partial^2 m}\right|_{m=r=s^*} = \frac{F_d(s^*)}{K(s^*)}\left(\frac{1}{\sigma_\alpha^2}-\frac{1}{\sigma_K^2}\right),$$

and $$\left.\frac{\partial^2 f_d(m,r)}{\partial^2 r}\right|_{m=r=s^*} = \frac{1}{K(s^*)}\left(\frac{F_d(s^*)}{\sigma_\alpha^2}-\left.\frac{\partial^2 F_d(r)}{\partial r^2}\right|_{m=r=s^*}\right),$$

Singular strategy. The singular strategy is obtained when the first derivative with respect to the mutant phenotype equals to 0. Since $F_d(s^*) \neq 0$ ($\forall$ d $\in$ [1;4]) as shown in section 1, the only solution and the unique singular strategy is the same for all the four fitness functions: $s^*=s_0$.

Evolutionary stability. The singular strategy is an evolutionary stable strategy if the second derivative with respect to the mutant strategy is negative. Since $F_d(s^*) \neq 0$ ($\forall$ d $\in$ [1;4]), the condition for s* to be an evolutionary stable strategy is the same for all the four fitness functions : $\sigma_\alpha^2 > \sigma_K^2$.

Convergence stability. The singular strategy is a convergent stable strategy if the second derivative with respect to the residents is larger than the second derivative with respect to the mutant phenotype. It is straightforward to show that such a condition is equivalent to:

$$\frac{F_d(s^*)}{\sigma_K^2} - \left.\frac{\partial^2 F_d(r)}{\partial^2 r}\right|_{m=r=s^*} > 0$$

For the second and fourth fitness functions, this inequality is equivalent to

$$2\frac{cK(s^*)}{\sigma_K^2} > 0$$

which is always satisfied since $cK(s^*) > 1$ for P^* to be positive (see equation 9 in the main text).

For the first fitness function this inequality can be written as:

79 $$\frac{1}{\sigma_K^2}\left(F_1(s^*)+\frac{k}{k+1}cK(s^*)\right)>0$$

80 which holds since $F_1(s^*)>0$ and $cK(s^*)>1$.

81 To evaluate the above inequality while using the third fitness function, it is useful to re-write
82 $F_3(r)$ as a function of A (defined in section 1):

83 $$F_3(r)=\frac{(A-1)cK(r)-A}{H-1}$$

84 Tedious but straightforward calculation then leads to:

85 $$\left.\frac{\partial^2 F_3(r)}{\partial^2 r}\right|_{m=r=s^*}=\frac{cK(s^*)}{\sigma_K^2}\frac{1-A}{H-1}$$

86 It then comes that s* is a convergent stable strategy if:

87 $$\frac{F_3(s^*)}{\sigma_K^2}-\frac{cK(s^*)}{\sigma_K^2}\frac{1-A}{H-1}>0$$

88 which holds since $F_3(s^*)>0$ and $A>>1$.

89 Accordingly, for all the four fitness functions, s* is always a convergent stable strategy.

90

91 *Invasion potential.* A singular strategy is an invasive strategy if the second derivative with
92 respect to the resident is positive. This is equivalent to:

93 $$\frac{F_d(s^*)}{\sigma_\alpha^2}-\left.\frac{\partial^2 F_d(r)}{\partial^2 r}\right|_{m=r=s^*}>0$$

94 Interestingly, the second derivatives (with respect to the residents strategy) are negative for
95 the four fitness functions:

96 $$\left.\frac{\partial^2 F_2(r)}{\partial^2 r}\right|_{m=r=s^*}=\left.\frac{\partial^2 F_4(r)}{\partial^2 r}\right|_{m=r=s^*}=-\frac{1}{\sigma_K^2}cK(s^*)<0,$$

97 $$\left.\frac{\partial^2 F_1(r)}{\partial^2 r}\right|_{m=r=s^*}=-\frac{cK(s^*)}{\sigma_K^2}\frac{k}{k+1}<0,$$

98 and $\left.\frac{\partial^2 F_3(r)}{\delta^2 r}\right|_{m=r=s^*}=\frac{cK(s^*)}{\sigma_K^2}\frac{1-A}{H-1}<0$ (since $A>>1$).

99 As $F_d(s^*)>0$ ($\forall$ d $\in$ [1;4])., we can conclude that s* is obviously always invasive.

100

101

102

Protected polymorphism. A protected polymorphism can arise around the singular strategy, when the second derivative with respect to the residents phenotype is larger than the opposite of the second derivative with respect to the mutant. This condition is equivalent to

$$\frac{2F_d(s^*)}{\sigma_\alpha^2} - \left.\frac{\partial^2 F_d(r)}{\partial^2 r}\right|_{m=r=s^*} - \frac{F_d(s^*)}{\sigma_K^2} > 0$$

For the second and fourth fitness functions, this condition is equivalent to:

$$\frac{2F_d(s^*)}{\sigma_\alpha^2} > 0 .$$

This condition always holds since $F_2(s^*) = F_4(s^*) > 0$.

For the first fitness function, it can be shown, using the two equalities $\left.\frac{\partial^2 F_1(r)}{\partial^2 r}\right|_{m=r=s^*} = -\frac{cK(s^*)}{\sigma_K^2}\frac{k}{k+1}$ and $F_1(s^*) = \frac{k}{k+1}(cK(s^*)-1)$, that the above condition becomes:

$$\frac{2F_1(s^*)}{\sigma_\alpha^2} + \frac{1}{\sigma_K^2}\left(\frac{k}{k+1}\right) > 0$$

This condition always holds since $F_1(s^*) > 0$.

For the third fitness function, it is convenient to re-write the above condition as a function of $A = H\left(\frac{k}{k+1}\right)$, which gives:

$$\frac{2}{\sigma_\alpha^2}\left(\frac{(A-1)cK(s^*) - A}{H-1}\right) - \frac{1}{\sigma_K^2}\left(\frac{cK(s^*)(1-A) - (A-1)cK(s^*) + A}{H-1}\right) > 0$$

Considering $A >> 1$, this is roughly equivalent to:

$$\frac{2A}{\sigma_\alpha^2}(cK(s^*)-1) + \frac{A}{\sigma_K^2}(2cK(s^*)-1) > 0$$

This condition holds since $cK(s^*)$ is expected to be much larger than 1.

Thus, for all the four fitness functions , a protected polymorphism can emerge around the singular strategy.

References

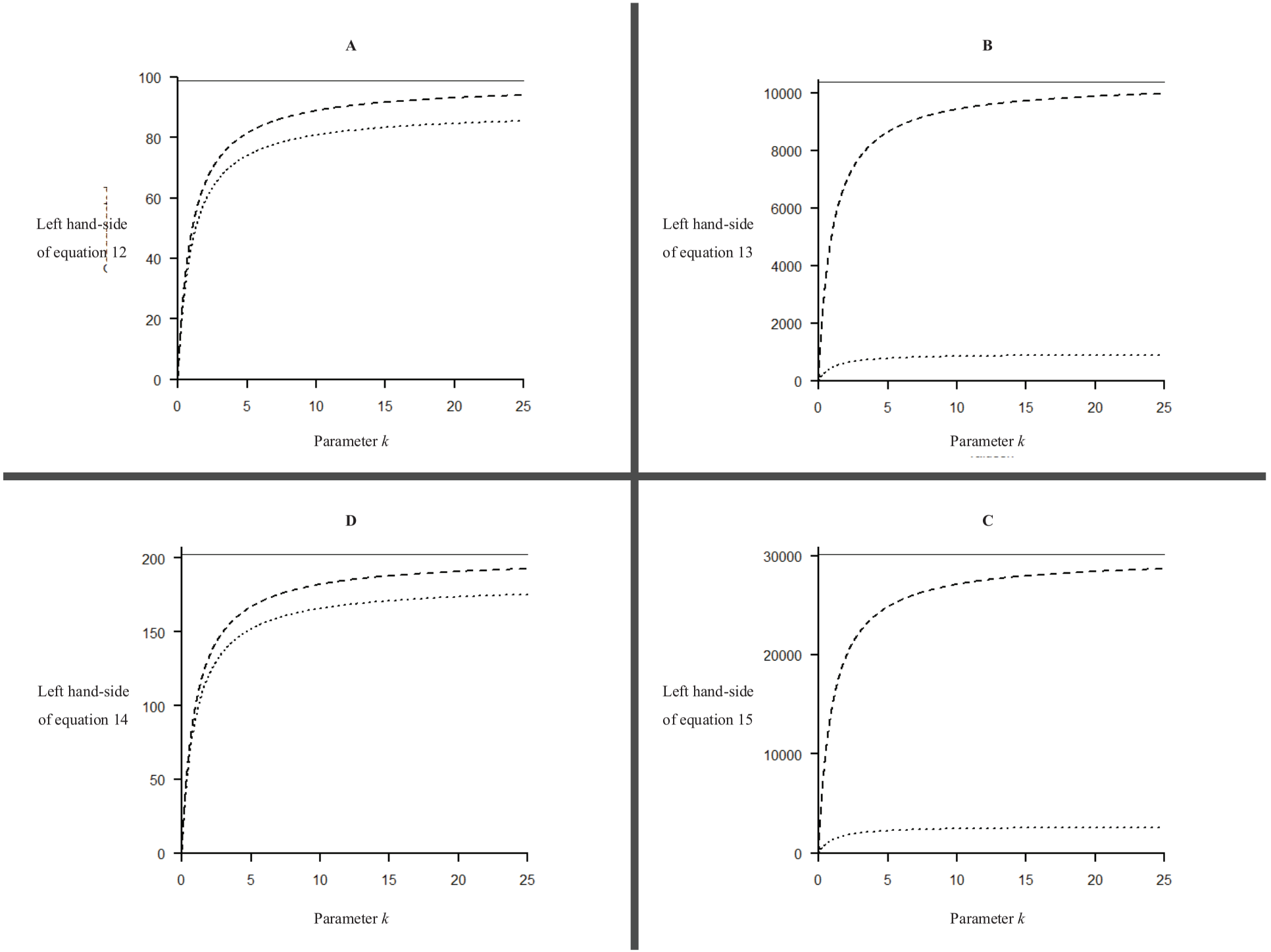
1. Metz, J. A. J., Geritz, S. A. H., Meszéna, G., Jacobs, F. J. A., van Heerwaarden, J. S. 1996 Adaptive dynamics, a geometrical study of the consequences of nearly faithful reproduction. In *Stochastic and spatial structures of dynamical systems* (eds S. J. van Strien & S. M. Verduyn Lunel), pp. 183-231. North Holland, Amsterdam, The Netherlands.

2. Geritz, S. A. H., Metz, J. A. J., Kisdi, E., Meszéna, G. 1997 The dynamics of adaptation and evolutionary branching. *Phys. Rev. Lett.* **78**, 2024-2027. (DOI 10.1103/PhysRevLett.78.2024)

3. Geritz, S. A. H., Kisdi, E., Meszena, G., Metz, J. A. J. 1998 Evolutionary singular strategies and the adaptive growth and branching of the evolutionary tree. *Evol. Ecol.*, **12**, 35-57. (DOI 10.1023/A:1006554906681)

Figures captions

Figure ESM 1. Evolutionary properties of the singularity $s^*=s_0$ with respect to the distribution of the mutants, and to the level of aggregation of the resident parasites. Panels A to D corresponds to the four evolutionary properties of s*, as evaluated in the adaptive dynamics approach; evolutionary stability, convergence stability, invasion potential and mutual invadability. The panels show the value of the quantities to be calculated to evaluate each of these properties (i.e. the left hand side of equations 12, 13, 14 and 15, respectively) with respect to the distribution of the mutant (d=1,2,3 as defined in the main text) and the level of aggregation of the resident (k). In each panel, the variations in function of k are displayed as a solid line for d=2, a dashed line for d=1, a and dotted line for d=3. The value of those quantities vary with respect to d and k (except for d=2, as expected from the analytical results), but they always remain positive illustrating that s* is a CSS, IP, PP, but not an ESS, and confirming that such a conclusion is independent of the distribution of the mutants and the level of aggregation of the residents. The values of parameters are H=10,000; c=1; σ_α=0.1; σ_K=0.9; K_{opt}=100 (=10 for d=3).


A
Left hand-side of equation 12
100
80
60
40
20
0
0
5
10
15
20
25
Parameter k
B
Left hand-side of equation 13
10000
8000
6000
4000
2000
0
0
5
10
15
20
25
Parameter k
D
Left hand-side of equation 14
200
150
100
50
0
0
5
10
15
20
25
Parameter k
C
Left hand-side of equation 15
30000
20000
10000
0
0
5
10
15
20
25
Parameter k

Chapitre 4

Diversification compétitive des macro-parasites : virulence, distribution et taux évolutifs

4.1 Introduction

Le modèle utilisé dans le chapitre 3 prend en compte deux caractéristiques essentielles des systèmes hôte-macro-parasites : le fractionnement de la population parasite et son agrégation au sein de la population hôte. Par contre, la théorie développée dans ce chapitre ne tient pas compte des conséquences éventuelles de la virulence des parasites. Comme discutée alors, ceci rend compte du fait que les macro-parasites ont souvent un faible pouvoir pathogène sur les individus hôtes qu'ils infectent (Thomas, *2002*; Brooker, *2010*). Néanmoins cette virulence, bien que faible pour de nombreuses espèces, existe et peut, pour certaines espèces, affecter significativement la survie ou la reproduction de leurs hôtes. C'est le cas notamment de certaines espèces d'helminthes affectant la santé de l'homme, telles que les schistosomes, ou d'animaux à forte valeur économique, comme certains parasites de poissons (Knudsen et al., *2002*)

De nombreux travaux traitent de l'interaction entre la virulence et la compétition intra-hôte chez les micro-parasites (Alizon & van Baalen, *2008*). Dans le contexte de la spéciation compétitive des macro-parasites, la virulence pourrait influencer les interactions entre parasites et entre hôtes et parasites, et par voie de conséquence les pressions de sélection disruptive et les conditions de spéciation. En effet si les hôtes viennent à mourir du fait de la virulence de leurs parasites, la disparition des hôtes les plus infectés doit se traduire par la disparition des portions de la population de parasites (les « infra-populations ») au sein desquelles les interactions compétitives sont les plus fortes. Ceci doit donc se traduire par une réduction de la pression de sélection disruptive, et donc limiter les phénomènes de diversification. Autrement dit la virulence doit, a priori, constituer un frein à la spéciation compétitive.

L'objectif du chapitre 4 est donc d'élargir le cadre théorique proposé dans le chapitre 3 pour étudier l'influence du mode vie des macro-parasites sur leurs conditions de spéciation en considérant un trait d'histoire de vie parasite supplémentaire, à savoir la virulence, et son interaction avec l'agrégation des parasites et la compétition intra-hôte. Le premier pas dans cette direction consiste à identifier la fonction de fitness d'invasion de parasites mutants, et d'en analyser les variations en fonction de l'agrégation et de la virulence.

Contrairement à ce qui avait été montré pour des parasites non-virulents, l'expression générale de la fitness du mutant est qualitativement différente de celle dérivée pour les espèces non-parasites. En outre l'effet de la virulence sur la fitness dépend du mode de co-distribution des mutants et des résidents. Comme précisé ci-dessus, la mort d'individus hôtes due a la virulence des parasites entraîne la disparition des infra-populations correspondante, et une réduction de la taille de la population des parasites résidents. Dans le cas où le mutant tend à infecter les mêmes individus hôtes que les résidents, le mutant ne bénéficie pas de la réduction de la taille de la population de résidents puisqu'il est également pénalisé par la mort des hôtes fortement infectés. Par contre, lorsque mutant et résidents sont distribués de manière

indépendante ou que le mutant tend à coloniser des hôtes non-infectés, cette réduction du nombre de résidents, et donc de compétiteurs, bénéficie à l'invasion du mutant car celui-ci tend à coloniser des individus hôtes globalement moins infectés. Dans le premier cas la virulence a donc toujours un effet négatif sur la fitness du mutant. Mais dans les deux autres cas, bien que la virulence contribue à réduire la fitness du mutant car celui-ci risque directement d'induire la mort de son hôte, cette effet peut être compensé par la réduction du contexte compétitif et avoir, de façon inattendue, un effet bénéfique pour l'invasion du mutant. Ces résultats constituent un premier pas indispensable pour comprendre l'influence de la virulence sur la compétition intra-hôte entre macro-parasites, mais ne fournissent pas directement les conditions de spéciation compétitive. Pour obtenir ces dernières, j'ai donc procédé à l'analyse évolutive de ces fonctions de fitness par les méthodes standards de dynamique adaptative.

Les conditions de spéciation compétitive prédites suite à l'analyse évolutive sont identiques à celles des parasites non-virulents, et donc des espèces non-parasites. Ces résultats permettent donc de conclure qu'aucun des 3 traits d'histoire de vie considérés – agrégation, fractionnement de la population et virulence – ne différencie les conditions de spéciation compétitive des espèces macro-parasites et des non-parasites.

Dans l'optique d'une théorie expliquant comment le mode de vie des espèces parasites pourrait influencer leur taux de spéciation adaptative et leur diversité, l'objectif du chapitre 4 est aussi de mieux quantifier l'influence des traits d'histoire de vie des macro-parasites sur leurs probabilités de spéciation compétitive. Pour cela je me suis d'abord intéressé à l'influence de ces traits d'histoire de vie sur le paysage adaptatif des mutants au travers de « Pairwise-Invasibility Plot » (PIP), comme souvent utilisé pour les espèces non-parasites. Ces PIP permettent de représenter graphiquement l'influence des paramètres sur la probabilité de remplir les différents critères nécessaires au branchement évolutif d'après les méthodes de dynamique adaptative. Puis j'ai dérivé l'expression générale de l'équation canonique décrivant la vitesse d'évolution du phénotype résident lorsque cette évolution est générée par une sélection stabilisante. Cette équation permet ainsi de quantifier l'effet des traits d'histoire de vie parasites sur le temps nécessaire à la population parasite pour accomplir la première étape vers un branchement évolutif : l'évolution vers la stratégie singulière prédite par les résultats de dynamique adaptative. Cette équation a ainsi permis d'apporter des premiers résultats quantitatifs sur l'effet du mode de vie des parasites sur le temps nécessaire pour accomplir cette première étape vers le branchement évolutif.

L'analyse des PIP produit des résultats conformes avec les prédictions de l'analyse évolutive selon lesquelles les conditions de spéciation compétitive chez les espèces macro-parasites sont les mêmes que pour les espèces non-parasites. Néanmoins, les résultats numériques issus de l'utilisation de l'équation canonique montrent que les traits d'histoire de vie des macro-parasites peuvent influencer leur taux d'évolution vers la stratégie singulière. Surtout, ces résultats montrent que, selon le niveau de virulence par exemple, les espèces macro-parasites peuvent évoluer à des taux supérieurs mais aussi inférieurs à ceux obtenus pour les espèces non-parasites. Sans anticiper sur les taux avec lesquels les macro-parasites accomplissent l'ensemble des étapes nécessaires à l'apparition d'un branchement évolutif, ces résultats représentent une première quantification de la capacité du mode de vie des espèces parasites à leur conférer des taux de spéciation compétitive différents des espèces non-parasites.

4.2 Competitive diversification of macro-parasites: virulence, distribution and evolutionary rates (article en préparation)

Competitive diversification of macro-parasites: virulence, distribution and evolutionary rates

Rascalou Guilhem[1] and Sébastien Gourbière[1,2*]

[1] Université de Perpignan Via Domitia, UMR 5244 CNRS-UPVD 'Ecologie et Evolution des Interactions', Perpignan 66100, France.

[2] University of Sussex, School of Life Sciences, Centre for the Study of Evolution, Brighton BN1 9QG, United Kingdom.

* corresponding author: Sébastien Gourbière [1,2]
[1] Univ. Perpignan Via Domitia, Ecologie et Evolution des Interactions, UMR 5244, F-66860 , Perpignan, France.
[2] CNRS, Ecologie et Evolution des Interactions, UMR 5244, F-66860 , Perpignan, France.
Tel: 33 (0)4 68 66 21 83. Fax: 33 (0)4 68 50 36 86. Email: gourbiere@univ-perp.fr

Introduction

The theory of adaptive speciation has been broadly expanded over the last two decades [Dieckmann et al., *2004*; Weissing et al. *2011*]. These theoretical studies describe how frequency and density dependent ecological interactions can lead to adaptive diversification, and they have strongly contributed to challenge the common view that sympatric speciation is of little importance to explain the observed level of species diversity [Dieckmann et al., *2004*]. The theory of adaptive speciation has stimulated a lot of empirical research which today provide us with a better understanding of the evolution of a wide range of organisms, such as plants [Savolainen et al., *2006* ; Gavrilets & Vose, *2007*], fungi [Giraud et al., *2010* ; Giraud & Gourbière, *2011*], algae [Jancek et al., *2008*], fishes [Barluenga et al., *2006* ; Gavrilets et al., *2007*]. However, this theory has paid virtually no attention to the diversification of parasites, even though they represent an important proportion of living species [Poulin & Morand, 2004], and despite that the origin of their high diversity is recurrently questioned [Price, *1980*, de Meeûs et al. *1998*]. Such a gap in the theoretical literature on adaptive speciation is surprising since parasites are thought to have a great potential for sympatric speciation [de Meeûs et al., *1998*; Giraud, *2006*], and because the ecological interactions with their host as well as between them influence their population dynamics [Pedersen & Fenton, *2006*], their micro-evolution [Mideo *2009*], and the level of diversity in their communities [Lo & Morand, *2000*].

One particular form of adaptive speciation is 'competitive speciation', in which diversification results from competitive interaction between con-specific individuals [Dieckmann et al., *2004*, pages 8-9]. The potential for intraspecific competition to allow for sympatric diversification of non-parasite species has been investigated for more than 10 years both theoretically [Dieckmann & Doebeli., *1999*; Weissing et al. *2011*] and empirically [Dieckmann et al., *2004*], and such interactions are central to the evolution and the diversity of several groups of sympatric parasite species [Gourbière & Mallet, *2010*]. A fundamental and still unaddressed question is thus; what is the influence of the parasite lifestyle on the conditions and rates of competitive speciation ? In the absence of a firm theory quantifying the effect of the specificities of parasite life histories such as fragmentation of the population between host individuals, overdispersed distribution of individuals among the host population (aggregation), or parasite virulence [Combes *2001*; Poulin *2006*], there is little hope to answer this question.

In a first attempt to investigate the influence of parasitic lifestyle on competitive speciation, we adapted the existing theory to account for these key aspects of macro-parasites life-history [Rascalou et al., *2012*]. We focused on the 'pleiotropic scenario' whereby a magic trait subject to divergent natural selection also contributes to non-random mating [Dieckmann & Doebeli, *1999*]. The proposed theory deals with a quantitative character that determines the competitive ability of individuals and which pleiotropically serves as a clue for mating choice. Such a trait typically includes the body mass [Steinauer *2009*], or the size of anchors in monogeans colonizing fish gills [Šimková et al., *2002*]. We modelled parasite aggregation among hosts, parasite reproduction and within-host intraspecific competition as well as larvae dispersal between hosts according to the standard theoretical literature on the ecology of macro-parasite [Anderson & May, *1992*]. Using the same 'adaptive dynamic' approach as previously used to study diversification of non-parasite species [Dieckmann & Doebeli, *1999*; Doebeli & Dieckmann, *2000*], we demonstrated that, although the fitness of individuals depends on the specific features of the macro-parasites lifestyle, the conditions for competitive diversification are the same as for non-parasite species.

The model used in [Rascalou et al., *2012*] did not consider any virulence of macro-parasites, which is consistent with a common view that many macro-parasite species, do not significantly affect the survival of their host [e.g., Thomas 2002, Brooker 2010]. However, for many other species, there are clear evidences that macro-parasites are virulent to their hosts. These include human helminths such as schistosome flatworms responsible for anemia [Friedman et al., *2005*], as well as many parasites affecting livestocks or wild fauna such as cattle [Over et al., *1992*] and fishes [Knudsen et al., *2002*]. Hypothetically, parasite virulence and aggregation among host, a key feature of macro-parasite lifestyle [Combes *2001*; Poulin *2006*] could interact to weaken the disruptive selection generated by within-host competitive interactions between parasites [Rascalou et al., *2012*]. Because the macro-parasites are typically highly aggregated among hosts [Shaw et al., *1998*], virulence induces the death of the most highly infected host individuals and their parasites [Dobson & Hudson, *1992*]. In the context of adaptive diversification associated to competitive interactions, this also means that wherever competition and disruptive selection manifest themselves at the strongest levels, their selective effects on parasite evolution will be partially counterbalanced by the effects of virulence.

We built on the emerging theory of competitive speciation of macro-parasite species [Rascalou et al., *2012*] to account for parasite virulence and to investigate how much the interplay between aggregation and virulence affects the level of post-zygotic isolation induced by frequency- and density- dependent selection due to within-host competition, and ultimately the condition for competitive speciation? We further expand the previous theory to investigate not only the condition of competitive speciation, but also the time required for parasite adaptive diversification. There is little consideration to the time required for diversification in the literature on adaptive speciation (but see [Gavrilets, *2004*]). Theoretical predictions focus on the condition for ecological interaction to produce disruptive selection, and implicitly assume that such conditions would stay constant over a sufficient time for speciation. While such an assumption has been criticized, and while theory offers the possibility to make qualitative predictions on the effect of competition on temporal rates of diversification, it has never been attempted so far. We give a first quantification of the effect of the features of macro-parasites life-history on their probability of competitive diversification, by using a canonical equation describing the temporal dynamics of the average phenotypic composition of a population of macro-parasites under stabilizing selection [Dieckmann et al., *2004*]. Eventually, through the use of this same canonical equation, we also compare the evolutionary rates predicted for macro-parasite species with those predicted for non-parasite species.

Materials and Method

Model for a polymorphic population of macro-parasites

We expanded the model of Rascalou et al. (2012) by accounting for the virulence of macro-parasites. In this previous model, we considered a polymorphic population of macro-parasites whereby individuals differ with respect to a quantitative trait determining the part of a gradient of resource they are able to exploit, and, accordingly, the level of competitive interaction between individuals with different quantitative trait value [Dieckmann & Doebeli, *1999*]. Individuals where distributed among hosts according to a negative binomial law, and they were competing within each host according to a Lotka-Voltera function. Reproduction occurred within-host followed by larvae dispersal between hosts, both described according to typical in the field [Anderson & May, *1992*]. All these assumptions were highly consistent with the theory on ecological character displacement and competitive speciation on one side, and with the theory of macro-parasite ecology on the other, which we brought together for the first time.

We introduce here an additional host mortality induced by the parasite, assuming that virulence V is the same for all parasites, so that such a mortality is proportional to the total number of parasites present inside a host individual. Those assumptions lead to an infinite system of ordinary differential equations describing the rate of variation of the number $H_{n_r,n_m}(t)$ of hosts harbouring n_r and n_m parasites with phenotype r and m, respectively, keeping n_m as a constant:

$$\begin{aligned}\left.\frac{dH_{n_r,n_m}}{dt}\right|_{n_m} = & -\ (r)\,(n_r)H_{n_r,n_m}(t) - (n_r+1)H_{n_r+1,n_m}(t) \\ & +\ (r)\,H_{n_r-1,n_m}(t) - H_{n_r,n_m}(t) - V\,n_r + n_m\,H_{n_r,n_m} \\ & -\ (r,r)\left(\frac{n_r^2}{K(r)}H_{n_r,n_m}(t) - \frac{n_r+1^{\,2}}{K(r)}H_{n_r+1,n_{mi}}(t)\right) \\ & -\ (r,m)\left(\frac{n_r n_m}{K(r)}H_{n_r,n_m}(t) - \frac{n_r+1\,n_m}{K(r)}H_{n_r+1,n_m}(t)\right)\end{aligned} \qquad \text{Eq. 1.}$$

where , , V, , and K are typical parameters of models for host-macro-parasites systems [Diekmann & Heesterbeek, *2000*], as described in table 1.

Describing similarly the variations of $H_{n_r,n_m}(t)$ with n_r as a constant, and summing over n_r and n_m, one derives a couple of ordinary differential equations describing the change in the number of individuals of two competing phenotypes r and m:

$$\frac{dP(r)}{dt} = \sum_{n_r,n_m} \frac{dH_{n_r,n_m}}{dt}\bigg|_{n_m} = - \ (r)P(r) + \ (r)H - V \sum_{n_r,n_m} n_r + n_m \ H_{n_r,n_m}(t)$$

$$- \ (r,r) \sum_{n_r,n_r} \frac{n_r^2}{K(r)} H_{n_r,n_m}(t) - \ (r,m) \sum_{n_r,n_m} \frac{n_r n_m}{K(r)} H_{n_r,n_m}(t) \qquad \text{Eq. 2a.}$$

$$\frac{dP(m)}{dt} = \sum_{n_m,n_r} \frac{dH_{n_m,n_r}}{dt}\bigg|_{n_r} = - \ (m)P(m) + \ (m)H - V \sum_{n_r,n_m} n_r + n_m \ H_{n_r,n_m}(t)$$

$$- \ (m,m) \sum_{n_m,n_m} \frac{n_m^2}{K(m)} H_{n_r,n_m}(t) - \ (r,m) \sum_{n_r,n_m} \frac{n_r n_m}{K(m)} H_{n_r,n_m}(t) \qquad \text{Eq. 2b.}$$

The invasion fitness function of macro-parasites

General expression. The general expression of the invasion fitness $f(m,r)$ of a mutant with trait value *m* in a population of residents of trait value *r* was derived from equations 2a and 2b, assuming that the residents are at their population dynamics equilibrium (see Appendix I):

$$f_d(m,r) = c - \left(V + \frac{(m,r)}{K(m)} \right) Z_d(r) \qquad \text{Eq 3}$$

with $Z_d(r) = S_d(m,r)/P(m)$.

Quantity c is the intrinsic fitness of every parasite in absence of interaction with other parasites and their host, which accounts for the standard survival and reproduction of adults within the host as well as dispersal of the larvae stage between hosts as follows;

$$c = - \ + \frac{H}{H+v},$$

where , v and stand for the rates of production of larvae by adults, death of larvae, and of host infection, respectively.

$S_d(m,r)$ is the average number (or average 'effective density') of resident individuals with phenotype r, the mutants of phenotype m are expected to interact with either directly through competition or indirectly through its effect on the host. Accordingly, $Z_d(r)$ stands for the average number of residents per mutant individual. Those two quantities are functions of parameters appearing in Eq. 2a and b, whose precise forms depend on the assumption about the relative distribution of mutants and residents among hosts.

Distribution of mutant and resident. Three assumptions (d=1, 2, 3) can be made to describe a broad range of potential situations in a simple way. One can assume that mutant infect hosts at random (d=1), or that they parasitize the same hosts than residents, which we refer to as 'co-distribution' (d=2), or that they tend to distribute in the hosts which are not yet been infected by other (residents) parasites, which we refer to as 'inverse distribution' (d=3). Those are typical assumptions on the spatial co-distribution of interacting species, which have been extensively used to investigate the condition for coexistence of competitive non-parasitic species [Anazawa *2012*] or host-parasitoid interactions [Rohani & Ruxton, *1999*]. Under each

of these three assumptions, the probability for a mutant parasite to colonize a host already infected with n_r residents can be described mathematically as $\frac{1}{H}$ for d=1, $\frac{n_r}{P(r)^*}$ for d=2, and $\frac{1-\frac{n_r}{P(r)^*}}{H-1}$ for d=3 [Rascalou et *al.*, *2012*].

Direct and indirect interactions between mutant and resident. Combining these probabilities with the partition of residents among hosts, which we assumed to follow a negative binomial distribution, one can calculate the average effective density of residents a mutant individual is expected to interact with, $S_d(m,r)$. The mathematical expression of $S_d(m,r)$ that we derived for d=1, 2 and 3, and under the standard assumption of a negative binomial distribution, are given in table 2. The formulae of $Z_d(r)$ then follow from basic algebra, whereby the total number of resident parasites is replaced by its expression at population dynamics equilibrium. Such equilibrium value can be found by solving Eq. 2a = 0, and is equal to

$$P(r)^* = H\frac{k}{k+1}\left(\frac{c(r)K(r)}{1+VK(r)}-1\right)$$

where k is the usual measure of parasite 'aggregation' among hosts (see Gaba and Gourbiere *2008*, for a meta-review of field values). The expressions of $Z_d(r)$ are given in table 2, and they allow completing the definition of the fitness functions given in Eq. 3. In order to ensure that the size of the residents population *P(r)** is always positive, one can define a maximal value of virulence $V^{\max} = c - \frac{1}{K(r)}$.

An immediate result is that, while the form of the invasion fitness of a non-virulent mutant was mathematically similar to the fitness function derived for non-parasitic individuals [Rascalou et al., *2012*], to account for virulence leads to a qualitatively different result. Although the first two terms appearing in Eq. 3 are similar to the invasion fitness of non-parasites and non-virulent parasites, virulence now adds a negative contribution on fitness as the parasite induced death of hosts can prevent invasion of the mutant. However, virulence has an antagonistic effect, which is to reduce parasite abundance itself. This will reduce $Z_d(r)$ and lead to less competitive and host-mediated interactions for the mutant. We shall investigate the net result of these two effects, and its interaction with the aggregation of parasites.

Evolutionary analysis.

The three fitness functions defined according to the assumptions described above depend on the life-history of the parasites (c, k), their effect on hosts (V) and competitive interaction with other parasites ( ), as well as the size of the host population H and the maximal number of parasites (i.e., the carrying capacity) an individual host can sustain (K). Despite their relative simplicity, it remains hard to anticipate the individual and synergetic effects of these different components on the evolutionary dynamics of the quantitative trait. We thus first looked in a systematic way at the influence of the distribution of individuals among hosts (parameter k and assumptions d=1,2,3), virulence V) and within-host competition (parameter) on the invasion fitness function of macro-parasites.

We then looked at the possible evolutionary dynamics resulting from this fitness functions using the standard background of Adaptive Dynamics [Geritz et al., *1997, 1998*]. This method is well tailored for the objective of this paper as it allows identifying the conditions where selection switches from directional to disruptive at a so-called 'branching point' characterized by a given value of the quantitative trait under study, referred to as an 'evolutionary singularity' [Geritz et al., *1997, 1998*]. Around such branching point, a monomorphic population can adaptively evolve to a polymorphic one, and this typically leads to the evolution of two or more phenotypic clusters. Under the pleiotropic scenario, those phenotypic clusters can readily be interpreted as incipient species since the quantitative trait determines simultaneously both pre- and post-zygotic isolation [Dieckmann & Doebeli, *1999*]. Conditions for the existence of such branching point are then equivalent to conditions for within-host duplication [Rascalou et al., *2012*]. Evolutionary singularities and conditions for them to be a branching point are routinely determined according to simple rules on the first and second derivatives of the fitness function of the mutant with respect to variables m and r [Geritz et al., *1997, 1998*]. Specifically, an evolutionary singularity is the value of the trait (s*) where the gradient of selection vanishes:

$$\left.\frac{f_d(m,r)}{m}\right|_{m=r=s^*} = 0$$

Such an evolutionary singularity is a branching point, if i) this singularity is not an evolutionary stable strategy, ii) directional selection leads the trait to evolve towards such a value, but iii) once the singular strategy has invade the population it can be invaded by individual with alternative strategies, among which iiii) couples of alternative strategies are able to invade each other [Geritz et al., *1997, 1998*]. The latter condition ensures that some (protected) polymorphism can emerge around the singular strategy, leading to the coexistence of two or more phenotypic clusters. Condition i) requires

$$\left.\frac{^2 f_d(m,r)}{^2 m}\right|_{m=r=s^*} \quad 0$$

While conditions ii) iii) and iiii) requires, respectively;

$$\left.\frac{^2 f_d(m,r)}{^2 r}\right|_{m=r=s^*} - \left.\frac{^2 f_d(m,r)}{^2 m}\right|_{m=r=s^*} \quad 0,$$

$$\left.\frac{^2 f_d(m,r)}{^2 r}\right|_{m=r=s^*} \quad 0,$$

and

$$\left.\frac{^2 f_i(m,r)}{^2 r}\right|_{m=r=s^*} + \left.\frac{^2 f_i(m,r)}{^2 m}\right|_{m=r=s^*} \quad 0$$

These rules were applied to the three fitness functions (d=1,2,3) to look for the effect of parasite life-history and parasites direct and indirect interactions on the condition for within-host adaptive speciation of macro-parasites.

Rate of adaptive evolution

According to the canonical equation of adaptive dynamics [Dieckmann et al., *2004*], the temporal dynamics of the average phenotype of a population ($F(m)$) under stabilizing selection depends on the product of two terms: the evolutionary rate coefficient, and the selection derivative. The first one describes the rate of evolution of the population towards the evolutionary singularity, and depends on the rate of mutation of the phenotype ($_m$), the standard deviation of mutations ($_m$), as well as the size of the population of residents at dynamical equilibrium ($P(r)^*$). The second term describes the direction of the evolution, which will be towards the evolutionary singularity if the derivative of the mutant fitness with respect to the mutant phenotype is positive ($\frac{f(m,r)}{m}>0$), or away from the singularity if this derivative is negative ($\frac{f(m,r)}{m}<0$). The general expression of the canonical equation thus reads;

$$\frac{F(m)}{t} = \frac{1}{2} \; _m \; ^2_m P(r)^* \frac{f(m,r)}{m}$$

and using the expression of the mutant fitness (equ. 3) one can obtain an expression of the canonical equation for the adaptive dynamics of macro-parasites, which depends on the co-distribution of mutant and residents among hosts (d):

$$\frac{F_d(m)}{t} = \frac{1}{2} \; _m \; ^2_m P(r)^* . - Z_d(r) \; \frac{(m,r)}{K(m)} \left(\frac{m - opt}{^2_K} - \frac{m - r}{^2} \right)$$

Equ. 4

In order to quantify the effect of macro-parasites life history on their rate of adaptive evolution, we run stochastic simulations of the evolution of the average phenotype of macro-parasites for different degrees of aggregation and virulence. This enabled us to quantify the influence of these parameters on the time required for the parasite population to reach the evolutionary singularity, and thus, to complete the first necessary step before evolutionary branching can result from divergent selection.

RESULTS

The invasion fitness of macro-parasites

How does the distribution of mutants and residents hosts affect the invasion fitness?

The variation of the fitness functions with respect to the level of aggregation of the residents in hosts (*k*) are directly linked to the variation of the number of residents that mutant individuals have to interact with while attempting to establish in the population ($Z_d(r)$). Clearly those variations also depend on the hypothesis on the co-distribution of mutant and resident individuals. Let's first consider the situation of 'co-distribution' (d=2), where mutant and resident individuals colonize the same hosts. Interestingly, under such assumption, both the number of residents, and the invasion fitness of the mutant are independent of the level of

aggregation (Figure 1B). As a matter of fact, when mutant and residents are co-aggregated (d=2), a stronger aggregation among the host population means that the mutant is more likely to colonise hosts that harbour higher amounts of residents, and thus, to suffer stronger competition. Nevertheless, a stronger aggregation also means that these highly infected hosts are less numerous. Under the simple assumption that the probability for a mutant to colonise a host with n_r resident is equal to $\frac{n_r}{P(r)^*}$, these two opposite effects cancel out. Our model can then be seen as a neutral model, which will allow investigating the effect of any departure from the above assumption on the fitness of the mutant.

Under the other two hypotheses on resident and mutant co-distributions, we indeed obtain different patterns. When mutant and residents are not co-aggregated (d=1,3), then a stronger aggregation among the host population does not imply that the mutant is more likely to colonise highly infected hosts. Besides, this still means that these highly infected hosts are less numerous, which results into a mutant fitness benefitting from a stronger aggregation (figure 1B). .In both case, as k increases, the distribution of the residents tends towards a random distribution among hosts, and the level aggregation ultimately has virtually no effect on the mutant fitness (figure 1B).

Figure 1 also shows that the segregation of mutant and residents lowers the level of interaction ($Z_2(r) > Z_1(r) > Z_3(r)$, panel A) and in consequence favours the invasion of a mutant ($f_2(m,r) \quad f_1(m,r) \quad f_3(m,r)$, panel B), and it can be shown mathematically that these two inequalities always hold. More importantly, as for non-virulent parasites [Rascalou et al., *2012*], the virulent mutant fitness is independent of the level of aggregation within the host population when mutant and residents are co-aggregated (d=2, table 2), while it benefits from stronger aggregation when this co-distribution is random (d=1) or inverse (d=3) (table 2).

How does virulence (V) affects the invasion fitness of macro-parasites?

An immediate result is that, while the form of the invasion fitness of a non-virulent mutant was mathematically similar to the fitness function derived for non-parasitic individuals [Rascalou et al., *2012*], to account for virulence leads to a qualitatively different result. Although the first two terms appearing in equation 3 are similar to the invasion fitness of non-parasites and non-virulent parasites, virulence has a negative impact on the number of residents $Z_d(r)$ a mutant individual interacts with. There is indeed an antagonistic effect to virulence, which is to reduce parasite abundance itself. This is well reflected by the negative relationship between $Z_d(r)$ and V, and this should lead to less competitive and host-mediated interactions, and thus, increased mutant fitness.

But there is another additional component explicitly related to V. This term can effectively be interpreted as the effect of the host-mediated interaction that typically appears between virulent parasites [Dobson *1985*]. In this case, it describes the lost of mutants, and the subsequent reduction in mutant invasion fitness, which is associated to the death of hosts induced by co-infecting residents. It should nonetheless not be concluded that virulence has a systematically linear and detrimental effect on mutant fitness.

It is straightforward to show that the function $Z_d(r)$ is negatively correlated with virulence

(V). Therefore, we can predict from the general expression of $f_d(m,r)$ (equation 3) that the effect of virulence on the invasive fitness of a mutant is bothly negative (by increasing the sum of virulence and competition) and positive (by reducing the term $Z_d(r)$). The coexistence of this two antagonist effects becomes more obvious and intuitive once the general expression of $f_d(m,r)$ has been reformulated:

$$f_d(m,r) = c - VZ_d(r) - \frac{(m,r)}{K(m)} Z_d(r) \qquad \text{Equ. 5}$$

The negative effect of virulence on the mutant invasive fitness (second term in equation 5) is due to the fact that if parasites virulence increases, then residents becomes more likely to kill their hosts, and thus, to kill the host where a mutant parasite emerges. On the other side, the increased mortality of hosts will also cause an increased mortality of resident parasites, and thus, a reduction of the size of the residents population at dynamical equilibrium (see equation S4 in Appendix I). This would benefit to the mutant invasive fitness, because this mutant would have to interact with fewer competitors (reduction of $Z_d(r)$ in the 3rd term of equation 5), and fewer residents would be likely to kill the host where this mutant emerges (reduction of $Z_d(r)$ in the 2nd term of equation 5).

Before addressing the global qualitative effect of virulence on the invasive fitness of a mutant parasite, it should be kept in mind that we are considering here a virulent mutant parasite emerging within a population of resident parasites who are characterized with exactly the same level/intensity of virulence. Indeed, the value of virulence in this model is phenotype-independent (see section 'Model for a polymorphic population of virulent macro-parasites' and table 1), and our conclusions on the effect of virulence do not apply to the numerous models used to study the evolution of parasite virulence [Dieckmann et al., *2002*].

It can be shown that when mutant and residents are co-aggregated (d=2), then the mutant fitness is negatively correlated with virulence (figure 2B and Appendix I). On the other side, when this co-distribution is random (d=1) or inverse (d=3), then virulence can have a positive effect on the mutant fitness (figure 2A and 2C). This correlation is positive for any value of parameter V within the range]0, $V^{\max}$ [, or only when virulence is beyond a threshold value V_d^{thr} which depends on the parasites growth rate (c), the residents carrying capacity ($K(r)$), the mutant carrying capacity ($K(m)$), and the intensity of competition between one mutant and one resident individual ((m,r)) for d=1 and 3; as well as on the size of the hosts population (H) and the level of aggregation of parasites among this population (k) for d=3 (Appendix I).

As the effect of both competition [Rascalou et al., *2012*] and aggregation on the mutant invasive fitness also differ according to the relative distribution of mutant and residents, these results reinforce the idea that the influence of macro-parasites life-history traits on the mutant invasive fitness is closely linked to the of mutant and residents co-distribution.

Evolutionary dynamics and adaptive duplication of macro-parasites

Conditions for adaptive diversification. Details of the mathematical derivation of the results on conditions to be verified (see 'Evolutionary analysis' in Materials and method) for adaptive diversification to occur are given in an Appendix II.

Evolutionary singularities can be identified by solving:

$$\left.\frac{f_d(m,r)}{m}\right|_{m=r=s^*} = -\frac{Z_d(s^*)}{K(s^*)}\left(\frac{s^*-s_0}{\frac{2}{K}}\right) = 0$$

Since $Z_d(s^*)$ 0 (d [1;3]), the only solution and the unique singular strategy is the same for all the three fitness functions: $s^*=s_0$.

This evolutionary singularity is evolutionary stable (ESS) if:

$$\left.\frac{^2 f_d(m,r)}{^2 m}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{K(s^*)}\left(\frac{1}{^2} - \frac{1}{\frac{2}{K}}\right) < 0$$

Since $Z_d(s^*)$ 0 (d [1;3]) (see Appendix I), the condition for s* to be an evolutionary stable strategy is the same for all the three fitness functions : ^{2} $\frac{2}{K}$.

The evolutionary singularity is a convergent stable (CSS) strategy if:

$$\left.\frac{^2 f_d(m,r)}{^2 r}\right|_{m=r=s^*} - \left.\frac{^2 f_d(m,r)}{^2 m}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{\frac{2}{K}} - VK(s^*)+1\left.\frac{^2 Z_d(r)}{^2 r}\right|_{m=r=s^*} \quad 0,$$

an invasive strategy (IP) if:

$$\left.\frac{^2 f_d(m,r)}{^2 r}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{^2} - VK(s^*)+1\left.\frac{^2 Z_d(r)}{^2 r}\right|_{m=r=s^*} \quad 0,$$

and a protected polymorphism (PP) could appear in the vicinity of the singular strategy if:

$$\left.\frac{^2 f_i(m,r)}{^2 r}\right|_{m=r=s^*} + \left.\frac{^2 f_i(m,r)}{^2 m}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{\frac{2}{K}} - VK(s^*)+1\left.\frac{^2 Z_d(r)}{^2 r}\right|_{m=r=s^*} \quad 0.$$

Evaluating these inequalities according to the different function $Z_d(r)$ and their second derivative with respect to r, it appears that these three conditions are always verified for each of the three fitness functions (see Appendix II). As for non-virulent parasites [Rascalou et al., *2012*], the expression of these conditions when the mutant distribution is independently (d=1) or inversely (d=3) correlated with the resident distribution depends on the aggregation level. However, for all the three fitness functions for virulent parasites, these conditions also depend on another parasite life-history trait; the virulence of the parasite. This means that, unlike for

non-virulent parasites [Rascalou et al., *2012*], such conditions differ from non-parasite species even if the mutant distribution is positively correlated with the resident distribution d=2).

Pairwise-invasibility plots(PIP). Pairwise-invasibility plots (PIP) are frequently used to study and illustrate variations of the conditions of adaptive speciation [Dieckmann et al., *2004*]. For each assumption on the mutant and resident co-distributions (d=1 to 3), we used those plots to confirm or not the conditions of adaptive diversification as predicted by our analytical results (see previous point).

When mutant and residents are positively co-distributed (d=2), patterns displayed by PIP (figure 3) are consistent with our analytical results, as well as with PIP typically obtained for non-parasite species [Dieckmann et al., *2004*]. The mutant fitness is positive above the axis *w2* ($f_{d=2}(m,r)\big|_{m=r}$) for values of the mutant phenotype which are less than the evolutionary singularity, and below this same axis for values greater than this singularity. This confirms that the evolutionary singularity is convergent stable (CSS) and this property is verified when $_K$ $_C$ (figure 3A) but also when $_K$ $_C$ (figure 3B). This singularity is also an invasive strategy (IP) when $_K$ $_C$ and $_K$ $_C$, since it represents a minimum of the mutant fitness along the axis *w3* ($f_{d=2}(m,r)\big|_{m=s*}$). Similarly, a protected polymorphism (PP) can appear around this singularity in both cases, since the mutant fitness is always positive along the axis *w3* ($f_{d=2}(m,r)\big|_{m=-r}$). As predicted by analytical results, the only property of the singular strategy that changes with the ratio $_K/\ _C$ is the evolutionary stability (ESS). When $_K$ $_C$, the singular strategy represents a maximum along the axis *w1* ($f_{d=2}(m,r)\big|_{r=s*}$) and is thus evolutionary stable, while it becomes a minimum along this axis when $_K$ $_C$, which means that the evolutionary strategy is then not evolutionary stable and confirms the prerequisite for adaptive diversification to occur as predicted by analytical results.

When mutant and resident are segregated (d=1,3), the mutant fitness is always positive (figure 4A) or almost always positive for particular values of parameters (figure 4B) (see figure S1 in Appendix III for d=3). This means that properties CSS (axis w2) and PP are always verified, but such PIP do not allow to study the effect of ratio $_K/\ _C$ on properties ESS and IP. However, by plotting the variations of $f_{d=1}(m,r)\big|_{m=s*}$ (axis *w3*, figure 5A), we can verify that the singular strategy is a minimum along the axis *w3*, and thus, an invasive strategy (IP). Similarly, by plotting the variations of (axis *w1*), we can verify that the singular strategy is a maximum – and thus evolutionary stable - along the axis *w1* when $_K$ $_C$ (figure 5B), and a minimum – and thus not an evolutionary stable strategy – when $_K$ $_C$ (figure 5C). Similar results are obtained for d=3 (see figure S2 in Appendix III).

On the basis of these PIP and the complementary plots, analytical results are confirmed and we can conclude that, as for non-parasite species, adaptive speciation in macro-parasites requires $_K$ $_C$, whatever the assumption on mutant and residents distributions (d).

Evolutionary rate. According to the general expression of the canonical equation (equation 4), both aggregation and virulence can have antagonistic effects on the variations of $\frac{F_d(m)}{t}$ when mutant and residents are segregated (d=1,3). On one side, for any hypothesis of mutant end resident co-distribution, increased aggregation or virulence will reduce the size of the

residents population at equilibrium *P(r)**, and thus, the rate of evolution towards the singular strategy. But on the other side, increased aggregation or virulence will also reduce the mutant invasive fitness if mutant and residents are positively co-distributed (d=2), while it can promote the mutant invasion if it does not infect the same hosts as residents (d=1,3) (see section 'The invasion fitness of macro-parasites' for further explanation). Numerical results on the average time required to reach the singular strategy s* for different values of parameter *k* and *V* allow quantifying the net effect of these parameters on the evolutionary rate towards s* (table 4).

When aggregation is increased (from *k*=0.1 to *k*=20), the average time to reach s* decreases for each d. When mutant and residents are positively co-distributed (d=2), the longer average time (from 1.3 to 16.6) is clearly due to reduction of *P(r)*,* as the mutant fitness $f_2(m,r)$ is independent of parameter *k*. When mutant and residents are segregated (d=1,3), this longer average time (from 2.5 to 8.4 for d=1, from d=7 to 12.1 fro d=3) is also due to reduction of *P(r)**, which means that such reduction has a stronger negative effect on the evolutionary rate than the positive effect due to better mutant invasive fitness. More interestingly, we can notice that the average time when parasites are strongly aggregated (*k*=0.1) is shorter for d=1 (8.4) and d=3 (12.1) than for d=2 (16.6). Despite the fact that such differences are not statistically significant (see table 4 for p-values), this is consistent with the prediction that aggregation increases the invasion fitness of the mutant when it does not infect the same hosts as residents (d=1,3), and thus, confers a shorter time to reach the evolutionary singularity.

Similar trends are observed when considering the effect of virulence (*V*). Whatever the hypothesis on resident and mutant co-distribution (d), increased virulence (from 0 to 0.1) leads to longer average time to reach the singular strategy s*. Once again, this is consistent with the predictions on the effect of virulence. For d=2, virulence reduces both *P(r)** and the mutant fitness $f_2(m,r)$, and thus has negative effect on the evolutionary rate towards s*. When mutant and residents are segregated (d=1,3), the negative effect of virulence through reduction of *P(r)** seems to be stronger than the positive effect through increased mutant fitness, and the global effect of virulence on the evolutionary rate is eventually negative. However, as for aggregation (*k*), the average time to reach s* is always shorter for d=1,3 than for d=2 (and this difference is statistically significant for *V*=0.05 and *V*=0.1, table 4). Despite the globally negative effect of virulence on the evolutionary rate, this difference confirms the prediction that, in comparison with the case when mutant and residents are positively co-distributed (d=2), virulence generate larger evolutionary rate when mutant and residents are segregated (d=1,3).

Stochastic simulations also enabled comparison of evolutionary rates between macro-parasite and non-parasite species. This required the use of a similar canonical equation for non-parasites species, that is, free of parasitic features, and which reads

$$\frac{F(m)}{t} = \frac{1}{2} \; {}_{m} \; {}^{2}{}_{m} N(r)^* \frac{f(m,r)}{m},$$

where the size of the resident non-parasite population at equilibrium is $N(r)^* = K(r)$, and where the derivative of the mutant fitness with respect to the mutant phenotype $\frac{f(m,r)}{m}$ takes the same form as for non-virulent macro-parasites in the case when mutant and residents are positively segregated (d=2, [Rascalou et al., *2012*]):

$$. - cK(r)\ \frac{(m,r)}{K(m)}\left(\frac{m-opt}{\frac{2}{K}}-\frac{m-r}{2}\right).$$

As the only difference here between non-parasite and macro-parasite species relies on the significance of the carrying capacity *K(r)* [Rascalou et al., *2012*], we calculated the average time to reach the evolutionary singularity s* in non-parasite species for different values of $K(s_0)$, that is, the size of the residents population at the optimal strategy s_0 (table 5) Four increasing values were chosen: the size of $N(s_0)^*$ would be equal to the size of a residents population of macro-parasites at equilibrium i) within one single host individual, $(= K(s_0))$; ii) within a whole host population with aggregation (k=0.1) but no virulence (V=0) ,$(= P(s_0)^*|_{V=0})$; iii) within a whole host population with aggregation and virulence (V=0.01), $(= P(s_0)^*|_{V=0.01})$; iiii) and within a whole host population but with homogeneous distribution and no virulence, $(= H.K(s_0)|_{V=0})$.

As expected, variations of the carrying capacity has strong effect on the average time to reach the evolutionary singularity, as it ranges from 2857 for the smallest value of $K(s_0)$ - when it is equal the parasites equivalent within one single host individual, to 0.5 when for the largest value - when $K(s_0) = H.K(s_0)|_{V=0}$.

When comparing the average time between non-parasites and non-virulent macro-parasites aggregated among their hosts (third line in table 5), macro-parasites appear to reach the evolutionary singularity s* within a shorter time (4.7, 5.8 and 4.4 for d=1,2,3 respectively) than non-parasites (7.6). However, this difference is statistically significant. On the other side, when comparing the average time between non-parasites and virulent macro-parasites aggregated among their hosts (fourth line in table 5), macro-parasites appear to reach the evolutionary singularity s* within a longer time (8.4, 16.6 and 12.1 for d=1,2,3 respectively) than non-parasites (4.5). And this difference is statistically significant for the case when mutant and residents are positively segregated (d=2).

Non virulent macro-parasite species can thus reach the evolutionary singularity within shorter time than non-parasite species, but virulence can slowdown such evolution to the extend where it takes actually more time longer than for non-parasite species.

Discussion

We expanded the theory proposed in Rascalou et al. (*2012*) to account for the virulence of macroparasites to contribute further to set up the first theoretical framework for the study of adaptive speciaton in macro-parasites. This background is rooted in the standard modelling of the ecology of macro-parasites [Anderson & May, *1992*] and in the theoretical literature of ecological character displacement and competitive speciation [Geritz et al., *1997*, *1998*; Dieckmann et al., *2004*]. It describes typical life history traits of macro-parasites, such as the fragmentation and aggregation of the parasite population among hosts, and virulence of the parasite, to allow investigating their influence and interaction during competitive diversification of macro-parasites. Within this framework, we produced neutral predictions under the null assumption that mutant and residents tend to infect the same host individuals, and we considered two schematic departures from this standard situation; one where mutants colonize hosts randomly and one where mutant tend to avoid hosts already infected by residents.

The conditions for competitive diversification of macro-parasite species were found to be similar to those obtained for non-virulent parasites under the null assumption on parasite distributions (d=2) as well as under the two alternative distributions (d=1,3). This suggests that the deleterious effects of the parasites on their hosts do not have an impact on the rate of parasite adaptation to the exploitation of a resource gradient. This confirms that key differences in the life-history of macro-parasites and non-parasite species, such as the level of aggregation [Rascalou et al., *2012*] and, here, the level of virulence, are somewhat irrelevant to the condition for competitive diversification. Our analytical predictions, made by the adaptive dynamics machinery, have been confirmed by the use of pairwise invisibility plot and ongoing simulations of competitive speciation in macro-parasites using (even more robust) individual-based models are also supporting our analytical conclusions.

Although the assumption about the co-distributions of mutant and residents has no effect on the condition for the existence of a branching point, it can be anticipated that it will have some importance for further development of the theory of competitive diversification in macro-parasites species, especially if one is to include sexual reproduction more explicitly. Indeed, according to the theory developed for non-parasites species, competitive speciation then also involves the evolution of assortative mating [Dieckman & Doebeli, *1999*]. In the case of macro-parasites species, if mutants tend to infect hosts which are less infected, then they would have to face a limited availability of sexual partners. Such 'rare phenotypes disadvantage' has been predicted to have great impact on the population genetics of nematode species [Galvani & Gupta, *1998*], and it is of primary importance during adaptive diversification along a resource gradient [Gourbiere *2004*; Gourbiere & Mallet, *2005*]. In other words, while basic features of macro-parasites are predicted not to have an effect on the condition for a branching point to exist, and a genetic polymorphism to emerge around such point of diversification, they are still likely to influence the polymorphic evolution once such genetic polymorphism has been established. The condition of speciation through non-pleiotropic scenario, which involves the co-evolution of sexual traits, would thus be likely to lead to qualitatively different conclusions. This remains to be explored, and would probably require more specific modelling as sexual clue and recognition mechanism differ between parasite taxa [Boag et al., *2001*]

A second important result of this contribution was gain from the use of the canonical

equation of the adaptive dynamics. This equation is usually confined to highly mathematical papers, and not used by adaptive dynamics practitioners, despite it can potentially gives important information about the time required to reach a branching point, whereby the population diversify. Such pieces of information clearly are valuable additions to the knowledge typically gained about the conditions required for such a point to exist. We derived the canonical equation for macro-parasites species, and used it to look at the influence of macro-parasites life history traits on their rate of evolution towards a branching point. We then showed that, although they do not have effect on the condition for adaptive diversification, both aggregation and virulence had an effect on the time required to reach a branching point. Aggregation was shown to increase the time to reach branching point because it lowered the evolutionary rate by reducing the size of the residents population at dynamical equilibrium. Virulence had also a negative impact on the rate of adaptive evolution since it not only reduced the size of the residents population, but also, in the case of the neutral model, reduced the mutant invasive fitness. Interestingly, combination of strong aggregation and low virulence could result in higher rates of evolution in parasites than in non-parasite species, while evolution could be faster under opposite condition. Although such an approach needs to be expanded over a wider range of biological conditions with larger number of simulation for each combination of parameters to allow for more powerful statistical tests, there are clear tendencies. Besides, PIP obtained for non-neutral model (d=1,3) show that the evolutionary singularity is a convergent strategy, but also that mutation towards a phenotype that is further away from this singularity can also invade. This suggests that the conclusion on the rate of competitive diversification can also depend on the distribution of mutation effects. A very natural and promising follow up to this study would thus be to compare the distribution of the effects of mutations between parasite and non-parasite species, and to look for their consequence on the rate of competitive diversification. Finally, the canonical equation enables to investigate the time required to complete the first stage of adaptive diversification; reaching an evolutionary branching point. However, as pointed out in the previous paragraph, a complete picture also require a quantification of the influence of macro-parasites features on their rate of divergence between incipient species, which is likely to involve the evolution of sexual trait.

These developments would contribute to take the development of a theory of adaptive evolution of parasites a step further by looking at the co-evolution between ecological trait, such as the quantitative trait considered in this study, and sexual mating traits, whose phenotypic and genetic evolution makes the core of the theoretical and empirical studies of speciation.

References

Anazawa M. 2012 Interspecific Competition Models Derived from Competition Among Individuals. *Bull Math Biol*. [Epub ahead of print]

Anderson, RM. & May, RM. 1992. *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Barluenga, M., Stölting, K. N., Salzburger, W., Muschick, M., Meyer, A. 2006 Sympatric speciation in Nicaraguan crater lake cichlid fish. *Nature* 439, 719-723.

Boag, P. R., Newton, S. E., Gasser, R. B. 2001 Molecular aspects of sexual development and reproduction in nematodes and schistosomes. *Adv. Parasitol.* 50, 153-198.

Brooker S 2010 Estimating the global distribution and disease burden of intestinal nematode infections: adding up the numbers – a review. *Int J Parasitol* 40:1137-1144.

Combes C. 2001 *Parasitism: the ecology and evolution of intimate interactions.* University Of Chicago Press.

Coyne, J. A. & Orr, H. A. 2004 *Speciation.* Sinauer Associates, Sunderland, MA.

Dieckmann, U. & Doebeli, M. 1999 On the origin of species by sympatric speciation. *Nature* 400, 354-367.

Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K. 2002 *Adaptive dynamics of infectious diseases: in pursuit of virulence management.* Cambridge University Press.

Dieckmann U, Doebeli M, Metz JAJ, Tautz D. 2004 *Adaptive speciation*. Cambridge University Press.

Diekmann, O. & Heesterbeek, JAP. 2000 *Mathematical epidemiology of infectious diseases*. Wiley-Blackwell.

Dobson, AP. 1985 The population dynamics of competition between parasites. *Parasitology* 92, 675-682.

Dobson, A.P. & Hudson, P.J. 1992. Regulation and stability of a free-living host-parasite system, Tricho-strongylus tenuis in red grouse. II. Population models. *J Anim Ecol.* 61, 487-500.

Doebeli, M. & Dieckmann, U. 2000 Evolutionary branching and sympatric speciation caused by different types of ecological interactions. *Am. Nat.* 156, S77-S101.

Friedman, JF, Kanzaria, HK, McGarvey, ST. 2005. Human schistosomiasis and anemia: the relationship and potential mechanisms. *Trends Parasitol.* 21(8):386-92.

Gaba S, Gourbière S. 2008 To delay once or twice: the effect of hypobiosis and free-living stages on the stability of host-parasite interactions. *J R Soc Interface*. 5(25):919-28.

Galvani A & Gupta S 1998 The effects of mating probability on the population genetics of nematodes. *J Helminthol* 72, 295-300.

Gavrilets, S. 2004 *Fitness landscapes and the origin of species (Monographs in Population Biology)*. Princeton University Press.

Gavrilets, S. & Vose, A. 2007 Case studies and mathematical models of ecological speciation. 2. Palms on an oceanic island. *Mol. Ecol.* 16, 2910-2921.

Gavrilets, S., Vose, A., Barluenga, M., Salzburger, W., Meyer, A. 2007 Case studies and mathematical models of ecological speciation. 1. Cichlids in a crater lake. *Mol. Ecol.* 16, 2893-2909.

Geritz, S. A. H., Metz, J. A. J., Kisdi, E., Meszéna, G. 1997 The dynamics of adaptation and evolutionary branching. *Phys. Rev. Lett.* 78, 2024-2027.

Geritz, S. A. H., Kisdi, E., Meszéna, G., Metz, J. A. J. 1998 Evolutionary singular

893 strategies and the adaptive growth and branching of the evolutionary tree. *Evol. Ecol.* 12, 35-57.

Giraud T 2006 Speciation in parasites: host switching does not automatically lead to allopatry. *Trends Parasitol* 22:151-152.

Giraud, T., Gladieux, P., Gavrilets, S. 2010 Linking the emergence of fungal plant diseases with ecological speciation. *Trends Ecol. Evol.* 25, 387-395.

Giraud, T. & Gourbière, S. 2011 The tempo and modes of evolution of reproductive isolation in fungi. *Manuscript in revision*

Gourbière, S. 2004 How do natural and sexual selection contribute to sympatric speciation ? *J. Evol. Biol.* 17, 1207-1309.

Gourbière, S. & Mallet, J. 2005 Has adaptive dynamics contributed to the understanding of adaptive and sympatric speciation ? *J. Evol. Biol.* 18, 1201-1204

Gourbière, S. & Mallet, J. 2010 Are species real ? The shape of the species boundary with exponential failure, reinforcement, and the “missing snowball”. *Evolution* 64, 1-42.

Jancek, S., Gourbière, S., Moreau, H., Piganeau, G. 2008 Clues about the genetic basis of adaptation emerge from comparing the proteomes of two *Ostreococcus* ecotypes (Chlorophyta, Prasinophyceae). *Mol. Biol. Evol.* 25, 2293-2300.

Knudsen, R., Amundsen, PA., Klementsen, A. 2002 Parasite-induced 994 host mortality: indirect evidence from a long-term study. *Env. Biol. Fishes* 64, 257-265.

Lo, C. M. & Morand, S. 2000 Spatial distribution and coexistence of monogenean gill parasites inhabiting two damselfishes from Moorea island in French Polynesia. *J. Helminthol.* 74, 329-336

de Meeûs T, Michalakis Y, Renaud F 1998 Santa Rosalia revisited: or why are there so many kinds of parasites in the garden of earthly delights ? *Parasitol Today* 14:10-13.

Mideo, N. 2009 Parasite adaptations to within-host competition. *Trends Parasitol.* 25, 261-268.

Over HJ, Jansen J, van Olm PW 1992 *Distribution and impact of helminth diseases of livestock in developing*. Food and Agriculture Organization (FAO) of the United Nations, Rome. Available at http://www.fao.org/DOCREP/004/T0584E/T0584E00.HTM.

Pedersen, A. B. & Fenton, A. 2006 Emphasizing the ecology in parasite community ecology. *Trends Ecol. Evol.* 22, 133-139.

Poulin R, Morand S 2004 *Parasite Biodiversity*, Smithsonian Books, Washington.

Poulin R. 2006 *Evolutionary Ecology of Parasites.* Princeton University Press.

Price PW 1980 *Evolutionary Biology of Parasites*, Princeton University Press, Princeton.

Rascalou G, Šimková A, Morand M, Gourbière S 2012 Within-host competition and diversification of macro-parasites. *J R Soc Interface.* [Ahead of print]

Rohani P & Ruxton GD. 1999 Dispersal-induced instabilities in host-parasitoid metapopulations. *Theor Popul Biol.*, 55(1):23-36.

Savolainen, V., Anstett, M.C., Lexer, C., Hutton, I., Clarkson, J. J., Norup, M. V., Powell, M. P., Springate, D., Salamin, N., Baker, W. J. 2006 Sympatric speciation in palms on an oceanic island. *Nature* 441, 210-213.

Shaw DJ, Grenfell BT, Dobson AP 1998 Patterns of macroparasite aggregation in wildlife host populations. *Parasitology* 177, 597-610.

Šimková, A., Ondračková, M., Gelnar, M., Morand, S. 2002 Morphology and coexistence of congeneric ectoparasite species: reinforcement of reproductive isolation ? *Biol. J. Linn. Soc.* 76, 125-135.

Steinauer ML. 2009 The sex lives of parasites: investigating the mating system and mechanisms of sexual selection of the human pathogen *Schistosoma mansoni*. *Int J Parasitol*., 39(10):1157-63.

Thomas JD 2002 The ecology of fish parasites with particular reference to helminth parasites and their salmonid fish hosts in Welsh rivers: a review of some of the central questions. *Adv Parasitol* 52:1-154.

Weissing, F. J., Edelaar, P., van Doorn, G. S. 2011 Adaptive speciation theory: a conceptual review. *Behav. Ecol. Sociobiol.* 65, 461-480.

Tables and figures captions

Table 1. Parameters symbol and definition.

Symbol	Definition
(r), (m)	Natural mortality rate of parasite individuals with phenotype r and m, respectively
(r), (m)	Colonization rate of parasite individuals with phenotype r and m, respectively
$(r,m) = (m,r)$	Strength of within-host competition between parasite individuals with phenotype r and m.
$K(r)$, $K(m)$	Carrying capacity of parasite individuals with phenotype r and m, respectively
V	Host induced-mortality due to parasite virulence, independently of phenotype r or m.
, K	Standard deviation of the strength of competition and the carrying capacity, respectively
$K(s_0)$	Maximal phenotypic carrying capacity
s_0	Intermediate trait value associated with the maximal phenotypic carrying capacity
c	Parasites growth rate, independently of phenotype r or m
H	Size of the host population
k	'Clumping' parameter of the law of negative binomial distribution [Shaw et al., *1998*]

Table 2. Definition of function $Z_d(r)$ under different assumptions of the respective distribution of mutant and resident individuals. This distribution (d) can be random (where the mutant distributes irrespectively of the number of residents), co-aggregated (where mutant distributes among the hosts as the residents do) and an inversely aggregated (where mutant preferentially colonizes hosts harbouring a few individual residents).

Mutant distribution (d)	**Function** $Z_d(r)$
Random (d=1)	$\frac{k}{k+1}\left(\frac{cK(r)}{1+VK(r)}-1\right)$
Co-aggregation (d=2)	$\frac{cK(r)}{1+VK(r)}$
Inverse-aggregation (d=3)	$\frac{H\left(\frac{k}{k+1}\right)\left(\frac{cK(r)}{1+VK(r)}-1\right)-\frac{cK(r)}{1+VK(r)}}{H-1}$

Table 3. Influence of macro-parasites life-history traits on the mutant invasive fitness. Results for the influence of mutant and residents co-distribution and the influence of aggregation apply for both virulent and non-virulent macro-parasites.

Life-history traits	**Mutant and resident co-distribution (d)**		
	Random (d=1)	**Co-aggregated (d=2)**	**Inverse (d=3)**
Spatial segregation	$f_2(m,r)$ $f_1(m,r)$ $f_3(m,r)$		
Stronger aggregation	Positive	Null	Positive
Stronger virulence	Positive for V within $]0,V^{\max}[$ or within $[V_1^{thr},V^{\max}[$	Negative	Positive for V within $]0,V^{\max}[$ or within $[V_3^{thr},V^{\max}[$

Table 4.. Average time to reach the evolutionary singularity s*, for different mutant and residents co-distribution (d), and different levels of aggregation (k) and virulence (V). Time unit is generations. For each combination of parameters values, average times were calculated for a total of 10 simulations. P-values calculated using a student test are given between parenthesis, and average time statistically different (p-value<0.05) from those obtained for the neutral model (d=2) are indicated by '***'. For each simulation, the phenotype of the resident population at initial time was set as r = 0.5, and could evolve within values ranging from 0 to 2, with r = 1 being the evolutionary singularity. When not mentioned in the table, values used for parameters were $_m$=0.001, $_m$=1/20, H=10000, k=0.1, c=1, $K(s_0)=100$, =0.4 , $_K$=0.6, V=0.01.

	d=1	**d=2**	**d=3**
Agregation (*k*)			
***k*=0.1**	8.4 *(0.068)*	16.6	12.1 *(0.436)*
***k*=1**	4.5 *(0.263)*	3.1	3.9 *(0.403)*
***k*=20**	2.5 *(0.074)*	1.3	7.0 *(0.014)***
Virulence (*V*)			
***V*=0**	4.7 *(0.632)*	5.8	4.4 *(0.523)*
***V*=0.01**	8.4 *(0.068)*	16.6	12.1 *(0.436)*
***V*=0.05**	40.8 *(0.003)***	137.6	39.0 *(0.003)***
***V*=0.1**	43.9 *(0.001)***	517.2	71.7 *(0.002)***

Table 5. Average time to reach the evolutionary singularity s*, for non-parasite species, and different values of $K(s_0)$. Time unit is generations. For each combination of parameters values, average times were calculated for a total of 10 simulations. P-values calculated using a student test are given between parenthesis, and average time statistically different (p-value<0.05) from those obtained for non-parasite species are indicated by '***'. For each simulation, the phenotype of the resident population at initial time was set as r = 0.5, and could evolve within values ranging from 0 to 2, with r = 1 being the evolutionary singularity. Values used for parameters were $_m$=0.001, $_m$=1/20, H=10000, k=0.1, c=1, , =0.4 , $_K$=0.6, V=0.01.

Value of $N(s_0)$*	**Non-parasite species**	**Macro-parasite species (p-value)**		
		d=1	d=2	d=3
$= K(s_0) = 100$	2857.4			
$= P(s_0)*\big\|_{V=0} = 44{,}545$	7.6	4.7 *(0.934)*	5.8 *(0.319)*	4.4 *(0.947)*
$= P(s_0)*\big\|_{V=0.01} = 90{,}000$	4.5	8.4 *(0.777)*	16.6 *(0.021)***	12.1 *(0.362)*
$= H.K(s_0)\big\|_{V=0} = 1{,}000{,}000$	0.5			

Figure 1. Variations of function $Z_d(r)$ (A) and $f_d(m,r)$ (B) in function of aggregation (k). Solid line: d=2, dashed line: d=1, dotted line: d=3. Values used for parameters are H=10000, c=1, $K(s_0)=100$, $_K$=0.9, V=0.01.

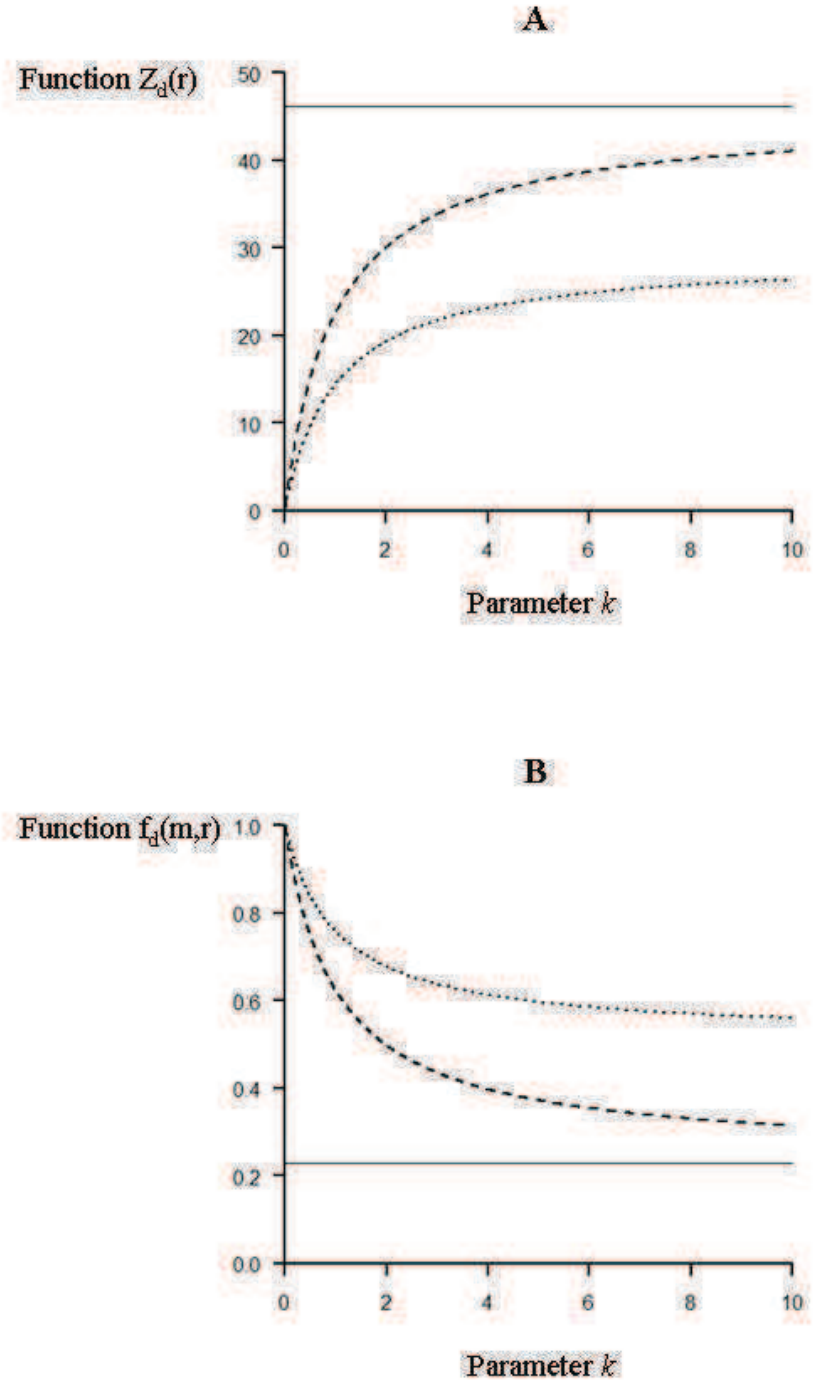


Figure 2. Variations of function $f_d(m,r)$ for d=1 (A), d=2 (B) and d=3 (C), in function of virulence (V) and aggregation (k=10: solid line, k=1: dashed line, k=0.1: dotted line). Values used for parameters are H=10000, c=1, $K(s_0)=100$ (=50 for d=3), =0.1 , $_K$=0.9, V=0.01, m=0.5, r=0.4.

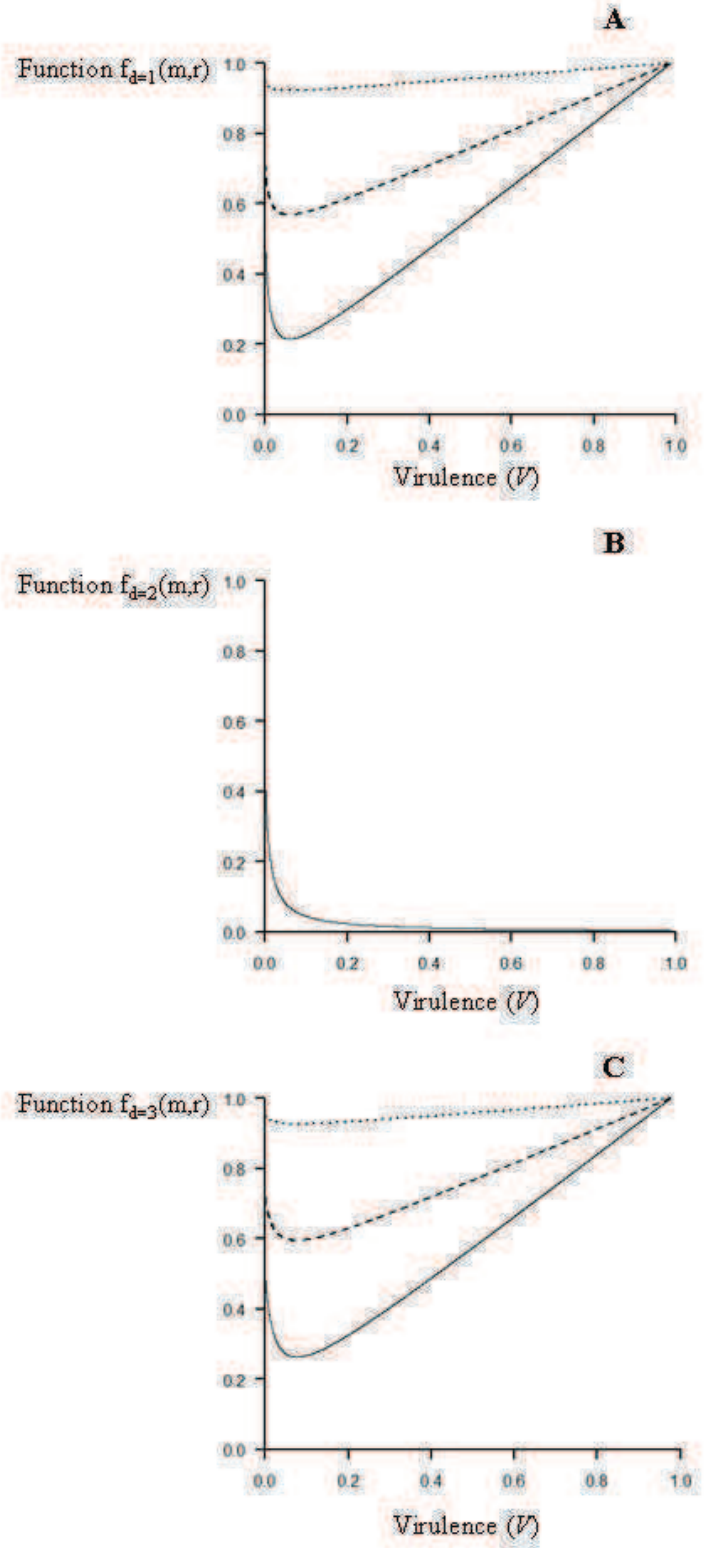


Figure 3. Pairwise-invasibility plot for d=2. $_K$ $_C$ (A) and $_K$ $_C$ (B). Grey and white areas correspond to positive and negative mutant fitness, respectively. Values used for parameters are H=10000, k=0.5, c=1, $K(s_0)=100$, =0.4 (A) or 0.6 (B), $_K$=0.6 (A) or 0.4 (B), V=0.01.

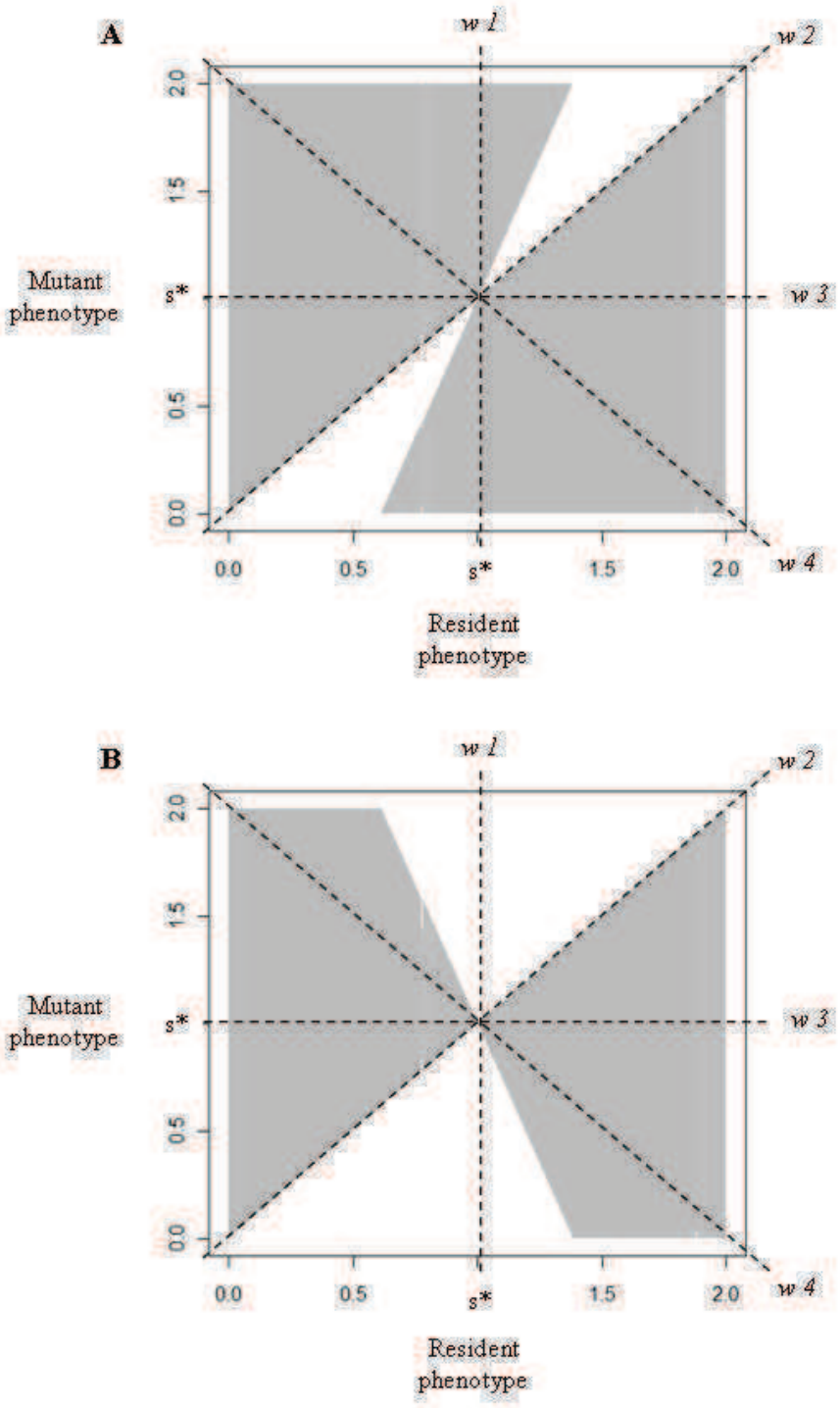


Figure 4. Pairwise_invasibility plot for d=1. k=0.5 (A) and k=1,000,000 (B). Grey and white areas correspond to positive and negative mutant fitness, respectively. Values used for parameters are H=10000, c=1, $K(s_0) = 100$, =0.4 , $_K$=0.6, V=0.01.

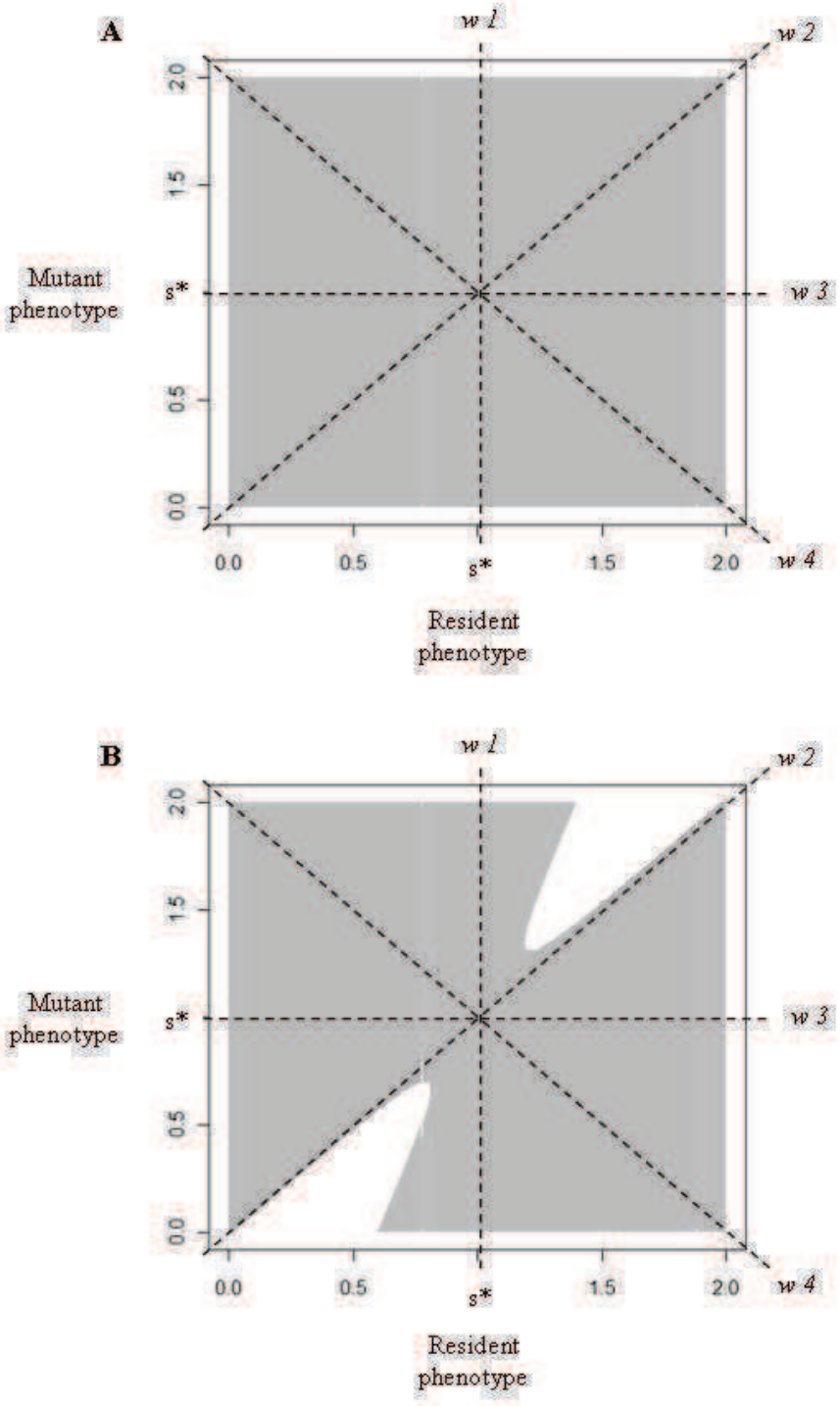
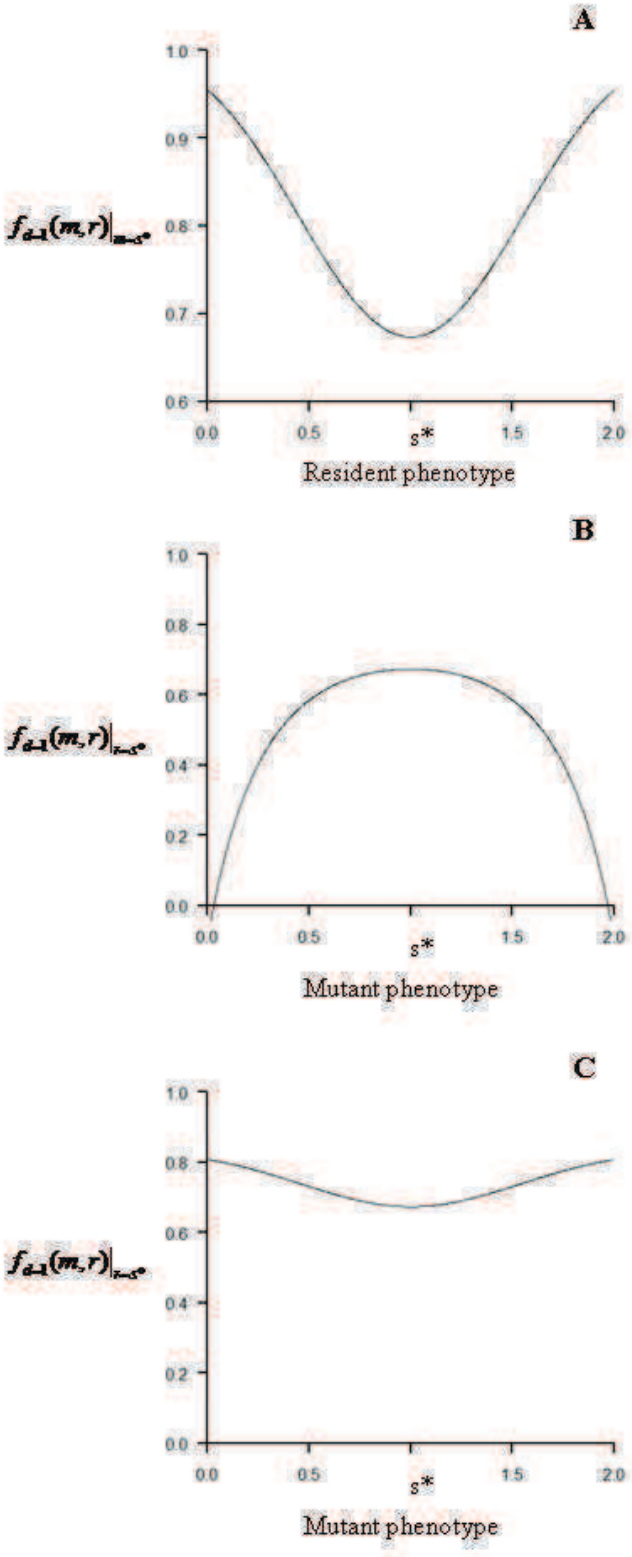


Figure 5. Plot of $f_{d=1}(m,r)\big|_{m=s^*}$ (axis *w3* in figure 4) in function of resident phenotype (A), and plot of $f_{d=1}(m,r)\big|_{r=s^*}$ (axis *w1* in figure 4) in function of mutant phenotype for $_K$ $_C$ (B) and $_K$ $_C$ (C). Values used for parameters are *H*=10000, c=1, $K(s_0)=100$, =0.4 (A & C) or 0.6 (B), $_K$=0.6 (A&C) or 0.4 (B), *V*=0.01, *k*=0.5.



Appendix I: the invasion fitness function of macro-parasites

The general expression of the mutant invasion fitness

According to equation 1 in the main text, one can derives a couple of ordinary differential equations describing the change in the number of individuals of two competing phenotypes r and m:

$$\frac{dP(r)}{dt} = \sum_{n_r,n_m} \frac{dH_{n_r,n_m}}{dt}\bigg|_{n_m} = -\ (r)P(r) + \ (r)H - V\sum_{n_r,n_m} n_r + n_m\ H_{n_r,n_m}(t)$$

$$- \ (r,r)\sum_{n_r,n_r} \frac{n_r^2}{K(r)} H_{n_r,n_m}(t) - \ (r,m)\sum_{n_r,n_m} \frac{n_r n_m}{K(r)} H_{n_r,n_m}(t) \quad \text{Eq. S1a.}$$

$$\frac{dP(m)}{dt} = \sum_{n_m,n_r} \frac{dH_{n_m,n_r}}{dt}\bigg|_{n_r} = -\ (m)P(m) + \ (m)H - V\sum_{n_r,n_m} n_r + n_m\ H_{n_r,n_m}(t)$$

$$- \ (m,m)\sum_{n_m,n_m} \frac{n_m^2}{K(m)} H_{n_r,n_m}(t) - \ (r,m)\sum_{n_r,n_m} \frac{n_r n_m}{K(m)} H_{n_r,n_m}(t) \text{ Eq. S2b.}$$

with parameters being defined in table 1.
Using the same assumptions as for non-virulent parasites [Rascalou et al., *2012*], the sum within the last competition term of equation S2b can be approximated as

$$S(m,r) = \sum_{n_r,n_m} n_r n_m H_{n_r,n_m} \approx P(m)\sum_{n_r} n_r H^*_{k_r} p(n_r)$$

where $p(n_r)$ is the probability for a mutant parasite to colonize a host already infected with n_r residents (see main text for the expression of $p(n_r)$ in function of the form of the mutant and residents co-distribution).

Considering that the mutant is rare, we can expect n_m to take only two possible values: 1 or 0, with probability $P(m)$ and 1-$P(m)$, respectively. The virulence term in equation S2b can then be approximated as follows:

$$\sum_{n_r,n_m} n_r + n_m\ H_{n_r,n_m} \approx P(m)\sum_{n_r} n_r H^*_{n_r} p(n_r) + \ 1 - P(m)\ \sum_{n_r} n_r H^*_{n_r} p(n_r)$$

However, the second term here does not contribute to the variations of $\frac{dP(m)}{dt}$ (equation S2b), therefore we only keep

$$\sum_{n_r,n_m} n_r + n_m\ H_{n_r,n_m} = P(m)\sum_{n_r} n_r H^*_{n_r} p(n_r) = S(m,r)$$

Including the sum $S(m,r)$ within equation 2Sb, one can derive a first expression of the mutant fitness within a resident population as

$$f(m,r) = \frac{dP(m)}{P(m)dt} = -\ (m) + \frac{H}{H+v} - \left(V + \frac{(m,r)}{K(m)}\right)\frac{S(m,r)}{P(m)} \qquad \text{Eq. S3}$$

Using the ordinary differential equations describing the change in the number of resident individuals (r) without mutant (m):

$$\frac{dP(r)}{dt} = - \ (r)P(r) + \frac{H}{H+v}P(r) - \left(V + \frac{(r,r)}{K(r)}\right)\left(\frac{P(r)^2}{H}\left(\frac{k+1}{k}\right) + P(r)\right)$$

(see table 1 for definition of parameters), we can obtain the expression of the size of the resident population at dynamical equilibrium:

$$P(r)^* = H\left(\frac{k}{k+1}\right)\left(\frac{c(r)K(r)}{1+VK(r)} - 1\right) \qquad \text{Eq. S4}$$

Finally, by introducing *P(r)** as well as the different expressions of $p(n_r)$ into the sum $S(m,r)$ of equation S3, we can obtain a general expression of the mutant invasion fitness of macro-parasites depending on the form of the co-distribution of mutant and residents (d):

$$f_d(m,r) = c - \left(V + \frac{(m,r)}{K(m)}\right)Z_d(r) \qquad \text{Eq. S5}$$

where function $Z_d(r)$ is equal to $\frac{S(m,r)}{P(m)}$, and is described in table 2 for each mutant and residents co-distribution (d).

The sign of function $Z_d(r)$

Clearly, $Z_2(r)$ 0 . As the size of the residents population *P(r)** requires $\frac{cK(r)}{1+VK(r)}>1$ to be positive (equation S4), then $Z_1(r)$ is necessarily always positive. For d=3, we first take $A = H\left(\frac{k}{k+1}\right)$, and $Z_3(r)$ can then be re-expressed as $\frac{\frac{cK(r)}{1+VK(r)} \ A-1 \ -A}{H-1}$. Assuming that *A*>>1, and given that $\frac{cK(r)}{1+VK(r)}>1$, then $Z_3(r)$ is always positive.

In conclusion, the function $Z_d(r)$ is always positive for mutant and residents co-distribution: $Z_d(r)$ 0 (d [1; 3]).

The effect of virulence on the mutant invasion fitness

Mutant and residents positive co-distribution (d=2). Introducing $Z_2(r)$ into the general expression of $f_d(m,r)$ (equation S5) for d=2, it comes

$$f_2(m,r) = \frac{c - \frac{(m,r)}{K(m)}cK(r)}{1+VK(r)}$$

Therefore $f_2(m,r)$ is an inverse function of virulence V . Clearly, increased virulence has a negative effect on the mutant fitness when this mutant is co-aggregated with residents (d=2). Thou virulence reduces the size of the resident population $P^*(r)$ by killing hosts, a co-aggregated distribution means that dying hosts are also those colonised by the emerging

mutant. As a result, only the negative effect of virulence remains within the function of mutant fitness $f_2(m,r)$.

Mutant and residents independent co-distribution (d=1). The effect of virulence V on $f_1(m,r)$ can be investigated through the study of the sign of $\frac{f_1(m,r)}{V}$ in function of *V*.

The general condition for $\frac{f_1(m,r)}{V}>0$ – that is, for a positive effect of virulence - is

$V^2K(r)^2+2VK(r)+1-cK(r)+\frac{(m,r)}{K(m)}cK(r)^2 \quad 0$.

Therefore, solutions V such as $\frac{f_1(m,r)}{V}>0$ depend on the sign of $1-cK(r)+\frac{(m,r)}{K(m)}cK(r)^2$ and/or on the sign of Δ, the discriminant of $\frac{f_1(m,r)}{V}=0$:

$$\Delta = 4cK(r)^3\left(1-\frac{(m,r)}{K(m)}K(r)\right)$$

Given that $K(r)^2 \quad 0$, we know that the shape of $\frac{f_1(m,r)}{V}$ in function of V is concave. The, as a result of graphic analysis, we know that :

- if $\Delta \quad 0$ then no value of V is a solution for $\frac{f_1(m,r)}{V}=0$, which means that $\frac{f_1(m,r)}{V}$ is always positive, and thus, that the virulence has a positive effect on $f_1(m,r)$ for any value of V (within $]0,V^{\max}[$). A general condition for $\Delta \quad 0$ is $(m,r) \quad \frac{K(m)}{K(r)}$.

- if $\Delta \quad 0$, then $\frac{f_1(m,r)}{V}=0$ has two solutions

$$V_1=\frac{-2K(r)-\sqrt{\Delta}}{2K(r)^2} \text{ and } V_2=\frac{-2K(r)+\sqrt{\Delta}}{2K(r)^2}$$

It can be easily demonstrated that V_1 is strictly negative.

We know by graphical analysis that $V_2 \quad 0$ if $1-cK(r)+\frac{(m,r)}{K(m)}cK(r)^2>0$, and $V_2 \quad 0$ if $1-cK(r)+\frac{(m,r)}{K(m)}cK(r)^2<0$, but there is no general condition giving a strict sign to $1-cK(r)+\frac{(m,r)}{K(m)}cK(r)^2$. Similarly, if we try to resolve the inequality $V_2 \quad 0$, this gives:

$$(m,r) \quad \frac{K(m)}{K(r)}\left(1-\frac{1}{cK(r)}\right).$$

Regarding the sign of the derivative function if $\Delta \quad 0$, this means that $\frac{f_1(m,r)}{V}$ is positive only beyond a threshold value $V_{d=1}^{thd}=V_2=\sqrt{c\left(\frac{1}{K(r)}-\frac{(m,r)}{K(m)}\right)}-\frac{1}{K(r)}$

Another condition for V to have a positive effect on $f_1(m,r)$ is that $V^{thd} < V^{\max}$. This is equivalent to $c - \frac{1}{K(r)} + \frac{(m,r)}{K(m)} > 0$.

However, a condition for $P(r)^* > 0$ is $c - V - \frac{1}{K(r)}$ 0, thus $c - \frac{1}{K(r)}$ 0, which ensures that the inequality $V^{thd} < V^{\max}$ is always verified, and thus, that $V_{d=1}^{thd}$ is always below $V^{\max}$ indeed. In terms of variations of the fitness $f_1(m,r)$ in function of V, this means that if Δ 0, then the virulence has a negative effect on $f_1(m,r)$ within the range $]0; V_{d=1}^{thd}[$, and positive within $]V_{d=1}^{thd}\ V^{\max}[$.

It can be showed that $1 - \frac{1}{cK(r)}$ 1, which means that $\frac{K(m)}{K(r)}\left(1 - \frac{1}{cK(r)}\right)$ $\frac{K(m)}{K(r)}$.

Eventually, we can thus summarise the results on the influence of V on the fitness $f_1(m,r)$ as in table S1, where this effect depends on the intensity of the competition.

Table S1. Effect of V on the mutant invasion fitness when d=1.

Condition	(m,r) $\frac{K(m)}{K(r)}\left(1 - \frac{1}{cK(r)}\right)$	$\frac{K(m)}{K(r)}\left(1 - \frac{1}{cK(r)}\right)$ (m,r)
Effect of V on the fitness function $f_1(m,r)$	Negative within $]0; V_{d=1}^{thd}[$, positive within $]V_{d=1}^{thd}; V^{\max}[$	Always positive

Mutant and residents inverse co-distribution (d=3). As for the independent co-distribution (d=1), the effect of the virulence V on $f_3(m,r)$ can be investigated through the study of the sign of $\frac{f_3(m,r)}{V}$ in function of V. The general condition for $\frac{f_3(m,r)}{V} > 0$ – that is, for a positive effect of virulence - is

$V^2 XK(r)^2 + 2VXK(r) + X + cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r) - 1\right)$ 0, with $X = H\frac{k}{k+1}$.

Therefore, solutions V such as $\frac{f_3(m,r)}{V} > 0$ depend on the sign of

$X + cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r) - 1\right)$ and/or on the sign of Δ, the discriminant of $\frac{f_3(m,r)}{V} = 0$:

$\Delta = 4XcK(r)^3\ X - 1\left(1 - \frac{(m,r)}{K(m)}K(r)\right)$

Given that $XK(r)^2$ 0, we know that the shape of $\frac{f_3(m,r)}{V}$ in function of V is concave. As a result of graphic analysis, we then know that:

- if Δ 0 then no value of V is a solution for $\frac{f_3(m,r)}{V} = 0$, which means that $\frac{f_3(m,r)}{V}$ is always positive, and thus, that the virulence has a positive effect on $f_3(m,r)$ for any value of

V (within $]0,V^{\max}[$). Assuming that X>>1, a general condition for Δ 0 is (m,r) $\frac{K(m)}{K(r)}$.

- if Δ 0, then $\frac{f_3(m,r)}{V}$=0 has two solutions

$V_1 = \frac{-2XK(r)-\sqrt{\Delta}}{2XK(r)^2}$ and $V_2 = \frac{-2XK(r)+\sqrt{\Delta}}{2XK(r)^2}$

It can be easily demonstrated that V_1 is strictly negative.

We know by graphical analysis that V_2 0 if $X+cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r)-1\right)$>0, and V_2 0 if $X+cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r)-1\right)$<0, but there is no general condition giving a strict sign to $X+cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r)-1\right)$. Similarly, if we try to resolve the inequality V_2 0, this gives:

$\sqrt{\frac{cK(r)(X-1)\left(\frac{(m,r)}{K(m)}K(r)-1\right)}{X}}$>1, which turns out be exactly the same condition as obtained through graphical analysis. Finally, assuming that X>>1, we can approximate this condition to $\sqrt{cK(r)-\frac{(m,r)}{K(m)}cK(r)^2}$ 1, which is exactly the same as when mutant and residents are independently distributed (d=1).

It can be showed that $1-\frac{X}{X-1}\frac{1}{cK(r)}$ 1, which means that $\frac{K(m)}{K(r)}\left(1-\frac{X}{X-1}\frac{1}{cK(r)}\right)$ $\frac{K(m)}{K(r)}$. Eventually, we can thus summarise the results on the influence of V on the fitness $f_3(m,r)$ in table S2, as made for $f_1(m,r)$ in table S1, where this effect depends on the intensity of the competition.

Table S2. Effect of V on the mutant invasion fitness when d=3.

Condition	(m,r) $\frac{K(m)}{K(r)}\left(1-\frac{X}{X-1}\frac{1}{cK(r)}\right)$	$\frac{K(m)}{K(r)}\left(1-\frac{X}{X-1}\frac{1}{cK(r)}\right)$ (m,r)
Effect of V on the fitness function $f_3(m,r)$	Negative within $]0;V_{d=3}^{thd}[$, positive within $]V_{d=3}^{thd};V^{\max}[$	Always positive.

In conclusion, the influence of virulence on $f_3(m,r)$ is the same as on $f_1(m,r)$, as summarised in table S1. The only slight difference is that threshold value $V_{d=3}^{thd}$ for d=3 is slightly below $V_{d=1}^{thd}$ since $V_{d=3}^{thd}=\sqrt{\frac{X-1}{X}c\left(\frac{1}{K(r)}-\frac{(m,r)}{K(m)}\right)}-\frac{1}{K(r)}$ and $\frac{X-1}{X}$<1. The main consequence of this difference is that, given the same value for other parameters, the range]

$V_{d=3}^{thd}; V^{\max}$[is wider than] $V_{d=1}^{thd}, V^{\max}$[. In other words, when mutant and residents are inversely co-distributed (d=3), the virulence has a positive effect on $f(m,r)$ for a few more values of V than when mutant and residents are independently distributed (d=1).

Appendix II: Adaptive dynamics

The three derivatives to be evaluated for m=r= s* are:

$$\left.\frac{f_d(m,r)}{m}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{K(s^*)}\left(\frac{(s_0 - s^*)}{\frac{2}{K}}\right),$$

$$\left.\frac{{}^2 f_d(m,r)}{{}^2 m}\right|_{m=r=s^*} = \frac{Z_d(s^*)}{K(s^*)}\left(\frac{1}{2} - \frac{1}{\frac{2}{K}}\right),$$

and $$\left.\frac{{}^2 f_d(m,r)}{{}^2 r}\right|_{m=r=s^*} = \frac{1}{K(s^*)}\left(\frac{Z_d(s^*)}{2} - VK(s^*)+1 \left.\frac{{}^2 Z_d(r)}{{}^2 r}\right|_{m=r=s^*}\right).$$

Singular strategy. The singular strategy is obtained when the first derivative with respect to the mutant phenotype equals to 0. Since $Z_d(s^*)$ 0 (d [1;3]), the only solution and the unique singular strategy is the same for all the three fitness functions: **s*=s$_0$.**

Evolutionary stability. The singular strategy is an evolutionary stable strategy if the second derivative with respect to the mutant strategy is negative. Since $Z_d(s^*)$ 0 (d [1;3]), the condition for s* to be an evolutionary stable strategy is the same for all the three fitness functions : ^{2} $\frac{2}{K}$.

Convergence stability. The singular strategy is a convergent stable strategy if the second derivative with respect to the resident is larger than the second derivative with respect to the mutant phenotype. It is straightforward to show that such a condition is equivalent to:

$$\frac{Z_d(s^*)}{\frac{2}{K}} - VK(s^*)+1 \left.\frac{{}^2 Z_d(r)}{{}^2 r}\right|_{m=r=s^*} \quad 0$$

It can be easily demonstrated that $\left.\frac{{}^2 Z_2(r)}{{}^2 r}\right|_{m=r=s^*} = 0$. For the second fitness function, this inequality is thus equivalent to $\frac{Z_2(s^*)}{\frac{2}{K}}$ 0, which is always satisfied since $Z_2(s^*)$ 0 and $\frac{2}{K}$ 0.

It can be easily demonstrated that $\left.\frac{{}^2 Z_1(r)}{{}^2 r}\right|_{m=r=s^*} = \frac{k}{k+1}\left.\frac{{}^2 Z_2(r)}{{}^2 r}\right|_{m=r=s^*} = 0$. For the first fitness function, this inequality is thus equivalent to $\frac{Z_1(s^*)}{\frac{2}{K}}$ 0, which is always satisfied since $Z_1(s^*)$ 0 and $\frac{2}{K}$ 0.

It can be easily demonstrated that $\left.\frac{{}^2 Z_3(r)}{{}^2 r}\right|_{m=r=s^*} = \frac{X-1}{H+1}\left.\frac{{}^2 Z_2(r)}{{}^2 r}\right|_{m=r=s^*} = 0$, with $X = H\frac{\mathrm{k}}{\mathrm{k}+1}$. For the third fitness function, this inequality is thus equivalent to $\frac{Z_3(s^*)}{\frac{2}{K}}$ 0, which is always satisfied since $Z_3(s^*)$ 0 and $\frac{2}{K}$ 0.

Invasion potential. A singular strategy is an invasive strategy if the second derivative with respect to the resident is positive. This is equivalent to:

$$\frac{Z_d(s^*)}{2} - VK(s^*)+1 \left.\frac{^2Z_d(r)}{^2r}\right|_{m=r=s^*} \quad 0 .$$

We know from the analysis of the conditions for the singular strategy to be a convergent stable strategy that $\left.\frac{^2Z_d(r)}{^2r}\right|_{m=r=s^*} = 0$, this inequality is thus equivalent to $\frac{Z_d(s^*)}{2} \quad 0$.

As $Z_d(s^*) \quad 0$ and $^2 \quad 0$, therefore this inequality is always verified for any d [1;3].

Protected polymorphism. A protected polymorphism can arise around the singular strategy, when the second derivative with respect to the residents phenotype is larger than the opposite of the second derivative with respect to the mutant. This condition is equivalent to

$$\frac{Z_d(s^*)}{\frac{2}{K}} - VK(s^*)+1 \left.\frac{^2Z_d(r)}{^2r}\right|_{m=r=s^*} \quad 0 .$$

It can be noticed that this is exactly the same condition as for the singular strategy to be a convergent stable strategy (see above). As this condition has been demonstrated to be always verified for all the co-distribution hypothesis (d), then we can also conclude that a protected polymorphism can arise around the singular strategy for any d [1;3].

Appendix III: Pairwise-invasibility plots (PIP) for d=3

Figure S1. Pairwise_invasibility plot for d=3. k=0.5 (A) and k=50 (B). Grey and white areas correspond to positive and negative mutant fitness, respectively. Values used for parameters are H=10000, c=1, $K(s_0) = 100$, =0.4 , $_K$=0.6, V=0.01.

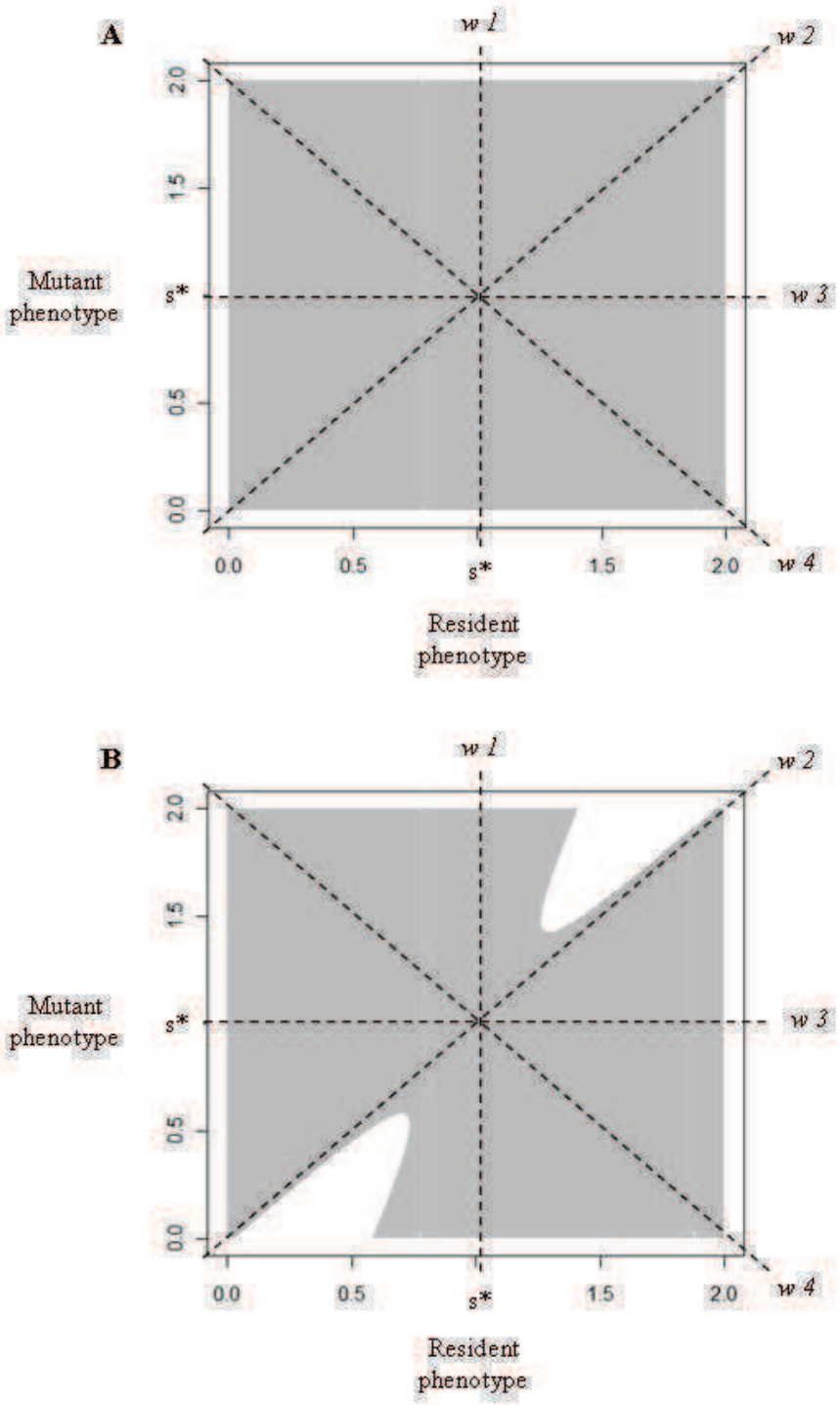
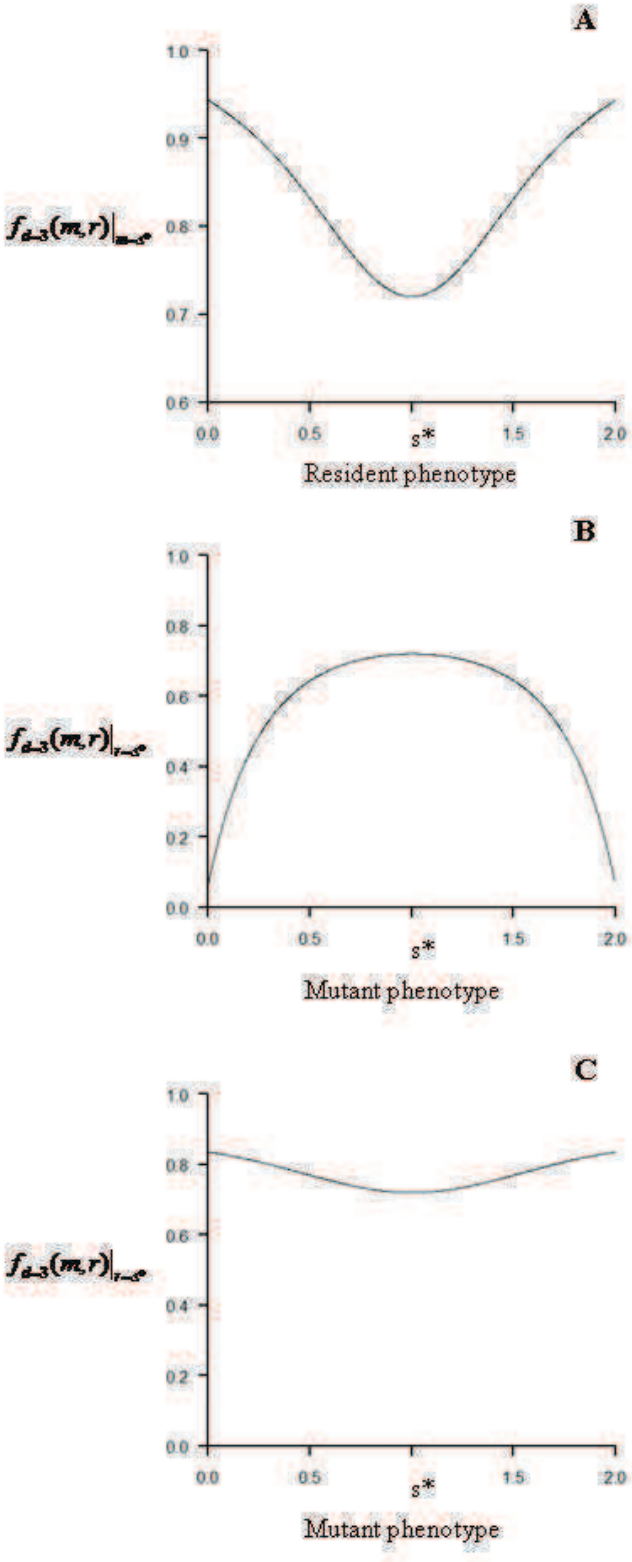


Figure S2. Plot of $f_{d=3}(m,r)\big|_{m=s^*}$ (axis *w3* in figure S1) in function of resident phenotype (A), and plot of $f_{d=3}(m,r)\big|_{r=s^*}$ (axis *w1* in figure S1) in function of mutant phenotype for $_K$ $_C$ (B) and $_K$ $_C$ (C). Values used for parameters are H=10000, c=1, $K(s_0)=100$, =0.4 (A & C) or 0.6 (B), $_K$=0.6 (A&C) or 0.4 (B), V=0.01, k=0.4.



Chapitre 5

Discussion

Afin de contribuer à une meilleure compréhension de l'écologie, l'évolution et le contrôle des maladies tropicales négligées j'ai fait appel pendant cette thèse à des approches théoriques comparatives (chapitre 2) et généralistes (chapitres 3 et 4). L'avantage des approches généralistes est qu'elles permettent d'explorer simplement des interactions potentielles entre différents processus éco-évolutifs dans le cadre de cette thèse. Les approches comparatives permettent également de mieux comprendre les interactions possibles entre différents processus en combinant l'utilisation de modèles empruntés aux approches généralistes, et des estimations de paramètres issues de diverses revues d'expérimentations et d'observations en milieu naturel. Elles permettent ainsi de proposer des « lois » établies théoriquement dans des domaines de paramètres réalistes sur le plan biologique, et contribuent à la fois à créer un lien formel entre les théories les plus abstraites et les données, et à comparer des situations biologiques, ici le nombre de maladies modélisées, entre elles. La généralité des lois obtenues dépend bien sûr du nombre de situations envisagées. Malgré leur intérêts respectifs, aucune de ces approches ne fournit de résultats sur le fonctionnement de systèmes particuliers qui permettraient une confrontation fine des prédictions et des données. Dans cette dernière partie de ma thèse, j'ai souhaité discuter de la façon dont cette limite pourrait être dépassée. Pour chacune des deux thématiques abordées dans ces trois chapitres - transmission des maladies vectorielles dans des populations puits et diversification compétitive des macro-parasites - je m'intéresse donc à la généralisation de mes résultats en les discutant pour d'autres maladies/parasites et en identifiant quelques systèmes biologiques spécifiques dont l'étude par des approches théoriques analogues à celles proposées apporterait des résultats. Enfin, je profite de ce dernier chapitre pour discuter du lien entre ces contributions théoriques et le contrôle des maladies infectieuses, et ce au travers d'exemples concrets (maladies vectorielles) ou plus abstraits (diversification des macro-parasites).

5.1 Transmission des maladies vectorielles dans des populations puits

Le chapitre 2 a permis de montrer que les probabilités d'émergence et les niveaux de persistence des maladies vectorielles transmises dans des populations puits peuvent être préoccupants, et ce malgré de faibles densités vectorielles. Il apparaît aussi que dans ce contexte, les niveaux de transmission sont avant tout déterminés par la démographie et le comportement alimentaire des vecteurs. Ces conclusions sont communes aux 6 maladies vectorielles considérées, mais leur généralisation à l'ensemble des maladies vectorielles affectant l'homme, et plus largement les animaux, reste néanmoins à établir. Je vais donc dans un premier temps essayer d'anticiper si ces conclusions sont susceptibles de s'appliquer aux autres maladies vectorielles et ceci à la vue des caractéristiques de ces dernières. Dans un deuxième temps je présente quelques cas d'études de transmission dans des populations puits pour lesquels le chapitre 2 apporte des résultats supplémentaires. Pour finir, je m'intéresserai plus particulièrement à l'un des processus dont j'ai montré qu'il doit avoir une grande influence sur la transmission des maladies vectorielles dans les populations puits: la migration des vecteurs. Je conclue donc cette première partie du chapitre 5 en discutant de l'intérêt de mieux comprendre les capacités migratoires des vecteurs, ainsi que les liens entre la migration et les caractéristiques biologiques et épidémiologiques de ces vecteurs.

5.1.1 La transmission dans des populations puits suit-elle les mêmes lois générales pour toutes les maladies vectorielles ?

Un grand nombre de maladies vectorielles sont dues à l'infection par des arbovirus, c'est-à-dire des virus qui, comme la dengue ou l'encéphalite japonaise, sont transmis par des arthropodes hématophages: certaines espèces de moustiques, mouches, ou tiques. Les arbovirus ont souvent beaucoup de points communs: les symptômes causés (encéphalite), la durée de la phase infectieuse (très courte), l'acquisition d'une immunité post-infection et l'existence d'hôtes animaux domestiques (CDCa; Weaver & Reisen, *2010*). Ces caractéristiques sont celles dont j'ai tenues compte pour modéliser la transmission de la dengue et de l'encéphalite japonaise (voir notamment « Text S1 » dans le chapitre 2), et l'on peut donc raisonnablement penser que la transmission des autres maladies arbovirales (fièvre jaune, chickungunya, virus du Nil occidental, etc), dans des populations puits de moustiques ou de mouches, a de bonnes chances de suivre les mêmes lois générales.

Certaines maladies vectorielles affectent exclusivement des populations animales. Ces populations animales peuvent avoir de fortes valeurs économiques pour l'homme. Le contrôle des vecteurs dans les zones d'élevage fait alors partie des stratégies employées pour lutter contre ces maladies (Peter et al., *2005*). Tout comme dans le cas de la lutte contre les maladies à vecteurs affectant l'homme, lorsque le bétail reste exposé à des vecteurs immigrants depuis des zones non-traitées, il existe un risque résiduel de transmission. Une telle situation peut se rencontrer par exemple pour la forme animale de la trypanosomiase africaine, appelée maladie du sommeil chez l'homme, qui affecte nombreux élevages bovins en Afrique. Une des stratégies de lutte contre les espèces de mouche tsétsé vectrices de la maladie consiste à débroussailler les zones de patûrage, afin d'en faire un habitat moins favorable aux vecteurs (Symeonakis et al., *2007*). Néanmoins, la mobilité des mouches et leur fort pouvoir de réinvasion représentent une limite à l'efficacité de cette stratégie de contrôle (Hargrove, *2000*). La trypanosomiase africaine animale partage de nombreux points communs avec sa forme humaine, notamment une durée relativement longue de la phase infectieuse (de plusieurs semaines à plusieurs mois selon l'espèce pathogène (CFSPH, *2009*)). Là aussi, on peut donc s'attendre à ce que la démographie et le comportement alimentaire des vecteurs soient les principaux déterminants de la transmission dans les populations puits. La plupart des maladies arbovirales humaines sont des zoonoses et sont donc plutôt spécifiques des espèces animales (CDCa; Weaver & Reisen, *2010*). Lorsque ces maladies sont transmises par des moustiques (comme les diverses encéphalites équines par exemple) ou des mouches (comme la fièvre catharrale), on peut anticiper que les mêmes conclusions puissent être tirées sur les facteurs déterminant la transmission dans des populations puits. Néanmoins, pour certaines arboviroses par exemples, la transmission dans les populations animales peut se traduire par de fortes augmentations de la mortalité ou par une réduction de la fertilité des hôtes infectés (CFSPH, *2007*). Sous l'hypothèse que la virulence des pathogènes entraîne une régulation des populations hôtes animales par les populations de parasites, on peut donc s'attendre à ce que l'effet de cette virulence sur la transmission dans des populations puits soit plus fort pour les maladies animales que pour les maladies humaines.

Pour d'autres maladies vectorielles au contraire, il existe des différences marquées avec les 6 maladies considerées, et il est alors fort possible que les conclusions données au chapitre 2 ne soient plus valables. C'est le cas par exemple des helminthiases transmises par des mouches, comme l'onchocerciase, ou des moustiques, comme la filariose lymphatique. Les pathogènes à l'origine de ces maladies sont des macro-parasites, un type de parasites pour lequel on sait que la densité des charges parasitaires a de fortes conséquences sur la

transmission (Churcher et al., *2005*). Qui plus est, les temps de maturation de ces pathogènes au sein de leur hôte, et donc le délais avant que cet hôte ne devienne infectieux, peut être beaucoup plus long que pour les micro-parasites considérés jusqu'à présent (de plusieurs mois à un an (CDCb)). Comparé aux maladies discutées jusqu'à présent, on peut alors penser que la transmission dans des populations puits dépend davantage de la virulence et des interactions hôtes-pathogènes. Nombreux pathogènes sont aussi transmis par des tiques: arbovirus responsable de la fièvre Congo-Crimée, bactérie responsable de la borréliose, protozoaire responsable de la babésiose, etc (Dobler *2010*; Estrada-Peña et al., *2012*). Or les tiques représentent des vecteurs très différents des moustiques, mouches ou punaises, et leur caractéristiques biologiques peuvent avoir de fortes conséquences sur la transmission des pathogènes. Leur durée de vie et le temps entre deux repas sanguins peuvent durer plusieurs années, les temps de contacts hématophagiques peuvent durer plusieurs mois, les individus peuvent intéragir et se reproduire sur leur hôte, et leur dispersion sur de grandes distances se fait typiquement grâce au transport par les hôtes infestés par le vecteur (Bowman & Nuttall, *2009*). Dans le cas où la probabilité de transmission du pathogène à l'hôte augmente avec la durée de ce contact hématophagique (Konnai et al., *2007*), on peut donc s'attendre à ce que la transmission de maladies dans des populations puits de tiques soit elle aussi fortement influencée par la longévité ainsi que le comportement alimentaire des vecteurs. De même, on peut s'attendre à ce que cette transmission dépende fortement des capacités migration des tiques, mais selon des mécanismes différents des moustiques, mouches ou punaises puisque dans le cas des tiques les taux d'immigration des vecteurs seraient fortement liés aux taux d'immigration des hôtes eux-mêmes.

La conclusion du chapitre 2 selon laquelle la démographie et le comportement alimentaire des vecteurs sont les principaux facteurs influencant la transmission dans des populations s'applique donc probablement à nombreuses maladies vectorielles.

5.1.2 Quelques cas d'études auxquels le chapitre 2 apporte des résultats supplémentaires

Ré-émergence de la maladie du sommeil dans les foyers historiques d'Afrique de l'ouest et d'Afrique centrale. Le contrôle des populations de mouches tsétsé a permit dans les années 1960 de contrôler la maladie du sommeil dans nombreux foyers de transmission d'Afrique de l'ouest et d'Afrique centrale (Artzrouni & Gouteux, *1996*). En général ce contrôle vectoriel s'effectue par l'utilisation d'insecticides ou de pièges disposés en périphérie de l'habitat humain (Brun et al., *2010*), là où se fait l'essentiel des contacts hommes-vecteurs et donc la transmission de la maladie. Néanmoins, suite à l'interruption ou la réduction de l'effort de contrôle dans certains foyers, la maladie a ré-émergé au sein des populations humaines. Les origines de ce phénomène ont fait l'objet de plusieurs travaux expérimentaux (Bouyer et al., *2009*) et théoriques (Gouteux & Artzrouni, *2000*). L'hypothèse testée par ces travaux est que la transmission de la maladie du sommeil dans ces foyers se fait par des populations puits de vecteurs, qui sont alimentées par les populations de mouches épargnées par les efforts de contrôle. D'après les travaux de Gouteux et Artzrouni (2000), les ré-émergences observées dépendent de deux facteurs principaux: la forte capacité de ré-invasion des mouches tsé-tsé du fait de leur comportement de dispersion, et l'existence d'une transmission « à bas bruit » du fait d'une longue phase infectieuse et asymptomatique chez l'homme . Les multiples travaux théoriques testant cette hypothèse ne permettent pas de conclure de manière définitive sur l'influence relative de ces deux processus. Ceci est peut-être du au parti-pris des auteurs de ne quantifier que l'influence de ces deux mécanismes, sans considérer la sensibilité de leur système aux variations d'autres paramètres. Les résultats du chapitre 2 pour la maladie du sommeil confirment l'effet prépondérant de ces deux processus, mais mettent davantage en

avant l'effet des vecteurs immigrants que celui de la phase infectieuse. Surtout, l'approche numérique utilisée dans le chapitre 2 et la paramétrisation du modèle selon des valeurs plus spécifiques permettrait peut-être d'apporter des conclusions encore plus robustes.

Invasion des triatomines vectrices de la maladie de Chagas. Un exemple particulierement bien étudié de transmission par des populations puits de vecteurs est celui de la transmission de la maladie de Chagas dans la péninsule du Yucatan au Mexique. Dans les villages de cette péninsule, l'habitat humain est infesté par des populations de triatomines incapables de s'établir durablement dans cet habitat domestique où se fait la transmission à l'homme. Ceci tient au contrôle vectoriel qui y est mis en place et/ou au fait que les punaises y sont incapables de se reproduire (Gourbière et al., *2008*). Ces populations sont donc fortement alimentées par l'immigration provenant des habitats sylvatique et péridomestique (Barbu et al 2010, 2011). Des situations analogues ont été observées pour d'autres espèces de vecteurs de la maladie, au centre du Mexique (Salazar Schettino et al., *2007*), à Belize (Polonio et al., *2009*) et au Brésil (Carbajal de la Fuente et al., *2007*). Dans la péninsule du Yucatan, bien que la dynamique et le controle des populations de ces triatomines - qualifiées de « non-domiciliées » - aient fait l'objet de nombreux travaux dans les dix dernières années, la transmission du pathogène n'a pas encore été étudiée quantitativement. Les résultats du chapitre 2, et notamment l'expression du R_0 (« reproductive number ») qui y est dérivée, peuvent donc fournir des informations complémentaire sur ce système. Un rapide calcul réalisé sur la base des données entomologiques et épidémiologiques disponibles, conduit à la conclusion que le taux d'immigration quotidien nécessaire à l'émergence de la maladie en milieu domestique (i.e., $R_0 > 1$) est d'environ 0,7 individu par par jour et par habitation. Ceci représente l'immigration d'une punaise environ toutes les 2 semaines, et une densité de punaises d'approximativement 2,8 individus par maison, ce qui est cohérent avec les résultats obtenus dans le chapitre 2. Dans la mesure où la densité vectorielle dans cette région évolue entre 1 et 40 punaises par maison, avec une moyenne de 20 (Nouvellet et al., *en préparation*), cela signifie qu'il faudrait des pulvérisation d'insecticides capables de réduire la densité vectorielle d'environ 86%, un taux légèrement supérieur à ceux estimé par Barbu et al. (*2011*) sur la base de modèles décrivant uniquement la démographie des vecteurs. Un autre aspect important de ce résultat est que la transmission domestique via ces triatomines « non-domiciliées » est vraisemblablement due à l'immigration régulière de triatomines infectées, et qu'il est très peu probable qu'un cycle de transmission se maintienne au sein des maisons uniquement grâce à l'immgration de vecteurs dont aucun ne serait porteur du pathogène. Autrement dit, la transmission domestique serait surtout due à l'introduction du périodique du pathogène par des vecteurs immigrants, et ce bien qu'il existe des hôtes domestiques infectés susceptibles de servir de réservoirs. Ceci s'explique notamment par la très faible probabilité de transmission du vecteur vers l'hôte, qui ne permet pas au vecteur de s'infecter ni de transmettre pendant son temps de transit dans l'habitat domestique.

Le paradoxe de la transmission de la leishmaniose viscérale dans l'état du Bihar, Inde. L'état du Bihar, au nord-est de l'Inde, habrite une des populations du pays les plus à risque de contracter la leishmaniose viscérale (Singh et al., *2010*). Ceci est notamment du à la colonisation de nombreuses zones ripariennes par la mouche *Phlebotomus argentipes*, vectrice de la maladie. Suites à de graves épidémies dans les années 1990, les efforts de lutte contre la maladie ont nécessité la pulvérisation extra-domiciliaire d'insecticides afin de contrôler les populations de vecteurs. Depuis, dans le sud du Bihar, la leishmaniose viscérale est efficacement contrôlée, et les pulvérisations d'insecticide ont été réduites (Kumar et al., *2009*). Au contraire, dans le nord de l'état, la leishmaniose viscérale continue de représenter un problème de santé publique, nécessitant de maitenir l'effort de contrôle par des

pulvérisations régulières. L'usage d'insecticide depuis les années 1990 a donc abouti à une situation surprenante à l'échelle du Bihar: les densités vectorielles les plus grandes sont observées dans le sud, là où le contrôle des vecteurs est désormais rare ou interrompu, mais où la maladie est sous contrôle, alors que ces densités sont bien moindres dans le nord en raison du maintien du contrôle vectoriel parce que la maladie y persiste à des niveaux d'incidence problématiques (Kumar et al., *2009*). Il est donc probable que la transmission dans les régions du nord du Bihar se fasse au sein de populations puits de *P. argentipes*, alimentées par des individus migrants depuis les regions du sud de l'état ou depuis les états voisins. Cette hypothèse pour expliquer la situation entomo-épidémiologique dans la partie Nord du Bihar est crédibilisée par les résultats du chapitre 2, qui prédisent qu'une faible population de vecteurs alimentées par des immigrants peut suffir à générer de forts taux de circulation de ce pathogène au sein de la population humaine. Les prévalences d'infections observées dans ces zones sont en effet qualitativement comparable à celles prédites sur la base du modèle que j'ai développé. En outre la susceptibilité des hommes au parasite est généralement réduite par le contact avec la salive des vecteurs (Silva et al., *2005*). Dans le nord du Bihar, les populations exposées à de plus faible densités vectorielles pourraient donc être davantage susceptibles au pathogène que les populations du sud de l'état. Ces différences pourraient donc également contribuer à expliquer le maintien d'une forte transmission au nord. Néanmoins, le chapitre 2 a montré que la transmission de la leishmaniose viscérale dépend beaucoup plus de la démographie et du comportement des vecteurs, que de la probabilité de transmission du vecteur à l'homme. Ceci suggère donc que la plus forte susceptibilité humaine au parasite doit jouer un role secondaire dans le maintien de la transmission à l'homme dans le nord de cet état. Par la même occasion ceci confirme qu'il est nécessaire d'améliorer la lutte contre la leishmaniose par un effort accru et plus efficace du contrôle vectoriel (Kumar et al., *2009*), et ce malgré l'éventuelle augmentation de susceptibilités qui pourrait être liée à une réduction des densités vectorielles.

Les résultats du chapitre 2, et leur possible extansion en intégrant des informations plus spécifiques aux systèmes étudiés, pourraient donc contribuer directement à une meilleure compréhension de la dynamique épidémiologique observée dans des foyers de transmission particuliers, ainsi qu'à une meilleure appréciation des effets – possiblement contradictoires comme dans la cas de la leishmaniose viscérale dans l'état du Bihar – des contrôles vectoriels. Une suite extrêmement intéressante à donner aux travaux de cette partie de ma thèse serait en effet de décliner les modèles proposés en incluant des informations sur ces trois systèmes particuliers pour lesquels il existe suffisament de connaissances empiriques. Ceci permettrait à la fois de faire progresser la connaissance de ces systèmes (comme je l'ai esquissé pour la transmission de la maladie de Chagas dans la péninsule du Yucatan), mais également de tester la robustesse des résultats géneraux obtenus ici.

5.1.3 Que sait-on des capacités migratoires des vecteurs, et des éventuels liens entre migration, biologie et statut épidémiologique des individus migrants ?

Depuis les années 2000, de plus en plus de travaux théoriques s'intéressent à l'influence de la dispersion des vecteurs sur le degré de connection entre leur populations (Killeen et al., *2003*), et sur ses conséquences en terme d'hétérogénéité spatiale des abondances de vecteurs (Barbu et al., *2010*), de taux de contacts hôte-vecteur et des probabilités de transmission (Smith et al., *2004*). Nombreux travaux expérimentaux tentent aussi de faire le lien entre la distribution spatiale de données épidémiologiques et le mouvement des vecteurs (Bhunia et al., *2011*; Himeidan et al., *2011*).

Néanmoins, il existe très peu de données quantitatives sur les taux de dispersion ou de migration des vecteurs. Or, d'après les résultats du chapitre 2, le taux de migration des vecteurs est un des facteurs les plus déterminants pour la transmission dans des populations puits. Il apparaît donc crucial d'obtenir davantage d'estimations de ces taux de migration. A l'échelle populationnelle, des lâchés-recaptures donnent une idée des capacités de dispersion en terme de distance maximale parcourue (Service 1997; Baber et al., *2010*), et des études de génétique des populations permettent (au prix de diverses hypothèses) de quantifier des taux de migration entre populations (Krafsur *2003;* da Costa-Ribeiro et al*., 2007*). Il existe également une riche littérature sur les différentes facteurs influencant le mouvement des vecteurs, en particulier les moustiques (Service 1997). Selon la distance considérée, la mobilité des vecteurs peut dépendre notamment du transport par le vent (Molyneux et al., *1979*), par leurs hôtes ou par la circulation de marchandises (Tatem et al., 2006), mais aussi de leur comportement alimentaire ou reproducteur, et de l'intéraction entre comportement et structure de leur environnement (Service 1997; Pates & Curtis, *2005*). D'après la littérature théorique et empirique, la relation entre hétérogénéité de l'environnement et comportement migratoire des vecteurs peut avoir des conséquences sur leur paramètres biologiques et épidémiologiques (Smith et al., *2004*). Ainsi, dans le cas par exemple des moustiques vecteurs de la dengue (Smith et al., *2004*), l'âge des individus peut être positivement corrélé à leur distance de dispersion ou à leur prévalence d'infection. De telles relations sont susceptibles d'avoir un effet important sur la transmission dans les populations puits, puisque d'après les résultats du chapitre 2 la longévité des vecteurs dans la population puit – et donc leur âge/espérance de vie au départ ou à l'arrivée de leur migration – est aussi un des facteurs déterminants de la probabilité d'émergence et des prévalences attendues.

Dans la mesure où la mise en place des stratégies de contrôle des maladies vectorielles suit souvent des critères relatifs à la dispersion spatiale des vecteurs (Carter et al., *2000*; Pates & Curtis, *2005*; Barbu et al., *2011*), nul doute que l'étude et le contrôle des maladies vectorielles bénéficieraient grandement d'une meilleure connaissance des capacités migratoires des vecteurs, mais aussi des relations entre migration et paramètres biologiques et épidémiologiques des vecteurs. Il serait ainsi intéressant de compléter les approches décrites ci-dessus par des méthodes plus fines permettant d'estimer l'intégralité des « noyaux de dispersion » par des approches indirectes reposant sur la modélisation spatiale, qu'elle soit statistique (Levy et al., *2008*; Zu Dohna et al., *2009*) ou dans le meilleur des cas mécaniste (Barbu et al., 2010). A terme, il sera aussi indispensable d'étudier la dispersion à l'échelle individuelle pour mieux comprendre les effets de ce processus sur la dynamique des populations de vecteurs, et par la suite l'évolution de ce trait d'histoire de vie en réponse aux effets du parasites (Nouvellet et al 2011) et éventuellement en réponse aux stratégies de contrôle employées.

5.2 Diversification compétitive des macro-parasites

Les chapitres 3 et 4 ont permis d'adapter une théorie développée pour les espèces non-parasites afin de mieux comprendre la spéciation adaptative des parasites et l'influence de leur mode de vie sur leur diversité. Ces premiers pas dans le développement d'une telle théorie ont été effectués au sein d'un cadre théorique très général et abstrait, qui n'indique pas forcément de manière très intuitive quel type de modèle biologique parmi les nombreuses espèces de macro-parasites serait le plus adéquat pour tester cette théorie. C'est pourquoi, dans un premier temps, je vais décrire les principales caractéristiques requises pour que des modèles biologiques puissent servir à tester cette théorie, et proposer quelques espèces candidates. Un

second point que je souhaite discuter est le lien entre la théorie développée et lien avec le contrôle des maladies dues à des macro-parasites, comme par exemple les helminthiases, qui représentent la moitié des 18 maladies tropicales négligées considérées dans le premier chapitre de cette thèse.

5.2.1 Quel modèle biologique pour étudier la diversification compétitive chez les macro-parasites ?

La première condition à remplir pour tout modèle candidat est évidemment l'existence d'une compétition intra-spécifique ou inter-générique pour une ressource intra-hôte et limitante. Une telle compétition a été démontrée chez nombreux helminthes parasites de vertébrés : monogènes parasites des branchies de poissons (Lo & Morand, *2000*), nématodes parasites du tube digestif de vertébrés (Moore & Simberloff, *1990*; Stancampiano et al., *2010*). Pour des raisons techniques et éthiques il est beaucoup plus difficile d'étudier ce phénomène chez les helminthes parasites de l'homme, mais il est intéressant de constater que chez d'autres vertébrés la compétition intra-hôte a été démontrée pour des espèces ou groupes d'helminthes intestinaux proches de ceux qui parasitent l'homme, comme certains nématodes parasites d'oiseaux (Dezfuli et al., *1992*). Typiquement, la ressource limitante pourrait être distribuée selon un gradient spatial, comme c'est probablement le cas pour monogènes dans les branchies de poissons (Šimková et al., *2004*), ou pour les ressources alimentaires exploitées par les helminthes parasites des intestins de vertébrés (Stock & Holmes, 1988; Stancampiano et al., *2010*).

Une deuxième condition requise est que cette compétition intra-hôte mette en jeu un caractère quantitatif dont la valeur détermine la quantité de ressources qu'un individu peut exploiter. Surtout, le caractère en question doit être impliqué dans une interaction compétitive dont l'intensité est à la fois densité-dépendante – qui dépend du nombre de compétiteurs - et fréquence-dépendante – qui dépend de la fréquence des individus porteurs des différents phénotypes associés au caractère en question. Un tel caractère peut notamment être d'ordre morphométrique, comme la taille, la forme du corps, ou le mode de nutrition, qui pour certains vers intestinaux varient avec le positionnement au sein du tube digestif (Canaris & Kinsella, *2001*); ou de certains organes, comme les pièces haptorales de certaines espèces de monogènes dont la taille peut varier avec le point d'accrochage des vers au sein de la branchie de leur poisson hôte (Šimková et al., *2002*). Ce caractère pourrait aussi être d'ordre comportemental, comme par exemple les capacités de dispersion intra-hôte. En effet on peut envisager que, selon sa mobilité, un individu puisse accéder à plus ou moins de ressources lorsque celles-ci ont une distribution spatiale hétérogène, comme c'est le cas chez de nombreux helminthes intestinaux (Shostak & Dick, 1989).

Tester cette théorie nécessite en outre d'être capable de comparer la distribution des ressources et de l'intensité de la compétition entre individus de phénotypes différents.. De ces deux paramètres, la distribution de la compétition semble le plus difficile à estimer. En effet, l'impossibilité d'observer directement nombreuses espèces de macro-parasites telles que les helminthes intestinaux oblige à sacrifier leurs hôtes, ce qui rend alors impossible le suivi de d'helminthes au sein d'un même individu hôte. Pour contourner cet obstacle, l'étude de la compétition chez les macro-parasites passe peut-être par l'utilisation d'espèces libres, comme *Caenorhabditis elegans,* un nématode dont la biologie (Murray et al., *2011*) mais aussi la génomique (*C. elegans* Sequencing Consortium, *1998*) sont déjà très étudieés.

Enfin, il existe de nombreuses perspectives de développement pour cette théorie, et

donc de critères supplémentaires pour l'identification de modèles biologiques candidats. Toutes ces perspectives viseraient à prendre en compte d'autres caractéristiques susceptibles d'influencer leur évolution et leur diversité par des processus adaptatifs : types de reproduction (Kunz, *2002*) et donc de scénarios d'isolement reproducteurs (Dieckmann & Doebeli, *1999*), mode(s) de distribution des ressources (celle-ci peut par exemple être bimodale, comme lorsqu'elle correspond à deux organes différents au sein de l'hôte (voir « Discussion » dans le chapitre 3)), types de compétitions intra-hôte (Mideo, *2009*).

5.2.2 Quel lien entre diversification adaptative et contrôle des macro-parasites ?

Evolution de la résistance aux traitements

L'une des questions les plus récurrentes au sujet de l'évolution des parasites est celle de l'évolution de la résistance aux traitements chémothérapiques. En effet l'apparition de résistance à ces traitements a été observée chez des micro-parasites (Goldberg et al., *2012*) comme chez des macro-parasites, tels que les schistosomes ou les nématodes (Geerts & Gryseels, *2000*). Dans le cas des espèces d'helminthes, ce phénomène est de plus en plus observé chez les parasites du bétail, mais il devient aussi un problème important chez les parasites de l'homme, avec le risque qu'il contraigne les stratégies de lutte mises en place contre certaines helminthiases humaines (Geerts & Gryseels, *2000*; Smits *2009*).

Les mécanismes à l'origine de l'évolution de la résistance aux traitements chez les helminthes sont encore mal connus (Geerts & Gryseels, *2000*), mais ce processus évolutif est clairement adaptatif (Jackson, *1993*; Churcher & Basañez, *2008*). Pour mieux comprendre les origines de cette résistance, la théorie développée au cours de cette thèse sur la diversification intra-hôte doit probablement viser à prendre en compte l'ensemble des interactions intra-hôtes auxquelles sont soumis les macro-parasites. En effet si les hôtes fournissent l'habitat et les ressources exploitées par leurs parasites, ces mêmes hôtes participent aussi aux pressions auxquelles doivent faire face ces macro-parasites puisque ceux-ci doivent lutter contre le sytème immunitaire et/ou les traitements employés par leurs hôtes. Autrement dit, la diversité des interactions hôte-parasite est telle que ces derniers sont donc susceptibles d'évoluer simultanément à la fois selon leur capacité à acquérir les ressources intra-hôtes, et selon leur capacité à échapper ou résister aux mécanismses de défense de l'hôte. Il semble tout à fait possible que l'évolution de traits liés à l'exploitation des ressources et l'évolution en réponse aux chémotherapies et/ou au système immunitaire soient deux processus interagissant.. L'expression de phénotypes résistants peut en effet avoir un coût se répercutant sur d'autres traits d'histoire de vie des parasites, et éventuellement ceux impliqués dans l'exploitation des ressources. C'est le cas par exemple chez certains nématodes tels que *Onchocerca volvulus* ou certaines espèces de la famille des Trichostrongyloidae , qui lorsqu'ils sont résistants peuvent également être moins fertiles ou moins mobiles (Gill & Lacey, *1998*; Bourguinat et al., *2006,* 2007). Sous l'hypothese d'un tel trade-off, les individus investissant dans l'exploitation d'un maximum de ressources (par exemple par une mobilité accrue) verraient leur avantage sélectif réduit du fait d'une moindre capacité de résistance à l'hôte ou au traitement. Or la réduction d'abundance de ces parasites se traduirait directement par une réduction de l'intensité de la compétition et donc de la pression de sélection disruptive qui y est associée. Autrement dit, en réduisant l'abundance des parasite, on réduit aussi le potentiel de diversification. Il est important de préciser que ceci n'est pas lié à la simple réduction du réservoir de variabilité génétique (du fait de la plus petite taille de population), mais le résultat d'un changement de type de sélection qui n'est possible que parce que celle-ci (liée à la compétition) est densité dépendente. Cependant, dans le même temps, les individus investissant moins dans

l'exploitation des ressources, et qui s'adaptent alors généralement à des ressources moins abondantes afin de réduire les niveaux de compétition intraspecifiques qui leur sont défavorables, peuvent alors exprimer des capacités de résistance. Dans ce cas ces individus augmenteraient en fréquence en présence de traitement et/ou de forte réponse immunitaire, et ceci limiterait les effets délétères de la sélection sexuelle qui les affecte génerallement en raison de leur faible nombre (Gourbière *2004*; Kirkpatrick & Nuismer, *2004*). L'apparition de tels individus résistants aux traitements pourrait ainsi accélérer les phénomènes de diversification lies à la compétition intra-hôte. Autrement dit, la balance entre sélection naturelle et sélection sexuelle qui permet la diversification et la spéciation compétitive pourrait être modifiée par les traitement antiparasitaire ou la réponse de l'hôte. En en retour, cette diversification compétitive pourrait accélérer et contribuer à maintenir une majorité d'individus résistants au sein de l'espèce ou de la population exposée aux traitements. Bien entendu ce scénario, qui correspond à un « modèle verbal », doit être testé quantitativement sur la base d'approches analogues à celles développées dans les chapitres 3 et 4 de cette thèse, avant que des hypotheses sur le rôle des traitements et du système immunitaire des hôtes puissent être retenues et testées expérimentallement.

Diversité des hôtes et risques de zoonoses

Comme je l'ai décris dans le chapitre 1 pour les maladies tropicales négligées, la diversité des hôtes peut avoir de fortes conséquences sur l'écologie et le contrôle des parasites. Cette diversité peut correspondre à différentes espèces ou populations d'hôtes, ou même à différents types d'individus au sein d'une même population (par exemple différentes classes d'âge). On sait aussi que cette diversité, notamment la diversité d'espèce d'hôtes, peut influencer voir favoriser l'évolution et la diversité des parasites (Emelianov *2007*). Lorsque ces espèces d'hôtes sont elles-même sympatriques, cette évolution par changement d'hôte peut se faire par diversification adaptative, comme cela a été démontrée chez certaines champignons parasites d'arbres (Giraud et al., *2010*). Pour les macro-parasites, une telle diversification adaptative due à la diversité d'hôtes pourrait avoir des conséquences sur les risques et le contrôle des zoonoses par exemple. Nombreux helminthes sont ainsi capables d'infecter à la fois l'homme et d'autres espèces animales, mais pour certains d'entre eux l'homme ne constitue qu'un hôte accidentel auquel ils ne sont, a priori, pas ou peu adaptés. C'est le cas par exemple de nombreuses espèces d'helminthes dont les hôtes les plus communs sont des espèces animales domestiques ou des poissons (Robinson & Dalton, *2009*). Dans le cas d'une lutte contre les helminthes par administration de chémothérapies aux animaux infectés ou susceptibles de l'être, les individus capables d'infecter des hôtes humains pourraient posséder un avantage sélectif si ces hôtes humains ne sont pas traités et constituent donc des refuges. Lorsque ces espèces animales, comme les animaux domestiques ou le bétail, sont sympatriques de l'homme, l'action des chémothérapies appliquées aux hôtes animaux pourrait donc favoriser l'émergence de parasites mieux adaptés à l'homme selon des processus de diversification adaptative (Giraud et al., *2010*), et donc augmenter les risques de zoonoses. A une époque où le traitement des animaux est tel qu'il peut conduire à la rapide évolution de leurs parasites (évolution de la résistance par exemple), le développement d'une théorie de la diversification adaptative des parasites prenant en compte la diversité d'hôtes permettrait donc de mieux évaluer si ces risques de zoonoses sont purement spéculatifs, ou au contraire, représentent des perspectives plausibles et qu'il faut donc chercher à mieux apréhender.

Conclusion générale

Que ce soit pour l'étude de la transmission des maladies vectorielles ou de la diversification compétitive des macro-parasites, les approches développées au cours de cette thèse sont enracinées dans la littérature théorique classique en écologie et épidemiologie (Anderson & May, *1992*; Smith et al., *2012*). Celle la même qui a servit à la fois à établir des principes généraux et à réaliser des travaux plus spécifiques sur l'écologie et le contrôle de systèmes biologiques particuliers (voir chapitre 1). Malgré le manque d'un certain nombre de données empiriques (chapire 5), ces théories écologiques ont donc généralement pu être testées et exploitées, tout du moins leur principales prédictions. En ce qui concerne plus spécifiquement les maladies tropicales négligées, il reste néanmoins des domaines très peu abordés, notamment l'évolution de la transmission de ces maladies (voir chapitre 1). L'étude des maladies tropicales négligées bénéficierait donc grandement de plus grands apports théoriques, en particulier ceux faisant le lien entre micro-évolution des parasites et vecteurs et les méthodes employées pour leur contrôle. Il est en effet assez évident que les grands efforts faits au cours des dernières années voire décennies pour protéger les populations humaines dans le monde entier ont conduit à des processus d'adaptation de ces derniers. Ceci laisse les pouvoirs publiques dans des situations très difficiles, par exemple pour lutter contre les vecteurs de maladies aussi répandues que la malaria, la dengue ou la maladie de Chagas. Il est donc prévisible que des situations épidemiques de moins en moins controlables soient de plus en plus dramatiques. Les approches théoriques ont ici un rôle essentiel à jouer dans l'optimisation du temps de recherche mobilisé collectivement dans la lutte contre les parasites qui continuent à nous affecter. En facilitant l'identification de principes communs et des spécificités de l'évolution de la transmission de ces divers maladies, ces approches peuvent permettrent de mutualiser les efforts de recherche et ainsi de gagner un temps précieux dans des contextes difficiles sur les plans scientifiques, financiers et éthiques.

Références bibliographiques

Abad-Franch F, Ferraz G, Campos C, et al. (2010) Modeling disease vector occurrence when detection is imperfect: infestation of Amazonian palm trees by triatomine bugs at three spatial scales. *PLoS Negl Trop Dis.* 4:e620.

Alizon S, van Baalen M (2008) Multiple Infections, Immune Dynamics, and the Evolution of Virulence. Am Nat 172(4):E150-68.

Altizer S, Bartel R, Han BA (2011) Animal migration and infectious disease risk. *Science* 331:296-302.

Anderson, RM. & May, RM. (1992). *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Artzrouni M. & Gouteux JP. (1996) A compartmental model of sleeping sickness in central Africa. *J Biol Syst*., 4(4):459-477

Arguin PM, Marano N, Freedman DO (2009) Globally mobile populations and the spread of emerging pathogens. *Emerg Infect Dis.* 15(11):1713-4.

Baber I, Keita M, Sogoba N et al. (2010) Population size and migration of *Anopheles gambiae* in the Bancoumana Region of Mali and their significance for efficient vector control. *PLoS One* 21:e10270.

Barbu C, Dumonteil E, Gourbière S (2010). Characterization of the dispersal of non-domiciliated Triatoma dimidiata through the selection of spatially explicit models. *PLoS Negl Trop Dis* 4(8):e777.

Barbu C, Dumonteil E, Gourbière S (2011). Evaluation of spatially targeted strategies to control non-domiciliated Triatoma dimidiata vector of Chagas disease. *PLoS Negl Trop Dis* 5(5):e1045.

Barluenga M, Stölting KN, Salzburger W, et al. (2006) Sympatric speciation in Nicaraguan crater lake cichlid fish. *Nature* 439:719-723.

van den Berg H, Zaim M, Yadav RS, et al. (2012) Global trends in the use of insecticides to control vector-borne diseases. *Environ Health Perspect.* 120(4):577-82.

Bhunia GS, Kesari S, Chatterjee N, et al. (2011) Incidence of visceral leishmaniasis in the Vaishali district of Bihar, India: spatial patterns and role of inland water bodies. *Geospat Health.* 5(2):205-15.

Bourguinat C, Pion SD, Kamgno J, et al. (2006) Genetic polymorphism of the beta-tubulin gene of *Onchocerca volvulus* in ivermectin naïve patients from Cameroon, and its relationship with fertility of the worms. *Parasitology*. 132(2):255-62.

Bourguinat C, Pion SDS, Kamgno J, et al. (2007) Genetic Selection of Low Fertile *Onchocerca volvulus* by Ivermectin Treatment. *PLoS Negl Trop Dis* 1(1): e72.

Bouyer J, Balenghien T, Ravel , et al. (2009) Population sizes and dispersal pattern of tsetse flies : rolling over the river ? *Mol Ecol* 18:2787-2797.

Bowman AS & Nuttall PA (2009) *Ticks: biology, disease and control.* Cambridge University Press.

Brooker S (2010) Estimating the global distribution and disease burden of intestinal nematode infections: adding up the numbers – a review. *Int J Parasitol* 40:1137-1144.

Brun R, Blum J, Chappuis F, et al. (2010) Human African trypanosomiasis. *Lancet* 375 :148-159.

C. elegans Sequencing Consortium. (1998) Genome sequence of the nematode *C. elegans*: a platform for investigating biology. *Science.* 282(5396):2012-8.

Canaris AG, Kinsella JM. (2001) Helminth parasites in six species of shorebirds (Charadrii) from the coast of Belize. Mem Inst Oswaldo Cruz. 96(6):827-30.

Carbajal de la Fuente AL, Minoli SA, Lopes CM, et al. (2007) Flight dispersal of the Chagas disease vectors *Triatoma brasiliensis* and *Triatoma pseudomaculata* in northeastern Brazil. *Acta Trop* 101: 115–119.

Carter R, Mendis KN, Roberts D (2000) Spatial targeting of interventions against malaria. *Bulletin of the World Health Organization*, 78: 1401–1411.

Center for Disease Control and Prevention (CDC).
- a. Information on arboviral encephalitides. Disponible en ligne à http://www.cdc.gov/
- b. Onchocerciasis. Disponible en ligne à www.cdc.gov/parasites/onchocerciasis/disease.html

Center for Food Security and Public Health (CFSPH)
- (2007). JAPE_A2007. Disponible en ligne à www.cfsph.iastate.edu/Factsheets/pdfs/japanese_encephalitis.pdf.
- (2009) African animal trypanosomiasis. Disponible en ligne à www.cfsph.iastate.edu/Factsheets/pdfs/trypanosomiasis_african.pdf

Churcher TS & Basáñez MG. (2008) Density dependence and the spread of anthelmintic resistance. *Evolution.* 62(3):528-37.

Churcher TS, Ferguson NM, Basáñez MG. (2005) Density dependence and overdispersion in the transmission of helminth parasites. *Parasitology* 131(Pt 1):121-32.

Cohen JE. (2004) Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better. *PLoS Biol* 2(12):e439.

Colwell DD, Dantas-Torres F, Otranto D (2011) Vector-borne parasitic zoonoses: emerging scenarios and new perspectives. *Vet Parasitol* 182(1):14-21.

Conteh L, Engels T, Molyneux DH (2010) Socioeconomic aspects of neglected tropical diseases. *Lancet* 375(9710):239-47.

Cooney CM (2011) Climate Change and Infectious Disease: Is the Future Here? *Environ Health Perspect.* 119(9):a394–a397.

da Costa-Ribeiro MC, Lourenço-de-Oliveira R, Failloux AB. (2007) Low gene flow of *Aedes aegypti* between dengue-endemic and dengue-free areas in southeastern and southern Brazil. *Am J Trop Med Hyg*. 77(2):303-9.

Coutinho F, Massad E, Menezes R, et al. (1999) A theoretical model of the evolution **of** v irulence in sexually transmitted HIV/AIDS. *Rev Saude Publica* 33(4):329-33.

Coyne JA, Orr HA (2004) *Speciation.* Sinauer Associates, Sunderland, MA.

Derraik JGB (2006) A Scenario for Invasion and Dispersal of *Aedes albopictus* (Diptera: Culicidae) in New Zealand. *J Med Entomol* 43(1):1D8.

Dezfuli BS, Volponi S, Beltrami I, et al. (2002) Intra- and interspecific density-dependent effects on growth in helminth parasites of the cormorant, *Phalacrocorax carbo sinens*is. Parasitology. 124(5):537-44.

Dias PC (1996) Sources and sinks in population biology. *Trends Ecol Evol* 11:326-330.

Dieckmann U & Doebeli M (1999) On the origin of species by sympatric speciation. *Nature* 400:354-367.

Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K (2002) *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management*. Cambridge University Press. 552p.

Dieckmann U, Doebeli M, Metz JAJ, Tautz D (2004) *Adaptive speciation*. Cambridge University Press.

Diekmann O & Heesterbeek JAP (2000) *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis, and Interpretation*. John Wiley and Sons. 303p.

Dobler G. (2010) Zoonotic tick-borne flaviviruses. *Vet Microbiol*. 140(3-4):221-8.

Doebeli M, Dieckmann U (2000) Evolutionary branching and sympatric speciation caused by different types of ecological interactions. *Am Nat* 156:S77-S101.

Dumonteil E, Ramirez-Sierra MJ, Ferral J, et al. (2009) Usefulness of community participation for the fine temporal monitoring of house infestation by non-domiciliated triatomines. *J Parasitol* 95:469-471.

Emelianov I (2007) How adaptive is parasite species diversity ? *Int J Parasitol* 37:851-860.

Emerson PM, Ngondi J, Biru E, et al. (2008) Integrating an NTD with one of "The big three": combined malaria and trachoma survey in Amhara Region of Ethiopia. *PLoS Negl Trop Dis* 2(3):e197.

Enserink M (2008) Entomology. A mosquito goes global. *Science* 320(5878):864-6.

Estrada-Peña A, Ayllón N, de la Fuente J. (2012) Impact of climate trends on tick-borne pathogen transmission. *Front Physiol.* 3:64.

Feasey N, Wansbrough-Jones M, Mabey DCW, et al. (2010) Neglected tropical diseases. *British Medical Bulletin* 93:179–200.

Fenwick A (2012) The global burden of neglected tropical diseases. *Public Health* 126(3):233-6.

Fincham JE, Markus MB, Adams VJ (2003) Could control of soil-transmitted helminthic infection influence the HIV/AIDS pandemic. *Acta Trop* 86:315–333.

First WHO report on neglected tropical diseases 2010: working to overcome the global impact of neglected tropical diseases.
www.who.int/neglected_diseases/2010report/en/index.html

Frew SE, Liu VY, Singer PA (2009) A business plan to help the 'global South' in its fight against neglected diseases. *Health Aff (Millwood)* 28(6):1760-73.

Gavrilets S (2004) *Fitness landscapes and the origin of species (Monographs in Population Biology)*. Princeton University Press.

Gavrilets S, Vose A (2007) Case studies and mathematical models of ecological speciation. 2. Palms on an oceanic island. *Mol Ecol* 16:2910-2921.

Gavrilets S, Vose A, Barluenga M, et al. (2007) Case studies and mathematical models of ecological speciation. 1. Cichlids in a crater lake. *Mol Ecol* 16:2893-2909.

Geerts S, Gryseels B (2000) Drug resistance in human helminths: current situation and lessons from livestock. *Clin Microbiol Rev* 13:207–222.

Gill JH & Lacey E. (1998) Avermectin/milbemycin resistance in trichostrongyloid nematodes. *Int J Parasitol.* 28(6):863-77.

Giraud T (2006) Speciation in parasites: host switching does not automatically lead to allopatry. *Trends Parasitol* 22:151-152.

Giraud T, Gladieux P, Gavrilets S (2010) Linking the emergence of fungal plant diseases with ecological speciation. *Trends Ecol Evol* 25:387-395.

Giraud T, Gourbière S (2011) The tempo and modes of evolution of reproductive isolation in fungi. *Manuscript in revision.*

Githeko AK, Lindsay SW, Confalonieri UE, et al. (2000) Changement climatique et maladies à transmission vectorielle: une analyse régionale. *Bull World Health Org* 78:1136-1147.

Gold MR, Stevenson D, Fryback DG (2002) HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annu Rev Public Health* 23:115-134.

Goldberg DE, Siliciano RF, Jacobs WR Jr (2012) Outwitting Evolution: Fighting Drug-Resistant TB, Malaria, and HIV. *Cell* 148(6):1271-83.

González C, Wang O, Strutz SE, et al. (2010) Climate change and risk of leishmaniasis in North America: Predictions from ecological niche models of vector and reservoir species. *PLoS Negl Trop Dis* 4:e585.

Gourbière, S. (2004) How do natural and sexual selection contribute to sympatric speciation ? *J. Evol. Biol.* 17, 1207-1309.

Gourbière S, Dumonteil E, Rabinovich JE, et al. (2008) Demographic and dispersal constraints for domestic infestation by non-domiciliated Chagas disease vectors in the Yucatán peninsula, Mexico. *Am J Trop Med Hyg* 78:133-139.

Gourbière S, Mallet J (2010) Are species real ? The shape of the species boundary with exponential failure, reinforcement, and the "missing snowball". *Evolution* 64(1):1-24.

Gouteux JP, Marc Artzrouni M (2000). Persistance et résurgence de la maladie du sommeil à *Trypanosoma brucei gambiense* dans les foyers historiques. Approche biomathématique d'une énigme épidémiologique. Life Sciences 323:351–364.

Hargrove JW (2000) A theoretical study of the invasion of cleared areas by tsetse flies (Diptera: Glossinidae). *Bulletin of Entomological Research* 90, 201–209.

Himeidan YE, Elzaki MM, Kweka EJ, et al. (2011) Pattern of malaria transmission along the Rahad River basin, Eastern Sudan. *Parasit Vectors.* 16;4:109.

Hotez PJ, Molyneux DH, Fenwick A, et al. (2006) Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. *PLoS Med* 3(5):e102.

Hotez PJ, Molyneux DH, Fenwick A, et al. (2007) Control of Neglected Tropical Diseases. *N Engl J Med* 357:1018-27.

Hotez PJ (2008) Neglected Infections of Poverty in the United States of America. *PLoS Negl Trop Dis* 2(6):e256.

Jackson F. (1993) Anthelmintic resistance--the state of play. *Br Vet J.* 149(2):123-38.

Jancek S, Gourbière S, Moreau H, et al. (2008) Clues about the genetic basis of adaptation emerge from comparing the proteomes of two *Ostreococcus* ecotypes (Chlorophyta, Prasinophyceae). *Mol Biol Evol* 25:2293-2300.

Kealey A & Smith R (2010) Neglected tropical diseases: infection, modeling, and control. *J Health Care Poor Underserved* 21(1):53-69.

Killeen GF, Knols BGJ, Gu W (2003). Taking malaria transmission out of the bottle: implications of mosquito dispersal for vectorcontrol interventions. *The Lancet Infectious Diseases* 3:297-303.

Kirkpatrick M & Nuismer SL. (2004) Sexual selection can constrain sympatric speciation. *Proc Biol Sci.* 271(1540):687-93.

Knudsen R, Amundsen PA, Klementsen A (2002) Parasite-induced host mortality: indirect evidence from a long-term study. *Env Biol Fishes* 64:257-265.

Koella JC & Boëte C (2003) A model for the coevolution of immunity and immune evasion in vector-borne diseases with implications for the epidemiology of malaria. *Am Nat* 161(5):698-707.

Konnai S, Yamada S, Imamura S, et al. (2007) Attachment duration required for Rhipicephalus appendiculatus to transmit Theileria parva to the host. Vector Borne Zoonotic *Dis.* 7(2):241-8.

Kovats RS, Campbell-Lendrum DH, McMichael AJ, et al. (2001) Early effects of climate change: do they include changes in vector-borne diseases ? *Philos Trans R Soc Lond B Biol Sci* 356:1057-1068.

Krafsur ES. (2003) Tsetse fly population genetics: an indirect approach to dispersal. *TRENDS in Parasitol.* 19(4), 162-166.

Kubiak RJ, Arinaminpathy N, McLean AR (2010) Insights into the evolution and emergence of a novel infectious disease. *PLoS Comput Biol* 6(9). pii:e1000947.

Kumar V, Kesari S, Kumar AJ, et al. (2009). Vector density and the control of kala-azar in Bihar, India. *Mem Inst Oswaldo Cruz 104*(7):1019-1022.

Kunz W. (2002) When is a parasite species a species? Trends Parasitol. 18(3):121-4.

Levy MZ, Quíspe-Machaca VR, Ylla-Velasquez JL, et al. (2008) Impregnated netting slows infestation by *Triatoma infestans*. *Am J Trop Med Hyg*. 79(4):528-34.

Lord CC (2007) Modeling and biological control of mosquitoes. *J Am Mosq Control Assoc* 23(2 Suppl):252-64.

Luz PM, Struchiner CJ, Galvani AP (2010) Modeling Transmission Dynamics and Control of Vector-Borne Neglected Tropical Diseases. *PLoS Negl Trop Dis* 4(10):e761.

Lo CM & Morand S (2000) Spatial distribution and coexistence of monogenean gill parasites inhabiting two damselfishes from Moorea island in French Polynesia. *J Helminthol* 74:329-336.

May RM (2007) Parasites, people and policy: infectious diseases and the Millennium Development Goals. *Trends Ecol Evol* (10):497-503.

de Meeûs T, Michalakis Y, Renaud F (1998) Santa Rosalia revisited: or why are there so many kinds of parasites in the garden of earthly delights ? *Parasitol Today* 14:10-13.

Mideo N. (2009) Parasite adaptations to within-host competition. Trends Parasitol. 25(6):261-8.

Midzi N, Mtapuri-Zinyowera S, Mapingure MP, et al. (2010) Consequences of polyparasitism on anaemia among primary school children in Zimbabwe. *Acta Trop* 115(1-2):103-11.

Molyneux DH, Baldry DA, Fairhurst C. (1979) Tsetse movement in wind fields: possible epidemiological and entomological implications for trypanosomiasis and its control. *Acta Trop*. 36(1):53-65.

Moore J, Simberloff D (1990) Gastrointestinal helminth communities of bobwhite quail. *Ecology* 7(1):344-359.

Murray RL, Kozlowska JL, Cutter AD. (2011) Heritable determinants of male fertilization success in the nematode *Caenorhabditis elegans*. *BMC Evol Biol*. 14;11:99.

Mwangi TW, Bethony JM, Brooker S (2006) Malaria and helminth interactions in humans: an epidemiological viewpoint. *Ann Trop Med Parasitol* 100(7):551-70.

National Center for Biotechnology Information (NCBI), Pubmed.
www.ncbi.nlm.nih.gov/pubmed/

Organisation Mondiale de la Santé (OMS).
www.who.int/gho/mortality_burden_disease/en/index.html

Osei-Atweneboana MY, Eng JK, Boakye DA, et al. (2007) Prevalence
and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. *Lancet* 369:2021–2029.

Osnas EE, Dobson AP (2012) Evolution of virulence in heterogeneous host communities under multiple trade-offs. *Evolution* 66(2):391-401.

Otto SP, Day T (2001) *A Biologist's Guide to Mathematical Modeling in Ecology and Evolution*. Princeton University Press. 752p.

Pates H, Curtis C (2005). Mosquito behaviour and vector control. *Annu. Rev. Entomol* 50:53-70.

Payne L, Fitchett JR (2010) Bringing neglected tropical diseases into the spotlight. *Trends Parasitol* 26(9):421-3.

Pedersen AB & Fenton A (2007) Emphasizing the ecology in parasite community ecology. *TRENDS in Ecology and Evolution* 22(3): 133-139.

Peter RJ, Van den Bossche P, Penzhorn BL, Sharp B. (2005) Tick, fly, and mosquito control--lessons from the past, solutions for the future. *Vet Parasitol.* 132(3-4):205-15.

Pinkerton SD (2011) HIV Transmission Rate Modeling: A Primer, Review, and Extension. *AIDS Behav* (Epub ahead of print).

Polonio R, Ramirez-Sierra MJ, Dumonteil E (2009) Dynamics and distribution of house infestation by *Triatoma dimidiata* in central and southern Belize. *Vector Borne Zoonotic Dis*

9: 19–24.

Poulin R (1999) Speciation and diversification of parasite lineages: an analysis of congeneric parasite species in vertebrates. *Evol Ecol* 13:455–67.

Poulin R, Morand S (2004) *Parasite Biodiversity*, Smithsonian Books, Washington.

Price PW (1980) *Evolutionary Biology of Parasites*, Princeton University Press, Princeton.

Pulliam HR (1988) Sources, sinks, and population regulation. *American Naturalist* 132:652-661.

Raghavendra K, Barik TK, Reddy BP, et al. (2011) Malaria vector control: from past to future. *Parasitol Res* 108(4):757-79.

Robinson MW, Dalton JP. (2009) Zoonotic helminth infections with particular emphasis on fasciolosis and other trematodiases. *Philos Trans R Soc Lond B Biol Sci.* 364(1530):2763-76.

Rogers DJ, Randolph SE, Kuzoe FA (1984) Local variation in the population dynamics of *Glossina palpalis palpalis* (Robineau-Desvoidy) (Diptera: Glossinidae). I. Natural population regulation. *Bull Entomol Res* 74:403-423.

Salazar Schettino PM, Rosales Pina JS, Rojas Wastavino G, et al. (2007) *Triatoma mexicana* (Hemiptera: Reduviidae) in Guanajuato, Mexico: house infestation and seasonal variation. *Mem Inst Oswaldo Cruz* 102: 803–807.

Sarkar S, Strutz SE, Frank DM, et al. (2010) Chagas disease risk in Texas. *PLoS Negl Trop Dis* 4(10) pii:e836.

Service, MW (1997) Mosquito (Diptera: Culicidae) Dispersal—The Long and Short of It. *J Med Entomol.* 34(6), 579-588.

Shostak AW & and Dick TA (1989) Helminth Position within the Intestine of Naturally Infected Pike (*Esox lucius*) Relative to Host Stomach Contents. *The Journal of Parasitology* 75(6), 905-910.

Silva F, Gomes R, Prates D, et al. (2005). Inflammatory cell infiltration and high antibody production in BALB/c mice caused by natural exposure to *Lutzomyia longipalpis* bites. *Am J Trop Med Hyg. 72*:94-98.

Šimková, A., Ondračková, M., Gelnar, M., Morand, S. (2002) Morphology and coexistence of congeneric ectoparasite species: reinforcement of reproductive isolation ? *Biol. J. Linn. Soc.* 76, 125-135.

Šimková A, Morand S, Jobet E, et al. (2004) Molecular phylogeny of congeneric monogenean parasites (*Dactylogyrus*): a case of intrahost speciation. *Evolution* 58:1001-1018.

Singh SP, Picado A, Boelaert M, et al. (2010) The epidemiology of *Leishmania donovani* infection in high transmission foci in India. *Trop Med Int Health.* 15(2):12-20.
Smith DL, Dushoff J, McKenzie FE (2004) The risk of a mosquito-borne infection in a

heterogeneous environment. *PLoS Biol* 2(11): e368.

Smith DL, Battle KE, Hay SI, et al. (2012) Ross, macdonald, and a theory for the dynamics and control of mosquito-transmitted pathogens. *PLoS Pathog* 8(4):e1002588.

Smits HL (2009) Prospects for the control of neglected tropical diseases by mass drug administration. *Expert Rev Anti Infect Ther. 7(1), 37-56.*

Stancampiano L, Mughini Gras L, Poglayen G. (2010) Spatial niche competition among helminth parasites in horse's large intestine. *Vet Parasitol.* 170(1-2):88-95.

Stock, T. M. & Holmes, J. C. (1988) Functional relationships and microhabitats distributions of enteric helminths of grebes (Podicipedidae): the evidence for interactive communities. *J. Parasitol.* 74, 214-227.

Sundar S, Makharia A, More DK, et al. (2000) Short-course of oral miltefosine for treatment of visceral leishmaniasis. *Clin Infect Dis* 31:1110–1113.

Symeonakis E, Robinson T, Drake N. (2007) GIS and multiple-criteria evaluation for the optimisation of tsetse fly eradication programmes. *Environ Monit Assess.* 124(1-3):89-103.

Tatem AJ, Rogers DJ, Hay SI (2006) Global transport networks and infectious disease spread. *Adv Parasitol* 62:293-343.

Thomas JD (2002) The ecology of fish parasites with particular reference to helminth parasites and their salmonid fish hosts in Welsh rivers: a review of some of the central questions. *Adv Parasitol* 52:1-154.

Varmus H, Klausner R, Zerhouni E, et al. (2003) Public health. Grand Challenges in Global Health. *Science* 302(5644):398-9.

Vazeille M, Jeannin C, Martin E, et al. (2008) Chikungunya: a risk for Mediterranean countries? *Acta Trop* 105(2):200-2.

Vitasek J (2004) A review of rabies elimination in Europe. *Vet Med Czech* 49(5):171–185.

Wahala WM, Silva AM (2011) The human antibody response to dengue virus infection.*Viruses* 3(12):2374-95.

Weissing FJ, Edelaar P, van Doorn GS (2011) Adaptive speciation theory: a conceptual review. *Behav Ecol Sociobiol* 65:461-480.

Weaver SC, Reisen WK. (2010) Present and future arboviral threats. *Antiviral Res*. 85(2):328-45.

de Wet N, Ye W, Hales S, et al. (2001) Use of a computer model to identify potential hotspots for dengue fever in New Zealand. *N Z Med J* 114(1140):420-2.

Winslow CEA (1951) The cost of sickness and the price of health. Word Health Organization. *Bull World Health Organ* 84(2):153–158.

Wonham MJ, Lewis MA, Renclawowicz J, et al. (2006) Transmission assumptions generate conflicting predictions in host-vector disease models: a case study in West Nile virus. *Ecol Lett* 9:706-725.

World Health Statistics 2011, Organisation Mondiale de la Santé, 171p. Disponible en ligne à http://www.who.int/gho/publications/world_health_statistics/EN_WHS2011_Full.pdf

Zu Dohna H, Cecere MC, Gurtler RE, et al. (2009). Spatial re-establishment dynamics of local populations of vectors of Chagas disease. *PLoS Negl Trop Dis*. 3(7):e490.

Guilhem Rascalou

Écologie, évolution et contrôle des maladies tropicales négligées

Annexes

Annexe A

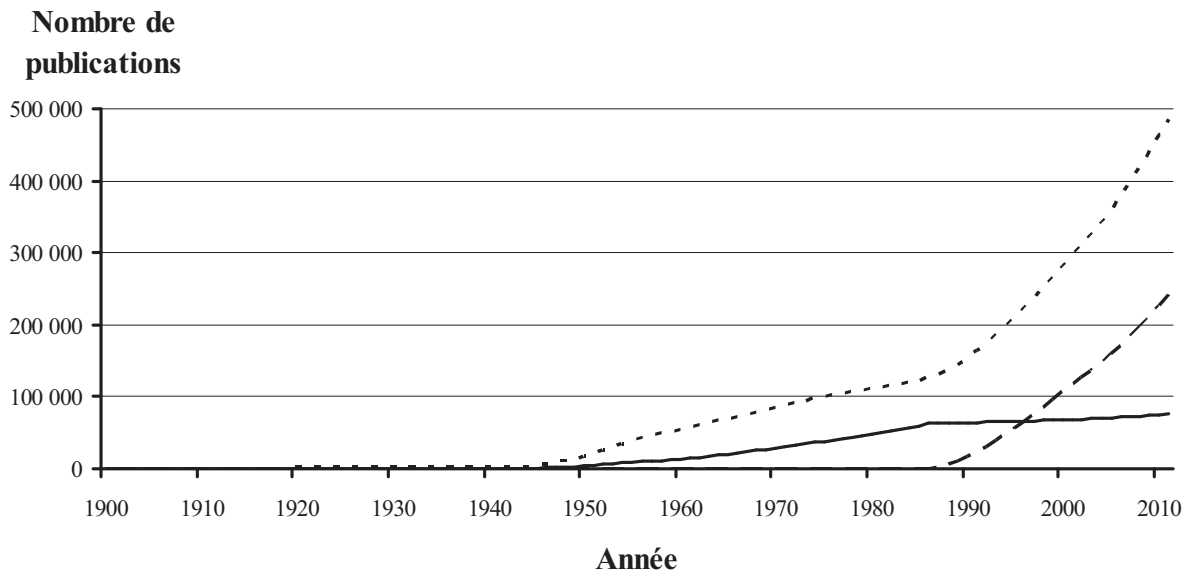
Détails des résultats du chapitre 1

A.1. Mots clefs utilisés dans Pubmed pour la recherche de publications par maladies.

Sida – HIV
Tuberculose – tuberculosis
Malaria – malaria
Total Big three – (HIV)OR(tuberculosis)OR(malaria)

Rage – rabies
Dengue – dengue
Lèpre – leprosy
Trachome – trachoma
Pian – yaws
Ulcère de Buruli – (Buruli)AND(ulcer)
Maladie du sommeil – ((sleeping)AND(sickness))OR((human)AND(African)AND(trypanosomiasis))
Leishmaniose – leishmaniasis
Maladie de Chagas - ((Chagas)AND(disease))OR((American)AND(trypanosomiasis))
Cysticercose - cysticercosis
Schistosomiase - (schistosomiasis)OR(bilharzia)
Helminthiases intestinales - (ascariasis)OR(trichocephaliasis)OR(ankylostomiasis)
Strongyloidose - strongyloidiasis
Echinococcose – echinococcosis
Filariose lymphatique – (lymphatic)AND(filariasis)
Onchocerciase – onchocerciasis
Fasciolase – (fascioliasis)OR(fasciolosis)
Dracunculose – (dracunculiasis)OR((Guinea)AND(worm))
Total maladie tropicales negligees (NTD) – Comme pour les Big three, les noms de toutes les maladies ont été inclus dans une seule et même recherche.

Figure A.1. Nombre de résultats Pubmed cumulés entre 1900 et 2011 pour le sida (tirés), les Big three (pointillés) et les maladies tropicales négligées (trait plein).



A.2. Publications sur l'écologie, l'évolution et le contrôle des maladies tropicales négligées.

Liste et thématique des travaux faisant appel à des modèles de types systèmes dynamiques.

La numérotation attribuée à chaque publication est ensuite réutilisée dans les tableaux A.1, A.2 et A.3 . La thématique dans laquelle chaque publication a été classée dans le chapitre 1 est indiquée par une étoile (*) pour Contrôle, deux étoiles (**) pour Evolution, et aucune étoile pour Ecologie.

Cysticercose

1* - Kyvsgaard NC, Johansen MV, Carabin H (2007). Simulating transmission and control of Taenia solium infections using a Reed-Frost stochastic model. Int J Parasitol. 37(5):547-58.

Dengue

2** - Adams B, Boots M (2006). Modelling the relationship between antibody-dependent enhancement and immunological distance with application to dengue. J Theor Biol. 242(2):337-46.

3 - Adams B, Boots M (2010). How important is vertical transmission in mosquitoes for the persistence of dengue? Insights from a mathematical model. Epidemics. 2(1):1-10.

4* - Atkinson MP, Su Z, Alphey N, Alphey LS, Coleman PG, Wein LM (2007). Analyzing the control of mosquito-borne diseases by a dominant lethal genetic system. Proc Natl Acad Sci U S A. 104(22):9540-5.

5 - Bacaër N, Gomes MG (2009). On the final size of epidemics with seasonality. Bull Math Biol. 71(8):1954-66.

6 - Barbazan P, Guiserix M, Boonyuan W, Tuntaprasart W, Pontier D, Gonzalez JP (2010). Modelling the effect of temperature on transmission of dengue. Med Vet Entomol 24(1):66-73.

7 - Bartley LM, Donnelly CA, Garnett GP (2002). The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Trans R Soc Trop Med Hyg. 96(4):387-97.

8 - Bianco S, Shaw LB, Schwartz IB (2009). Epidemics with multistrain interactions: the interplay between cross immunity and antibody-dependent enhancement. Chaos. 19(4):043123.

9 - Bianco S, Shaw LB (2011). Asymmetry in the presence of migration stabilizes multistrain disease outbreaks. Bull Math Biol. 73(1):248-60.

10* - Brownstein JS, Hett E, O'Neill SL (2003). The potential of virulent Wolbachia to modulate disease transmission by insects. .J Invertebr Pathol. 84(1):24-9.

11* - Burattini MN, Chen M, Chow A, Coutinho FA, Goh KT, Lopez LF, Ma S, Massad E (2008). Modelling the control strategies against dengue in Singapore. Epidemiol Infect. 136(3):309-19.

12 - de Castro Medeiros LC, Castilho CA, Braga C, de Souza WV, Regis L, Monteiro AM (2011). Modeling the dynamic transmission of dengue fever: investigating disease persistence. PLoS Negl Trop Dis.5(1):e942.

13 - Chikaki E, Ishikawa H (2009). A dengue transmission model in Thailand considering sequential infections with all four serotypes. J Infect Dev Ctries. 3(9):711-22.

14 - Chowell G, Diaz-Dueñas P, Miller JC, Alcazar-Velazco A, Hyman JM, Fenimore PW, Castillo-Chavez C (2007). Estimation of the reproduction number of dengue fever from spatial epidemic data. Math Biosci. 208(2):571-89.

15** - Christofferson RC, Mores CN (2011). Estimating the magnitude and direction of altered arbovirus transmission due to viral phenotype. PLoS One. 6(1):e16298.

16 - Coutinho FA, Burattini MN, Lopez LF, Massad E (2006). Threshold conditions for a non-autonomous epidemic system describing the population dynamics of dengue. Bull Math Biol. 68(8):2263-82.

17** - Cummings DA, Schwartz IB, Billings L, Shaw LB, Burke DS (2005). Dynamic effects of antibody-dependent enhancement on the fitness of viruses. Proc Natl Acad Sci U S A. 102(42):15259-64.

18 - Cummings DA, Iamsirithaworn S, Lessler JT, McDermott A, Prasanthong R, Nisalak A, Jarman RG, Burke DS, Gibbons RV (2009). The impact of the demographic transition on dengue in Thailand: insights from a statistical analysis and mathematical modeling. PLoS Med. 6(9):e1000139.

19 - Degallier N, Favier C, Boulanger JP, Menkes C (2009). Imported and autochthonous cases in the dynamics of dengue epidemics in Brazil. Rev Saude Publica. 43(1):1-7.

20 - Derouich M, Boutayeb A, Twizell EH (2003). A model of dengue fever. Biomed Eng Online. 19;2:4.

21* - Devine GJ, Perea EZ, Killeen GF, Stancil JD, Clark SJ, Morrison AC (2009). Using adult mosquitoes to transfer insecticides to Aedes aegypti larval habitats. Proc Natl Acad Sci U S A. 106(28):11530-4.

22* - Egger JR, Ooi EE, Kelly DW, Woolhouse ME, Davies CR, Coleman PG (2008). Reconstructing historical changes in the force of infection of dengue fever in Singapore: implications for surveillance and control. Bull World Health Organ. 86(3):187-96.

23 - Esteva L, Vargas C (1998). Analysis of a dengue disease transmission model. Math Biosci. 150(2):131-51.

24 - Esteva L, Vargas C (1999). A model for dengue disease with variable human population. J Math Biol. 38(3):220-40.

25 - Esteva L, Vargas C (2000). Influence of vertical and mechanical transmission on the dynamics of dengue disease. Math Biosci. 167(1):51-64.

26 - Esteva L, Vargas C (2003). Coexistence of different serotypes of dengue virus. J Math Biol. 46(1):31-47.

27* - Esteva L, Mo Yang H (2005). Mathematical model to assess the control of Aedes aegypti mosquitoes by the sterile insect technique. Math Biosci. 198(2):132-47.

28 - Favier C, Schmit D, Müller-Graf CD, Cazelles B, Degallier N, Mondet B, Dubois MA (2005). Influence of spatial heterogeneity on an emerging infectious disease: the case of dengue epidemics. Proc Biol Sci. 272(1568):1171-7.

29 - Favier C, Degallier N, Rosa-Freitas MG, Boulanger JP, Costa Lima JR, Luitgards-Moura JF, Menkès CE, Mondet B, Oliveira C, Weimann ET, Tsouris P (2006). Early determination of the reproductive number for vector-borne diseases: the case of dengue in Brazil. Trop Med Int Health. 11(3):332-40.

30 - Feng Z, Velasco-Hernández JX (1997). Competitive exclusion in a vector-host model for the dengue fever. J Math Biol. 35(5):523-44.

31 - Ferguson NM, Donnelly CA, Anderson RM (1999). Transmission dynamics and epidemiology of dengue: insights from age-stratified sero-prevalence surveys. Philos Trans R Soc Lond B Biol Sci. 354(1384):757-68.

32 - Fischer DB, Halstead SB (1970). Observations related to pathogenesis of dengue hemorrhagic fever. V. Examination of agspecific sequential infection rates using a mathematical model. Yale J Biol Med. 42(5):329-49.

33 - Focks DA, Haile DG, Daniels E, Mount GA (1993). Dynamic life table model for Aedes aegypti (diptera: Culicidae): simulation results and validation. J Med Entomol. 30(6):1018-28.

34 - Focks DA, Daniels E, Haile DG, Keesling JE (1995). A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am J Trop Med Hyg. 53(5):489-506.

35 - Focks DA, Brenner RJ, Hayes J, Daniels E (2000). Transmission thresholds for dengue in terms of Aedes aegypti pupae per person with discussion of their utility in source reduction efforts. Am J Trop Med Hyg. 62(1):11-8.

36* - Garba SM, Gumel AB, Abu Bakar MR (2008). Backward bifurcations in dengue transmission dynamics. Math Biosci. 215(1):11-25.

37 - Heffernan JM, Smith RJ, Wahl LM (2005). Perspectives on the basic reproductive ratio. J R Soc Interface. (4):281-93.

38 - Hsieh YH, Chen CW (2009). Turning points, reproduction number, and impact of climatological events for multi-wave dengue outbreaks. Trop Med Int Health. 14(6):628-38.

39** - Huang Y, Magori K, Lloyd AL, Gould F (2007). Introducing desirable transgenes into insect populations using Y-linked meiotic drive - a theoretical assessment. Evolution. 61(4):717-26.

40** - Kawaguchi I, Sasaki A, Boots M (2003). Why are dengue virus serotypes so distantly related? Enhancement and limiting serotype similarity between dengue virus strains. Proc Biol Sci. 270(1530):2241-7.

41 - Luz PM, Codeço CT, Massad E, Struchiner CJ (2003). Uncertainties regarding dengue modeling in Rio de Janeiro, Brazil. *Mem Inst Oswaldo Cruz,* Rio de Janeiro, Vol. *98*(7): 871-878.

42** - Luz PM, Vanni T, Medlock J, Paltiel AD, Galvani AP (2011). Dengue vector control strategies in an urban setting: an economic modelling assessment. Lancet. 377(9778):1673-80.

43 - Maidana NA, Yang HM (2008). Describing the geographic spread of dengue disease by traveling waves. Math Biosci. 215(1):64-77.

44 - Margheri A, Rebelo C (2003). Some examples of persistence in epidemiological models. J Math Biol. 46(6):564-70.

45 - Massad E, Burattini MN, Coutinho FA, Lopez LF (2003). Dengue and the risk of urban yellow fever reintroduction in São Paulo State, Brazil. Rev Saude Publica. 37(4):477-84.

46 - Massad E, Ma S, Burattini MN, Tun Y, Coutinho FA, Ang LW (2008). The risk of chikungunya fever in a dengue-endemic area. J Travel Med. 15(3):147-55.

47 - Massad E, Wilder-Smith A (2009). Risk estimates of dengue in travelers to dengue endemic areas using mathematical models. J Travel Med. 16(3):191-3.

48 - Massad E, Coutinho FA, Burattini MN, Amaku M (2010). Estimation of R0 from the initial phase of an outbreak of a vector-borne infection. Trop Med Int Health. 15(1):120-6.

49** - Medlock J, Luz PM, Struchiner CJ, Galvani AP (2009). The impact of transgenic mosquitoes on dengue virulence to humans and mosquitoes. Am Nat. 174(4):565-77.

50* - Nagao Y, Koelle K (2008). Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever. Proc Natl Acad Sci U S A. 105(6):2238-43.

51 - Otero M, Solari HG, Schweigmann N (2006). A stochastic population dynamics model for Aedes aegypti: formulation and application to a city with temperate climate. Bull Math Biol. 68(8):1945-74. Epub 2006 Jul 11.

52 - Otero M, Schweigmann N, Solari HG (2008). A stochastic spatial dynamical model for Aedes aegypti. Bull Math Biol. 70(5) :1297-325

53 - Otero M, Solari HG (2010). Stochastic eco-epidemiological model of dengue disease transmission by Aedes aegypti mosquito. Math Biosci. 2010 Jan;223(1):32-46

54 - Patz JA, Martens WJ, Focks DA, Jetten TH (1998). Dengue fever epidemic potential as projected by general circulation models of global climate change. Environ Health Perspect. 106(3):147-53.

55* - Phuc HK, Andreasen MH, Burton RS, Vass C, Epton MJ, Pape G, Fu G, Condon KC, Scaife S, Donnelly CA, Coleman PG, White-Cooper H, Alphey L (2007). Late-acting dominant lethal genetic systems and mosquito control. BMC Biol. 5:11.

56* - Pinho ST, Ferreira CP, Esteva L, Barreto FR, Morato e Silva VC, Teixeira MG (2010). Modelling the dynamics of dengue real epidemics. Philos Transact A Math Phys Eng Sci. 368(1933):5679-93.

57 - Pongsumpun P, Tang IM (2001). A realistic age structured transmission model for dengue hemorrhagic fever in Thailand. Southeast Asian J Trop Med Public Health. 32(2):336-40.

58 - Pongsumpun P, Patanarapelert K, Sriprom M, Varamit S, Tang IM (2004). Infection risk to travelers going to dengue fever endemic regions. Southeast Asian J Trop Med Public Health. 35(1):155-9.

59 - Pongsumpun P, Garcia Lopez D, Favier C, Torres L, Llosa J, Dubois MA (2008). Dynamics of dengue epidemics in urban contexts. Trop Med Int Health. 13(9):1180-7.

60 - Recker M, Blyuss KB, Simmons CP, Hien TT, Wills B, Farrar J, Gupta S (2009). Immunological serotype interactions and their effect on the epidemiological pattern of dengue. Proc Biol Sci. 276(1667):2541-8.

59 - Schwartz IB, Shaw LB, Cummings DA, Billings L, McCrary M, Burke DS (2005). Chaotic desynchronization of multistrain diseases. Phys Rev E Stat Nonlin Soft Matter Phys. 72(6 Pt 2):066201.

60 - Shaw LB, Billings L, Schwartz IB (2007). Using dimension reduction to improve outbreak predictability of multistrain diseases. J Math Biol.55(1):1-19.

61 - Smith DL, Dushoff J, McKenzie FE (2004). The risk of a mosquito-borne infection in a heterogeneous environment. PLoS Biol. 2(11):e368.

62 - Stoddard ST, Morrison AC, Vazquez-Prokopec GM, Paz Soldan V, Kochel TJ, Kitron U, Elder JP, Scott TW (2009). The role of human movement in the transmission of vector-borne pathogens. PLoS Negl Trop Dis. 3(7):e481.

63* - Supriatna AK, Soewono E, van Gils SA (2008). A two-age-classes dengue transmission model. Math Biosci. 216(1):114-21.

67* - Thomé RC, Yang HM, Esteva L (2010). Optimal control of Aedes aegypti mosquitoes by the sterile insect technique and insecticide. Math Biosci. 223(1):12-23.

68 - Tran A, Raffy M (2006). On the dynamics of dengue epidemics from large-scale information. Theor Popul Biol. 69(1):3-12.

64 - Wearing HJ, Rohani P (2006). Ecological and immunological determinants of dengue epidemics. Proc Natl Acad Sci U S A. 103(31):11802-7.

69 - Wikramaratna PS, Simmons CP, Gupta S, Recker M (2010). The effects of tertiary and quaternary infections on the epidemiology of dengue. PLoS One. 5(8):e12347.

70 - Yang HM, Macoris Mde L, Galvani KC, Andrighetti MT (2011). Follow up estimation of Aedes aegypti entomological parameters and mathematical modellings. Biosystems. 103(3):360-71.

Echinococcose

71 - Azlaf R, Dakkak A, Chentoufi A, El Berrahmani M (2007). Modelling the transmission of Echinococcus granulosus in dogs in the northwest and in the southwest of Morocco. Vet Parasitol. 145(3-4):297-303. Epub 2007 Feb 7.

72 - Budke CM, Jiamin Q, Craig PS, Torgerson PR (2005). Modeling the transmission of Echinococcus granulosus and Echinococcus multilocularis in dogs for a high endemic region of the Tibetan plateau. Int J Parasitol. 35(2):163-70. Epub 2005 Jan 6.

73* - Hansen F, Tackmann K, Jeltsch F, Wissel C, Thulke HH (2003). Controlling Echinococcus multilocularis-ecological implications of field trials. Prev Vet Med. 60(1):91-105.

74* - Harris RE, Revfeim KJ, Heath DD (1980). Simulating strategies for control of Echinococcus granulosus, Taenia hydatigena and T. ovis. J Hyg (Lond). 84(3):389-404.

75 - Heinzmann D, Barbour AD, Torgerson PR (2009). Compound processes as models for clumped parasite data. Math Biosci. 222(1) :27-35.

76 - Ishikawa H, Ohga Y, Doi R (2003). A model for the transmission of Echinococcus multilocularis in Hokkaido, Japan. Parasitol Res. 91(6):444-51. Epub 2003 Oct 17.

77 - Ishikawa H (2006). Mathematical modeling of Echinococcus multilocularis transmission. Parasitol Int. 55 Suppl:S259-61.

78 - Kapel CM, Torgerson PR, Thompson RC, Deplazes P (2006). Reproductive potential of Echinococcus multilocularis in experimentally infected foxes, dogs, raccoon dogs and cats. Int J Parasitol. 36(1):79-86.

79 - Ming R, Tolley HD, Andersen FL, Chai J, Chang Q (1992). Frequency distribution of Echinococcus granulosus in dog populations in the Xinjiang Uygur Autonomous Region, China. Vet Parasitol. 43(3-4):233-41.

80 - Ming R, Tolley HD, Andersen FL, Chai J, Sultan Y (1992). Frequency distribution of Echinococcus granulosus hydatid cysts in sheep populations in the Xinjiang Uygur Autonomous Region, China. Vet Parasitol. 44(1-2):67-75.

81 - Roberts MG, Lawson JR, Gemmell MA (1986). Population dynamics in echinococcosis and cysticercosis: mathematical model of the life-cycle of Echinococcus granulosus. Parasitology. 92 (Pt 3):621-41.

82* - Roberts MG,Lawson JR , Gemmell MA (1987). Population dynamics in echinococcosis and cysticercosis: mathematical model of the life-cycles of Taenia hydatigena and T. ovis. Parasitology. 94 (Pt 1):181-97.

83* - Roberts MG (1994). Modelling of parasitic populations: cestodes. Vet Parasitol. 54(1-3):145-60.

84* - Roberts MG, Aubert MF (1995). A model for the control of Echinococcus multilocularis in France. Vet Parasitol. 56(1-3):67-74.

85* - Takumi K, Van der Giessen J (2005). Transmission dynamics of Echinococcus multilocularis; its reproduction number, persistence in an area of low rodent prevalence, and effectiveness of control. Parasitology. 131(Pt 1):133-40.

86* - Takumi K, de Vries A, Chu ML, Mulder J, Teunis P, van der Giessen J (2008). Evidence for an increasing presence of Echinococcus multilocularis in foxes in The Netherlands. Int J Parasitol. 38(5):571-8.

87 - Torgerson PR, Williams DH, Abo-Shehada MN (1998). Modelling the prevalence of Echinococcus and Taenia species in small ruminants of different ages in northern Jordan. Vet Parasitol. 79(1):35-51.

88* - Torgerson PR (2003). The use of mathematical models to simulate control options for echinococcosis. Acta Trop. 85(2):211-21.

89 - Torgerson PR, Burtisurnov KK, Shaikenov BS, Rysmukhambetova AT, Abdybekova AM, Ussenbayev AE (2003). Modelling the transmission dynamics of Echinococcus granulosus in sheep and cattle in Kazakhstan. Vet Parasitol. 114(2):143-53.

90 - Torgerson PR (2006). Canid immunity to Echinococcus spp.: impact on transmission. Parasite Immunol. 28(7):295-303.

91* - Torgerson PR (2006). Mathematical models for the control of cystic echinococcosis. Parasitol Int. 55 Suppl:S253-8.

92 - Vervaeke M, Davis S, Leirs H, Verhagen R (2006). Implications of increased susceptibility to predation for managing the sylvatic cycle of Echinococcus multilocularis. Parasitology. 132(Pt 6):893-901. Epub 2006 Feb 3.

Fasciolase

93 - Gettinby G, Hope-Cawdery MJ, Graingen JN (1974). Forecasting the incidence of fascioliasis from climatic data. Int J Biometeorol. 18(4):319-23.

94* - Smith G (1982). An analysis of variations in the age structure of Fasciola hepatica populations in sheep. Parasitology. 84(1):49-61.

95* - Smith G (1984). Chemotherapy of ovine fascioliasis: use of an analytical model to assess the impact of a series of discrete doses of anthelmintic on the prevalence and intensity of infection. Vet Parasitol. 16(1-2):95-106.

96* - Smith G (1984). The impact of repeated doses of anthelmintic on the intensity of infection and age structure of *Fasciola hepatica* populations in sheep. Vet Parasitol. 16(1-2):107-15.

97 - Smith G (1987). The regulation of trematode populations by density-dependent processes. Int J Parasitol. 17(2):541-8.

98* - Goodall EA, McIlroy SG, McCracken RM, McLoughlin EM, Taylor SM (1991). A Mathematical Forecasting-Model For the Annual Prevalence of Fascioliasis. Agricultural Systems. 36(2):231-240.

Filariose lymphatique

99 - Bundy DA, Grenfell BT, Rajagopalan PK (1991). Immunoepidemiology of lymphatic filariasis: the relationship between infection and disease. Immunol Today. 12(3):A71-5.

Helminthiases intestinales

100* - Bundy DA, Thompson DE, Cooper ES, Golden MH, Anderson RM. (1985). Population dynamics and chemotherapeutic control of Trichuris trichiura infection of children in Jamaica and St. Lucia. Trans R Soc Trop Med Hyg. 79(6):759-64.

101* - Chan MS, Guyatt HL, Bundy DA, Medley GF (1994). The development and validation of an age-structured model for the evaluation of disease control strategies for intestinal helminths. Parasitology. 109 (Pt 3):389-96.

102* - Chan MS (1997). The global burden of intestinal nematode infections--fifty years on. Parasitol Today. 13(11):438-43.

103* - Chan MS, Bradley M, Bundy DA (1997). Transmission patterns and the epidemiology of hookworm infection. Int J Epidemiol. 26(6):1392-400.

104 - Churcher TS, Ferguson NM, Basáñez MG (2005). Density dependence and overdispersion in the transmission of helminth parasites. Parasitology. 131(Pt 1):121-32.

105* - Croll NA, Anderson RM, Gyorkos TW, Ghadirian E (1982). The population biology and control of Ascaris lumbricoides in a rural community in Iran. Trans R Soc Trop Med Hyg. 76(2):187-97.

106 - Croll NA, Blair A (1973). Inherent movement patterns of larval nematodes, with a stochastic model to simulate movement of infective hookworm larvae. Parasitology. 67(1):53-66.

107 - Galvani AP. (2005). Age-dependent epidemiological patterns and strain diversity in helminth parasites. J Parasitol. 91(1):24-30.

108* - Guyatt HL, Bundy DA (1991). Estimating prevalence of community morbidity due to intestinal helminths: prevalence of infection as an indicator of the prevalence of disease. Trans R Soc Trop Med Hyg. 85(6):778-82.

109* - Guyatt HL, Bundy DA (1993). Estimation of intestinal nematode prevalence: influence of parasite mating patterns. Parasitology. 1993 Jul;107 (Pt 1):99-105.

110* - Medley GF, Guyatt HL, Bundy DA (1993). A quantitative framework for evaluating the effect of community treatment on the morbidity due to ascariasis. Parasitology. 106 (Pt 2):211-21.

111* - Sabatelli L, Ghani AC, Rodrigues LC, Hotez PJ, Brooker S (2008). Modelling heterogeneity and the impact of chemotherapy and vaccination against human hookworm. J R Soc Interface. 5(28):1329-41.

112 - Sengupta ME, Thamsborg SM, Andersen TJ, Olsen A, Dalsgaard A (2011). Sedimentation of helminth eggs in water. Water Res. 45(15):4651-60.

113 - Smith G, Schad GA (1989). Ancylostoma duodenale and Necator americanus: effect of temperature on egg development and mortality. Parasitology. 99 Pt 1:127-32..

114* - Thein-Hlaing, Than-Saw, Myat-Lay-Kyin (1991). The impact of three-monthly age-targetted chemotherapy on Ascaris lumbricoides infection. Trans R Soc Trop Med Hyg. 85(4):519-22.

115 - Walker M, Hall A, Basáñez MG (2010). Trickle or clumped infection process? A stochastic model for the infection process of the parasitic roundworm of humans, Ascaris lumbricoides. Int J Parasitol. 40(12):1381-8.

116 - Zhang YX (1987). A compound catalytic model with both reversible and two-stage types and its applications in epidemiological study. Int J Epidemiol. 16(4):619-21.

Leishmaniose

117* - Bacaër N, Guernaoui S (2006). The epidemic threshold of vector-borne diseases with seasonality: the case of cutaneous leishmaniasis in Chichaoua, Morocco. J Math Biol. 53(3):421-36.

118 - Chaves LF, Hernandez MJ (2004). Mathematical modelling of American cutaneous leishmaniasis: incidental hosts and threshold conditions for infection persistence. Acta Trop. 92(3):245-52.

119* - Chaves LF, Hernandez MJ, Dobson AP, Pascual M (2007). Sources and sinks: revisiting the criteria for identifying reservoirs for American cutaneous leishmaniasis. Trends Parasitol. 23(7):311-6.

120 - Dye C (1988). The epidemiology of canine visceral leishmaniasis in southern France: classical theory offers another explanation of the data. Parasitology. 96 (Pt 1):19-24.

121* - Dye C, Wolpert DM (1988). Earthquakes, influenza and cycles of Indian kala-azar. Trans R Soc Trop Med Hyg. 82(6):843-50.

122 - Dye C, Williams BG (1993). Malnutrition, age and the risk of parasitic disease: visceral leishmaniasis revisited. Proc Biol Sci. 254(1339):33-9.

123* - Dye C (1996). The logic of visceral leishmaniasis control. Am J Trop Med Hyg. 55(2):125-30.

124** - Garnick E (1992). Niche breadth in parasites: an evolutionarily stable strategy model, with special reference to the protozoan parasite Leishmania. Theor Popul Biol. 42(1):62-103.

125 - Hasibeder G, Dye C, Carpenter J (1992). Mathematical modelling and theory for estimating the basic reproduction number of canine leishmaniasis. Parasitology. 105 (Pt 1):43-53.

126* - Mubayi A, Castillo-Chavez C, Chowell G, Kribs-Zaleta C, Ali Siddiqui N, Kumar N, Das P (2010). Transmission dynamics and underreporting of Kala-azar in the Indian state of Bihar. J Theor Biol. 262(1):177-85.

127* - Palatnik-de-Sousa CB, Batista-de-Melo LM, Borja-Cabrera GP, Palatnik M, Lavor CC (2004). Improving methods for epidemiological control of canine visceral leishmaniasis based on a mathematical model. Impact on the incidence of the canine and human disease. An Acad Bras Cienc. 76(3):583-93.

128 - Rabinovich JE, Feliciangeli MD (2004). Parameters of Leishmania braziliensis transmission by indoor Lutzomyia ovallesi in Venezuela. Am J Trop Med Hyg. 70(4):373-82.

129 - Rogers DJ (1988). The dynamics of vector-transmitted diseases in human communities. Philos Trans R Soc Lond B Biol Sci. 321(1207):513-39.

130 - Williams BG, Dye C (1997). Infectious disease persistence when transmission varies seasonally. Math Biosci. 145(1):77-88.

131* - Woolhouse ME, Dye C, Etard JF, Smith T, Charlwood JD, Garnett GP, Hagan P, Hii JL, Ndhlovu PD, Quinnell RJ, Watts CH, Chandiwana SK, Anderson RM (1997). Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc Natl Acad Sci U S A. 94(1):338-42.

Lèpre

132 - Fischer E, De Vlas S, Meima A, Habbema D, Richardus J (2010). Different mechanisms for heterogeneity in leprosy susceptibility can explain disease clustering within households. PLoS One. 5(11):e14061.

133* - Lechat MF, Misson JY, Vellut CM, Misson CB, Bouckaert A (1974). Un modèle épidémiométrique de la lèpre. Bull World Health Organ. 51(4):361-73.

134* - Lechat MF, Misson CB, Vanderveken M, Vellut CM, Declercq EE (1987). A computer simulation of the effect of multidrug therapy on the incidence of leprosy. Ann Soc Belg Med Trop. 67(1):59-65.

135 - Lietman T, Porco T, Blower S (1997). Leprosy and tuberculosis: the epidemiological consequences of cross-immunity. Am J Public Health. 87(12):1923-7.

136* - Meima A, Gupte MD, van Oortmarssen GJ, Habbema JD (1999). SIMLEP: a simulation model for leprosy transmission and control. Int J Lepr Other Mycobact Dis. 67(3):215-36.

137* - Meima A, Irgens LM, van Oortmarssen GJ, Richardus JH, Habbema JD (2002). Disappearance of leprosy from Norway: an exploration of critical factors using an epidemiological modelling approach. Int J Epidemiol. 31(5):991-1000.

Maladie de Chagas

138* - Barbu C, Dumonteil E, Gourbière S (2009). Optimization of control strategies for non-domiciliated Triatoma dimidiata, Chagas disease vector in the Yucatán Peninsula, Mexico. PLoS Negl Trop Dis. 3(4):e416.

139 - Barbu C, Dumonteil E, Gourbière S (2010). Characterization of the dispersal of non-domiciliated Triatoma dimidiata through the selection of spatially explicit models. PLoS Negl Trop Dis. 4(8):e777.

140 - Berezovskaya FS, Novozhilov AS, Karev GP (2007). Population models with singular equilibrium. Math Biosci. 208(1):270-99. Epub 2006 Nov 10.

141* - Castillo-Riquelme M, Chalabi Z, Lord J, Guhl F, Campbell-Lendrum D, Davies C, Fox-Rushby J (2008). Modelling geographic variation in the cost-effectiveness of control policies for infectious vector diseases: the example of Chagas disease. J Health Econ. 27(2):405-26.

142* - Cohen JE, Gürtler RE (2010). Modeling household transmission of American trypanosomiasis. Science. 293(5530):694-8.

143 - Devillers H, Lobry JR, Menu F (2008). An agent-based model for predicting the prevalence of Trypanosoma cruzi I and II in their host and vector populations. J Theor Biol. 255(3):307-15.

144 - Gourbière S, Dumonteil E, Rabinovich JE, Minkoue R, Menu F (2008). Demographic and dispersal constraints for domestic infestation by non-domicilated chagas disease vectors in the Yucatan Peninsula, Mexico. Am J Trop Med Hyg. 78(1):133-9.

145 - Inaba H, Sekine H (2004). A mathematical model for Chagas disease with infection-age-dependent infectivity. Math Biosci. 190(1):39-69.

146 - Kribs-Zaleta C (2010). Estimating contact process saturation in sylvatic transmission of Trypanosoma cruzi in the United States. PLoS Negl Trop Dis. 4(4):e656.

147* - Massad E (2008). The elimination of Chagas' disease from Brazil. Epidemiol Infect. 136(9):1153-64.

148** - Menu F, Ginoux M, Rajon E, Lazzari CR, Rabinovich JE (2010). Adaptive developmental delay in Chagas disease vectors: an evolutionary ecology approach. PLoS Negl Trop Dis. 4(5):e691.

149* - Roberts MG, Heesterbeek JA (2003). A new method for estimating the effort required to control an infectious disease. Proc Biol Sci. 270(1522):1359-64.

150 - Velasco-Hernández JX (1994). A model for Chagas disease involving transmission by vectors and blood transfusion. Theor Popul Biol. 46(1):1-31.

Maladie du sommeil

151* - Artzrouni M, Gouteux JP (1996). Control strategies for sleeping sickness in Central Africa: a model-based approach. Trop Med Int Health. 1(6):753-64.

152 - Artzrouni M, Gouteux JP (2001). A model of Gambian sleeping sickness with open vector populations. IMA J Math Appl Med Biol. 18(2):99-117.

153** - Baker RD, Maudlin I, Milligan PJ, Molyneux DH, Welburn SC (1990). The possible role of Rickettsia-like organisms in trypanosomiasis epidemiology. Parasitology. 100 Pt 2:209-17.

154* - Chalvet-Monfray K, Artzrouni M, Gouteux JP, Auger P, Sabatier P (1998). A two-patch model of Gambian sleeping sickness: application to vector control strategies in a village and plantations. Acta Biotheor. 46(3):207-22.

155 - Gouteux JP, Artzrouni M (2000). Persistance et résurgence de la maladie du sommeil à *Trypanosoma brucei gambiense* dans les foyers historiques. Approche biomathématique d'une énigme épidémiologique. C R Acad Sci III. 323(4):351-64.

156 - Gouteux JP (2005). Évaluation du risque dans la maladie du sommeil : apport de la modélisation mathématique. Parasite. 12(3):259-64.

157* - Gutierrez AP, Gilioli G, Baumgärtner J (2009). Ecosocial consequences and policy implications of disease management in East African agropastoral systems. Proc Natl Acad Sci U S A. 106(31):13136-41.

158* - Habtemariam T (1989). Utility of epidemiologic simulation models in the planning of trypanosomiasis control programs. Ann Soc Belg Med Trop. 69 Suppl 1 :109-24.

159 - Lord CC, Barnard B, Day K, Hargrove JW, McNamara JJ, Paul RE, Trenholme K, Woolhouse ME (1999). Aggregation and distribution of strains in microparasites. Philos Trans R Soc Lond B Biol Sci. 354(1384) :799-807.

160 - Rogers DJ (1988). A general model for the African trypanosomiases. Parasitology. 97 (Pt 1):193-212.

161 - Rogers DJ (1989). The development of analytical models for human trypanosomiasis. Ann Soc Belg Med Trop. 69 Suppl 1:73-88; discussion 144.

Onchocerciase

162* - Alley WS, van Oortmarssen GJ, Boatin BA, Nagelkerke NJ, Plaisier AP, Remme JH, Lazdins J, Borsboom GJ, Habbema JD (2001). Macrofilaricides and onchocerciasis control, mathematical modelling of the prospects for elimination. BMC Public Health. 1:12.

163* - Basáñez MG, Boussinesq M (1999). Population biology of human onchocerciasis. Philos Trans R Soc Lond B Biol Sci. 354(1384):809-26.

164* - Basáñez MG, Ricárdez-Esquinca J (2001). Models for the population biology and control of human onchocerciasis. Trends Parasitol. 17(9) :430-8.

165 - Basáñez MG, Collins RC, Porter CH, Little MP, Brandling-Bennett D (2002). Transmission intensity and the patterns of Onchocerca volvulus infection in human communities. Am J Trop Med Hyg. 67(6):669-79.

166 - Basáñez MG, Razali K, Renz A, Kelly D (2007). Density-dependent host choice by disease vectors: epidemiological implications of the ideal free distribution. Trans R Soc Trop Med Hyg. 101(3):256-69. Epub 2006 Nov 16.

167* - Basáñez MG, Pion SD, Boakes E, Filipe JA, Churcher TS, Boussinesq M (2008). Effect of single-dose ivermectin on Onchocerca volvulus: a systematic review and meta-analysis. Lancet Infect Dis. 8(5):310-22.

168 - Churcher TS, Ferguson NM, Basáñez MG (2005). Density dependence and overdispersion in the transmission of helminth parasites. Parasitology. 131(Pt 1):121-32.

169 - Duerr HP, Dietz K, Buttner DW, Schulz-Key H (2001). A stochastic model for the aggregation of Onchocerca volvulus in nodules. Parasitology. 123(Pt 2):193-201.

170* - Duerr HP, Leary CC, Eichner M (2006). High infection rates at low transmission potentials in West African onchocerciasis. Int J Parasitol. 36(13):1367-72.

171* - Duerr HP, Eichner M (2010). Epidemiology and control of onchocerciasis: the threshold biting rate of savannah onchocerciasis in Africa. Int J Parasitol. 40(6):641-50.

172 - Filipe JA, Boussinesq M, Renz A, Collins RC, Vivas-Martinez S, Grillet ME, Little MP, Basáñez MG (2005). Human infection patterns and heterogeneous exposure in river blindness. Proc Natl Acad Sci U S A. 102(42):15265-70. Epub 2005 Oct 10.

173* - Plaisier AP, van Oortmarssen GJ, Remme J, Habbema JD (1991). The reproductive lifespan of Onchocerca volvulus in West African savanna. Acta Trop. 48(4):271-84.

174* - Plaisier AP, van Oortmarssen GJ, Remme J, Alley ES, Habbema JD (1991). The risk and dynamics of onchocerciasis recrudescence after cessation of vector control. Bull World Health Organ. 69(2):169-78.

175* - Plaisier AP, Alley ES, Boatin BA, Van Oortmarssen GJ, Remme H, De Vlas SJ, Bonneux L, Habbema JD (1995). Irreversible effects of ivermectin on adult parasites in onchocerciasis patients in the Onchocerciasis Control Programme in West Africa. J Infect Dis. 172(1):204-10.

176* - Plaisier AP, Alley ES, van Oortmarssen GJ, Boatin BA, Habbema JD (1997). Required duration of combined annual ivermectin treatment and vector control in the Onchocerciasis Control Programme in west Africa. Bull World Health Organ. 75(3):237-45.

177** - Poolman EM, Galvani AP (2006). Modeling targeted ivermectin treatment for controlling river blindness. Am J Trop Med Hyg. 75(5):921-7.

178* - Remme J, Ba O, Dadzie KY, Karam M (1986). A force-of-infection model for onchocerciasis and its applications in the epidemiological evaluation of the Onchocerciasis Control Programme in the Volta River basin area. Bull World Health Organ. 64(5):667-81.

179* - Remme J, De Sole G, van Oortmarssen GJ (1990). The predicted and observed decline in onchocerciasis infection during 14 years of successful control of Simulium spp. in west Africa. Bull World Health Organ. 68(3):331-9.

180* - Winnen M, Plaisier AP, Alley ES, Nagelkerke NJ, van Oortmarssen G, Boatin BA, Habbema JD (2002). Can ivermectin mass treatments eliminate onchocerciasis in Africa? Bull World Health Organ. 80(5):384-91.

Pian

181* - Gart JJ, de Vries JL (1966). The mathematical analysis of concurrent epidemics of yaws and chickenpox. J Hyg (Lond). 64(4):431-9.

182* - Gart JJ (1968). The mathematical analysis of an epidemic with two kinds of susceptibles. Biometrics. 24(3):557-66.

Rage

183* - Anderson RM, Jackson HC, May RM, Smith AM (1981). Population dynamics of fox rabies in Europe. Nature. 289(5800):765-71.

184 - Bolzoni L, De Leo GA, Gatto M, Dobson AP (2008). Body-size scaling in an SEI model of wildlife diseases. Theor Popul Biol. 73(3):374-82.

185 - Bolzoni L, Dobson AP, Gatto M, De Leo GA (2008). Allometric scaling and seasonality in the epidemics of wildlife diseases. Am Nat. 172(6):818-28.

186 - Childs JE, Curns AT, Dey ME, Real LA, Feinstein L, Bjørnstad ON, Krebs JW (2000). Predicting the local dynamics of epizootic rabies among raccoons in the United States. Proc Natl Acad Sci U S A. 97(25):13666-71.

187 - Cleaveland S, Dye C (1995). Maintenance of a microparasite infecting several host species: rabies in the Serengeti. Parasitology. 111 Suppl:S33-47.

188* - Coleman PG, Dye C (1996). Immunization coverage required to prevent outbreaks of dog rabies. Vaccine. 14(3):185-6.

189 - Cruickshank I, Gurney WS, Veitch AR (1999). The characteristics of epidemics and invasions with thresholds. Theor Popul Biol. 56(3):279-92.

190 - Dimitrov DT, Hallam TG, Rupprecht CE, Turmelle AS, McCracken GF (2007). Integrative models of bat rabies immunology, epizootiology and disease demography. J Theor Biol. 245(3):498-509.

191 - Dimitrov DT, Hallam TG, Rupprecht CE, McCracken GF (2008). Adaptive modeling of viral diseases in bats with a focus on rabies. J Theor Biol. 255(1):69-80. Epub 2008 Aug 13.

192 - Duke-Sylvester SM, Bolzoni L, Real LA (2011). Strong seasonality produces spatial asynchrony in the outbreak of infectious diseases. J R Soc Interface. 8(59):817-25. Epub 2010 Oct 20.

193* - Eisinger D, Thulke HH, Selhorst T, Müller T (2005). Emergency vaccination of rabies under limited resources -- combating or containing? BMC Infect Dis. 5:10.

194* - Evans ND, Pritchard AJ (2001). A control theoretic approach to containing the spread of rabies. IMA J Math Appl Med Biol. 18(1):1-23.

195* - Eisinger D, Thulke HH (2008). Spatial pattern formation facilitates eradication of infectious diseases. J Appl Ecol. 45(2):415-423.

196* - Fowler AC (2000). The effect of incubation time distribution on the extinction characteristics of a rabies epizootic. Bull Math Biol. 62(4):633-55.

197 - George DB, Webb CT, Farnsworth ML, O'Shea TJ, Bowen RA, Smith DL, Stanley TR, Ellison LE, Rupprecht CE (2011). Host and viral ecology determine bat rabies seasonality and maintenance. Proc Natl Acad Sci U S A. 108(25):10208-13.

198 - Gordon ER, Curns AT, Krebs JW, Rupprecht CE, Real LA, Childs JE (2004). Temporal dynamics of rabies in a wildlife host and the risk of cross-species transmission. Epidemiol Infect. 32(3) :515-24.

199* - Greenhalgh D (1992). Vaccination in density-dependent epidemic models. Bull Math Biol. 54(5):733-58.

200* - Hampson K, Dushoff J, Bingham J, Brückner G, Ali YH, Dobson A (2007). Synchronous cycles of domestic dog rabies in sub-Saharan Africa and the impact of control efforts. Proc Natl Acad Sci U S A. 104(18):7717-22.

201 - Ireland JM, Norman RA, Greenman JV (2004). The effect of seasonal host birth rates on population dynamics: the importance of resonance. J Theor Biol. 231(2):229-38.

202 - Jeltsch F, Müller MS, Grimm V, Wissel C, Brandl R (1997). Pattern formation triggered by rare events: lessons from the spread of rabies. Proc Biol Sci. 264(1381):495-503.

203* - Källén A, Arcuri P, Murray JD (1985). A simple model for the spatial spread and control of rabies. J Theor Biol. 116(3):377-93.

204* - Macdonald DW, Bacon PJ (1982). Fox society, contact rate and rabies epizootiology. Comp Immunol Microbiol Infect Dis. 5(1-3):247-56.

205* - Massad E, Coutinho FA, Burattini MN, Sallum PC, Lopez LF (2001). A mixed ectoparasite--microparasite model for bat-transmitted rabies. Theor Popul Biol. 60(4):265-79.

206* - Murray JD, Stanley EA, Brown DL (1986). On the spatial spread of rabies among foxes. Proc R Soc Lond B Biol Sci. 229(1255):111-50.

207 - Naulin JM (2002). A contribution of sparse matrices tools to matrix population model analysis. Math Biosci. 177-178:25-38.

208* - Panjeti VG, Real LA (2011). Mathematical models for rabies. Adv Virus Res. 79:377-95.

209 - Radcliffe J, Rass L (1983). Wave solutions for the deterministic non-reducible n-type epidemic. J Math Biol. 17(1):45-66.

210 - Radcliffe J, Rass L (1984). The spatial spread and final size of the deterministic non-reducible n-type epidemic. J Math Biol. 19(3):309-27.

211 - Rhodes CJ, Atkinson RP, Anderson RM, Macdonald DW (1998). Rabies in Zimbabwe: reservoir dogs and the implications for disease control. Philos Trans R Soc Lond B Biol Sci. 353(1371):999-1010.

212* - Russell CA, Real LA, Smith DL (2006). Spatial control of rabies on heterogeneous landscapes. PLoS One. 1:e27.

213* - Sallum PC, Almeida MF, Massad E (2000). Rabies seroprevalence of street dogs from São Paulo City, Brazil. Prev Vet Med. 44(3-4):131-9.

214* - Selhorst T, Thulke HH, Müller T (2001). Cost-efficient vaccination of foxes (Vulpes vulpes) against rabies and the need for a new baiting strategy. Prev Vet Med. 51(1-2):95-109.

215 - Singer A, Kauhala K, Holmala K, Smith GC (2009). Rabies in northeastern Europe--the threat from invasive raccoon dogs. J Wildl Dis. 45(4):1121-37.

216* - Smith GC, Harris S (1991). Rabies in urban foxes (Vulpes vulpes) in Britain: the use of a spatial stochastic simulation model to examine the pattern of spread and evaluate the efficacy of different control régimes. Philos Trans R Soc Lond B Biol Sci. 334(1271):459-79.

217* - Smith GC, Wilkinson D (2003). Modeling control of rabies outbreaks in red fox populations to evaluate culling, vaccination, and vaccination combined with fertility control. J Wildl Dis. 39(2):278-86.

218* - Suppo C, Naulin JM, Langlais M, Artois M (2000). A modelling approach to vaccination and contraception programmes for rabies control in fox populations. Proc Biol Sci. 267(1452):1575-82.

219 - Swart JH (1989). Hopf bifurcation and stable limit cycle behavior in the spread of infectious disease, with special application to fox rabies. Math Biosci. 95(2):199-207.

220* - Thulke HH, Eisinger D, Selhorst T, Müller T (2008). Scenario-analysis evaluating semergency strategies after rabies re-introduction. Dev Biol (Basel). 131:265-72.

221* - Tischendorf L, Thulke HH, Staubach C, Müller MS, Jeltsch F, Goretzki J, Selhorst T, Müller T, Schlüter H, Wissel C (1998). Chance and risk of controlling rabies in large-scale and long-term immunized fox populations. Proc Biol Sci. 265(1399):839-46.

222* - Woolhouse ME, Haydon DT, Bundy DA (1997). The design of veterinary vaccination programmes. Vet J. 153(1):41-7.

Schistosomiase

223 - Allen EJ, Victory HD Jr (2003). Modelling and simulation of a schistosomiasis infection with biological control. Acta Trop. 87(2):251-67.

224 - Anderson RM, May RM (1979). Prevalence of schistosome infections within molluscan populations: observed patterns and theoretical predictions. Parasitology. 79(1):63-94.

225 - Barbour AD (1978). Macdonald's model and the transmission of bilharzia. Trans R Soc Trop Med Hyg. 72(1):6-15.

226 - Bradley DJ, McCullough FS (1973). Egg output stability and the epidemiology of Schistosoma haematobium. II. An analysis of the epidemiology of endemic S. haematobium. Trans R Soc Trop Med Hyg. 67(4):491-500.

227 - Bradley DJ, May RM (1978). Consequences of helminth aggregation for the dynamics of schistosomiasis. Trans R Soc Trop Med Hyg. 72(3):262-73.

228** - Brown SP, Grenfell BT (2001). An unlikely partnership: parasites, concomitant immunity and host defence. Proc Biol Sci. 268(1485):2543-9.

229* - Carabin H, Chan MS, Guyatt HL (2000). A population dynamic approach to evaluating the impact of school attendance on the unit cost and effectiveness of school-based schistosomiasis chemotherapy programmes. Parasitology. 121 (Pt 2):171-83.

230** - Castillo-Chavez C, Feng Z, Xu D (2008). A schistosomiasis model with mating structure and time delay. Math Biosci. 211(2):333-41. Epub 2007 Nov 22.

231 - Chan MS, Isham VS (1988). A stochastic model of schistosomiasis immuno-epidemiology. Math Biosci. 151(2):179-98.

232* - Chan MS, Nsowah-Nuamah NN, Adjei S, Wen ST, Hall A, Bundy DA (1998). Predicting the impact of school-based treatment for urinary schistosomiasis given by the Ghana Partnership for Child Development. Trans R Soc Trop Med Hyg. 92(4):386-9.

233* - Chan MS, Guyatt HL, Bundy DA, Booth M, Fulford AJ, Medley GF (1995). The development of an age structured model for schistosomiasis transmission dynamics and control and its validation for Schistosoma mansoni. Epidemiol Infect. 115(2):325-44.

234* - Chan MS, Anderson RM, Medley GF, Bundy DA (1996). Dynamic aspects of morbidity and acquired immunity in schistosomiasis control. Acta Trop. 62(2):105-17.

235* - Chan MS, Bundy DA (1997). Modelling the dynamic effects of community chemotherapy on patterns of morbidity due to Schistosoma mansoni. Trans R Soc Trop Med Hyg. 91(2):216-20.

236* - Chan MS, Montresor A, Savioli L, Bundy DA (1999). Planning chemotherapy based schistosomiasis control: validation of a mathematical model using data on Schistosoma haematobium from Pemba, Tanzania. Epidemiol Infect. 123(3):487-97.

237* - Chen Z, Zou L, Shen D, Zhang W, Ruan S (2010). Mathematical modelling and control of schistosomiasis in Hubei Province, China. Acta Trop. 115(1-2):119-25.

238 - Coutinho FA, Griffin M, Thomas JD (1981). A model of schistosomiasis incorporating the searching capacity of the miracidium. Parasitology. 82(1):111-20.

239 - Coyne MJ, Smith G (1991). The regulation of mortality and fecundity in Schistosoma mattheei following a single experimental infection in sheep. Int J Parasitol.;21(8):877-82.

240 - De Vlas SJ, Gryseels B, Van Oortmarssen GJ, Polderman AM, Habbema JD (1992). A model for variations in single and repeated egg counts in Schistosoma mansoni infections. Parasitology. 104 (Pt 3):451-60.

241* - Feng Z, Li CC, Milner FA (2002). Schistosomiasis models with density dependence and age of infection in snail dynamics. Math Biosci. 177-178:271-86.

242* - Fukuhara K, Phompida S, Insisiengmay S, Kirinoki M, Chigusa Y, Nakamura S, Matsuda H, Ishikawa H (2011). Analysis of the effectiveness of control measures against Schistosoma mekongi using an intra- and inter-village model in Champasak Province, Lao PDR. Parasitol Int. [Epub ahead of print]

243* - Fulford AJ, Butterworth AE, Ouma JH, Sturrock RF (1995). A statistical approach to schistosome population dynamics and estimation of the life-span of Schistosoma mansoni in man. Parasitology. 110 (Pt 3):307-16.

244 - Gibson LR, Li B, Remold SK (2010). Treating cofactors can reverse the expansion of a primary disease epidemic. BMC Infect Dis. 10:248.

245 - Giovanelli A, Vieira MV, da Silva CL (2003). Apparent competition through facilitation between Melanoides tuberculata and Biomphalaria glabrata and the control of schistosomiasis. Mem Inst Oswaldo Cruz. 98(3):429-31. Epub 2003 Jul 18.

246 - Goddard MJ (1978). On Macdonald's model for schistosomiasis. Trans R Soc Trop Med Hyg. 72(2):123-31.

247* - Gray DJ, Williams GM, Li Y, McManus DP (2008). Transmission dynamics of Schistosoma japonicum in the lakes and marshlands of China. PLoS One. 3(12):e4058.

248* - Gurarie D, King CH (2005). Heterogeneous model of schistosomiasis transmission and long-term control: the combined influence of spatial variation and age-dependent factors on optimal allocation of drug therapy. Parasitology. 130(Pt 1):49-65.

249* - Gurarie D, Seto EY (2009). Connectivity sustains disease transmission in environments with low potential for endemicity: modelling schistosomiasis with hydrologic and social connectivities. J R Soc Interface. 6(35):495-508. Epub 2008 Sep 9.

250 - Gurarie D, King CH, Wang X (2010). A new approach to modelling schistosomiasis transmission based on stratified worm burden. Parasitology. 137(13):1951-65.

251* - Hairston NG (1965). An analysis of age-prevalence data by catalytic models. A contribution to the study of bilharziasis. Bull World Health Organ. 33(2):163-75.

252* - Hisakane N, Kirinoki M, Chigusa Y, Sinuon M, Socheat D, Matsuda H, Ishikawa H (2008). The evaluation of control measures against Schistosoma mekongi in Cambodia by a mathematical model. Parasitol Int. 57(3):379-85.

253* - Hu H, Gong P, Xu B (2010). Spatially explicit agent-based modelling for schistosomiasis transmission: human-environment interaction simulation and control strategy assessment. Epidemics. 2(2):49-65.

254* - Ishikawa H, Ohmae H, Pangilinan R, Redulla A, Matsuda H (2006). Modeling the dynamics and control of Schistosoma japonicum transmission on Bohol island, the Philippines. Parasitol Int. 55(1):23-9. Epub 2005 Oct

255 - Jobin WR, Michelson EH (1967). Mathematical simulation of an aquatic snail population. Bull World Health Organ. 37(4):657-64.

256** - King CH, Muchiri EM, Ouma JH (2000). Evidence against rapid emergence of praziquantel resistance in Schistosoma haematobium, Kenya. Emerg Infect Dis. 6(6):585-94.

257* - Kuris AM (1973). Biological control: implications of the analogy between the trophic interactions of insect pest-parasitoid and snail-trematode systems. Exp Parasitol. 33(2):365-79.

258* - Lee KL, Lewis ER (1976). Delay time models of population dynamics with application to schistosomiasis control. IEEE Trans Biomed Eng. 23(3):225-33.

259* - Liang S, Maszle D, Spear RC (2002). A quantitative framework for a multi-group model of Schistosomiasis japonicum transmission dynamics and control in Sichuan, China. Acta Trop. 82(2):263-77.

260* - Liang S, Spear RC, Seto E, Hubbard A, Qiu D (2005). A multi-group model of Schistosoma japonicum transmission dynamics and control: model calibration and control prediction. Trop Med Int Health. 10(3):263-78.

261* - Liang S, Seto EY, Remais JV, Zhong B, Yang C, Hubbard A, Davis GM, Gu X, Qiu D, Spear RC (2007). Environmental effects on parasitic disease transmission exemplified by schistosomiasis in western China. Proc Natl Acad Sci U S A. 104(17):7110-5. Epub 2007 Apr 16.

262* - Macdonald G (1965). The dynamics of helminth infections, with special reference to schistosomes. Trans R Soc Trop Med Hyg. 59(5):489-506.

263* - Mangal TD, Paterson S, Fenton A (2008). Predicting the impact of long-term temperature changes on the epidemiology and control of schistosomiasis: a mechanistic model. PLoS One. 3(1):e1438.

264* - Milner FA, Zhao R (2008). A deterministic model of schistosomiasis with spatial structure. Math Biosci Eng. 5(3):505-22.

265 - Morand S, Pointier JP, Théron A (1999). Population biology of Schistosoma mansoni in the black rat: host regulation and basic transmission rate. Int J Parasitol. 29(5):673-84.

266** - Morand S, Southgate VR, Jourdane J (2002). A model to explain the replacement of Schistosoma intercalatum by Schistosoma haematobium and the hybrid S. intercalatum x S. haematobium in areas of sympatry. Parasitology. 124(Pt 4):401-8.

267* - Mushayabasa S, Bhunu CP (2011). Modeling schistosomiasis and HIV/AIDS codynamics. Comput Math Methods Med. 846174.

268* - Nåsell I (1977). On transmission and control of schistosomiasis, with comments on Macdonald's model. Theor Popul Biol. 12(3):335-65.

269* - Nåsell I (1978). Mating for schistosomes. J Math Biol. 12;6(1):21-35.

270 - Polman K, de Vlas SJ, Gryseels B, Deelder AM (2000). Relating serum circulating anodic antigens to faecal egg counts in Schistosoma mansoni infections: a modelling approach. Parasitology. 121 Pt 6:601-10.

271 - Remais J, Liang S, Spear RC (2008). Coupling hydrologic and infectious disease models to explain regional differences in schistosomiasis transmission in southwestern China. Environ Sci Technol. 42(7):2643-9.

272 - Remais J, Zhong B, Carlton EJ, Spear RC (2009). Model approaches for estimating the influence of time-varying socio-environmental factors on macroparasite transmission in two endemic regions. Epidemics. 1(4):213-20.

273* - Riley S, Carabin H, Marshall C, Olveda R, Willingham AL, McGarvey ST. (2005). Estimating and modeling the dynamics of the intensity of infection with schistosoma japonicum in villagers of leyte, Philippines. Part II: Intensity-specific transmission of S. japonicum. The schistosomiasis transmission and ecology project. Am J Trop Med Hyg. 72(6):754-61.

274 - Riley S, Carabin H, Bélisle P, Joseph L, Tallo V, Balolong E, Willingham AL, Fernandez TJ, Gonzales RO, Olveda R, McGarvey ST (2008). Multi-host transmission dynamics of Schistosoma japonicum in Samar province, the Philippines. PLoS Med. 5(1):e18.

275* - Spear RC, Hubbard A, Liang S, Seto E (2002). Disease transmission models for public health decision making: toward an approach for designing intervention strategies for Schistosomiasis japonica. Environ Health Perspect. 110(9):907-15.

276 - Tchuem Tchuenté LA, Morand S, Imbert-Establet D, Delay B, Jourdane J (1996). Competitive exclusion in human schistosomes: the restricted distribution of Schistosoma intercalatum. Parasitology. 113 (Pt 2):129-36.

277* - Williams GM, Sleigh AC, Li Y, Feng Z, Davis GM, Chen H, Ross AG, Bergquist R, McManus DP (2002). Mathematical modelling of schistosomiasis japonica: comparison of control strategies in the People's Republic of China. Acta Trop. 82(2):253-62.

278* - Woolhouse ME, Etard JF, Dietz K, Ndhlovu PD, Chandiwana SK (1988). Heterogeneities in schistosome transmission dynamics and control. Parasitology. 117 (Pt 5):475-82.

279 - Woolhouse ME, Chandiwana SK (1990). Population dynamics model for Bulinus globosus, intermediate host for Schistosoma haematobium, in river habitats. Acta Trop. 47(3):151-60.

280 - Woolhouse ME, Chandiwana SK (1990). The epidemiology of schistosome infections of snails: taking the theory into the field. Parasitol Today. 6(3):65-70.

281 - Woolhouse ME (1991). On the application of mathematical models of schistosome transmission dynamics. I. Natural transmission. Acta Trop. 49(4):241-70.

282* - Woolhouse ME, Watts CH, Chandiwana SK (1991). Heterogeneities in transmission rates and the epidemiology of schistosome infection. Proc Biol Sci. 245(1313):109-14.

283 - Woolhouse ME, Taylor P, Matanhire D, Chandiwana SK (1991). Acquired immunity and epidemiology of Schistosoma haematobium. Nature. 351(6329):757-9.

284* - Woolhouse ME (1992). On the application of mathematical models of schistosome transmission dynamics. II. Control. Acta Trop. 50(3):189-204.

285* - Woolhouse ME (1995). Human schistosomiasis: potential consequences of vaccination. Vaccine. 13(12):1045-50.

286 - Woolhouse ME, Hasibeder G, Chandiwana SK (1996). On estimating the basic reproduction number for Schistosoma haematobium. Trop Med Int Health. 1(4):456-63.

287* - Woolhouse ME, Dye C, Etard JF, Smith T, Charlwood JD, Garnett GP, Hagan P, Hii JL, Ndhlovu PD, Quinnell RJ, Watts CH, Chandiwana SK, Anderson RM (1998). Heterogeneities in the transmission of infectious agents: implications for the design of control programs. Proc Natl Acad Sci U S A. 94(1):338-42.

288 - Yang HM, Coutinho FA, Massad E (1997). Acquired immunity on a schistosomiasis transmission model - fitting the data. J Theor Biol. 188(4):495-506.

289 - Yang HM, Yang AC (1998). The stabilizing effects of the acquired immunity on the schistosomiasis transmission modeling--the sensitivity analysis. Mem Inst Oswaldo Cruz. 93 Suppl 1:63-73.

290 - Yang HM (2003). Comparison between schistosomiasis transmission modelings considering acquired immunity and age-structured contact pattern with infested water. Math Biosci. 184(1):1-26.

291* - Zhang P, Feng Z, Milner F (2007). A schistosomiasis model with an age-structure in human hosts and its application to treatment strategies. Math Biosci. 205(1):83-107. Epub 2006 Aug 4.

292* - Zhao R, Milner FA (2008). A Mathematical model of Schistosoma mansoni in Biomphalaria glabrata with control strategies. Bull Math Biol. 70(7):1886-905. Epub 2008 Jul 31.

Strongyloïdose

293** - Fenton A, Paterson S, Viney ME, Gardner MP (2004). Determining the optimal developmental route of Strongyloides ratti: an evolutionarily stable strategy approach. Evolution. 58(5):989-1000.

Trachome

294*- Assaad FA, Maxwell-Lyons F (1966). The use of catalytic models as tools for elucidating the clinical and epidemiological features of trachoma. Bull World Health Organ. 34(3):341-55.

295 - Blake IM, Burton MJ, Bailey RL, Solomon AW, West S, Muñoz B, Holland MJ, Mabey DC, Gambhir M, Basáñez MG, Grassly NC (2009). Estimating household and community transmission of ocular Chlamydia trachomatis. PLoS Negl Trop Dis. 3(3):e401.

296* - Gambhir M, Basáñez MG, Turner F, Kumaresan J, Grassly NC (2007). Trachoma: transmission, infection, and control. Lancet Infect Dis. 7(6):420-7.

297* - Gambhir M, Basáñez MG, Burton MJ, Solomon AW, Bailey RL, Holland MJ, Blake IM, Donnelly CA, Jabr I, Mabey DC, Grassly NC (2009). The development of an age-structured model for trachoma transmission dynamics, pathogenesis and control. PLoS Negl Trop Dis. 3(6):e462.

298* - Lietman T, Porco T, Dawson C, Blower S (1999). Global elimination of trachoma: how frequently should we administer mass chemotherapy? Nat Med. 5(5):572-6.

299* - Lietman TM, Gebre T, Ayele B, Ray KJ, Maher MC, See CW, Emerson PM, Porco TC; TANA Study Group (2011). The epidemiological dynamics of infectious trachoma may facilitate elimination. Epidemics. 3(2):119-24.

300* - Ray KJ, Porco TC, Hong KC, Lee DC, Alemayehu W, Melese M, Lakew T, Yi E, House J, Chidambaram JD, Whitcher JP, Gaynor BD, Lietman TM (2007). A rationale for continuing mass antibiotic distributions for trachoma. BMC Infect Dis. 7:91.

301* - Ray KJ, Lietman TM, Porco TC, Keenan JD, Bailey RL, Solomon AW, Burton MJ, Harding-Esch E, Holland MJ, Mabey D (2009). When can antibiotic treatments for trachoma be discontinued? Graduating communities in three African countries. PLoS Negl Trop Dis. 3(6) :e458.

302* - Sundaresan TK, Assaad FA (1973). The use of simple epidemiological models in the evaluation of disease control programmes: a case study of trachoma. Bull World Health Organ. 48(6):709-14.

Tableau A.1. Références pour le tableau XX : grandes problématiques étudiées pour l'écologie des maladies tropicales négligées. Abbréviations: Ch=maladie de Chagas, De=dengue, Ec=échinococcose, HI=helminthiases intestinales, Le=leishmaniose, On=onchocerciase, Ra=rage, Sc=schistotmiase, , So=maladie du sommeil.

Problématiques	Maladies	Références
Diversité des agents pathogènes	De	8, 9, 13, 20, 26, 30-32, 59, 60, 64, 69
	Ch	143,
	HI	107, 112, 113
	On	169
	Sc	276
	So	159
Densité-dépendance de la dynamique intra-hôte	Ec	81
	HI	104
	On	168, 172
	Sc	239, 270
Agrégation au sein de la population hôte	Ec	71, 75
	HI	104, 115
	On	168, 169
	Sc	227, 231, 250
Vecteurs ou hôtes intermédiaires	Ch	139, 143-146, 150
	De	3, 6, 7, 12, 14, 16, 23, 25, 28, 29, 33-35, 41, 43-46, 51-54, 61, 64, 68, 70
	Ec	76, 77, 81, 87, 88, 92
	Le	120, 125, 128-130
	On	165, 166, 172
	Sc	223-225, 238, 245, 246, 255, 272, 279, 280
	So	152, 155, 156, 159, 160
Hôtes définitifs non-humains	Ch	143, 146
	Ec	71, 72, 75-78, 79-81, 90, 92
	Le	118, 120, 125, 129, 130
	Ra	184-186, 187, 189, 190-192, 197, 198, 201, 202, 207, 209, 211, 215, 219
	Sc	223, 239, 265, 274
	So	160, 161
Âge des hôtes humains et acquisition d'immunité	Ch	145
	De	8, 18, 31, 32, 57, 69
	HI	107, 116
	Le	122
	On	172
	Sc	226, 240, 281, 283, 288-290

Tableau A.2. Références pour le tableau XX : stratégies de contrôles des maladies tropicales négligées étudiées à l'aide de modèles de type systèmes dynamiques. Abbréviations: Ch=maladie de Chagas, De=dengue, Ec=échinococcose, HI=helminthiases intestinales, Le=leishmaniose. On=onchocerciase, Ra=rage, Sc=schistotmiase, , So=maladie du sommeil.

Stratégie de contrôle	Maladies	Références
Aménagement de l'habitat humain	Ch	138, 142
	De	50
	Sc	237, 241, 253, 254, 258, 260-263, 268, 269, 277, 284
	So	158
Traitement ou vaccination des hôtes intermédiaires	Ec	74, 82, 88, 91
Contrôle des vecteurs ou hôtes intermédiaires	Ch	138, 141, 142, 147
	De	4, 10, 11, 21, 22, 27, 50, 55, 56, 67
	Le	117, 123,
	On	163, 170, 173, 174, 176, 178, 179
	Sc	237, 248, 249, 253, 254, 257-263, 268, 269, 273, 277, 282, 284, 287
	So	151, 154, 157, 158
Traitement ou vaccin des hôtes définitifs non-humains	Ec	73, 74, 83-85, 88, 91
	Le	121, 123, 131
	Ra	183, 188, 193-196, 199, 200, 203, 205, 206, 208, 212-214, 217, 218, 220-222
	Sc	237, 277, 247
	So	157, 158
Contrôle des hôtes définitifs non-humains	Ch	142
	Ec	86
	Le	123, 127
	Ra	183, 194, 196, 203, 204-206, 208, 216-218
	So	158
Education, campagne préventive	Ec	88, 91
	De	11, 50
	Sc	241, 242, 252, 284
Surveillance, traitement des hôtes humains	Ch	141, 149
	HI	100-103, 105, 108-111, 114
	Le	126
	On	162-164, 167, 170, 171, 175, 176, 180
	Sc	229, 232-237, 241-243, 248, 252-254, 258-264, 267-269, 273, 275, 277, 282, 287, 291, 292
	So	151
Vaccin des hôtes humains	De	36, 63
	Le	123
	HI	111
	Sc	285

Tableau A.3. Références pour le tableau XX : travaux théoriques sur l'écologie, l'évolution et le contrôle des NTD s'adressant à des pays riches et tempérés.

Maladies	**Références**
Rage	183, 186, 189, 190, 192, 195, 197-199, 201, 203, 204, 206-208, 212, 214-218, 221
Echinococcose	73, 74, 76-78, 81-86, 92
Lèpre	135, 137
Fasciolase	93, 95
Leishmaniose	120, 125
Maladie de Chagas	146
Dengue	33, 54