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Benoît Randuineau

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Interactions entre pathogènes : quels impacts sur la santé publique ?

Thèse de Doctorat

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(mention Écologie et Évolution des pathogènes)

par

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Mis en page avec la classe thesul.

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Synthèse en Français

1 Introduction

Étudier la dynamique de population des pathogènes est à la fois un enjeu de santé publique et un champ d'application des idées, concepts et connaissances issues, entre autres, de l'Écologie. Afin de lutter contre un pathogène, il est utile de comprendre, notamment, sa transmission ou sa dispersion. Cette introduction présentera succinctement le développement des modèles en épidémiologie, en commençant par un bref historique soulignant à la fois les apports et un certain manque des modèles actuels à considérer les pathogènes comme les parties d'un écosystème plus large que le système hôte-pathogène. Dans une seconde partie, nous aborderons les connaissances actuelles concernant les interactions entre pathogènes, et nous verrons que l'identification de telles interactions reste difficile. Enfin, nous nous concentrerons brièvement sur les implications des interactions entre pathogènes pour la santé publique.

1.1 Modéliser les épidémies

S'inspirant des modèles de dynamique de population, des modèles ont rapidement été créés pour décrire la progression d'une épidémie au sein d'une population. Pour ce faire, une population est subdivisée en compartiments relatant de l'état des individus vis-à-vis du pathogène. Ces compartiments sont, principalement : les Susceptibles (S), qui peuvent se faire infecter, les Infectieux (I), qui sont porteurs du pathogènes et peuvent le transmettre, et les Résistants, ou Rétablis (R), qui sont immunisés au pathogène. Ainsi, la progression de la maladie se fait par passage des individus d'un compartiment à un autre. La structure d'un modèle simple est donc $S \xrightarrow{\lambda} I \xrightarrow{1/\gamma} R$, λ étant le taux de transmission et $1/\gamma$ la durée d'infection moyenne.

Une expression du taux de transmission λ a été définitivement validée au milieu du XX^{ÈME} siècle par analogie avec le principe d'action de masse utilisé en physique et en chimie [1]. D'après ce principe, si une population est bien mélangée, on a :

$$\lambda = \beta SI, \tag{1}$$

où β est le *taux de contact* du pathogène, proportionnel à la probabilité qu'un infectieux et un susceptible aient une *rencontre suffisante* à la transmission. Ainsi formulée, la transmission est densité-dépendante, car le taux de transmission dépendant de la densité I d'individu infectieux par unité d'espace. Au contraire, si ce taux dépend de la fréquence I/N d'infectieux dans la population, la transmission est dite fréquence-dépendante [2,3].

D'autres modèles peuvent inclure une perte d'immunité ou une période d'incubation matérialisée par un compartiment Exposés (E) précédant la période d'infectiosité.

De tels modèles permettent d'estimer le taux de reproduction de base du pathogène, ou R_0 [4,5]. Ce nombre indique le nombre d'infections secondaires créées par l'arrivée d'un infectieux

dans une population entièrement composée de susceptibles. S'il est supérieur à 1, une épidémie a lieu, sinon, le pathogène disparaît. Ce nombre permet également de calculer la limite épidémique, qui est la fréquence de susceptibles dans une population qu'il ne faut pas excéder pour éviter l'installation du pathogène dans cette population. Cette limite s'exprime comme suit [6–9] :

$$P_c = 1 - \frac{1}{R_0}. \quad (2)$$

De fait, un R_0 élevé sous-entend qu'une plus grande partie de la population ne doit pas être susceptible afin d'éviter l'apparition du pathogène dans la population. Cette protection de toute la population grâce à l'immunité d'une partie seulement constitue le principe d'immunité de groupe, qui est souvent l'objectif des campagnes de vaccination de masse.

Le R_0 ainsi que d'autres indicateurs utiles à la compréhension de la propagation d'un pathogène peuvent être estimés à partir de données mesurables, grâce aux enseignements des modèles épidémiologiques. On peut ainsi estimer le R_0 de la rougeole, de la rubéole, de la variole ou de la varicelle [8, 10], entre autres.

De nos jours, les modèles épidémiologiques se répartissent du très simple modèle mathématique dont le comportement est parfaitement étudié et connu à de très complexes et très spécifiques modèles utilisés pour obtenir des prédictions précises pour une situation donnée. On trouve ainsi des modèles spatialisés [11, 12], des modèles individus-centrés [12–18], des modèles d'épidémiologie sociale [19–24] et des modèles visant à rendre possible des expériences d'«épidémiologie virtuelle», remplaçant d'éthiquement impossibles expériences sur de vraies populations [25, 25–27].

1.2 Interactions entre pathogènes

Les travaux précédemment évoqués se concentrent généralement sur la relation entre l'hôte et le pathogène. Cependant les pathogènes, comme toutes les espèces, interagissent avec l'ensemble de leur écosystème, y compris les autres pathogènes. Les interactions entre différentes souches de la même espèce, ou entre pathogènes proches génétiquement, ont été étudiées depuis relativement longtemps [28–35], mais les interactions entre pathogènes non liés ne reçoivent encore qu'un intérêt limité [34, 36–40]. Pourtant, il a été montré que de telles interactions peuvent influencer la dynamique des épidémies [41–45]. Il est donc important de les connaître et de comprendre leurs conséquences.

Hélas, de telles interactions sont difficiles à identifier sans une forte présomption pré-existante, telle que celle qui a permis d'identifier la relation entre grippe et pneumonie [46]. Une telle approche «confirmative» n'est donc pas utilisable largement et à but exploratoire. Cependant, de nombreuses méthodes statistiques existent afin d'identifier des corrélations entre des variables ou dans des séries temporelles.

Dans d'autres domaines, des méthodes ont été développées pour faire la différence entre une simple corrélation, dont l'analyse est délicate, et une causalité, mettant en exergue une relation directe et orientée entre deux variables. On peut citer notamment la causalité de Granger [47] ou le transfert d'entropie [48, 49]. Ces méthodes ne demandent qu'à être testées en épidémiologie.

1.3 Interactions et Santé Publique

La possibilité d'effets secondaires des mesures de santé publique a déjà été soulevée, notamment la possibilité qu'un pathogène éradiqué soit remplacé par un autre, potentiellement plus virulent [50–55]. D'autres effets secondaires pourraient découler des interactions entre pathogènes.

On sait par exemple que certains pathogènes protègent contre d'autres infections ou réduisent la sévérité d'infections par d'autres pathogènes [56–59]. Que se passerait-il si cette protection était perdue du fait de l'éradication du pathogène ?

Plus les interactions sont complexes, comme celles existant entre les différents sérotypes de dengue [60–62], plus les effets secondaires d'interventions de santé publique peuvent être difficiles à prévoir. Il est donc important de mieux connaître ces interactions et de mieux comprendre leurs conséquences.

1.4 Les objectifs de la thèse

Cette thèse débute par une exploration de la bibliographie existante concernant les interactions entre pathogènes. Cette revue a pour but de recenser les différents types d'interactions et de souligner les progrès possibles dans le domaine. S'ensuit l'utilisation d'un modèle à deux pathogènes [63] pour explorer les effets possibles de certaines interactions et l'efficacité de différentes méthodes de détection des interactions entre pathogènes. Enfin, nous nous pencherons sur le cas particulier de la dengue pour illustrer les interférences entre interactions et mesures de santé publique.

2 Une nouvelle définition de la susceptibilité

Cette section passe en revue les mécanismes qui ont été documentés et les classe selon cinq grandes catégories. Les interactions intra-hôte ont été assez largement documentées [39, 44, 64] et, dans une moindre mesure, les interactions inter-hôtes l'ont été également [42, 43, 65]. D'une vue d'ensemble de ces différentes publications, il ressort les catégories d'interactions suivantes :

- **Immunité croisée.** L'immunité croisée est la protection partielle voire totale de l'hôte contre des pathogènes qui est conférée par l'infection par un pathogène proche génétiquement et/ou antigéniquement. Cette immunité-croisée est le résultat de la différenciation, lors de l'infection, de lymphocytes B en cellules B à mémoire. Lors de l'infection par un autre pathogène proche du pathogène originel, ces cellules mémoire peuvent être réactivées du fait d'antigènes similaires qui se lient aux récepteurs B des cellules mémoire. Du fait de cette réactivation, la réponse immunitaire de l'hôte à cette nouvelle infection est plus rapide et plus intense que la réaction normale.

Cela s'observe notamment entre les différentes souches de la grippe, pour laquelle la forte immunité-croisée entre les souches proches génétiquement est responsable de la dynamique évolutive du virus [66, 67]. Cela limite l'augmentation de la diversité au sein d'une même population et limite le succès de dispersion des souches mutantes à celles ayant accumulées un grand nombre de mutation [67].

- **Régulation croisée de l'immunité.** Le système immunitaire des vertébrés comporte un compromis (*trade-off*) fondamental entre l'immunité cellulaire, dite voie TH₁, et l'immunité humorale, dite voie TH₂ [68–70]. L'immunité cellulaire combat principalement les parasites intra-cellulaires, tandis que l'immunité humorale combat principalement les parasites extra-cellulaires. Ces deux voies sont régulées l'une par l'autre, si bien que la stimulation de l'une mène à l'inhibition de l'autre, sans jamais conduire à une désactivation totale cependant. De fait, un individu infecté à la fois par un pathogène intracellulaire et un pathogène extra-cellulaire va voir sa réaction immunitaire diminuée.

Les helminthes en particulier peuvent affecter l'immunité de leur hôte en augmentant leur susceptibilité [71], le taux de transmission de certains micro-parasites [72], voire les deux à la

fois [73, 74]. Ils peuvent également avoir un impact sur la sévérité des infections. La malaria cérébrale, l'une des formes les plus sévères de la malaria chez l'humain, est apparemment liée à une réaction immunitaire excessive [75]. L'infection par des helminthes, en diminuant la réponse immunitaire à la malaria, peut ainsi protéger l'hôte contre la forme la plus sévère de l'infection [38, 56, 57, 76, 77].

— **Immunosuppression.**

L'immunosuppression est la diminution de l'efficacité de l'ensemble du système immunitaire. Le virus de l'immunodéficience humaine (HIV) est l'exemple parangon de d'effet immunosuppresseur d'un pathogène. Lors de l'infection par le VIH, une phase aiguë suivie d'une phase chronique mène à la perte de nombreuses cellules CD4+T [78–80]. Cela conduit au syndrome d'immunodéficience acquise (SIDA), qui se traduit par une très forte susceptibilité à de nombreux pathogènes dits opportunistes [81, 82] et à des infections plus sévères [83].

Ainsi, les personnes souffrant du SIDA sont 37 fois plus susceptibles à la tuberculose humaine (TB) causée par *Mycobacterium Tuberculosis* [84]. L'émergence du HIV a ainsi causé la ré-émergence de la TB, qui avait été retirée des priorités de l'Organisation Mondiale de la Santé (OMS) dans les années 70 [85]. De plus, l'immunosuppression affecte également la sévérité de la TB, en accélérant sa progression. Enfin, la restauration des cellules CD4+T en cas de thérapie antirétrovirale contre le HIV peut causer une réaction immunitaire excessive contre la TB et causer un syndrome inflammatoire de reconstitution immunitaire (IRIS) mortel [86–89].

— **Réduction de la disponibilité des susceptibles.**

La réduction de la disponibilité des susceptibles, c'est-à-dire leur retrait de l'ensemble des individus accessibles pour un pathogène, peut-être due à l'infection par un autre pathogène. Par exemple, la mortalité liée à une maladie réduit de manière permanente le nombre de susceptibles dans la population pour tous les pathogènes, de même que la diminution de la fécondité de l'hôte par un pathogène va réduire le nombre naissances, et donc de susceptibles à la génération suivante [90–92]. Cette réduction peut également être temporaire dans le cas où une infection conduit à une période de convalescence, durant laquelle l'individu a moins de contact avec ses congénères et donc devient moins accessible pour les pathogènes. Cela s'observe notamment dans le cas des maladies infantiles, qui se transmettent à l'école [42].

— **Augmentation de la disponibilité des susceptibles ou perturbation de la protection comportementale.**

Cette interaction est la moins documentée dans la littérature. Une augmentation temporaire du nombre de susceptible dans la population peut être la conséquence de la présence d'un autre pathogène : par exemple, l'épidémie récente d'Ebola a perturbé fortement les programmes vaccinaux contre les maladies infantiles, empêchant ainsi la vaccination de 700 000 à 800 000 enfants [93, 94]. De plus, certaines maladies partagent un facteur de risque commun. De fait, l'infection par un pathogène implique une exposition accrue aux autres pathogènes qui sont transmis dans le même contexte. C'est le cas par exemple du HIV et de l'hépatite C qui se transmettent parmi les consommateurs de drogues par injection [95], ou des infections nosocomiales [96].

2.1 Interactions multiples

Un grand nombre de mécanismes d'interaction ont donc été décrits. Mais surtout, ces mécanismes ne sont pas exclusifs, et peuvent intervenir simultanément. Cette section est dédiée à

plusieurs modèles biologiques pour lesquels de multiples interactions peuvent avoir lieu simultanément, et à comment peut-on mieux les comprendre.

— **Immunosuppression et immunité croisée.**

Un pathogène peut à la fois causer une immuno-dépression globale et fournir une immunité-croisée ciblée. Cela pourrait être le cas entre les groupes de VIH-1 et VIH-2, bien que cela soit débattu depuis de nombreuses années [97–101]. Cette interaction double demeure difficile à identifier du fait que l’immunosuppression générale masque les effets d’une immunité croisée, dont l’existence a été confirmée par exemple entre VIH et VIS [102].

— **Immunosuppression et régulation.**

La régulation de la voie TH₁ lors de l’infection par des helminthes augmente la susceptibilité au VIH et la progression du virus [103–105]. Réciproquement, quelques études relatent un effet du VIH sur l’infection par des helminthes. L’immunosuppression pourrait à la fois augmenter la dissémination des helminthes en stimulant le développement larvaire [106] et diminuer l’excrétion d’œufs en causant la formation de granulomes [107–109].

— **Immunosuppression et réduction de la disponibilité des susceptibles.**

Exemple le plus simple, le VIH cause d’abord une immunodéficience, et les infections opportunistes qui suivent causent une forte mortalité [110]. De fait, l’effet du VIH est double et contradictoire, car il augmente la susceptibilité des hôte avant de diminuer leur nombre.

— **Immunité croisée et réduction de la disponibilité des susceptibles.**

À l’immunité croisée entre les souches de grippe s’ajoute une période de convalescence voire d’hospitalisation suivant l’infection [111, 112]. Cette période réduit la disponibilité des malades, ce qui pourrait augmenter les effets de l’immunité-croisée. De la même manière, une immunité croisée existerait entre les mycobactéries de la tuberculose et de la lèpre [113, 114]. De fait, la tuberculose aurait pu jouer un rôle dans le déclin de la lèpre en Europe [115]. De plus, la tuberculose est une maladie à très forte mortalité [87], et celle-ci peut avoir joué un rôle complémentaire dans la réduction du nombre de susceptibles à la lèpre, et donc dans son déclin.

— **Régulation et réduction de la disponibilité des susceptibles.**

Cette combinaison n’a pas été étudiée, et pourtant elle est potentiellement très importante entre les helminthes et les maladies infantiles. La régulation de la voie TH₁ lors de l’infection par des helminthes pourrait induire un risque élevé d’infection par certaines maladies infantiles [116]. De plus, ces maladies infantiles provoquent souvent une forte période de convalescence qui a de grandes conséquences sur la dynamique de la maladie [41]. Ces deux effets pourraient, en se combinant, avoir d’énormes conséquences de santé publique.

2.2 Conséquences pour la Santé Publique

Les études portant sur les interactions multiples simultanées sont, nous l’avons vu, rares. Cependant, l’expérience de cette revue bibliographique nous autorise à envisager les conséquences sur la santé publique de telles interactions, en se focalisant sur le dernier exemple présenté, la combinaison d’une régulation des voies immunitaires et de la réduction de disponibilité des susceptibles, et plus particulièrement sur l’exemple des helminthes *Fasciola hepatica* et de la maladie infantile *Bordetella pertussis*.

Dans un premier temps, sans aucune intervention, la présence de *F. hepatica* va diminuer la réponse immunitaire contre *B. pertussis*, donc contribuer à une plus grande transmission de cette dernière, et finalement à un plus grand nombre d’enfants en convalescence, non disponibles pour

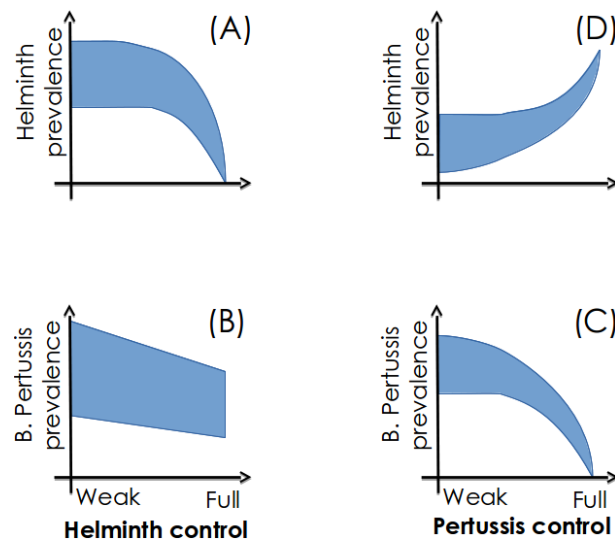


FIGURE 1. Représentation de l'impact possible de différentes mesures de santé publique contre *B. pertussis* et les helminthes sur la prévalence de chaque pathogène. (A) : Impact du contrôle des helminthes sur la prévalence des helminthes. (B) : Impact du contrôle des helminthes sur la prévalence de *B. pertussis*. (C) : Impact du contrôle de *B. pertussis* sur la prévalence de *B. pertussis*. (D) : Impact du contrôle de *B. pertussis* sur la prévalence des helminthes.

F. hepatica. Le nombre d'infection par *F. hepatica* va donc diminuer, et faire diminuer le nombre de co-infection par *B. pertussis*, rétablissant un plus grand nombre de susceptibles disponibles pour *F. hepatica*, et ainsi de suite.

Nous pouvons donc nous intéresser aux conséquences du contrôle de l'un ou l'autre de ces pathogènes sur la dynamique de chacun d'eux (Fig. 1). Dans un premier temps, le contrôle de *F. hepatica* pourrait être moins efficace que prévu car il réduirait le nombre d'individus en convalescence et donc augmenterait le nombre de susceptibles disponibles. Un fort contrôle devrait cependant se montrer efficace en dépassant l'effet du nombre de convalescents dans la population (Fig. 1, A). D'autre part, un faible contrôle de *F. hepatica* serait compensé par une augmentation du nombre de susceptibles disponibles pour *B. pertussis* et avoir donc peu d'effet sur celle-ci. En revanche, un fort contrôle devrait faire reculer *B. pertussis* du fait de la réduction du nombre de co-infectés transmettant mieux le pathogène (Fig. 1, B).

D'un autre côté, le contrôle faible de *B. pertussis* aurait peu d'effet sur *B. pertussis*, du fait de la diminution du nombre de personnes en convalescence. Un contrôle fort devrait en revanche palier à ce problème (Fig. 1, C). Enfin, la réduction du nombre de convalescents du fait du contrôle de *B. pertussis* devrait augmenter la disponibilité des susceptibles pour *F. hepatica*, et donc sa prévalence (Fig. 1, D). Les stratégies de contrôle contre les deux maladies étant généralement simultanées, il est important de noter que le succès de chacun d'eux dépendra fortement de l'efficacité de l'autre.

Comme le montre cet exemple, les interactions, qui ont surtout été étudiées indépendamment les unes des autres, peuvent avoir d'importantes conséquences quand elles sont impliquées simultanément. Le grand nombre d'observations ou de soupçons d'occurrence de telles combinaisons suggère que les pathogènes forment des communautés, comme n'importe quels organismes, comme cela a été suggéré dans l'idée de pathocénose introduite par Mirko Grmek [117]. Dans la Nature, il a été montré que les interactions entre pathogènes peuvent se révéler plus importantes

que les facteurs environnementaux dans la détermination de la prévalence des pathogènes [118].

Tout au long de cette section, nous avons vu que les interactions influent le plus souvent sur la susceptibilité réelle des populations. En effet, les interactions intra-hôte affectent le degré de susceptibilité de l'hôte aux autres pathogènes, tandis que les interactions inter-hôtes affectent le nombre d'individus susceptibles disponibles dans la population. Cela conduit logiquement à différencier la susceptibilité fondamentale de la population, qui découle simplement du nombre total d'individus susceptibles à un pathogène donné, et la susceptibilité réelle, qui prend en compte l'altération de susceptibilité et de disponibilité des individus en considérant l'historique personnel d'infection de chacun. L'estimation de cette susceptibilité réalisée, bien que difficile, serait un grand progrès pour la communauté scientifique et les autorités de santé publique.

3 Détection des interactions entre pathogènes

Comme nous l'avons vu, la connaissance et la prise en compte des interactions entre pathogènes peuvent s'avérer cruciales en matière de santé publique. De fait, il est nécessaire de disposer d'outils et de connaissances permettant de mieux connaître ces interactions et leurs conséquences sur les dynamiques de populations. Actuellement, l'identification des interactions se fait sur la base de forts soupçons biologiques. Lorsque l'on soupçonne l'existence d'une interaction, on utilise des approches confirmatives afin de confirmer l'existence de l'interaction et d'identifier plus précisément sa nature, en approximant la dynamique observée avec un modèle mécaniste incluant les mécanismes d'interaction dont on soupçonne l'implication [63]. On a ainsi pu quantifier l'interaction entre grippe et pneumocoque [46].

Cependant, il peut exister des interactions insoupçonnées. En ce cas, on ne dispose actuellement d'aucun outil permettant d'explorer largement les données afin d'identifier les interactions potentielles. Il y a donc un fort besoin pour un tel outil, et des méthodes exploratoires issues d'autres domaines scientifiques, en particulier les sciences économiques [47] ou la neurologie [119].

Dans cette section, nous nous penchons sur la pertinence de la causalité de Granger (GC) [120] et du Transfert d'Entropie (TE) [121] pour répondre à ce besoin. Ces deux méthodes visent à l'identification des causalités, c'est-à-dire des liens directs et orientés de cause à effet entre deux variables, en prenant en compte tout forçage extérieur et effets indirects, ce qui en font des outils plus puissants que les tests de corrélation.

Afin de tester leur application à l'épidémiologie, nous allons utiliser deux «boîtes à outils» (*toolboxes*) [119, 122] sur des données épidémiologiques issues d'un modèle à deux pathogènes permettant d'inclure un grand nombre des interactions décrites précédemment [63].

3.1 Le modèle

Le modèle utilisé est un modèle $S \rightarrow I \rightarrow C \rightarrow R$ (pour Susceptible, Infectieux, Convalescent, Résistant, resp.) à deux pathogènes originellement publié par Shresta *et al.* [63]. Ce modèle rend explicite toutes les combinaisons de statut par rapport aux deux pathogènes et inclus des mécanismes d'interaction par le biais d'une susceptibilité modifiée des individus si ils sont infectieux, convalescent ou résistant à l'un ou l'autre pathogène (Fig. 2)

Ce modèle inclus de la stochasticité démographique *via* la méthode de Gillespie [123] et de la stochasticité environnementale *via* un forçage saisonnier annuel commun aux deux pathogènes et auquel est adjoint un bruit blanc. Cela évite d'observer des similarités entre les dynamiques des deux pathogènes qui seraient uniquement liées au fait que les deux dynamiques découlent des mêmes mécanismes. Par exemple, sans stochasticité, si les deux pathogènes sont rigoureuse-

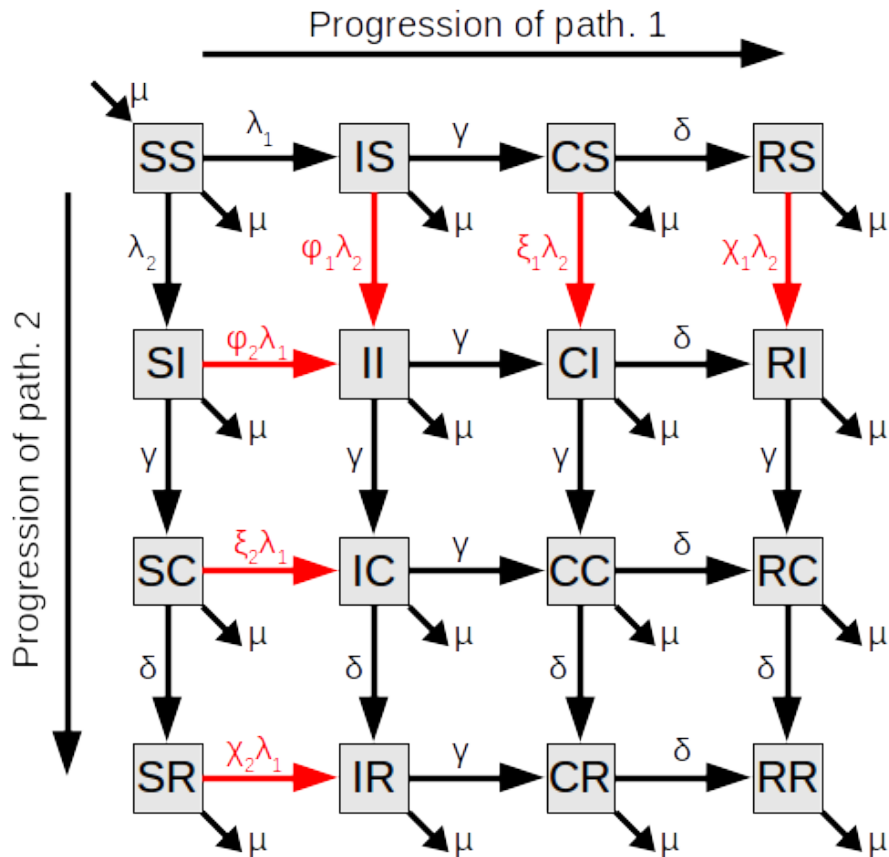


FIGURE 2. Diagramme du modèle à deux pathogènes. Chaque cadre représente un statut de l'hôte. Les flèches représentent les transitions entre les statuts. Les flèches rouges indiquent les transitions affectées par les interactions. Chaque compartiment regroupe les individus d'après leur statut vis-à-vis des deux pathogènes. S , I , C et R pour Susceptible, Infectieux, Convalescent and Résistant, respectivement. φ_i , ξ_i et χ_i sont les modifications de susceptibilité qui affectent les hôtes infectieux, convalescents et résistants (resp.) au pathogène i .

ment identiques, les dynamiques de chacun d'eux seraient également exactement identiques. La stochasticité permet d'éviter cela.

Afin de tester l'impact des caractéristiques des deux pathogènes sur les dynamiques, trois couples de pathogènes vont être utilisés. Le premier, dit "par défaut", est composé de deux pathogènes à fort taux de contact, avec une durée infection et une convalescence courtes et des taux de reproduction de base R_0 moyens. Cela correspond à la plupart des infections virales à forte transmissibilité [124, 125]. Le second, principalement destiné à éprouver les limites du modèle, comporte de très forts taux de contact, mais également une longue période d'infection et une longue convalescence, ce qui conduit à des R_0 extrêmement élevés, au-delà des R_0 observés dans la Nature. Le dernier enfin est constitué de très longues périodes d'infection et de convalescence, mais des taux de contact beaucoup plus faibles, qui correspondent à des infections chroniques à fort R_0 . Pour chaque simulation sont calculées l'aire sous la courbe, qui est un proxy du nombre total de cas, et la périodicité dominante.

Comportement du modèle Pour le premier jeu de paramètres, on constate que seules interactions modifiant la susceptibilité des individus résistants au premier pathogène ont un impact visible sur les dynamiques du second pathogène. Une susceptibilité diminuée (immunité croisée, par exemple) réduit le nombre de cas, tandis qu’une augmentation de susceptibilité (immunosuppression, par exemple) augmente peu le nombre de cas par rapport au cas sans interactions mais accélère la dynamique, avec une périodicité dominante plus courte.

Si l’on se penche sur les raisons de ce manque d’effet observable, on constate que la seule interaction ayant un effet visible concerne un compartiment, les résistants, dans lequel s’accumulent de nombreux individus, car situé en fin d’historique d’infection. Ainsi, avec les mêmes paramètres, parmi les individus susceptibles au second pathogène, on trouve 27.09% de résistants au premier pathogène, contre seulement 0.1075% et 0.04857% de convalescents et d’infectieux.

À l’aide de l’analyse de stabilité d’une version déterministe simplifiée du modèle, on peut déterminer ces proportions en fonction des paramètres du modèle. Ainsi, on a choisi les deux autres jeux de paramètres, celui à fort R_0 et celui à faible taux de contact, afin d’augmenter le nombre d’infectieux et de convalescents au premier pathogène parmi les susceptibles au second, afin de vérifier si cela modifie effectivement l’impact quantitatif des interactions sur les dynamiques.

Deux très forts R_0 affectent particulièrement la périodicité du second pathogène, en la déstabilisant, sans réellement changer l’impact des interactions sur le nombre de cas totaux par rapport aux paramètres précédents. En revanche, une faible transmission et de longues périodes d’infection et de convalescence augmentent l’impact d’une altération de susceptibilité lors de la convalescence.

3.2 Causalité de Granger

L’analyse de causalité de Granger (GCA) permet d’identifier la direction des relations entre les variables et de différencier les effets directs des biais [120]. La définition originelle de la GC est que « Y_t cause X_t si l’on est mieux capable de prédire X_t à partir de l’ensemble des informations disponibles qu’à partir de ce même ensemble privé de Y_t » [47]. Cette condition sous-entend que Y_t contient des informations exclusives qui ne sont présentes dans aucune autre variable et qui sont utiles pour prédire X_t . Ici, la capacité à prédire une variable se chiffre par l’erreur de prédiction d’un modèle auto-régressif multivarié (MVAR). Plus cette erreur est faible, meilleure est la prédiction.

Un MVAR est un modèle linéaire visant à prédire les valeurs d’une série temporelle en utilisant les valeurs passées de cette série temporelle et de celles d’autres variables. Il se construit en normalisant les données [126] dont on aura vérifié la stationnarité en terme de moyenne et de variance [119, 127], puis en construisant pour chaque instant t le vecteur A des coefficients que l’on multiplie aux n valeurs passées (Y_{t-1}, \dots, Y_{t-n}) de l’ensemble des variables explicatives (y compris X) pour estimer la valeur présente X_t . La significativité de la différence entre les erreurs de prédictions des différents modèles est ensuite testée.

Dans cette section, le calcul des causalités de Granger a été effectué au moyen de la *toolbox* proposée par Anil K. Seth [119].

3.3 Transfert d’Entropie

Le transfert d’entropie (TE) se base sur des principes issues de la théorie de l’information pour identifier les causalités entre des séries temporelles. Il respecte la définition de Granger de la causalité mais utilise l’*information mutuelle* plutôt que des modèles MVAR. Il s’agit d’un

indicateur symétrique qui quantifie la déviation de deux variables de l'indépendance et permet de calculer le-dit *transfert d'entropie*.

La difficulté de cette méthode est d'estimer les distributions, distributions jointes et distributions conditionnelles de chaque variable, qui sont nécessaires au calcul du TE. Cela peut se faire par différentes méthodes incluses dans la *toolbox* utilisée durant cette thèse, développée par Montalto *et al.* [122]. Ces méthodes incluent un estimateur linéaire (LIN), un estimateur "binning" (BIN) et un estimateur par plus proches voisins (NN), ces deux dernières étant des estimateurs non linéaires *a priori* plus adaptées aux systèmes complexes tels que le nôtre.

3.4 Application

Dans tous les résultats présentés ici, l'interaction est unidirectionnelle. La susceptibilité au second pathogène est modifiée en fonction du statut de l'individu par rapport au premier. Il n'y a également qu'une interaction à la fois. Il s'agit du cas le plus simple possible. L'analyse de causalité de Granger et le transfert d'entropie se sont tout deux révélés en deça des attentes pour l'identification des interactions incluses dans le modèle. Il est notable en premier lieu que les deux méthodes, à condition d'utiliser un estimateur linéaire (LIN) pour le transfert d'entropie, donnent des résultats très semblables. Les autres estimateurs (BIN et NN) se révèlent tout à fait inadaptés, ne détectant la plupart du temps aucune causalité, quelle que soit l'interaction présente dans les simulations.

De plus, si certaines interactions, particulièrement les interactions induisant une augmentation de la susceptibilité d'une proportion non négligeable de la population, sont détectés, il est difficile de dégager une règle permettant de prévoir si une interaction pourra être détectée ou non. Les interactions réduisant la susceptibilité sont parfois détectées également, tandis que dans la majorité des cas, un effet du second pathogène sur le premier, donc non-existante, est identifiée.

La détection dépend fortement des caractéristiques des pathogènes, les profils de causalités détectées étant très différents pour les trois jeux de paramètres. On constate globalement que les interactions ayant un impact visible sur les dynamiques ont tendance à conduire également à des détections de causalité, même erronées.

Enfin, il est important de noter que l'analyse de causalité de Granger, si elle n'est pas faisable sur des séries trop courtes, atteint son efficacité maximale avec des séries temporelles de 9 ans, soit environ 120 points, là où d'autres méthodes peuvent nécessiter des jeux de données de 40 années pour atteindre leur plein potentiel [63].

3.5 Discussion

Si nous avons précédemment mis en exergue l'importance des interactions entre pathogènes dans les dynamiques des maladies, cette étude montre que certaines interactions peuvent avoir un effet plus tempéré, voire invisible, à l'échelle des populations. Ainsi, pour qu'une interaction ait un impact sur la population dans son ensemble, il apparaît nécessaire que celle-ci modifie significativement la susceptibilité réalisée de la population. Une faible variation de cette susceptibilité peut n'avoir que très peu d'impact sur la dynamique du pathogène.

La causalité de Granger et le transfert d'entropie utilisant un estimateur linéaire donnent des résultats très similaires dans la plupart des cas. Cette observation a déjà été étudiée, et il a été montré que sous un certain nombre de conditions, difficilement vérifiables pour notre système, ces deux méthodes étaient équivalentes [128, 129].

Une des principales raisons possibles du manque de performance de l'analyse de causalité de Granger et du transfert d'entropie avec estimateur linéaire tient à la non-linéarité de notre

système. En effet, cette analyse nécessite que les modèles MVAR construits ou distributions utilisées soient efficaces, c'est-à-dire qu'ils expliquent une grande partie de la variance des séries temporelles. Or, ces modèles manquent de précision pour prédire des mécaniques non-linéaires. Cependant, ni diverses manipulation de données, telles que l'extraction de la phase, ni l'utilisation d'estimateur non-linéaires pour le transfert d'entropie, n'ont donné de meilleurs résultats. Cependant, des modèles non-linéaires non adaptés sont parfois moins performants que des modèles linéaires [130].

L'objectif de cette étude était d'obtenir une méthode exploratoire pour la détection des interactions, c'est-à-dire une méthode facile à mettre en place et pouvant être utilisée à grande échelle. Face aux piètres résultats de la causalité de Granger et du transfert d'entropie, il apparaît que les approches confirmatives demeurent mieux adaptées. Ces méthodes, basées sur l'inférence, estiment les interactions en estimant les paramètres de modèles mécanistes construit pour décrire la dynamique de pathogènes spécifiques. Construire de tels modèles nécessite un nombre conséquent de connaissances sur la biologie des pathogènes concernés et une suspicion concernant les mécanismes d'interactions possibles, qui doivent être intégrées au modèle [131]. De telles méthodes ont cependant démontré leur efficacité [46, 63].

4 Interactions et Santé Publique : cas de la vaccination contre la Dengue

La dengue est une maladie infectieuse transmise par les moustiques du genre *Aedes*. Ce pathogène est potentiellement présent dans 128 pays [132] et provoque environ 390 millions d'infections chaque année [133], dont 500 000 cas sévères requérant une hospitalisation et plus de 20 000 morts [134]. Il existe quatre sérotypes de ce virus (DENV-1, DENV-2, DENV-3, DENV-4), très proches génétiquement [135]. L'infection par un de ces sérotypes entraîne une immunité permanente à ce sérotype et une immunité temporaire aux autres, qui peut durer de deux mois à plusieurs années, en fonction des estimations [60, 61, 136–138].

La première infection est souvent asymptomatique, mais les ré-infections par d'autres sérotypes peuvent causer des formes sévères de la maladies (fièvre hémorragique, DHF, ou syndrome de choc, DSS). Les mécanismes en sont peu connus, mais l'une des hypothèses repose sur la présence d'anticorps due à la première infection qui se lie au virus sans pour autant le désactiver. Cette hypothèse est appelée *Antibody Dependant Enhancement* (ADE) [62, 139–141].

Les potentiels vaccins contre la dengue ont été l'objet d'énormes progrès ces dernières décennies. Plusieurs candidats sont en phase de tests cliniques [142]. L'un des plus avancé est le *Chimerivax*, ou CYD-TDV, développé par Sanofi-Pasteur [143–146]. La phase I des tests n'a révélé aucun effet secondaire [146], mais la phase II, menée sur 4 000 individus, a mis en avant un manque de protection contre le sérotype DENV-2 [147], et la phase III a confirmé, quoique tempéré également, ce défaut d'hétérogénéité de la protection fournie par le vaccin selon le sérotype [148].

La perspective d'une vaccination de masse avec un tel vaccin pose donc la problématique d'une potentiellement interférence entre son hétérogénéité et les nombreuses interactions entre sérotypes. Cette étude utilise un modèle à quatre sérotypes afin de visualiser l'effet de l'utilisation d'un tel vaccin dans les populations. Il s'agit en particulier de comparer ce vaccin hétérogène à un vaccin homogène hypothétique.

4.1 Le modèle

Le modèle utilisé pour simuler la dynamique de la dengue dérive de celui utilisé dans la section précédente. Les individus sont classés selon cinq catégories : susceptibles (S), infectieux (I), protégés (C, cette classe se substituant aux convalescents et servant à modéliser la période d'immunité-croisée suivant une infection), rétablis (R) et vaccinés (V). Toutes les combinaisons possibles de statut par sérotypes sont modélisés, menant non plus à une matrice de 4x4 mais à une hypermatrice de 5x5x5x5 compartiments.

La vaccination intervient à la naissance, avec une couverture vaccinale de 95% : 95% des nouveaux-nés reçoivent le vaccin, et sont donc protégés en fonction de l'efficacité du vaccin, calquée sur les résultats des test de phase II du Chimerivax (55.6%, 9.2%, 75.3% et 100% pour les sérotypes DENV-1, 2, 3 et 4 respectivement [147]) ou sur un vaccin homogène ayant la même efficacité moyenne (60%). De plus, les formes sévères (DHF et DSS) sont également recensées. 14% [134, 149] des infections primaires et 44% [134, 149] des infections secondaires entraînent de telles complications. Pour ce modèle, nous considérons que l'immunité donnée par le vaccin est comparable à celle donnée par une exposition au virus, et qu'une infection par un sérotype contre lequel le vaccin aura été inefficace présente donc un plus grand risque de complications.

Ce modèle parvient à saisir l'essentiel des caractéristiques de la dengue observées dans les données et est cohérent avec d'autres modèles à quatre sérotypes, avec des épidémies annuelles, causées par un ou plusieurs sérotypes à la fois, et une composante secondaire de 2-3 ans environ [65, 150]. L'introduction d'un vaccin hétérogène ne provoque pas de diminution remarquable du nombre de cas au cours des dix premières années, ni de diminution de la mortalité liées à la dengue. En revanche, le sérotype DENV-2, contre lequel le vaccin est le moins efficace, voit une augmentation de son nombre de cas.

Sur le plus long terme, 50 ans après le début de la campagne de vaccination, le nombre de cas des sérotypes DENV-1, 3 et 4 sont grandement réduits, et le nombre de cas sévères est diminué de moitié. En revanche, le nombre de cas de DENV-2 est augmenté de 44%. De fait, malgré une couverture vaccinale de 95%, ce vaccin ne permet pas d'aboutir à l'éradication de la dengue. En revanche, un vaccin homogène avec la même efficacité moyenne et la même couverture vaccinale permet de diminuer le nombre de cas sévères de plus de 97%.

4.2 Discussion

Cette étude, en se concentrant sur le candidat le plus avancé [144, 146–148, 151], montre que l'hétérogénéité du vaccin contre la dengue doit être une considération majeure, potentiellement plus importante que son efficacité moyenne. À court terme, l'introduction d'un vaccin hétérogène peut avoir des conséquences néfastes à cause de violentes épidémies dans les quelques années suivant la mise en place d'une politique vaccinale de vaccination de masse. Cela s'explique par l'altération de la compétition entre sérotypes qui bénéficie fortement au sérotype contre lequel le vaccin est le moins efficace. Ces effets sont en partie absorbés à long terme, et la mortalité due à la dengue finit par diminuer.

D'autres vaccins auraient pu être utilisés avec ce modèle. Cependant, la plupart des autres candidats sont bien moins avancés, ou leur développement est arrêté, ou les données d'efficacité par sérotype ne sont pas disponibles [142, 152, 153]. De plus, l'utilisation des résultats des test de phase III ne changent pas qualitativement les résultats obtenus. Ces résultats sont de plus robustes aux variations des paramètres épidémiologiques.

Les effets à court terme du vaccin sont définitivement un frein à son utilisation extensive. Même si les effets à long terme sont incontestables, un délai de deux générations avant l'observa-

bilité de résultats probants est difficile à soutenir, particulièrement dans un contexte où le refus vaccinal existe [154, 155]. Cependant, il est à noter que ce délai peut être lié à la vaccination concentrée sur les nouveaux-nés. Une campagne de vaccination commençant par une vaccination plus large, incluant, enfants, adolescents et adultes pourrait aider à réduire ce défaut, sans pour autant supprimer le problème de l'impossibilité d'éliminer totalement le pathogène. Cela pourrait éventuellement se voir compensé par la combinaison de la vaccination avec d'autres politiques de contrôle, telles que la lutte contre le vecteur, ou en ciblant spécifiquement les individus à haut risque de complications [156].

5 Conclusion

Cette thèse a permis de mettre en avant l'importance des interactions entre pathogènes en épidémiologie. Tout d'abord, il a été montré que, au-delà des nombreuses observations démontrant l'existence d'interactions entre certains pathogènes, ces interactions étaient susceptibles de se combiner. Cinq grands mécanismes d'interactions ont été établis : (i) l'immunité-croisée, (ii) la régulation des voies immunitaires, (iii) l'immunosuppression, (iv) la diminution de disponibilité des susceptibles, et (v) l'augmentation de disponibilité.

Ces cinq mécanismes ont été plus ou moins bien documentés, mais il ressort surtout qu'ils peuvent intervenir simultanément dans un même système, bien que les études se concentrant sur ce point soient rares. Par différents exemples, nous avons montré que la combinaison de plusieurs mécanismes d'interactions pouvait pourtant, potentiellement, avoir de très fortes répercussions pour la santé publique, et qu'il serait intéressant de développer un concept de susceptibilité réalisée d'une population, qui prendrait en compte l'impact des interactions sur la susceptibilité des individus, et donc, de la population.

Par l'intermédiaire de la modélisation, nous avons pu explorer l'impact de certains de ces mécanismes, pris indépendamment, sur la dynamique des pathogènes. Il est apparu que les interactions à court terme et affectant peu d'individus, c'est-à-dire affectant peu la susceptibilité réalisée de la population, avaient peu d'impact sur les dynamiques des pathogènes au niveau de la population. Les facteurs importants pour estimer l'impact d'une interaction sur la dynamique sont : (i) la force de l'interaction, c'est-à-dire à quelle point la susceptibilité de l'individu est modifiée, et (ii) l'exposition des individus à l'interaction.

Du fait du potentiel manque d'impact à grande échelle des interactions, il est difficile de les identifier sur la base des données populationnelles. Les approches exploratoires de causalité de Granger et de Transfert d'Entropie se révèlent non adaptées, ce qui oblige encore à utiliser des méthodes plus compliquées à mettre en œuvre, car nécessitant de se concentrer sur des pathogènes en particulier, des connaissances avancées de la biologie de ces pathogènes et de forts soupçons sur l'existence d'un mécanisme d'interaction particulier entre eux.

Malgré tout, les interactions peuvent avoir de grandes implications pour la santé publique. Le cas de la dengue, avec ses quatre sérotypes et leur schéma d'interactions complexe, pose des problèmes à l'instauration de la vaccination. En effet, un vaccin hétérogène, en perturbant l'équilibre entre les quatre sérotypes, peut avoir des conséquences néfastes à court terme sur les populations. Il est susceptible de fortement favoriser celui contre lequel il est le moins efficace en diminuant la compétition pour les susceptibles.

Les pathogènes ne devraient donc pas être considérés comme des entités indépendantes les unes des autres. Il est important de considérer la communauté formée par l'ensemble des pathogènes circulant dans une population, et de comprendre que la prévalence d'un pathogène peut dépendre de la prévalence d'autres [117, 118, 157–161].

5.1 Perspectives

Il ressort de cette thèse un manque de la littérature en matière d'interactions multiples. Peu nombreuses sont les études se concentrant sur la co-occurrence de plusieurs mécanismes d'interactions dans le même système, bien que nombreux soient les systèmes dans lesquels il est très probable de pouvoir faire de telles observations. Les faibles résultats des outils d'analyses testés durant cette thèse montrent qu'il y a toujours un besoin pour un moyen simple et efficace d'identifier les interactions, la difficulté de formellement prouver leur occurrence restant un frein au développement de la littérature. Plusieurs autres outils pourraient encore être testés, comme des approches par "copula" [162, 163] ou par modélisation d'espace d'état combiné à la cohérence partielle normalisée [164].

Comprendre la dynamique de tels systèmes, où plusieurs interactions sont en action, peut s'avérer vital pour la santé publique. En la matière, il y a un large champ disponible pour les approches théoriques et la modélisation. Les quelques modèles qui existent sont encore peu connus et peu explorés. Comprendre parfaitement le comportement de modèles théoriques aide à appréhender les systèmes réels desquels ils s'inspirent.

Introduction

Studying pathogens' population dynamics is both a crucial issue for Public Health [165] and a growing research field for Ecology [166]. Understanding how a pathogen spreads into an animal or human population is a key to find effective ways to fight it and restrain its transmission [3]. If medical sciences and clinical studies allow us to fight diseases at the individual level [167], population dynamics help maximizing the impact of medications at the population scale [168]. This introduction will focus on the development of models for epidemiology, i.e. the follow-up of the number of ill persons within a population.

Fighting diseases has always been a priority for mankind. Infectious diseases, caused by pathogens that are transmitted from one host to another, represent a consequent and specific part of all diseases. Infectious diseases have always been studied. Early Egyptians, Chinese, Greek and Roman civilizations already kept tracks of severe plagues [169]. First model designed in the intent to understand epidemics has been made by BERNOULLI in 1760 [170]. First mention of the possibility that vaccination of a part of a population might protect the whole population against a pathogen appears in 1840 in the second annual report of the Registrar-General of Births, Deaths and Marriages of England and Wales [171].

In the 60s, the improvements in sanitation, antibiotics and vaccination make people believe that infectious diseases would soon be eliminated. However, infectious diseases still circulated in the 'developing' countries and some diseases emerged or re-emerged [172]. Thus, interest in infectious diseases has been revived. Understanding how epidemics start, spread and decay is of great interest to protect the populations. It leads to better approaches to decrease the transmission of the diseases, by identifying vulnerable sub-populations or elaborate better public health policies. For example, epidemiological models have enable pulse vaccination. Pulse vaccination explicitly considers the dynamic of the host-pathogen system [173]. It aims to periodically vaccinate a defined proportion of the population in order to compensate births and maintain the number of susceptible individuals below a threshold [174, 175], without the huge cost of classical mass vaccination strategies. We will now see how these models have been developed and used.

1 Modelling Infectious Diseases

Inspired by population dynamics, models have been built to describe the course of an infection within a population. The first step is to consider two populations: the hosts and the pathogens. Mimicking the structure of the Lotka-Volterra prey-predator system [176], the preys are the hosts that can be infected by the pathogen while the predators are the pathogens that can infect hosts. However, the population of pathogen is of secondary interest. Instead we are interested in the number of infected (and infectious) individuals in the host population. However, with the assumption that 'predation' (i.e. transmission of the disease) depends more of the number of infectious individuals than in the total number of pathogens, it appears that modelling

the number of vulnerable individuals and the number of infectious individuals within the host population would be a better choice.

Thus the population is split in several groups, or ‘compartments’, according to the status of individuals toward the pathogen. Fundamental compartments are ‘Susceptible’ (S), for individuals who can be infected by the pathogen, ‘Infectious’ (I), for individuals who can transmit the pathogen to susceptible individuals, and ‘Resistant’ (R), for the individuals immune to the pathogen. Course of the disease is movement of individuals from one compartment to another. It is built similarly to the Lotka-Volterra system but instead of several population from the same community, we model several sub-populations from the same population. In order to fit the specificity of each pathogen, compartments can be added or removed. The fundamental model is the Susceptible - Infectious - Resistant model. Considering that the time scale of an epidemic is not comparable to the time scale of demography, births and deaths can be neglected. Thus, the model structure is $S \xrightarrow{\lambda} I \xrightarrow{1/\gamma} R$, with λ the rate of infection and $1/\gamma$ the infectious period, and the ODE system is:

$$\frac{dS}{dt} = -\lambda \tag{1}$$

$$\frac{dI}{dt} = \lambda - \gamma I \tag{2}$$

$$\frac{dR}{dt} = \gamma I \tag{3}$$

One of the first key issue that have to be overcome to model an infectious disease is: why do epidemics often end before the infection of all susceptibles? How to model the transmission of the pathogen from an infectious individual to a susceptible individual? What is this λ ? Two potential answer to the first question raised, leading to a major controversy in the early XXTH century. Some maintained that this was due to a loss of “virulence” of the infectious agent [177] and others argued that it reflected the interaction between the proportion of susceptible, infectious and resistant fraction of the population [178]. Despite both having support from observations and mathematical reasoning [179], the introduction of the “mass action principle” from physical and chemical science once and for all validated the later [1].

The analogy between chemical reactions and transmission of a pathogen define, given that the population is well-mixed, without segregation based on the status toward the disease, that

$$\lambda = \beta SI, \tag{4}$$

with β the *contact rate* of the pathogen, i.e. a parameter proportional to the probability that a susceptible and an infectious have a sufficient encounter (*contact*) to cause the transmission of the pathogen from the infectious to the susceptible. This is for the case were the total population N is constant or the transmission is dependant of the density (the number per unit of space) of infectious in the population. Transmission may also depend of the proportion of infectious in the population: this is *frequency-dependant* transmission,

$$\lambda = \beta_n S \frac{I}{N}. \tag{5}$$

If N is constant, i.e. the demography is neglected in the model, we simply have $\beta = \beta_n/N$. But with explicit demography, there is no direct equality between density-dependant contact rate β and frequency-dependant contact rate β_n .

Density-dependant transmission is used for supposedly well-mixed populations, where the number of encounters a susceptible makes is dependant of the density of the population. The

more individuals per unit area (or volume), the more encounters will occur. But in the case of, e.g., sexually transmitted diseases (STDs), the number of encounters depends mainly of the mating system and may be independent of the host density [2]. In this case the risk of infection is dependant of the proportion of infectious individuals in the population [3].

Other classical models are the SIRS model, $S \xrightarrow{\beta SI} I \xrightarrow{\gamma I} R \xrightarrow{\alpha R} S$, with loss of immunity, that can be used for influenza, or the SEIR model, $S \xrightarrow{\beta SI} E \xrightarrow{\varepsilon E} I \xrightarrow{\gamma I} R$, with a temporary incubation period during which a newly infected host is not infectious, E standing for “exposed”.

1.1 Basic reproductive rate, Epidemic threshold and Herd immunity

Modelling the dynamics of a disease gives clues on some of its key characteristics, by assessing such questions as (*sic*): “Can the infection be stably maintained in the population? Is it endemic or epidemic? What is the time course [...] of the infection when introduced into a virgin population?” [180]. Notably, the ‘Basic Reproductive Rate’, or basic reproduction number, usually noted R_0 , is a prominent concept in infectious diseases modelling [4, 5]. This number represents the average number of subsequent infection caused by a single infected individual introduced in a fully naïve, susceptible population. If $R_0 < 1$, the invasion will fail and the pathogen will disappear from the population, and if $R_0 > 1$, the pathogen will become either endemic or epidemic.

For a simple SIR model with no demography, we have

$$R_0 = \frac{\beta}{\gamma}. \quad (6)$$

Estimating the R_0 of a pathogen gives serious clues to answer the three previous questions. Even if the first theoretical basis of a quantitative estimation of herd immunity have been made before the introduction of R_0 in the context of infectious diseases [178, 181], the basic reproductive rate is closely related to the “Epidemic Threshold”, the maximum frequency of susceptible that must not be exceeded in a population in order to ensure the *herd immunity* of the population and prevent the spread of the disease [6–9]. Staying in the context of a SIR model, this threshold is

$$P_c = 1 - \frac{1}{R_0}. \quad (7)$$

The higher the R_0 , the more individuals have to be immune before the infection can fade out. Thus, the aim of eradication campaigns based on mass vaccination is to reach this threshold by granting vaccine-induced immunization to a large part of the population.

The basic reproductive number R_0 is the main of three precious indicators. The second is the contact number σ , i.e. the average number of contacts sufficient for infection if the contacted individual is susceptible made by an infectious individual during the infectious period. The last is the replacement number R , the average number of secondary infection produced by an infectious individual during the whole course of the infection. By using data of the fraction of susceptible at the beginning and at the end of epidemics, it is possible to estimate σ for specific diseases like rubella, influenza or the Epstein-Barr virus [10].

Thanks to formulas derived from SIR or SEIR models, data on average ages of infection and average life times can be used to estimate R_0 for some viral diseases for which acquired immunity is permanent, such as measles, chickenpox, mumps, rubella, poliomyelitis or smallpox [8, 10]. For pathogen with temporary immunity, like pertussis, reliable estimations of R_0 , σ or R are more difficult, but computer simulation of age-structured SIRS models inform us of the potential efficacy of several vaccination strategies [182, 183].

The stability of the endemic equilibrium, i.e. the equilibrium with a constant number of infectious individuals in the population, can be estimated for MSEIRS (M standing for mother-to-child transmission of immunity), MSEIR [184], SEIR [185, 186] with various specificity such as varying total population size [187], infectious power of latent (E) and immune (R) individuals [188], SIR, SIRS and SEIS [10, 187, 189, 190] models.

1.2 Other developments of Epidemiology

Nowadays, models for epidemiology range from very simple, but very well analytically known, explicative models, as the one briefly described above, to very specific, complex and complicated predictive models. Those models aim to fit to specific situation in order to give a precise prediction of the spread of a disease within a given real population. The first improvement that can be added to a model is the spatial dimension of the spread of the pathogen. This spatial dimension has first been added by considering the dispersion of the disease as a wave travelling outward from a center point [11]. These models successfully predict the spread of pathogens between cities or between cities and rural areas [12].

A possible step is individual-based, spatially explicit models [12]. In such model, each individual is explicitly modelled. They are all different in some point, they interact with each other locally, they are mobile and their environment is heterogeneous. Thus, transmission is not anymore an approximation with e.g. a mass action law, but is the result of explicit movement and contacts of infectious and susceptible individuals. They are called individual-based models (IBM) [13, 14], discrete individual transmission models [15], microsimulation models [16] and more often agent-based model [17, 18].

IBM allows to assess the micro scale (e.g. village) of a pathogen dynamic, more precisely its propagation and its persistence. Very complex IBM, with extensive representation of the environment and its dynamic, of interactions between individuals and between individuals and their environment, and high flexibility of the model, allow epidemiologists to hope for “virtual epidemiology” experiments, i.e. using models and simulations to assess, validate and explore new hypothesis about pathogens [25]. This could be achieved by combining IBM with Geographical Information System (GIS) [25–27], but is also conceivable with reaction-diffusion ordinary differential equations [191, 192].

Another branch of modern epidemiology is Social Epidemiology [19]. This branch focuses on social determinant (individual attributes, behaviours, contextual influence ...) of the spread of a pathogen. Social epidemiology uses both individual-based model and social network analysis to understand and predict the spatial and temporal dynamics of a pathogen, or of health and diseases in general [20]. It helps understand the influence of the social disparities in population on the spread of a pathogen [21]. Moreover, it gives new insight on previously supposed non-communicable disease, by proving (e.g.) that obesity or smoking spreads along social network as a pathogen could do [22–24].

2 Pathogen-pathogen Interactions

However, most of those works, including contemporary, generally focus on a single host-pathogen relationship. Pathogen represents a significant part of all living species (or not-so-living in the case of viruses, as most of biologists do not consider them as ‘alive’ because they can’t reproduce themselves without hacking the reproduction abilities of their hosts [193–195]), and as any other living species, they interact with their ecosystem and the other species constituting it. This includes their host and all the other pathogens sharing the same host. These interactions

might be immunological, ecological, or evolutionary, and occur at many levels, from intra-host to ecosystem. Starting there, it becomes clear that such interaction may jeopardize the course of the infections and that understanding them is crucial.

If interactions between strains of the same pathogen, or between closely related pathogens have been studied since a while [28–30], interactions between unrelated pathogens nowadays receive a growing interest. Many clinical case-studies tends to show that co-infection of a single host by several pathogens affects the course of the infection of both pathogens, and that unexpected effects arise from the interaction of these pathogens [34, 36–40] at the host level. On the other hand, some theoretical studies focus on the dynamical impact of interactions at larger scales [41–45].

A typical SIR model with two pathogens focuses on the life-history of an individual. Considering that co-infection is not possible or negligible, two possible routes exist. Either the individual gets infected by the first pathogen, then become susceptible again, gets infected by the second pathogen, and become resistant, either the order of the infections is reversed [41]. Thus the model’s structure remains simple (see Fig. 1, A) and properly describes a competition for susceptible between the two pathogens. Studies of this model show that interactions at the population level, such as removal of susceptibles, can strongly force the periodicity of the epidemics. ROHANI *et al.* [41, 42] highlights that this competition, which occurs for example between measles and whooping cough, coerces the diseases with the longer infectious period (whooping cough) to follow the same biennial periodicity as the other disease (measles), while whooping cough in isolation has an annual dynamic.

A more complex model, with co infection, temporary or permanent cross-immunity or removal, and temporary or permanent immuno-suppression (Fig. 1, B) can be used to broadly explore the impact of immune-mediated and ecological interactions. VASCO *et al.* [43] used such model to test the stability of the coexistence of two interacting pathogens. They tested several scenarii for measles-pertussis or measles-rubella interactions. They showed that according to the strength and duration of the interaction, both diseases could stably coexist or compete in a way that the dynamics of the diseases are either synchronous or out of phase, following stable limit cycles or chaotic attractors.

However, such high-level, ecological interactions are uneasy to identify. There is no clinical evidences of such interactions, and they may be population-specific. In the case of measles and whooping cough, the competition is due to the social context of the infection. Both diseases are child-diseases which are commonly contracted at school. When a child is infected by one of these disease, he does not go to school anymore before the infection is cured. Thus, he is also removed from the pool of available susceptibles for the other disease. But many other, more inconspicuous interaction may exist.

3 Detecting Pathogens Interactions

Identifying interactions is one of the main objective of statistical analysis in this field. Some works already focused on statistical ways to identify interactions between pathogens from population-level data. One of them, which has been a major inspiration for this PhD, is the work of SHRESTHA *et al.* [63]. Using a two pathogen model including various interaction mechanisms, they produced epidemiological time series. Then, they *inferred* the nature of the interactions in the system with partially observed Markov processes [66, 196, 197]. This method tries to fit the data with a ‘process’ model and an observation model. The observation model describes the way data are collected from the reality, and the process model describes the epidemiological and

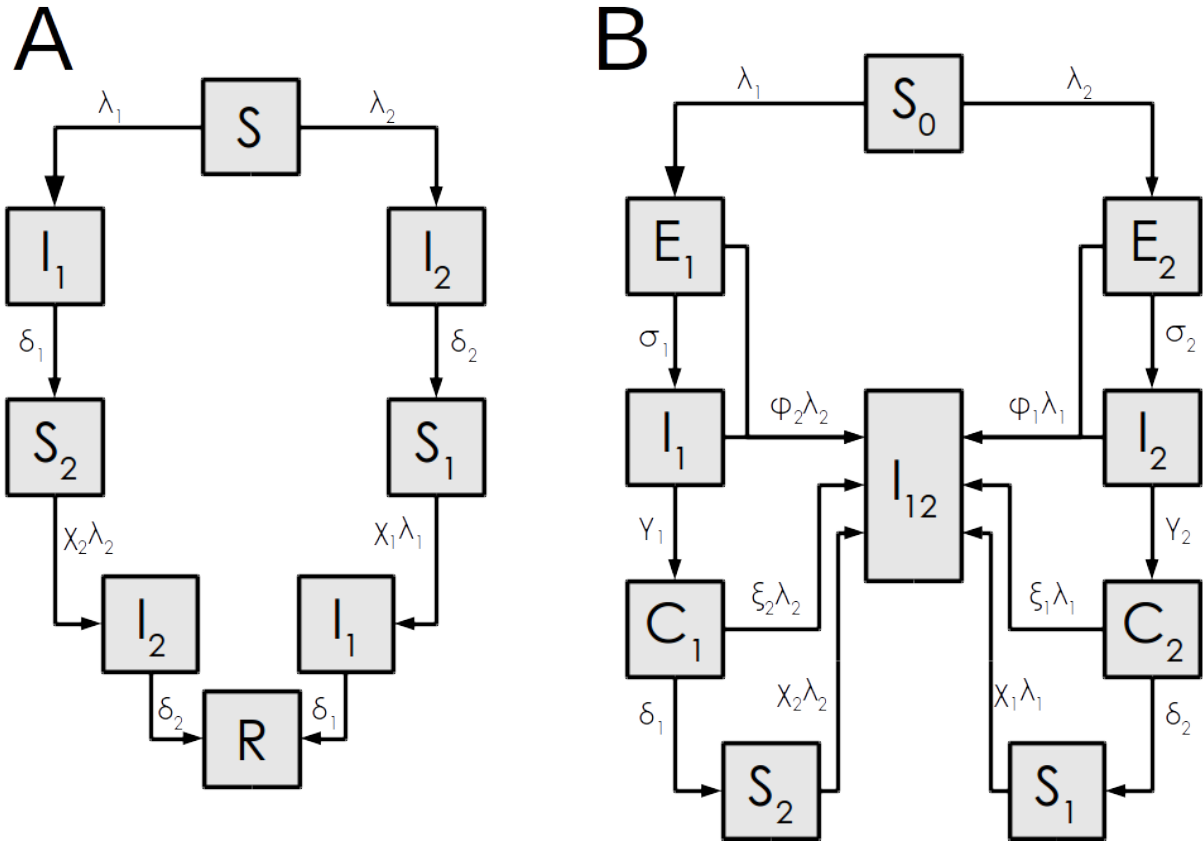


Figure 1. Schematics for two pathogens models. S or S_0 : susceptible to both pathogens. I_i : infectious to pathogen i . S_i : susceptible to pathogen i , recovered from the other. R : recovered from both pathogen. E_i : exposed to pathogen i . C_i : convalescent to pathogen i . χ_i : alteration of susceptibility when susceptible to pathogen i and recovered from the other. φ_i : alteration of susceptibility when exposed or infectious to pathogen i . ξ_i : alteration of susceptibility when convalescent to pathogen i . A: The probability of co infection is considered negligible and the latent period short enough to be ignored. The susceptibility to a pathogen after recovery from the other pathogen is different from the susceptibility when naïve to both pathogens. B: Co-infection is possible and latent period is not negligible. However we don't discriminate secondary infection in relation to the pathogen responsible for it and we don't follow life history of host after the second infection. Susceptibility of the host is modified differently if the host is exposed or infected, convalescent, or recovered.

demographic processes ruling the system.

This method, which is a confirmatory approach, is effective but relies on knowledge or hypothesis of both biological and demographic processes, and observation bias. In their paper, this distinguishes itself by the use of the very same model to produce the data and as process model in the analysis. Thus there is no doubt that the process model can reproduce the ‘reality’, i.e. the simulated dynamics. The main point of the inference is then to estimate the parameters used in the model to produce the data, these including the interaction parameters. Once the interaction parameters are estimated, one can conclude about the nature of the interaction existing in the data.

Such approach has been used by the same authors [46] to identify the interaction between Influenza and Pneumococcal Pneumonia. They developed a two pathogen SIRS model with three possible interaction mechanisms. Either (1) individuals infected with pneumococcal pneumonia contribute more to pneumococcal transmission if they have been recently infected with influenza, either (2) individuals recently infected with influenza are more susceptible to pneumococcal pneumonia, either (3) individuals infected with pneumococcal pneumonia are more likely to be reported, if recently infected with influenza. Their main result was that that influenza infection increase susceptibility to pneumococcal pneumonia 100-fold.

This result is striking but applying this method to real data required an extensive knowledge of the biology and the ecology of both pathogens, in order to use the appropriate model as process model and to restrain the space of biological parameters to be explored. Moreover, given the heaviness of the process, this method cannot be widely applied in order to explore unexpected interaction. On the contrary, it requires a strong biological presumption, because the right potential interaction have to be modelled. For example, in the case of influenza and pneumococcal pneumonia, if the interaction was a different one from the three included in the model, the results would have been “No interaction detected”. Biological suspicion of interaction exists for some pathogens, but not for many others, like those circulating in the same place at the same time, like childhood diseases and helminths [116, 198]. Thus, there is a need for exploratory approaches to identify interactions.

3.1 Correlation and Causality

Historically, one of the first role of exploratory statistical analysis is to identify correlation between variables. A correlation is a statistically significant link between two variables, meaning that knowledge about one of these variables gives partial knowledge about the other variable. However, a correlation is neutral and symmetrical. It does not induce a direct causation between the two variables, as it can be due, e.g., by a common external forcing (Fig 2, A). It could also result from a succession of causalities with intermediate variables (Fig 2, B) or a more complex pattern with retroaction (Fig 2, C).

Many methods have been created to identify correlation, either between punctual variables or between time series. Some are only “pairing” analysis, taking only a couple of variables into account, and others are multivariate. In the later case, there is an ‘observed’ variable and a set of ‘explicative’ variables. The analysis is used to identify which of these explicative variables ‘explain’ best the variance of the observed variable, i.e. which explicative variables are the most correlated to the observed variable. According to the method used, each variable might be continuous or discrete.

Further development of statistical sciences leads to the definition of statistical causality. Identifying causality as the direct influence of a variable on another is an ultimate goal of statistical analysis. Many different approaches has been created to discriminate ‘real’ causalities from simple

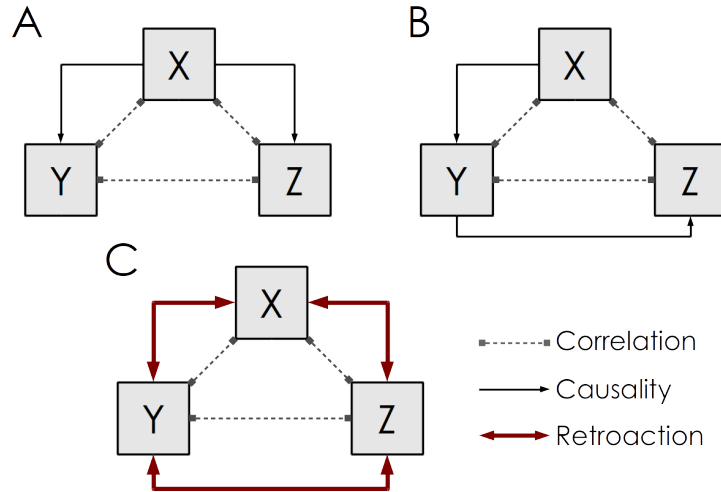


Figure 2. Several patterns of causalities that induce the same pattern of correlations. X , Y and Z are three variables. A: common external forcing of both Y and Z by X . B: Succession of causalities from X to Y and Y to Z , with no direct effect of X to Z . C: retroaction between all variables.

correlations. Restraining to exploratory ones, one of the oldest one is the Granger Causality [47], while most recent approaches are Convergent Cross-Mapping [199] or Transfer Entropy [48, 49]. Convergent Cross-Mapping being still poorly documented, we will focus on the two others.

4 Implications for Public Health

Acquiring the ability to broadly explore potential interactions, and thus identify unexpected interaction, might be of great help for Public Health. It has been proven that pathogen-pathogen interactions may affect the course of the disease at the population level, and it is possible that such interactions interfere with Public Health policies. Ecology does not lack of example of unexpected results of human intentional or non-intentional intervention on ecosystem. Invasive species and non-target effect of biological pest control are a flagrant example of such deleterious outcomes [200, 201].

Several authors already rose the issue of potential unexpected consequences of Public Health policies. Elimination of a disease may free a niche for another pathogen to replace it [50]. If this hypothesis has been rejected in the early years of the debate [202], it is nowadays gaining currency. Emergence of a pathogen in the niche of smallpox, declared eradicated in 1979 [203], is one of the most often invoked risk [51–53]. The same issue arises for the recently eradicated rinderpest [54], or close-to-eradication pathogens such as measles [55]. However, most of these questions are not directly related to interactions between pathogens, as they focus on the potential emergence of a new, previously unknown, pathogen to occupy a vacant niche.

This issue is close to the principle of competitive exclusion [204], stating that two species with the exact same niche cannot coexist at the same place and time, and that two species with overlapping niches will compete in a way that the best competitor will out-populate the other. But if this competition is altered by any mean (including human intervention), the excluded competitor may re-invade the system. Yet we saw in section 2 of this introduction that competition, e.g. for susceptible individuals, occurs between pathogens. Thus similarly, the release of this competition due to the decline or eradication of a pathogen achieved by Public Health

policies could facilitate the spread of its competitors, i.e., other pathogens.

Moreover, other types of interactions may interfere with Public Health. Several authors stated that infection by helminths *Ascaris lumbricoides* reduce the risk of suffering a severe cerebral malaria in case of simultaneous infection by *Plasmodium falciparum*, the main agent of human malaria [56,57]. More generally, simultaneous infection by helminths appears to reduce the severity of cerebral and mild malaria [58] and malaria-related acute renal failure and jaundice [59]. Thus, reducing the incidence of helminths, e.g. with targeted Public Health policies, could increase the burden of malaria.

Cross-protection occurs more often in related pathogens. Strong cross-immunity between antigenically similar strains of influenza is responsible for the evolutive dynamics of the virus [205,206] and the difficulty to eradicate the virus with vaccination [207–209]. For other pathogens such as dengue, the interaction pattern between strains is more complex, with short-term, temporary, cross-immunity and long-term higher susceptibility to severe form of the disease in case of reinfection [60–62]. Human intervention within such complex system may have unexpected consequences, and it is essential to invest the potential collusion between pathogen-pathogen interactions and Public Health policies. As experiment with Public Health are unthinkable, the need for theoretical models is here vital.

5 The objectives of this PhD

The objective of this PhD thesis is, in a first time, to review the evidences of intra- and inter-host interactions between pathogens, and to categorize them. This will be the object of chapter 1, that will specifically focus on the lack of investigations concerning multiple simultaneous interactions. Being based on a large set of evidences of the four main kind of isolated pathogen-pathogen interactions, it will show how these interactions may occurs simultaneously. Among other things, it rises the importance of the “realized susceptible pool”, i.e. the real number of individuals that are available for a pathogen, all interactions with other pathogens taken into account.

Chapter 2 will focus on the dynamical impacts of interactions between pathogen, and their detection from epidemiological data, using a two-pathogen model and several promising statistical causality tools. The aim of this chapter will be to develop and test exploratory approaches that could become standard, easy-to-use tools to test for the existence of interactions within any set of pathogens infecting the same population. It will yet bring out the difficulties of creating such framework firstly because of the lack of visible impact on incidence data of numerous interactions and secondly because of the limitation of ‘simple’ exploratory approaches.

Lastly, in chapter 3, a four-pathogen model will be used to study the specific case of dengue, a vector-born disease with four interacting serotype. More precisely, the problematic of the introduction of vaccines currently being developed will be the point of interest. In this chapter we will see that the homogeneity of the efficacy of such vaccine against the various serotype should be the main focus of the future development of the vaccine, as an heterogeneous vaccine could perturb the balance between serotypes and cause strongly deleterious effects before stabilization of the system.

This PhD aims to provide a large view of pathogen-pathogen interactions, from very specific case-studies to population-scale theoretical analysis. Most of the works presented hereafter are based on a multi-pathogen model with several interaction mechanisms inspired by the work of SHRESTHA *et al.* [63]. It uses both mathematical and computational analysis of derivatives of this model to assess the various questions addressed in this PhD, giving a great deal of room to

methodological aspects.

Chapter 1

Interactions between pathogens and the need for a new definition of population susceptibility

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1.1 Introduction

Host-pathogen interactions are among the most common dual-species interactions occurring in the natural world [210]. Because of the negative and sometimes devastating impacts pathogens can have on their hosts, a considerable amount of effort has been put towards understanding the processes that underlie many host-pathogen relationships, especially in humans [211]. These processes span from immunological responses of the host [212] to mechanisms of pathogen replication within the host [213] and pathogen transmission between hosts through space and time [214]. Such knowledge has been a crucial determinant of success in the constant fight against these pathogens [215–219].

More recently, it has been acknowledged that host-pathogen interactions are embedded within larger ecosystems, and that host pathogen-relationships involve more dimensions than just a single host and a single pathogen [117, 220, 221]. Indeed, pathogen transmission between two individual hosts, for example, can be influenced by climate [222], the presence of other species [221], and a range of socio-economic factors, such as vaccine refusal [223].

Among the numerous dimensions involved in the host-pathogen relationship, one of the least understood is the influence of other pathogens. Indeed, most of hosts, especially humans and animals, are exposed to an incredible diversity of pathogenic organisms [224]. Consequently, interactions between pathogens within a host, where the ecological, evolutionary, and epidemiological consequences of multiple infections are different from those in which a host supports only one parasite at a time, have been extensively studied, including their impacts on evolution of pathogen virulence, disease severity, or altered transmission potential [39, 44, 64]. Between-host interactions have also been documented, with potential impacts on disease dynamics through convalescence period or mortality [42, 43, 65]. However, these within-host and between-host mechanisms have typically been studied in isolation despite the likelihood that these interactions can act synergistically or antagonistically.

This work reviews the mechanisms that have been documented acting on the five main kinds of pathogen interactions, at both within-host and between-host scales. Then, we identify how these pathogen interactions can affect one-another and how consideration of these simultaneous interactions changes our understanding of disease ecology. Based on the most frequently encountered example in the field, the interaction between helminths and several childhood diseases, we discuss the potential consequences of uncoordinated Public Health strategies (which currently target only one aspect of the interaction). We finally argue that the myriad of pathogen interactions could be incorporated by estimating the “realized susceptible pool” of a given population, which would consider both partial protection conferred by current infection status or personal infection history as well as the unavailability of some hosts because the action of other pathogens such as mortality or morbidity they induce. Modeling the dynamics of such susceptibility, fluctuating in a non-linear manner, would allow for safer and more efficient design of Public Health strategies.

1.2 Parasite-parasite Interaction Mechanisms

Pathogens can interact through a large variety of mechanisms, may involve different strains from the same species as well as strains from different species, and often occur at multiple scales (within-host, within-population or across a meta-population). Here, we classify these interactions into five main categories (Fig. 1.1): (i) a resident pathogen that triggers cross-immunity conferring partial protection against a competing pathogen and thus decreases its fitness, (ii)

cross-regulation of immune functions that increases within-host replication and thus parasite transmission, (iii) immunosuppression that facilitates within-host replication and thus increases transmission, (iv) reduction in availability of susceptible hosts, through convalescence and/or mortality that decreases pathogen transmission and (v) increasing the availability of susceptible hosts, such as Public Health system failure avoiding massive vaccination and thus increase pathogen transmission, or increasing parasite transmission through disruption of behavioral resistance strategies. In this section, we briefly review, through the most striking examples, how these interactions each work in isolation.

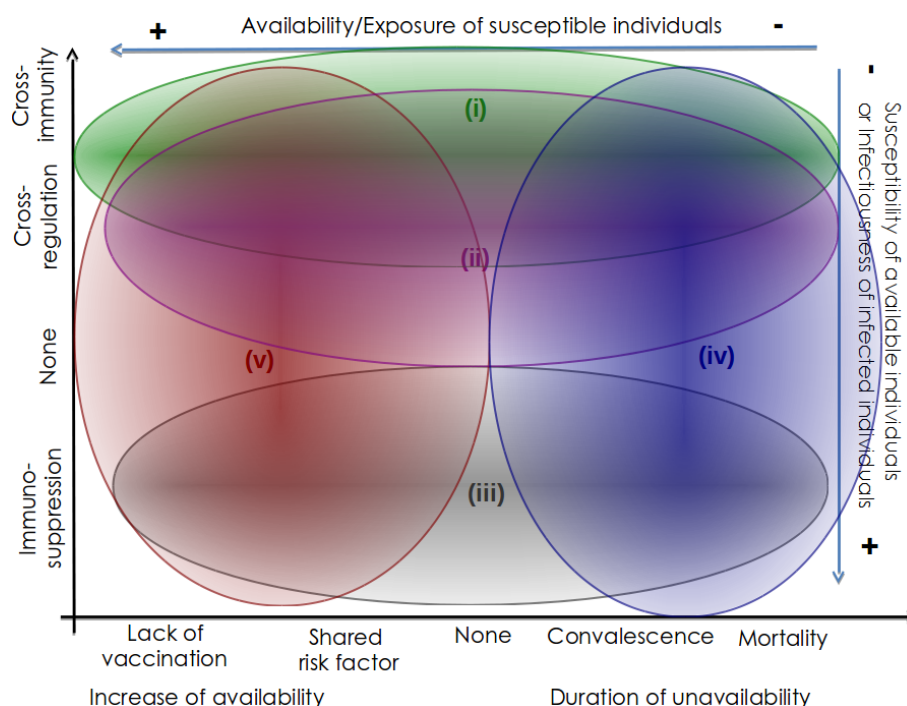


Figure 1.1. Schematic representation of five categories of interactions between pathogens. (i) Cross-immunity confers partial protection against a competing pathogen and thus decreases its fitness, (ii) cross-regulation of immune functions increases within-host replication and thus parasite transmission (iii) immunosuppression facilitates within-host replication and thus increases transmission (iv) Convalescence and/or mortality decreases availability of susceptible hosts and thus decreases transmission and (v) Public Health system failure, disruption of behavioral resistance or shared risk factors increases availability of susceptible hosts and thus increases transmission.

1.2.1 Cross-immunity

Cross-immunity is probably the most intuitive mechanism of pathogen-pathogen interaction. Upon infection, adaptive immunity can be triggered to fight against an invader. Following recognition of one or several antigens (external or fragmented molecules) of the parasite, stimulated B lymphocytes circulating in the blood will proliferate and produce antibodies targeting that specific parasite. Some of these activated B-cells will differentiate into memory B cells, which require much less time between re-activation and antibody secretion. Re-activation can occur if the host is exposed to the same pathogen again, but may also occur if an infection by another – likely closely-related – pathogen exposes the host to an antigen with similar binding affinity,

resulting in cross-immunity. This adaptive system induces a rapid and elevated response that, ideally, halts transmission, eliminates the parasite, and prevents future re-establishment. However, if the pathogen has mutated, the stimulated antibodies may be less efficient, providing only partial protection.

The most well-documented example of cross-immunity is between the influenza viruses, where within-host interactions have a very large impact on pathogen transmission at a population and meta-population scale. It has been shown in a semi-experimental system with a vaccine strain that the probability of becoming infected with a challenging strain decreases with the antigenic distance between the strains [66]. The consequences of this within-host interaction are huge at a population scale for this rapidly-mutating pathogen. Indeed, this cross-immunity mechanism limits the explosion of virus diversity in a given population, delaying the emergence of a new strain which has to have a sufficient antigenic distance from the previous one to be efficiently transmitted [67].

1.2.2 Immune cross-regulation

The immune system of vertebrate animals involves complex processes than are generally interdependent [212]. Among them, the trade-off between TH₁ and TH₂ immune pathways [68–70] is of particular interest for pathogen interactions (but see [225]). TH₁ mainly triggers “cellular immunity” to fight viruses and other intracellular pathogens through production of Cytotoxic T lymphocytes (CTLs) which will trigger destruction of infected cells, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. Meanwhile, TH₂ engages “humoral immunity” and up-regulates antibody production to fight extracellular organisms. The two pathways can down-regulate one-another, mediated by cell-signaling cytokines, but rarely reach full exclusivity. The result is that a co-infected individual with both an intracellular and an extracellular pathogen will have a weaker immune system reaction, which could increase within-host replication, pathogen transmission, and/or severity.

Helminths in particular have been demonstrated to skew host immunity in ways that could alter the outcomes of viral and bacterial infections [71,198,226,227]. The classic example concerns their interactions with micro-parasites [198,226] where the decreased immune response produced by helminth infection has been shown to increase host susceptibility to *Mycobacterium bovis* in African Buffalo [71], transmission rate of *Bordetella bronchiseptica* in mice [72] and susceptibility to and transmission rate of *Plasmodium falciparum* in humans [73,74].

Cross-regulation by helminths can also have implications for disease severity. Co-infection with helminths and *P. falciparum* can result in a protective effect against severe malaria [38,56,57,76,77]. Infection with helminths, especially *Ascaris spp.*, is associated with a stimulation of TH₂ lymphocytes [228]. This stimulation results in an increase of the IL-4/IFN γ ratio and the activation of the IgE-anti-IgE immune complexes. Meanwhile, the excessive immune reaction, resulting in an over-production of IFN γ , has been suggested to be a major predictor of cerebral malaria, the most lethal form of human malaria [75]. Such severity decrease in co-infected hosts have been observed not only in co-infection with helminths and can also involve other immune processes than TH₁/TH₂ balance, such as CD4+ T cell expansion as shown in mice co-infected by non-lethal malaria and lethal *P. berghei* NK65 strain [37].

1.2.3 Immunosuppression

Some pathogens can also significantly decrease the overall efficiency of the immune system. To this extent, Human Immunodeficiency Virus (HIV) is the most well-known example of an

immunosuppressive pathogen with facilitating effects. Upon HIV infection, an acute phase takes place, yielding a massive loss of memory-phenotype CD4+T cells [78, 79], followed by a chronic phase when CD4+T cells are slowly destroyed over a period of several years in untreated individuals [80], causing acquired immune deficiency syndrome (AIDS). Since CD4+T cells are an essential component of the vertebrate immune system, especially for protecting against within-cellular pathogens [212], HIV-infected individuals suffer dramatically higher susceptibility to a large number of opportunistic pathogens [81, 82], altered disease progression, and even loss of previously-acquired immunity [83].

The most striking example is probably the interaction between HIV and *Mycobacterium tuberculosis*, the agent responsible for human tuberculosis (TB), where HIV-positive people are 37 times more likely to become infected by this bacterium than those who are HIV-negative [84]. While TB disappeared from the world Public Health agenda during the 1970s, its incidence increased in a spectacular manner following the emergence of HIV one decade later [85]. It is worth pointing out that the potential epidemiological consequences of this interaction for TB re-emergence was suggested very early on, only several years after the description of HIV itself [229].

The immunosuppressive nature of HIV has also important consequences on TB severity. Indeed, the acceleration of *M. tuberculosis* replication within an HIV positive individual can accelerate TB disease progression from the latent form to the active one [230]. Moreover, and non-intuitively, restoring CD4+T cell level through Highly Active AntiRetroviral Therapy (HAART), which is generally prescribed to protect HIV-infected patient from opportunistic infection, can produce an excessive immune reaction to the bacterium, known as Immune Reconstitution Inflammatory Syndrome (IRIS), that results in high morbidity of TB [86–89].

1.2.4 Reducing availability of susceptible individuals

Reduction in the availability of susceptible individuals is known to have a large impact on epidemiological dynamics. Such reduction could be permanent and due to host population characteristics, such as the impact of demography or vaccination [231]. Nevertheless, despite rare evidence, these fluctuations could also be due to the presence of another pathogen. Pathogen-induced mortality will permanently decrease the number of susceptible individuals available for all pathogens in the ecosystem. Reduced fecundity induced by a pathogen will have, at a longer time-scale, the same consequences [90–92]. This has been proposed as a biological control solution to malaria mosquito *Anopheles gambiae* [232].

The presence of one pathogen can also temporarily decrease the number of susceptible individuals available for other parasites, like in a case of acute disease with significant convalescence period. Thus, 'removed' individuals are not only removed from the susceptible pool of the pathogen that infected them, but also, until the end of the convalescence, from the susceptible pool of all other pathogens. The most striking example is the interaction suggested between measles and pertussis, two childhood diseases with similar transmission potential. According to their epidemiological parameters, these diseases should exhibit similar epidemiological cycles. While the two-year periodicity of measles matches with theoretical expectations, the four-year seasonality of pertussis remained elusive for a long time. In 2003, ROHANI and colleagues showed that integrating a convalescence period, i.e., when a measles-infected child does not attend school, is enough to shift the pertussis periodicity to a 4-year cycle [42].

1.2.5 Increased availability of susceptible individuals or perturbation of behavioral resistance

Parasite-induced increases in the number of susceptible individuals are definitely less documented, despite such demographic event like “baby-boom” after the second world war has been suggested to had a potential impact on pathogen dynamics [231]. Nevertheless, a temporary increase in the number of susceptible individuals can also be the result of an interaction between pathogens. Recently, the Ebola outbreak in West Africa has had a very large impact on Public Health infrastructures in the affected countries [93]. As a consequence, between 700,000 and 800,000 children did not have access to routine vaccination against childhood diseases, such as measles [94]. A large outbreak, with significant mortality, is thus expected during the next months that could potentially yield more deaths than the ebola outbreak itself.

On the other hand, such increase can be due to strictly social factors. Several diseases, such as hepatitis C and HIV, share a common risk factor, namely iv drug abuse [95]. A common risk factor can be seen as the gathering of susceptible and infectious individuals in closely related network, thus increasing the number of potentially infectious contacts compared to the mean number of contacts in whole population. Similarly, diseases that require hospitalization of the host increase the host availability for hospital-acquired infections, which are high-ranked in the list of emerging infectious diseases [96].

1.3 Simultaneous Parasite-parasite Interactions: a Review of (non-existing) Studies

As previously highlighted, a large number of interaction mechanisms have been described, generally between high prevalence diseases. Furthermore, these interactions mechanisms are not mutually exclusive and thus likely operate simultaneously. In the following section, we illustrate several biological models where multiple interactions can take place and lay out the insights that can be garnered to improve our understanding of how these mechanisms may interact.

1.3.1 Immunity suppression and cross-immunity

A given pathogen could simultaneously yield partial cross-immunity against another pathogen and still producing a general immunosuppression. This could be the case of the interactions between HIV-1 and HIV-2 groups. The partial protection between different HIV groups has been debated for more than two decades since the initial experiment that showed partial protection in rhesus macaques [97]. Since then, empirical studies have contrasted its relevance on the field [98–101].

Both HIV groups are known to produce significant immunosuppression in infected hosts. Such double interactions may explain discrepancy between experimental studies, where modified viruses have recently confirmed the potential partial protection by testing cross-immunity between HIV and SIV [102], and empirical data showing that immunosuppression mechanism likely plays a larger role than cross-immunity because of its chronic nature. Though cross-immunity may be less important to overall individual health than the life-long spiral of ill effects from immuno-suppression, this does not negate the phenomenon nor the postulation that it could potentially play a larger role during the establishment phase of infection.

1.3.2 Immunity suppression and cross-regulation

It has been suggested early that helminth infections play a major role in the pathogenesis of HIV-1 infection in Africa and other developing areas [233]. Infection with helminths activates the TH₂ immune pathway, thus cross-regulating the TH₁ pathway. This facilitates the replication of HIV in co-infected hosts and accelerates the disease's progression [103]. Despite some tempering studies [234, 235], evidences are accumulating that helminth infection increases susceptibility to HIV and its replication [104, 105].

Evidences on the effect of HIV on helminth infection are more scattered, mostly because most studies focus solely on the effect of helminth on HIV. However, three main observations stand out. (i) Advanced infection with HIV suppress the pathological response to helminths, particularly *Schistosomia spp.*, and helminth eggs. Moreover, immune reconstitution following an antiretroviral therapy reactivates this pathological response, causing symptomatic enteritis [236, 237]. (ii) Co-infection with HIV reduces the excretion of schistosome eggs in animal models, because of granuloma formation [238], and humans [107–109]. (iii) Immuno-suppression from HIV could also facilitates dissemination of helminth by promoting larval development [106].

If the impact of helminth-induced cross-regulation on HIV is straight forward, the feedback of HIV-induced immunity suppression on helminths is more complicated. Several cellular-scale mechanisms are involved and the overall resulting effect on the host is still poorly known, and depends on the helminths species.

1.3.3 Immunity suppression and permanent reduction of susceptible abundance

HIV is probably the potentially most striking example of such interaction combination. Indeed, HIV is immunosuppressing significantly its host, but also exert a strong burden on human populations by killing millions [110]. As a consequence, disentangling the contribution of HIV burden and its immunosuppressive nature is extremely challenging, moreover because virulence of HIV is mainly due to co-infection with opportunistic diseases.

1.3.4 Cross-immunity and temporary decrease of susceptible abundance

The cross-immunity between influenza strains is now well-documented and quantified [66]. Similarly, influenza is an acute disease with a significant period of convalescence [111] and high hospitalization rate in non-vaccinated people [112], yielding a decreasing number of available susceptible individuals which would also have a decreased susceptibility because of cross-immunity. Interestingly, the cross-immunity has been thought to be a significant driver of influenza seasonality [239]. It would be thus especially relevant to decipher the respective contribution of the two mechanisms, where convalescence period may amplify cross-immunity effects.

1.3.5 Cross-immunity and permanent reduction of susceptible abundance

While influenza largely acts through removing susceptible individuals only temporarily, other infections can involve a permanent decrease of the susceptible pool. This could be the case for diseases caused by two *Mycobacteria*, namely *Mycobacterium tuberculosis* and *Mycobacterium leprae*. Indeed, some cross-immunity has been suggested since a while between these two pathogens [113, 114]. A modelling study has shown that *M. tuberculosis*, through such cross-immunity mechanism, may have contributed to the decline of leprosy in Western Europe [115]. However, *M. tuberculosis* is one of the most lethal disease in human populations [87], suggesting

that cross-immunity could have been completed by mortality for a larger decrease in susceptible abundance that may have contributed to outcompete leprosy from Europe.

1.3.6 Cross-regulation and temporary reduction of susceptible abundance

While not studied so far, a potentially high-profile combination of interactions exists between helminths and childhood diseases. On the one hand, while helminths can induce cross-regulation with micro-organisms through immune system [198], some empirical studies have suggested a role of helminths in susceptible abundance increase, with for instance a higher risk of exposure to *staphylococcus* infection in children when already infected by a nematode [116]. Similarly, infection by *Fasciola hepatica* has been documented to suppress the TH₁ response against *Bordetella pertussis*, allowing thus a higher replication of the bacterium and increase its transmissibility. On the other hand, childhood diseases are generally very acute and are known to produce temporary decrease in susceptible abundance through convalescence period that could have an impact on disease dynamics [41]. For instance, *B. pertussis* infection is associated with a temporarily decrease of the amount of susceptible individuals through its convalescence period. The Public Health consequences of such interaction combination are potentially enormous and will be discussed in the next section.

1.4 Simultaneous Pathogen Interactions and Public Health Strategies

Even if empirical evidences are sparse, we can nevertheless envision the consequences of Public Health strategies when simultaneous interactions are considered. Among all the examples discussed so far, the interactions between helminths and childhood disease is probably the example with the most important Public Health consequences. Indeed, helminths species affect up to 80% of children in developing countries [240] while childhood diseases, such as measles or pertussis, have affected almost everyone by the age of 20 in areas without vaccination [241]. It could be therefore expected that a large number of individuals live in areas where risk of infection by both types of pathogens is high.

We focus here on the specific example of *Fasciola hepatica* and *Bordetella pertussis* detailed previously, which involves cross-regulation and temporary decrease in susceptible abundance. First, without any control measures against each pathogen, presence of *F. hepatica* will reduce the immune response against *B. pertussis*, leading to an increased transmission (and potentially severity) and an increasing number of individuals in convalescence. Consequently, the number of available individuals for *F. hepatica* will temporarily decrease, impacting its prevalence and then the number of co-infected individuals with *B. pertussis*. This never-ending cycle highlights that the endemic equilibrium of both diseases should be inter-dependent.

We can now speculate about what should be the consequences of *F. hepatica* control for each pathogen (Fig. 1.2). First, these simultaneous interactions suggest that *F. hepatica* control should be, at least, less efficient than expected on its prevalence because a low control coverage will decrease the number of individuals in convalescence and thus increase the number of available individuals for *F. hepatica*. We could nevertheless expect a clear decline in *F. hepatica* prevalence when the number of available individuals will go below the expected number without *B. pertussis* (Fig. 1.2, A).

Regarding the consequences of *F. hepatica* control on *B. pertussis* transmission, we could expect a similar pattern, with limited effect for low control effort because the decreased number

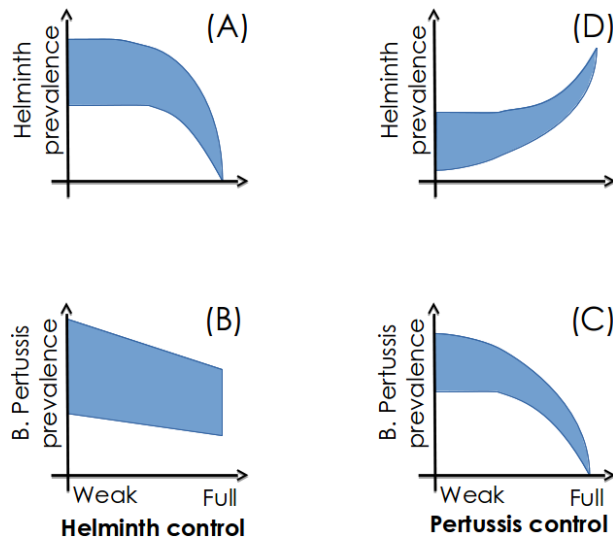


Figure 1.2. Representation of the potential impact of several Public Health measures against *B. pertussis* and helminths on each pathogen prevalence. (A): Impact of Helminth control on Helminth prevalence. (B): Impact of Helminth control on *B. pertussis* prevalence. (C): Impact of *B. pertussis* control on *B. pertussis* prevalence. (D): Impact of *B. pertussis* control on Helminth prevalence.

of *F. hepatica* infected individuals could be compensated by an increased number of available individuals for *B. pertussis*. Nevertheless, when *F. hepatica* prevalence will start to decline significantly, *F. hepatica* control should also decrease pertussis transmission because the number of co-infected individuals that can transmit more will decrease (Fig. 1.2, B).

The control measures against *B. pertussis* may also have non-intuitive outcomes. Indeed, for low control efficiency, the number of people in convalescence will decrease, which will increase the number of available individuals for helminths and thus potentially the number of co-infected individuals that could transmit more efficiently *B. pertussis*. As a consequence, pertussis control could be less efficient than expected for low control level (Fig. 1.2, C). Nevertheless, full control of pertussis will increase the number of available individuals for helminths, increasing then helminths prevalence (Fig. 1.2, D).

But the control programs are generally involved simultaneously, especially on this kind of high-prevalence disease. Therefore, the outcomes of each program will crucially depend on the efficiency of each other. Moreover, the magnitude of these interactions, which have been so far estimated in isolation from each other, will drive the final outcomes. This should be especially important for low-income countries where efficiency of control programs fluctuate through space and time [242].

1.5 How could we consider the myriad of interactions? Perspectives for a Global Health

As shown during previous sections, a large number of interactions can be involved simultaneously, whereas they have thus far largely only been explored in isolation. Considering their combined effects is likely to be crucial for Public Health strategies because they may dramatically change the outcomes of individual control measures. The occurrence of these interactions (summarized in Tables 1.1 and 1.2) shows that pathogens form communities like any kind of

organism [224], as Mirko GRMEK suggested by introducing the concept of pathocenosis [117], suggesting that pathogens form a biocenosis like any other kind of organisms. The importance of this community context has received an increasing amount of empirical attention. Within natural populations, TELFER *et al.* [118] show that interactions between parasites species are actually more important than host and environmental factors for determining pathogens prevalence. The Public Health consequences have already be highlighted, where elimination of some disease may have freed a niche for a new one to emerge [50]. Nevertheless, community ecology teaches us that predicting fluctuations in community structure is extremely challenging [243], especially when numerous interactions are involved, which is definitely the case for pathogen communities.

Interacting pathogens	Within-host mechanism	Between-host mechanism	Epidemiological impacts	Ref
<i>HIV / Mycobacterium tuberculosis</i>	HIV decreases immune response against TB	Increased susceptibility of TB and thus increased infection success, shared exposure among intra-venous drug users	TB has re-emerged significantly after beginning of the AIDS epidemic/Increased severity, even if HIV is treated	Getahun <i>et al.</i> [84]; Sester <i>et al.</i> [89]; Lienhardt <i>et al.</i> [85]; Fenner <i>et al.</i> [230]
<i>HIV / HCV</i>	HCV impacts lymphocyte and thus CD4+ T-cell production, also infected by HIV	Sharing the same transmission medium increases transmission rates.	Increased HCV disease progression and HIV severity	Eyster <i>et al.</i> [244]; Greub <i>et al.</i> [245]; Verucchi <i>et al.</i> [95]
<i>HIV / Malaria</i>	HIV decreases immune reaction against <i>Plasmodium falciparum</i> , <i>P. falciparum</i> produces specific cytokines that increase HIV viral load	Synergistic (mutual) facilitation of increased susceptibility and transmission rates.	Epidemiological dynamics and severity are coupled.	Cohen <i>et al.</i> [246]; Kublin <i>et al.</i> [247]; Abu-Raddad <i>et al.</i> [36]
<i>Helminth / Mycobacterium bovis</i>	Modulation of immune reaction against <i>Mycobacterium bovis</i>	Increased host susceptibility to <i>M. bovis</i>		Jolles <i>et al.</i> [71]
<i>Helminth / Bordetella bronchiseptica</i>	Modulation of immune reaction against <i>Bordetella bronchiseptica</i>	Increase transmission rate of <i>B. bronchiseptica</i>	Generation of super-shedders	Lass <i>et al.</i> [72]
<i>Helminth / Plasmodium falciparum</i>	Modulation of immune reaction against <i>P. falciparum</i> , decrease severity of malaria by avoiding excessive TNF α concentration	Increase susceptibility and transmission rate of <i>P. falciparum</i>	Anti-helminthic therapies can have unexpected impact on malaria transmission	Nacher <i>et al.</i> [74, 76]

Table 1.1. Pathogen interactions documented when compelling evidence about mechanisms exist. Part 1.

Interacting pathogens	Within-host mechanism	Between-host mechanism	Epidemiological impacts	Ref
<i>Helminth / Microparasites</i>	Top-down regulation through immune system modulation; bottom-up regulation through resource limitation			Graham [248]
<i>Myxoma / Trichostrongylus retortaeformis</i>	Immunomodulation against nematode	Increased susceptibility to nematode, elongated infectious period		Cattadori <i>et al.</i> [249]
<i>Plasmodium species in rodent</i>	Trade-off in competitive ability; competitively excluded genotypes have greater dispersal			Roode <i>et al.</i> [250]
<i>HIV / Ulcerative STDs</i>		Bleeding during intercourse that increases transmission rate of HIV		Fleming & Wasserheit [251]
<i>HIV / non-ulcerative STDs</i>	High recruitment of immune cells in genital tract, increasing their exposure to HIV	Increase in HIV susceptibility		Fleming & Wasserheit [251]
<i>Measles / Pertussis</i>		Measles convalescence period reduces number of individuals available for pertussis transmission.	Elongated periodicity for pertussis	Rohani <i>et al.</i> [42]

Table 1.2. Pathogen interactions documented when compelling evidence about mechanisms exist. Part 2.

Throughout this work, we have outlined how simultaneous interactions can be involved in structuring parasite communities at both within-host and between-host scales. Nevertheless, these interactions almost always occur on the “realized susceptibility” of the population. On this susceptibility, within-host interactions influence the level of susceptibility for each individual against a given pathogen while between-host interaction influence the number of susceptible individuals (Fig 1.3). It should be therefore fundamental to combine sociological data with serological assays in the population to estimate the real susceptibility of the population, and how this susceptibility will react with other Public Health programs. While challenging, such estimation represents an unique opportunity for both scientific community and Public Health authorities.

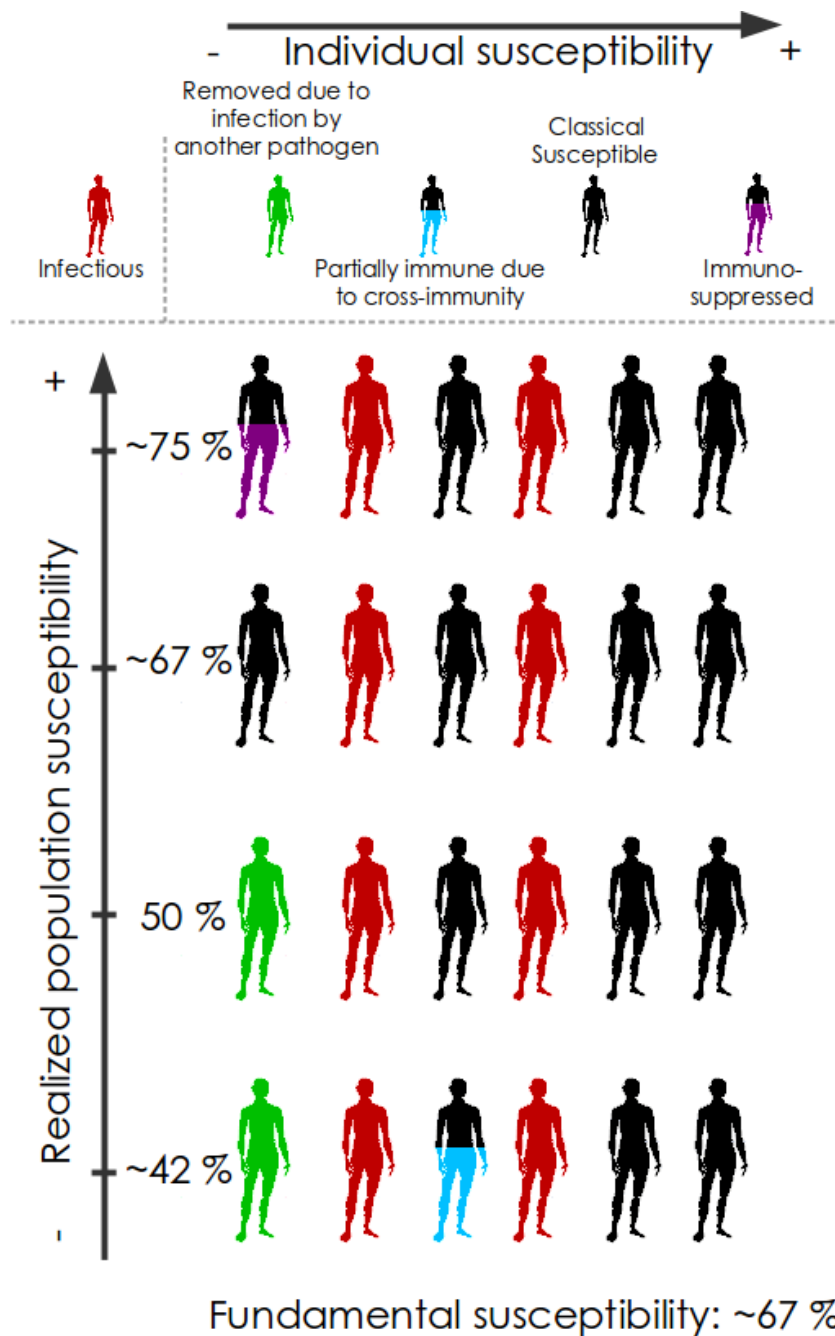


Figure 1.3. Illustration of the difference between classic susceptibility and realized susceptibility. Red individuals are infectious to the pathogen. Others are, classically speaking, susceptible to that pathogen. In reality, their susceptibility is dependant of their personal infection history. Green individuals are protected because of convalescence, perfect cross-immunity or permanent removal. Half-blue individuals are 50% less susceptible because of a partial cross-immunity. Half-purple individuals are 50% more susceptible because of immuno-suppression. Susceptibility of the population is expressed as the proportion of susceptible hosts within it. Realized susceptibility takes into account that all susceptible individuals are not equally susceptible.

Chapter 2

Detecting interactions between pathogens

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2.1 Introduction

Classical studies of infectious diseases system focus solely on the “host-pathogen” system. This approach has proven its efficacy on several systems. Eradication of smallpox thanks to vaccination [203, 252] and the great reduction of the number of deaths by vaccine preventable diseases such as whooping cough, diphtheria, tetanus, measles, mumps or rubella [253] have been achieved thanks to studies focused on a single host species and a single pathogen. Yet it becomes commonly admitted that it is important to study pathogens as a part of an ecosystem including not only their hosts, but also other pathogens that are infecting the same hosts [220, 254]. As a part of larger ecosystems, pathogens not only interact with their hosts [160, 255]. Interactions with other pathogens occurs too, between different serotypes of the same species or even between several species [242].

Those interactions can be observed at several scale, from intra-host direct competition to population-scale social interactions. At the intra-host level, *Plasmodium falciparum* and *Plasmodium vivax*, the two main agent of human malaria, are both limited in their intra-host reproduction by the availability of red blood cell. In case of co-infection of the same host by both species, *Pl. falciparum* competitively excludes *Pl. vivax* [35, 256]. Others intra-host interactions are driven by the immune system of the host. Acquired ImmunoDeficiency Syndrome (AIDS) greatly reduces the ability of the immune system to protect the host from infection by other pathogens. Such “cooperative” interaction may even be mutual, in the case of co-infection by both HIV and malaria for example [36]. Intra-host interactions may also be a consequence of a trade-off between the two main immune response paths, TH_1 and TH_2 [68–70]. Either way is specialized in fighting specific kinds of infections, and infection by a pathogen usually stimulates one of these two ways, reducing the expression of the other one. Thus, other pathogens can take advantage of this reduction to easily infect the host [249]. On the other hand, “negative” interactions can also be driven by the immune system. Partial cross-immunity often exists between closely related pathogen, e.g. different strains of influenza. Exposure to a strain confers long-lasting protection to the host against this specific strain and a partial cross-immunity to antigenetically similar strains too [29, 205]. Lastly inter-hosts dynamics can be responsible of interactions between pathogens too. Quarantine for example reduces the “effective susceptible pool”, i.e. the actual number of hosts available for the pathogens, and this may have strong effects on epidemiological dynamics [41, 42].

Those interactions raise crucial issues for epidemiological data interpretation and the design of Public Health policies. Most of known interactions have been clinically identified through case studies. Because of the individual scale of these observations it is difficult to scale them up to their consequences on the population. Nowadays, this is done with confirmatory approaches, by fitting mechanistic models to the data [63]. Such method made possible the quantification of the interaction between Influenza and Pneumococcal Pneumonia: influenza infection could increase susceptibility to pneumonia 100-fold [46]. However this requires strong biological presumption in order to use the right mechanistic model. Using a model that do not allow the actual interaction between the pathogens would inevitably lead to erroneous results.

In addition, all population-scale interactions does not have an individual-scale cause [41]. This suggests that an universal way to identify interactions, including population-scale ones, may lead to the identification of unexpected interactions. Thus, it is crucial to have tools to identify interactions at the population scale directly. These tools have to be easy to apply and independent of any prior knowledge or hypothesis about the pathogens dynamics. Being able to build the “interaction graph” of a set of pathogen may also help us to understand how communities of pathogens are organised [257].

Understanding how pathogens interact also helps anticipating the consequences of a disturbance of the pathogen community [258], that could be caused e.g. by Public Health policies. Some interactions should not be neglected, because they could work synergistically or antagonistically with Public Health. There is a need for a standard method to broadly identify interactions that could be population-specific. This method should be easy to use, reliable and able to identify any kind of interaction without complicated calibration and not based on prior knowledges about the pathogens.

2.2 Methodology

In this work, we investigate the pertinence of using the Granger Causality (GC) paradigm and Transfer Entropy (TE) to determine the interaction between pathogens from epidemiological time series. Granger Causality stands on the comparison of several auto-regressive (AR) and multi-variate auto-regressive (MVAR) model to determine the probability of existence of a directional interaction between several variables, and the intensity of this “causality” [47]. The main advantage of this method stands in the “causality” aspect. Granger Causality Analysis intends to identify precisely which variable has a direct impact of which other one, all confounding effect such as common external forcing taken into account [120]. Transfer Entropy stands on the detection of information flows between time series. Based on information theory, it also is a directional, non-parametric method. It uses estimated distributions of the variable to detect interactions between them. It does not intrinsically need any hypothesis about the structure of the time series, making it (theoretically) sensitive to any kind of interactions, including non-linear [121].

We used a Granger Causality Analysis toolbox written by Anil K. Seth [119] and a Transfer Entropy toolbox written by Montalto *et al.* [122]. These toolboxes were originally designed for neuroscience. We used them on time series generated by a two-pathogens model with several mechanisms of interactions [63]. We used the Granger Causality Analysis and Transfer Entropy to try to identify interactions from time-series only, without any informations about the model structure or parameters.

This work will focus on testing these promising tools to identify interactions. The mathematical model, that includes several interactions mechanism through alteration of susceptibility of the hosts (Fig. 2.1, A), will be used to produce epidemiological data (Fig. 2.1, B). These data will be analysed by GCA and TE (Fig. 2.1, C-D) and the detected causalities (Fig. 2.1, E) will be compared to the interaction parameters used in the model to determine which kind of interactions can be correctly detected by these tools, and to identify their applicability and their limits.

2.2.1 The Model

All analysis have been performed on temporal series from a two-pathogens epidemiological model. The model used here is designed to be the simplest that admits multiple interaction mechanisms, both permanent and temporary effects, and stochasticity. The two pathogens in the model may be two strains of a single species or genetically unrelated pathogens. The model stands on the paradigm of SIR modelling: the host population is structured in several compartment according to their status toward the pathogens. Dynamics of the diseases are flows between these compartments. This model, based on a model created by SHRESTHA *et al.* [63], uses a $S \rightarrow I \rightarrow C \rightarrow R$ (for Susceptible, Infectious, Convalescent, Resistant — or Recovered, resp.) path. Individuals are born susceptible to both pathogens. Convalescent compartment regroup individuals who are no longer infectious but still suffer any kind of consequences of the infection. These can

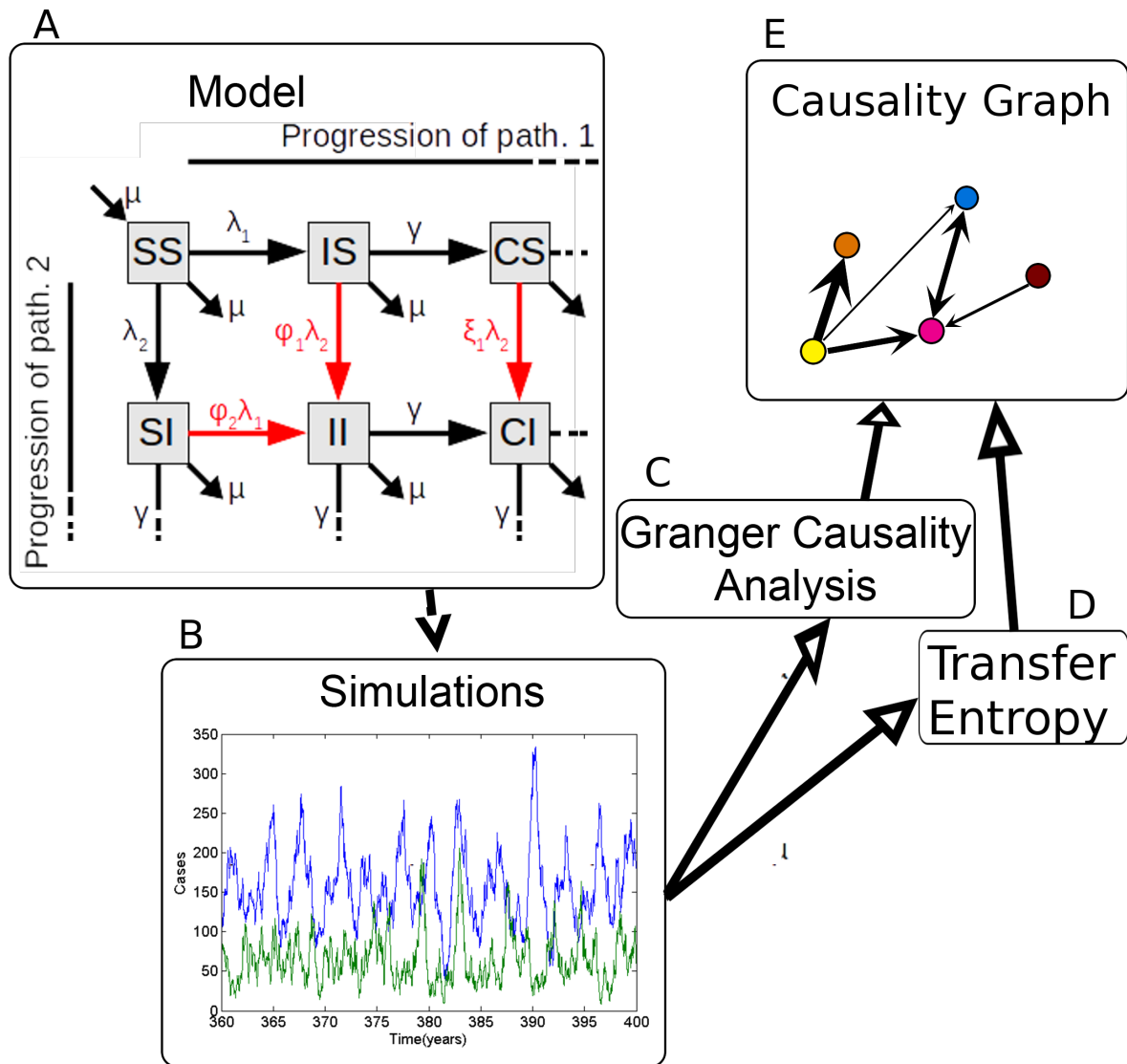


Figure 2.1. Schematics of the approach used in this work. A: Partial view of the two-pathogens model. Each box represents a host state. Arrows represent transition rates between states. Red arrows stand for transition affected by interactions. Complete view of the model in Fig. 2.2. B: Example of simulation from the model. Times series are weekly reports of new cases (incidence) for each pathogen. C-D: Causality analysis are performed on those time series. E: Results of Granger Causality Analysis and Transfer Entropy can be plotted as a causality graph. Arrows represent causalities. Wideness of the arrows represent the strength of the causality.

be biological consequences (weakness, alteration of the immune system ...) or social, ecological consequences (quarantine, hospitalization...). It might then represent, e.g., a temporary period of immuno-suppression, strain-transcending cross-immunity, a temporary period of enhanced susceptibility associated with Anti-Body Dependant Enhancement (ADE) [259], or temporary removal from the effective susceptible pool. resistant individuals are immune to the pathogen(s) that infected them but still susceptible to the others. Each possible combination of status for both diseases is explicitly modelled (Fig.2.2). Thus the model is bi-dimensional, and the progression of each disease follows one dimension.

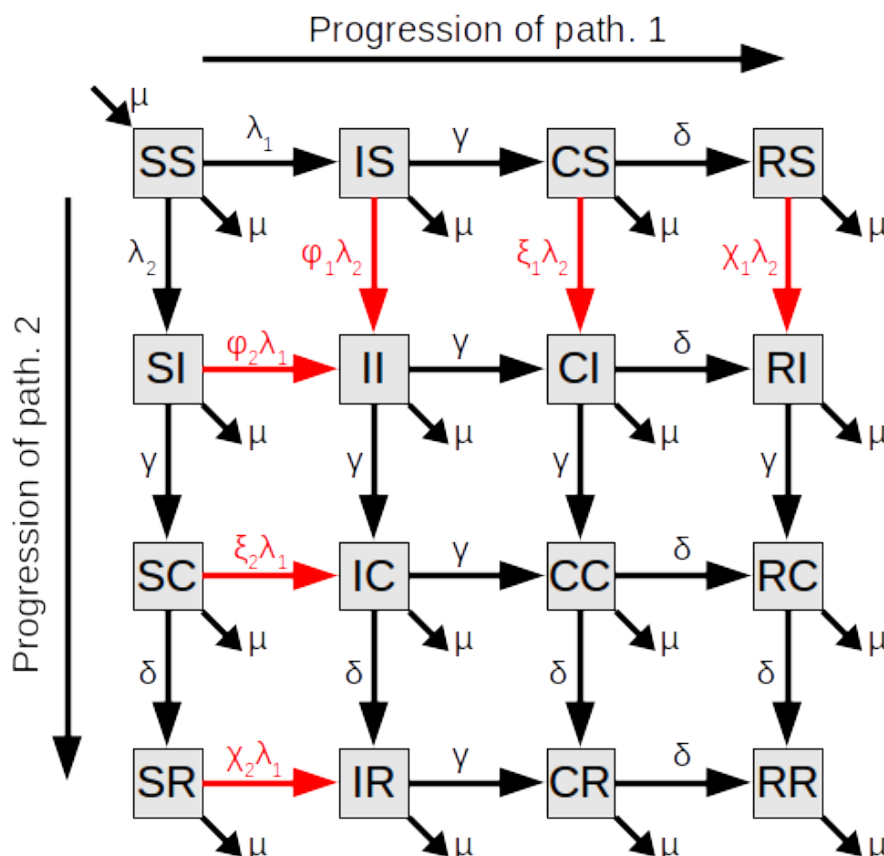


Figure 2.2. Diagram of the two-pathogen model. Each box represents a host state. Arrows represent transition rates between states. Red arrows stand for transition affected by interactions. Each compartment regroups individuals according to their status towards both pathogen. S , I , C and R stand for Susceptible, Infectious, Convalescent and Resistant, respectively. Red color highlights interactions between pathogens by alteration of susceptibility to infection. φ_i , ξ_i and χ_i are the modifications of susceptibility that affects infectious, convalescent and resistant (resp.) to pathogen i hosts.

Infection of new hosts may happen when an susceptible host S_i is exposed to pathogen i . Outcome of such exposure is based on two parameters. The first one is the contact rate β_i , which determine the force of infection λ_i of pathogen i . The second one depends on the history of the exposed host: in this model, pathogens interact when an individual currently or previously infected with pathogen j is exposed to pathogen i . A host which is or has been infected by pathogen j will experience a transmission rate of pathogen i , λ_i , altered a by positive parameters φ_j , ξ_j or χ_j . φ_j is used for the hosts currently infected by pathogen j (S_iI_j), ξ_j for the hosts

convalescent from a previous infection by pathogen j (S_iC_j), and χ_j for the hosts resistant to pathogen j (S_iR_j). Thus, an individual susceptible to both pathogens will be exposed to a transmission rate of λ_i for pathogen i , while an individual susceptible to pathogen i but infected by pathogen j will be exposed to a transmission rate of $\varphi_j\lambda_i$ for pathogen i . If all $\varphi_i = \xi_i = \chi_i = 1 \forall i$, the force of infection is always equal to λ_i : there is no interaction between pathogens and they are strictly independent. A value smaller than 1 induces a partial (or total if $\varphi = \xi = \chi = 0$) cross-protection (later called ‘obstructing interactions’), while a value greater than 1 induces a susceptibility enhancement (later called ‘facilitating interactions’). Those alterations of susceptibility can be either simultaneous to the infection if they occur on infectious individuals (φ) or delayed if they occur on convalescent or resistant individuals (ξ and χ , resp.). They may also be temporary, if they occur on infectious or convalescent individuals (φ and ξ , resp.), or permanent, if they occur on resistant hosts (χ). This model assumes that all pathogen interactions are driven by a modification of host susceptibility. In reality, interactions may also operate via infectiousness (see [65] for a model with modification of infectiousness). Demography is included in the model via the constant birth and death rate μ . Birth rate and death rate are equal and independent of the host status, so the population size is held constant (or nearly constant because of stochasticity). Forces of infection may be subject to a seasonal fluctuation according to the amplitude of seasonality η . This seasonal forcing is annual, the unit of time in the model being the year and the time-step between each point being a week.

The model is based on a deterministic skeleton given by the following system of ODE. We set the forces of infection to be frequency-dependant, with $\lambda_1 = (1 + \eta \cos(2\pi t)) \frac{\beta_1}{N} (X_{IS} + X_{II} + X_{IC} + X_{IR})$ and $\lambda_2 = (1 + \eta \cos(2\pi t)) \frac{\beta_2}{N} (X_{SI} + X_{II} + X_{CI} + X_{RI})$.

$$\frac{dX_{SS}}{dt} = \mu(N - X_{SS}) - \lambda_1 X_{SS} - \lambda_2 X_{SS} \quad (2.1)$$

$$\frac{dX_{IS}}{dt} = \lambda_1 X_{SS} - (\varphi_1 \lambda_2 + \mu + \gamma_1) X_{IS} \quad (2.2)$$

$$\frac{dX_{CS}}{dt} = \gamma_1 X_{IS} - (\xi_1 \lambda_2 + \mu + \delta_1) X_{CS} \quad (2.3)$$

$$\frac{dX_{RS}}{dt} = \delta_1 X_{CS} - (\chi_1 \lambda_2 + \mu) X_{RS} \quad (2.4)$$

$$\frac{dX_{SI}}{dt} = \lambda_2 X_{SS} - (\varphi_2 \lambda_1 + \mu + \gamma_2) X_{SI} \quad (2.5)$$

$$\frac{dX_{SC}}{dt} = \gamma_2 X_{SI} - (\xi_2 \lambda_1 + \mu + \delta_2) X_{SC} \quad (2.6)$$

$$\frac{dX_{SR}}{dt} = \delta_2 X_{SC} - (\chi_2 \lambda_1 + \mu) X_{SR} \quad (2.7)$$

$$\frac{dX_{II}}{dt} = \varphi_1 \lambda_2 X_{IS} + \varphi_2 \lambda_1 X_{SI} - (\mu + \gamma_1 + \gamma_2) X_{II} \quad (2.8)$$

$$\frac{dX_{IC}}{dt} = \gamma_2 X_{II} + \xi_2 \lambda_1 X_{SC} - (\mu + \gamma_1 + \delta_2) X_{IC} \quad (2.9)$$

$$\frac{dX_{IR}}{dt} = \delta_2 X_{IC} + \chi_2 \lambda_1 X_{SR} - (\mu + \gamma_1) X_{IR} \quad (2.10)$$

$$\frac{dX_{CI}}{dt} = \gamma_1 X_{II} + \varphi_1 \lambda_2 X_{IS} - (\mu + \gamma_2 + \delta_1) X_{CI} \quad (2.11)$$

$$\frac{dX_{CC}}{dt} = \gamma_1 X_{IC} + \gamma_2 X_{CI} - (\mu + \delta_1 + \delta_2) X_{CC} \quad (2.12)$$

$$\frac{dX_{CR}}{dt} = \gamma_1 X_{IR} + \delta_2 X_{CC} - (\mu + \delta_1) X_{CR} \quad (2.13)$$

$$\frac{dX_{RI}}{dt} = \delta_1 X_{CI} + \chi_1 \lambda_2 X_{RS} - (\mu + \gamma_2) X_{RI} \quad (2.14)$$

$$\frac{dX_{RC}}{dt} = \delta_1 X_{CC} + \gamma_2 X_{RI} - (\mu + \delta_2) X_{RC} \quad (2.15)$$

$$\frac{dX_{RR}}{dt} = \delta_1 X_{CR} + \delta_2 X_{RC} - \mu X_{RR} \quad (2.16)$$

Gillespie's method [123] is used to include demographic stochasticity in the model. Demographic stochasticity mimics the consequences of individual variability in the population and adds unpredictable fluctuations to the data [260]. That can facilitate the analyses by exciting the attractors. Time series of both pathogens are produced by the same mechanistic model. Thus, similarities in the dynamics, that could lead to the detection of correlations or causalities, could rise from the similarities in the processes behind the data, all interactions excluded. Because of this, one could argue that, even without any interactions in the model, the two pathogen are not independent. Dynamics produced in the time series by demographic stochasticity are independent. Thus, without any interaction, demographic stochasticity ensures differences in the dynamics of the two pathogens, even if they were strictly identical. On the other hand, environmental stochasticity is added to the model by the addition of a white noise to the seasonal forcing [261]. Following the exact opposite reasoning, this stochasticity ensures non-periodic component to the common forcing for the two pathogens.

Each event (birth, death, infection, convalescence, healing) is defined by its rate. The time between each event is given by an exponential distribution, which parameter is the inverse of the sum of rates. Each one of the 42 events has a probability proportional to its rate to be applied at each time step. In order to avoid extinction of a pathogen, we add a constant immigration term to the forces of infection of each pathogen. This immigration is a flat, temporary arrival of infectious individuals that transmit their infection to local individuals without being part of the demographic dynamics of the population. This process is independent of the contact rate. Saying, there is a constant rate of individuals that becomes infectious toward each pathogens by being exposed to immigrated infectious individuals. Simulations' length is 400 years. The first 350 years are discarded to keep only the stationary state. Each parameters set has 100 replicates. Final output data is weekly report of new cases (incidence).

Several parameters sets will be used (see Table 2.1). The first set of parameters is chosen in order to fulfil biological plausibility. The epidemiological parameters of both pathogens are chosen to reflect most of viral infections. Viral infection are characterised by short infectious periods with high contact rates [124, 125]. Convalescence period is very short. Moreover, those parameters allows to maintain significantly strong epidemics each year. Lower contact rates could cause quasi-extinction of the pathogens. Contact rates of the two pathogens are different in order to reduce similarities between dynamics that are not caused by interactions. Basic reproductive rates (R_0) are, not considering interactions, 5 and 10 for pathogen 1 and 2, respectively. These values are in the range of highly transmissible diseases. For comparison, R_0 estimates are around 2.2 for H1N1 influenza [262], 1.79 and 3.75 for two waves of Spanish flu (1918 epidemics) in Geneva (Switzerland) [263], 6.2 and 7.7 for measles [264], 27.1 for malaria [265], with most recent estimates ranging from around 1 to an arguable 3,000 [266], 3.5 – 6 for smallpox [267].

In order to get a first sight on the impact of interactions on diseases' dynamics, several indicators are computed. The first one is the *Main Periodic Component* (MPC). For each replicate of a simulation, the Fourier spectrum is calculated. The MPC for a given parameters set is the mean of periods associated with the highest peak of the spectrum of each replicate. This helps us understanding the influence of the interaction on temporal dynamics. Then, the *Area Under the Curve* (AUC) is calculated for each replicate, as a proxy of the total number of cases during

Param.	Description (<i>unit</i>)	Default Set		High R_0 Set		'Parsimonious' Set	
		Path.1	Path.2	Path.1	Path.2	Path.1	Path.2
N	Population Size (<i>individuals</i>)	1.000.000					
ω	Immigration Rate (<i>infectious ind.year⁻¹</i>)	7					
μ	Birth and death rate (<i>years⁻¹</i>)	0.02					
β_i	Contact Rate (<i>years⁻¹.ind⁻¹</i>)	600	1200	600	1200	100	200
$\frac{1}{\gamma}$	Mean Infectious period	3 <i>days</i>		1 <i>months</i>		6 <i>weeks</i>	
$\frac{1}{\delta}$	Mean Convalescence period	1 <i>week</i>		6 <i>months</i>		1 <i>year</i>	
R_0	Basic Reproductive Rate	~ 5	~ 10	~ 49	~ 99	~ 11	~ 23

Table 2.1. Parameter's values for the simulations.

the whole simulation. This indicates whether the interaction, which is at individual level, leads to stronger or weaker epidemics, at the scale of the population.

In every simulation used for this study, there is no interactions from pathogen 2 to pathogen 1 ($\varphi_2 = \xi_2 = \chi_2 = 1$). Only interactions from pathogen 1 to pathogen 2 may exist.

2.2.2 Granger Causality

Granger Causality Analysis (GCA) intents to detect causality between variables, that is, directional straight effects. The main advantage of this method is to overcome the standard "limit" of correlation, which only can show the existence of a link, either direct or indirect, between variables [268,269]. Granger Causality Analysis both allow us to identify the way the interaction goes and to discriminate direct effect and (e.g.) effect from a common external forcing [120].

GCA key-idea is that " Y_t is causing X_t if we are better able to predict X_t using all available information than if the information apart from Y_t had been used" [47]. In other words, if this condition is fulfilled, that means that Y_t contains exclusive informations that are not present in all the other time series and that are useful to predict the time series of interest, X_t . Here, "being better able to predict" a variable means that the standard predictive error of a multivariate autoregressive (MVAR) model is smaller [126,270]. A MVAR is a statistical linear model that aims to estimate a variable using the present and past values of this variable and other variable [126]. For Granger Causality Analysis, there is no aim to produce a parsimonious model in term of number of variables. On the contrary, the more variable, the more pertinent the analysis will be [120,271].

To build the MVAR models, we first normalize the data. Time series must be "covariance stationary" to be suitable for GCA [119,127], i.e. mean and variance of each variable do not vary with time [272]. If they are not, the MVAR models may have 'spurious regression' resulting from non-stationarities. This "covariance stationary" condition is tested by two separate tests: Augmented Dickey Fuller (ADF [273,274]) and Kwiatkowski, Phillips, Schmidt & Shin (KPSS [275]). These two tests are complementary in the way that the first uses the null hypothesis that there is no "unit root", the second tests against the null hypothesis that there is a "unit root". When the "covariance stationary" is successfully tested, the series are normalized. They are de-trended by subtracting the best-fitting line from each time series, then demeaning by removing the temporal mean from each observation of the time series. At the same time, the observations are divided

by the temporal standard deviation. Thus we obtain zero-mean times series, which is essential for MVAR models fitting [126].

To build the MVAR models themselves, we find the order n of the best MVAR model that uses all of the available data to predict X_t . The order of the model corresponds to the more ancient value of the variable that is used to predict X_t . That is, for an univariate case, the AR model are the $\{A_1, \dots, A_n\}$ coefficients that are applied to the $\{X_{t-1}, \dots, X_{t-n}\}$ past values of X to estimate X_t . For a bivariate case, with X_t and Y_t two times series, the MVAR model is:

$$X_t = \sum_{j=1}^n A_{11,j} X_{t-j} + \sum_{j=1}^n A_{12,j} Y_{t-j} + \varepsilon_{X(t)}, \quad (2.17)$$

where $\varepsilon_{X(t)}$ is the predictive errors on X_t .

The optimal order n is chosen by computing the Bayesian Information Criteria (BIC [276]) of all model of order within $[n_{min} : n_{max}]$ and choosing the order n that minimise the BIC for the model using all available data. The predictive error ε_U on X_t of this model is calculated. Then, a MVAR model of the same order n and using all available data except the time series Y_t is built. The predictive error ε_Y on X_t of this model is calculated. Finally, the amplitude, or strength, of the causality of Y_t on X_t is the logarithm of the relation between the variance of the errors, $\ln \frac{\text{var}(\varepsilon_Y)}{\text{var}(\varepsilon_U)}$. The significance of this causality is given by a Fisher test [277] based on the relative difference in error square sum of both models.

2.2.3 Transfer Entropy

Transfer Entropy (TE) still intends to identify causality between time-series. It complies with the Granger-Wiener definition of causality but does not use MVAR to estimate causalities. Instead it uses the properties of *Mutual Information*. Mutual Information is a symmetrical indicator that measures the deviation of two variables from independence. It is calculated from *Entropy* and *Conditional Entropy*. The entropy of a variable X quantify its unpredictability. If the probability mass function of X is $p(x) = \text{Prob}(X = x)$, then the entropy of X [278, 279] is:

$$H(X) = - \sum_x p(x) \log p(x) \quad (2.18)$$

Following the same structure, one can calculate the *Joint Entropy* and conditional entropy between two variables X and Y with joint distribution $p(x, y) = \text{Prob}(X = x, Y = y)$ and conditional distribution $p(x|y) = \text{Prob}(X = x|Y = y)$. Joint entropy is

$$H(X, Y) = - \sum_{x, y} p(x, y) \log p(x, y) \quad (2.19)$$

and conditional entropy is

$$H(X|Y) = - \sum_{x, y} p(x, y) \log p(x|y) \quad (2.20)$$

Given these entropies, the Mutual Information between X and Y is

$$I(X; Y) = H(X) - H(X|Y) = H(Y) - H(Y|X) \quad (2.21)$$

Given two stochastic processes X_t and Y_t , with $X_t^{\tau_X} = (X_t, X_{t-1}, \dots, X_{t-\tau_X+1})$ and $Y_t^{\tau_Y} = (Y_t, Y_{t-1}, \dots, Y_{t-\tau_Y+1})$ being the past τ_X and τ_Y values of X and Y , respectively, the *Transfer Entropy* [48] from Y to X is defined as:

$$T_{Y \rightarrow X} = H(X_{t+1}|X_t^{\tau_X}) - H(X_{t+1}|X_t^{\tau_X}, Y_t^{\tau_Y}) \quad (2.22)$$

One can recognize in eq.2.22 the Wiener-Granger Causality principle, as the difference of uncertainty about X_{t+1} given ‘all’ available informations (i.e. X_t^{TX} and Y_t^{TY}) and given ‘all’ available informations apart from Y_t^{TY} . If $T_{Y \rightarrow X} > 0$, that means that the uncertainty about X is reduced by the addition of informations from Y , and thus that Y causes X .

The whole point of Transfer Entropy is to estimate the probability mass functions, joint distributions and conditional distributions [280]. Several methods exist, some of them being well-described by MONTALTO *et al.* [122]. We used the *MuTE* Matlab™ toolbox they developed to estimate multivariate transfer entropy. This toolbox provides three entropy estimators based on different methods for distribution computation: a linear estimator (LIN) [128], a binning estimator (BIN) [281] and a nearest neighbour estimator (NN) [280]. For each of them, the components to be included in the embedding vectors used for the estimations can be either selected *a priori* and separately for each time series (uniform embedding, UE) [282] or selected progressively in order to include only the most informative components of each series (non-uniform embedding, NUE) [283].

Each of these methods have their specificity. Montalto *et al.* however conclude that the binning estimator with non-uniform embedding (BIN NUE) should be the best estimators for non-linear systems, being better to discriminate false positive from true positive [122], and that non-uniform embedding (NUE) is always better than its uniform counterpart (UE).

The work here being theoretical, we *know*, according to the model, that the only possible causal factors are the population in each compartment and the seasonal forcing. On the other hand, we know that most if not all epidemiological data are incidence data: we nearly never know the number of susceptible, convalescent nor resistant individuals. Because of this, we will only use incidence data and seasonality for the analysis of the simulations provided by the model.

2.3 Results

2.3.1 Model Behaviour

In all the following series of simulations, interactions are unidirectional: susceptibility toward the second pathogen is affected by the status of the host toward the first pathogen, whereas susceptibility toward the first pathogen is fixed. Each type of interactions is tested independently from the others, i.e. only one interaction parameter at a time is different from 1. Here, we are interested in the impact of the value of each interaction parameters on the dynamics of the second pathogen. The dynamics of the first pathogen is not impacted by any change in the interaction parameters. Single simulations of the model are shown in Fig. 2.3 and A.1. This is the most simple possible case: the interaction is unidirectional so we can discriminate false positives and false negatives. The epidemiological parameters of both pathogens (Table 2.1) are chosen to reflect most of viral infections, with high contact rates, but short infectious and, if any, convalescent periods. This is the case of, e.g., influenza, measles or noroviruses [284–286]. Contact rates of the two pathogens are different in order to avoid similarities between dynamics that are not caused by interactions.

First Glimpse: When we restrain interaction’s strength to low, biologically plausible, values, we observe that only interactions on resistant individual have a visible effect on pathogen’s dynamics (Fig. 2.3, C and F). One notable observation is that the effect on periodicity of interaction on resistant individuals does not inflect as the interaction changes from ‘obstructing’ to ‘facilitating’: the periodicity of the second pathogen dynamics keeps decreasing nearly linearly on the full range of interaction parameter values (Fig. 2.3 F). This period increases again only

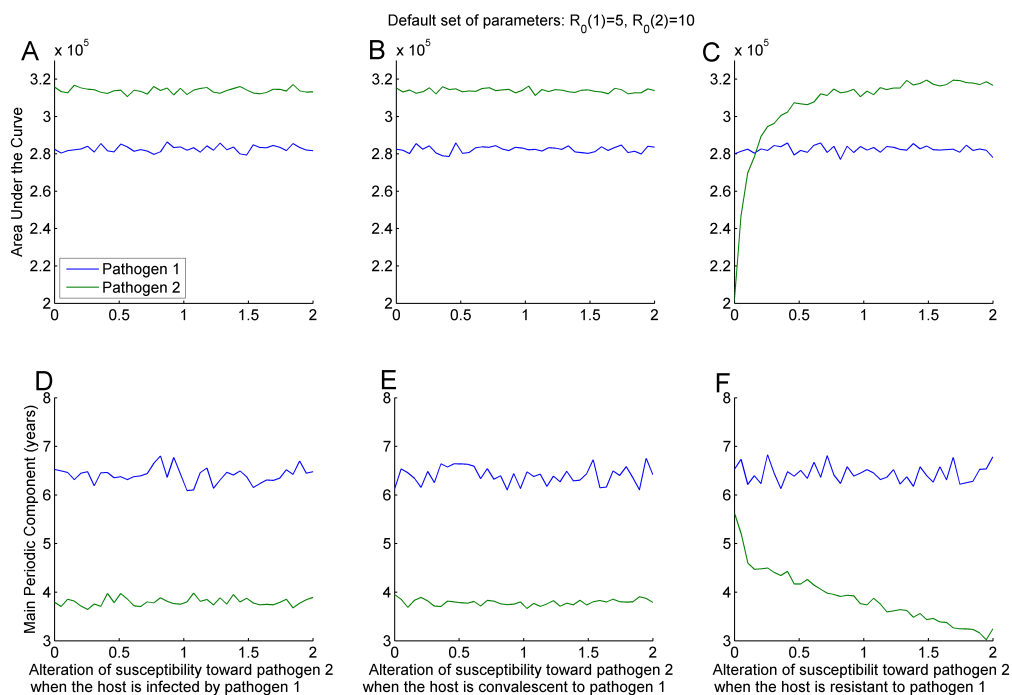


Figure 2.3. Values of the generic dynamics indicators according to each type of interaction with the default set of parameters. A-B-C: Total number of cases. This is an estimate based on the calculation of the area under the curve. D-E-F: Main Periodic Component, determined by the highest peak of the Fourier Spectra of each time series. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for pathogen 1 (resp. 2) are blue (resp. green). 40-years long examples of simulations for each minima and maxima of interaction strength are shown in side boxes. Parameters are shown in Table 2.1, Default Set.

for stronger positive interaction (see Fig. A.1 F). On the other hand, the total number of cases follows a logarithmic-like growth, reaching its saturation value before the interaction switch from obstructing to facilitating.

Alteration of susceptibility for infectious and convalescent individuals does not affect the monitored indicators. This might be explained by the number of individuals affected by these interactions. Indeed with this kind of epidemiological structure, most individuals are resistant to at least one pathogen. Without any interaction, in mean 27.09% ($\pm 4.6 \times 10^{-2}$ 95% CI) of individuals susceptible to pathogen 2 are resistant to pathogen 1, while only 0.1075% ($\pm 2.7 \times 10^{-3}$ 95% CI) and 0.04857% ($\pm 1.3 \times 10^{-3}$ 95% CI) of them are convalescent and infectious, respectively. The fewer individuals affected by the interaction are, the less visible effects of this interaction at the population scale is.

Explore the impact of the interaction: In order to assess this issue, we investigate the influence of model's parameters on the repartition of individuals susceptible to pathogen 2 according to their status toward pathogen 1 (Fig. 2.4). This is done analytically from the ODE system of the model (Eqs.2.1-2.16). In order to keep the system analytically solvable, interaction parameters ϕ , ξ and χ have to be fixed to 1 and seasonality factor η fixed to 0. From these ODE we establish the non disease-free equilibrium in order to obtain the analytic formulas for the proportion of susceptible, infectious, convalescent and resistant (resp.) to pathogen 1 that are susceptible to pathogen 2 in the population at equilibrium, $\frac{X_{SS}^*}{N}$, $\frac{X_{IS}^*}{N}$, $\frac{X_{CS}^*}{N}$ and $\frac{X_{RS}^*}{N}$. We get, given that $\beta_1 > \mu + \gamma_1$ and $\beta_2 > \mu + \gamma_2$, which are the stability conditions for the non-disease free equilibrium:

$$\frac{X_{SS}^*}{N} = \frac{\mu}{\lambda_1^* + \lambda_2^* + \mu} \quad (2.23)$$

$$\frac{X_{IS}^*}{N} = \frac{\mu \lambda_1^*}{(\gamma_1 + \lambda_2^* + \mu)(\lambda_1^* + \lambda_2^* + \mu)} \quad (2.24)$$

$$\frac{X_{CS}^*}{N} = \frac{\mu \gamma_1 \lambda_1^*}{(\gamma_1 + \lambda_2^* + \mu)(\lambda_1^* + \lambda_2^* + \mu)} (\delta_1 + \lambda_2^* + \mu) \quad (2.25)$$

$$\frac{X_{RS}^*}{N} = \frac{\gamma_1 \delta_1 (\mu + \gamma_2) \lambda_1^*}{(\gamma_1 + \lambda_2^*)(\lambda_1^* + \lambda_2^* + \mu)} (\delta_1 + \lambda_2^* + \mu) \quad (2.26)$$

$$(2.27)$$

with

$$\lambda_1^* = \frac{\beta_1}{N}(X_{IS}^* + X_{II}^* + X_{IC}^* + X_{IR}^*) = \frac{\mu \beta_1}{\mu + \gamma_1} - \mu$$

$$\lambda_2^* = \frac{\beta_2}{N}(X_{SI}^* + X_{II}^* + X_{CI}^* + X_{RI}^*) = \frac{\mu \beta_2}{\mu + \gamma_2} - \mu$$

From Eq.2.24 and Fig. 2.4B, we see that the proportion of individuals that are infectious to pathogen 1 and susceptible to pathogen 2, i.e. the individuals who would be affected by an alteration of susceptibility for infectious individuals (φ) is mainly affected by the infectious period of pathogen 1, while other parameters have little (or no, in the case of convalescence periods) influence. On the contrary, proportion of convalescent (Eq.2.25) and resistant (Eq.2.26) are more or less equally (but in different manners) influenced by all parameters (Fig. 2.4).

From these observations we conclude that to get a significant impact of the interaction on infectious individuals (φ), the infectious period of pathogen 1 has to be significantly higher, more

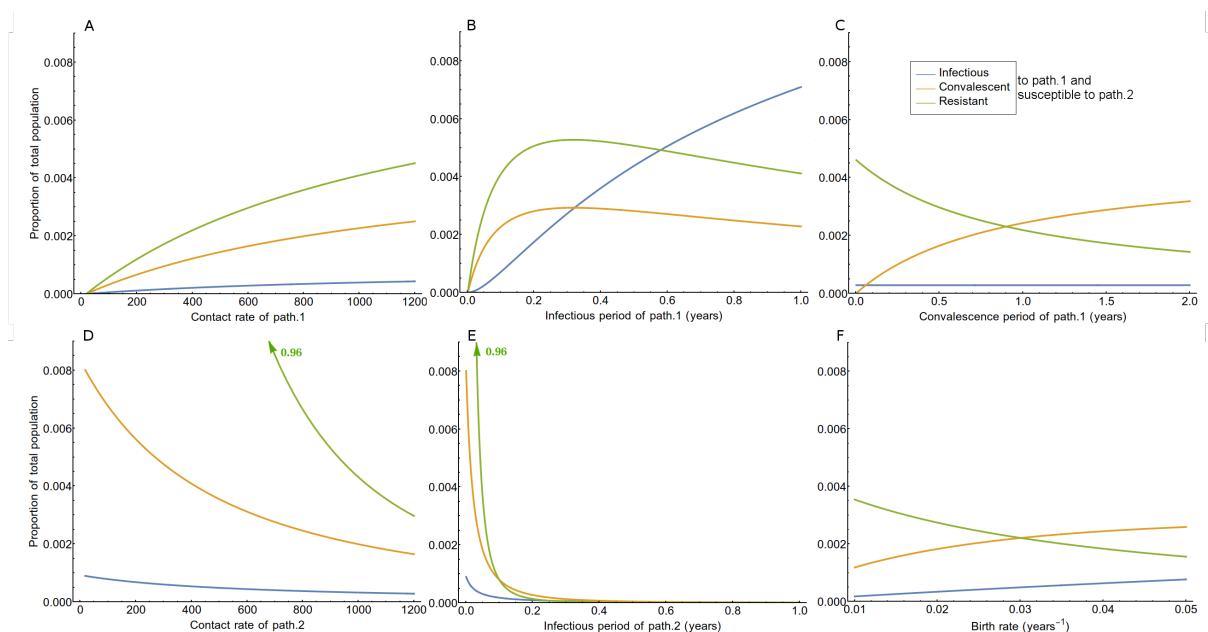


Figure 2.4. Repartition at equilibrium of susceptible to pathogen 2 according to their status toward pathogen 1, without any interaction nor seasonality. A & D: Repartition according to contact rate of path.1 and 2 (resp.), other parameters at default value. B & E: Repartition according to infectious period of path.1 and 2 (resp.), other parameters at default value. C: Repartition according to convalescence period of path.1, other parameters at default value. F: Repartition according to birth rate, other parameters at default value.

than one month seeming to be a minimum. Most respiratory viral infections have an infectious period of less than one week [287]. Diseases with infectious period longer than one month are, non exhaustively, Tuberculosis [288, 289] or HIV [290]. For most diseases, with short infectious period, an alteration of susceptibility to other pathogens during infectious period is likely to have no visible effect at the population scale (Fig. 2.3, A, D).

The proportion of convalescent individuals is increased by higher contact rate and longer convalescence period. It also increases with the infectious period of pathogen 1 as long as it does not exceed a threshold of about one month. The value of this threshold is dependant of the other parameters. Lastly, the proportion of resistant individuals is reduced by the convalescent period of pathogen 1, and contact rate and infectious period of pathogen 2. It is increased by the contact rate of pathogen 1 and affected by infectious period of pathogen 1 the same way as the proportion of convalescent is.

In order to insure a significant proportion of individuals potentially subject to all interactions, we can set $\beta_1 = 600, \beta_2 = 1200, \frac{1}{\gamma} = 1$ month, $\frac{1}{\delta} = 6$ months (Table 2.1, High R_0 Set, and Fig. 2.5). With those values we expect higher proportion of infectious and convalescent individuals within susceptible to pathogen 2 (4.53% and 13.9%, resp., according to Eqs. 2.24 and 2.25), due to longer infectious and convalescence period. However, with this set of parameters basic reproductive rates are very high ($R_0(1) = 49.9, R_0(2) = 99.8$), making these parameters good to test the model and the analysis' methods but unrealistic.

The whole point of this parameter's set is to test GCA and TE in an extremely favourable context, with high proportion of the population affected by the interactions. Indeed with these parameters, the estimate total number of cases for pathogen 2 is only affected by a decrease of susceptibility to pathogen 2 when the host are resistant to pathogen 1 (Fig. 2.5, C) but the main

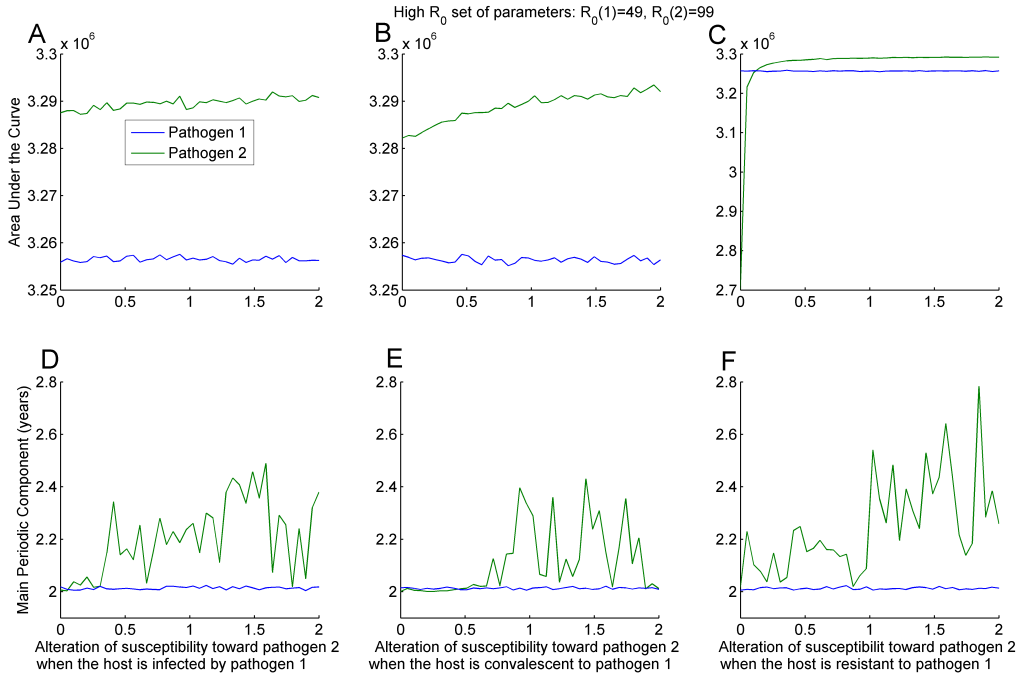


Figure 2.5. Values of the generic dynamics indicators according to each type of interaction with the ‘High R_0 ’ set of parameters. A-B-C: Total number of cases. This is an estimate based on the calculation of the area under the curve. D-E-F: Main Periodic Component, determined by the highest peak of the Fourier Spectra of each time series. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for pathogen 1 (resp. 2) are blue (resp. green). $\beta_1 = 600, \beta_2 = 1200, \frac{1}{\gamma} = 1 \text{ month}, \frac{1}{\delta} = 6 \text{ months}$. Other parameters are shown in Table 2.1, High R_0 Set.

periodic component of pathogen 2 varies with every interaction (Fig. 2.5, D-F), while it was only altered by the interaction on resistant individuals with default parameters (Fig. 2.3, F).

Lastly, in order to insure a significant proportion of individuals potentially subject to all interaction but without going to far away from realistic parameters, we can set $\beta_1 = 100, \beta_2 = 200, \frac{1}{\gamma} = 6 \text{ weeks}, \frac{1}{\delta} = 1 \text{ year}$. With those values, we still have a plausible basic reproductive rate ($R_0(1) = 11.3, R_0(2) = 22.6$) because of lower contact rates but we expect higher proportion of infectious and convalescent individuals within susceptible to pathogen 2 (1.23% and 8.11%, resp., according to the analytic values from Eqs. 2.24, 2.25), due to longer infectious and convalescence period.

With these parameters, only the alteration of susceptibility of infectious individuals has no visible effect on the number of cases and the periodicity of pathogen 2 (Fig. 2.6, A, D). Alteration of susceptibility of convalescent and resistant individuals induce a decrease of the periodicity of pathogen 2 as the susceptibility increases (Fig. 2.6, E, F). For convalescent individuals, it also slowly increases the total number of cases (Fig. 2.6, B), while for resistant individuals the increase is logarithmic-like (Fig. 2.6, C).

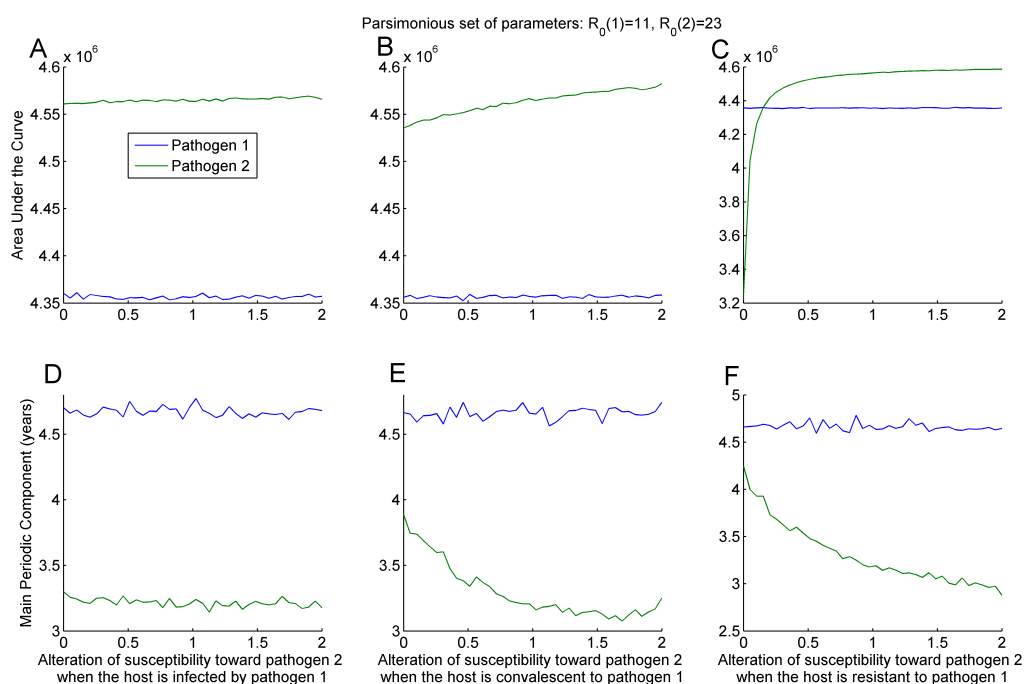


Figure 2.6. Values of the generic dynamics indicators according to each type of interaction with the ‘parsimonious’ set of parameters. A-B-C: Total number of cases. This is an estimate based on the calculation of the area under the curve. D-E-F: Main Periodic Component, determined by the highest peak of the Fourier Spectra of each time series. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for pathogen 1 (resp. 2) are blue (resp. green). $\beta_1 = 100, \beta_2 = 200, \frac{1}{\gamma} = 6 \text{ weeks}, \frac{1}{\delta} = 1 \text{ year}$. Other parameters are shown in Table 2.1, Parsimonious Set.

2.3.2 Granger Causality

Granger Causality Analysis have been done for each single simulation. For each set of parameters and each interaction parameter value, the number of simulations for which the causality is significant (p -values < 0.05) and mean amplitude of significant causalities are plotted (Fig. 2.7, 2.8 and A.2).

Default parameters: For our default, biologically plausible parameters (Table 2.1), we immediately observe, as expected, that interactions on infectious and convalescent individuals are not detected, as the number of significant causalities remains low and stationary whatever the interaction strength (Fig. 2.7, A-B). Results are slightly different for interactions on resistant individuals. The number of significant causalities from pathogen 1 to pathogen 2 increases steadily as the interaction parameter value increases, instead of the V-shaped expected curve. That is, obstructing interactions ($0 \leq \chi < 1$) lead to fewer detected causalities than no interactions ($\chi = 1$). The detection of this interaction does not follow the absolute value of the interaction strength. The amplitude of the significant causalities increases with the interaction parameter value for both causality from pathogen 1 to pathogen 2, which is the one expected from parameters. However, with stronger, but biologically unrealistic, interactions (Fig. A.2), GCA achieves to detect facilitating interactions, even if it does not correctly identify the direction of the interaction: causalities from pathogen 1 to pathogen 2 and from pathogen 2 to pathogen 1 are equally detected.

High R_0 set: Results of the Granger Causality Analysis (GCA) are very different for the unrealistic testing set of parameters, with very high R_0 (Fig. 2.8). Whatever the interaction, we have 100% false-positive detection of a causality from pathogen 2 to pathogen 1 (Fig. 2.8, A-C). Amplitude of the detected causalities from pathogen 2 to pathogen 1 are always slightly increasing with the interaction parameter value, whatever the type of interaction (Fig. 2.8, D-F). The proportion of detected causalities from pathogen 1 to pathogen 2) behaves differently for each interaction. For interaction on infectious individuals (Fig. 2.8, A), it nearly linearly increases with the interaction parameter value. For interaction on convalescent individuals (Fig. 2.8, B and E), it decreases when the interaction parameter is between 0 and 0.5 and increasing for higher values. For interaction on resistant individuals (Fig. 2.8, C and F), it decreases with the interaction parameter value. We still never observe the centred around 1, V-shaped curve that would characterise a good detection of the interaction.

Parsimonious set: With the ‘parsimonious’ set of parameters, i.e. quite high R_0 , with low transmission but long infectious and convalescent periods (Table 2.1), there is a 100% detection of both the real causality (from path.1 to path.2) and the false causality (from path.2 to path.1) (Fig. 2.9, A-C), whatever the interaction. Amplitudes of the detected false causality are slightly decreasing with the interaction parameter value for interactions modifying the susceptibility of infectious and convalescent hosts (Fig. 2.9, D, E). On the contrary, for interactions on resistant individuals, they increase strongly (Fig. 2.9, F). Concerning the right causality, amplitude slightly increases with the value of the interaction when it occurs on the infectious hosts (Fig. 2.9, D), while it exponentially decreases for the interactions on resistant individuals (Fig. 2.9, F). However, it is noteworthy that for the interaction on convalescent individuals, the amplitude of the detected causalities decreases for interaction value between 0 and 0.75, then stabilizes around 1 and slightly increases again after 1.5 (Fig. 2.9, E). This is the best result that GCA has achieved.

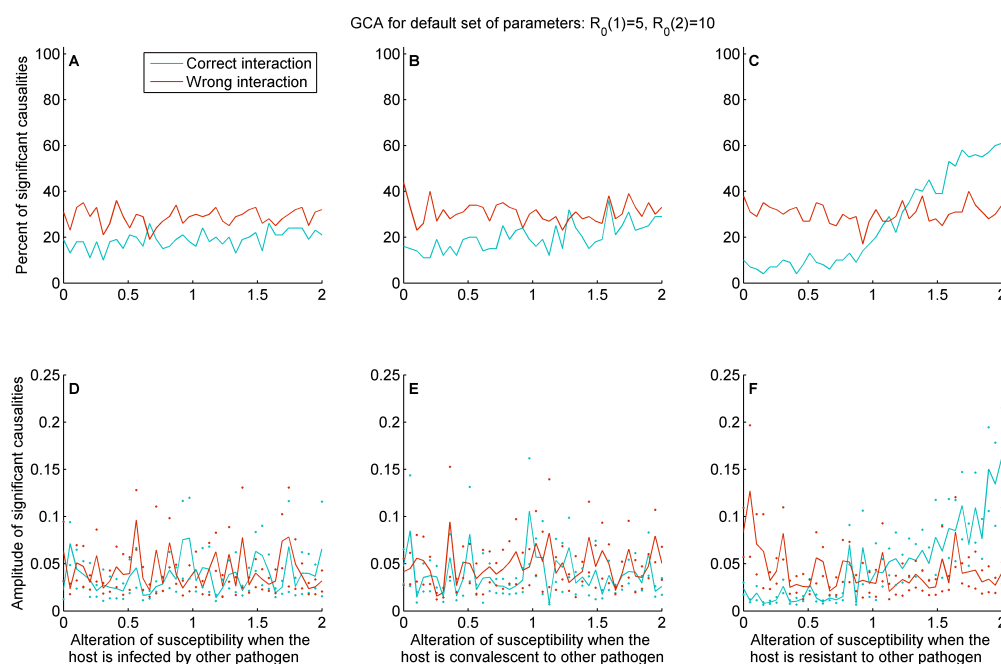


Figure 2.7. Values of Granger Causality analysis output according to each type of interaction with the default set of parameters. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for effect of pathogen 1 (resp. 2) on pathogen 2 (resp. 1) are blue (resp. red). Points delimit 95% confidence intervals. Other parameters are shown in Table 2.1, Default Set.

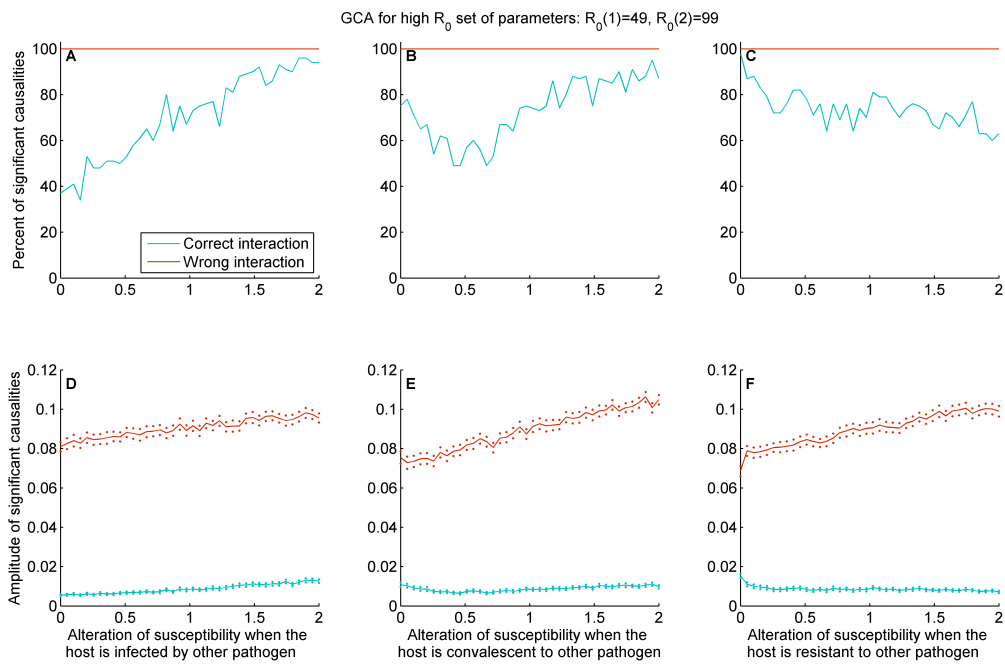


Figure 2.8. Values of Granger Causality analysis output according to each type of interaction with the ‘High R_0 ’ set of parameters. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for effect of pathogen 1 (resp. 2) on pathogen 2 (resp. 1) are blue (resp. red). Dotted lines delimit 95% confidence intervals. $\beta_1 = 600, \beta_2 = 1200, \frac{1}{\gamma} = 1$ month, $\frac{1}{\delta} = 6$ months. Other parameters are shown in Table 2.1, High R_0 Set.

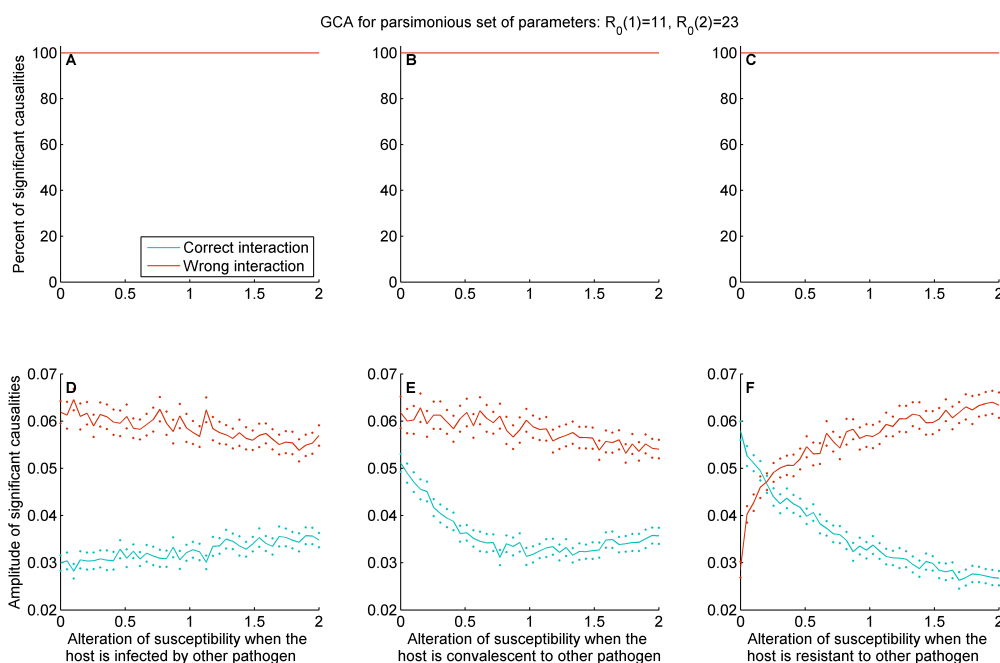


Figure 2.9. Values of Granger Causality analysis output according to each type of interaction with the ‘parsimonious’ set of parameters. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for effect of pathogen 1 (resp. 2) on pathogen 2 (resp. 1) are blue (resp. red). Dotted lines delimit 95% confidence intervals. $\beta_1 = 100$, $\beta_2 = 200$, $\frac{1}{\gamma} = 6$ months, $\frac{1}{\delta} = 1$ year. Other parameters are shown in Table 2.1, parsimonious Set.

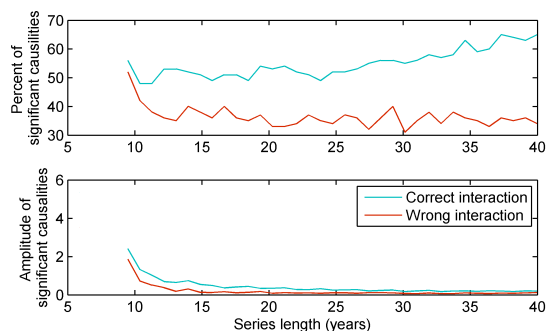


Figure 2.10. Values of Granger Causality analysis output according to the length of the time series (in years). A: Number of significant causalities. B: mean amplitude of significant causalities. Values for effect of pathogen 1 on pathogen 2 (resp. 2 on 1) are blue (resp. green). Parameters used can be found in 2.1, Default Set. $\varphi_1 = \xi_1 = \varphi_2 = \xi_2 = \chi_2 = 1$, $\chi_1 = 2$.

Series length: If the interaction included in the parameters can be detected by the Granger analysis, we observe that the length of the time series has an interesting qualitative impact on the detection of this interaction. Series shorter than 9 years are too short to run the analysis, resulting in the incapacity to compute proper amplitude and p-values for the interactions. This is equivalent to three pseudo-cycles of pathogen 2, its main periodic component being three years (Fig. 2.3), and ~ 110 points of monthly data. For series longer than 13 years, the significance of the interaction detected is independent of the length of the series (Fig. 2.10). For series between 9 and 12 years, amplitude of detected causalities decreases as well as the number of false positives for a causality from pathogen 2 to pathogen 1. Number of true positives slightly increases for series longer than 25 years. Thus, 12 years are sufficient to reach the optimal efficacy of the method. Weekly data allows slightly better performances than monthly data.

2.3.3 Transfer Entropy

Similarly to Granger Causality Analysis, Transfer Entropy has been computed for each simulation of each parameter set. The number of simulations for which the causality is significant (p-values < 0.05) and mean amplitude of significant causalities are plotted (Figs. 2.11, 2.12, A.3 and A.4).

Default parameters: Transfer entropy using linear estimator and our default set of parameters (Table 2.1) gives very similar results than Granger Causality analysis (Fig. 2.11). Interactions on infectious and convalescent individuals are not detected, the number of significant causalities remaining low whatever the interaction strength. Interactions on resistant individuals are partially detected, with growing proportion and strength of causalities from pathogen 1 to pathogen 2 for facilitating interactions. On the contrary, using a binning estimator leads to nearly no detection, including both false and true positives (Fig. A.3). Additionally, the very few causalities that are detected have a very low intensity compared to intensities detected by transfer entropy with a linear estimator. Nearest Neighbours estimator gives similar results than binning estimator.

High R_0 set: Results of the Transfer Entropy (TE) using linear estimator (LIN) still are quite similar to those of GCA for the unrealistic testing set of parameters with very high R_0 (Table 2.1). We still have 100% false-positive detection of a causality from pathogen 2 to pathogen 1 (Fig. 2.12, A-C). However for interaction on resistant individuals, the number of significant

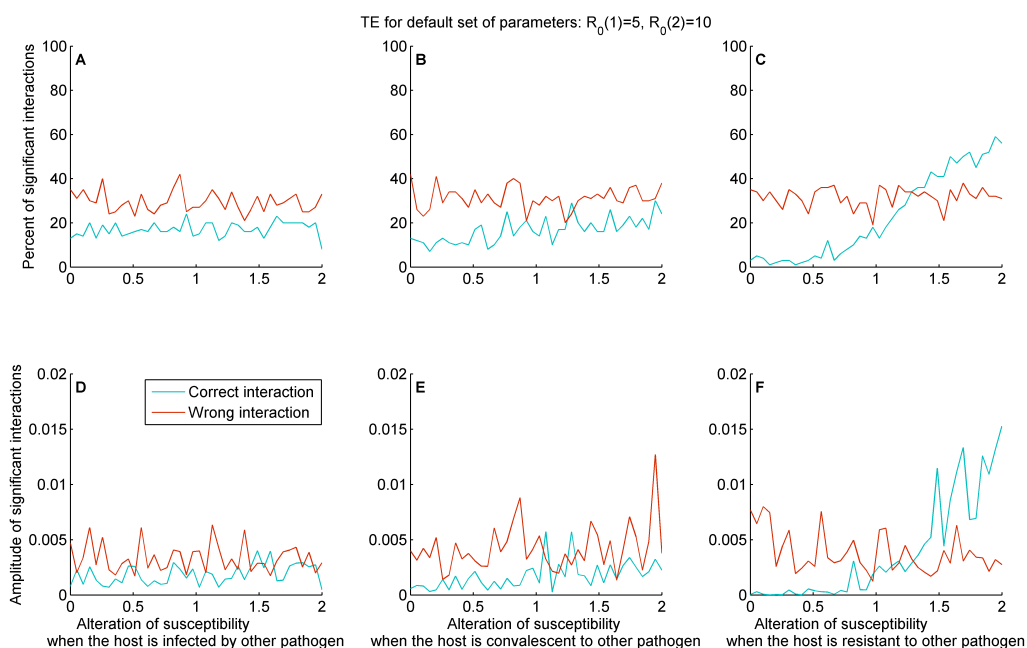


Figure 2.11. Values of LIN NUE Transfer Entropy analysis output according to each type of interaction with the default set of parameters. Top: number of simulations for each point where detected causalities are significant. Bottom: mean amplitude of the significant causalities. Left: Indicators values for a range of values of φ_1 . All others interaction parameters set to 1. Center: Indicators values for a range of values of ξ_1 . All others interaction parameters set to 1. Indicators values for a range of values of χ_1 . All others interaction parameters set to 1. Values for effect of pathogen 1 on pathogen 2 (resp. 2 on 1) are blue (resp. red). Other parameters are shown in table 2.1, Default Set.

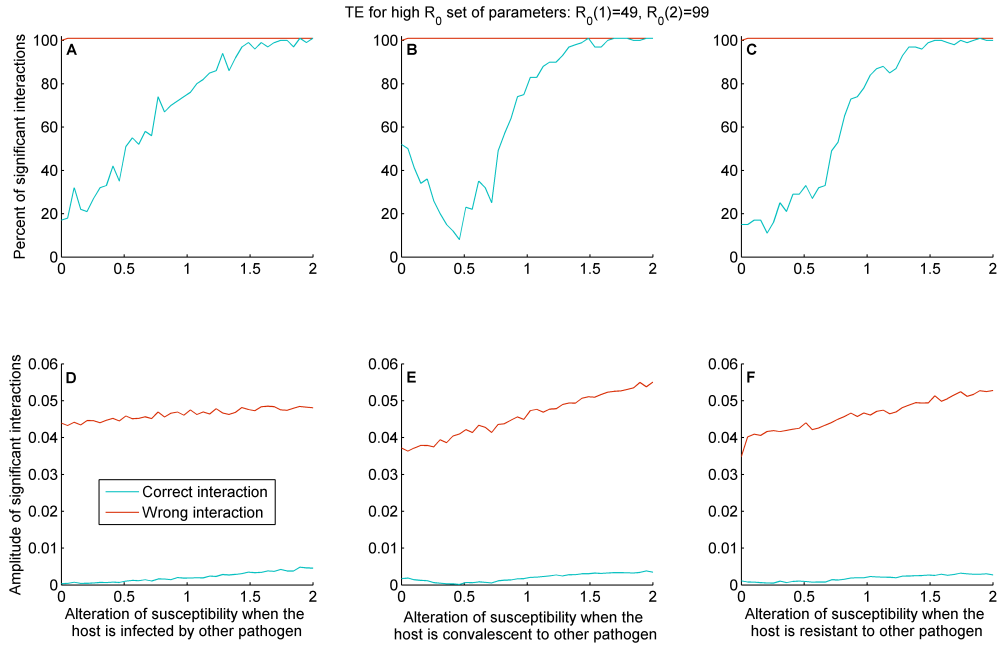


Figure 2.12. Values of LIN NUE Transfer Entropy output according to each type of interaction with the ‘High R_0 ’ set of parameters. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for effect of pathogen 1 (resp. 2) on pathogen 2 (resp. 1) are blue (resp. red).. $\beta_1 = 600$, $\beta_2 = 1200$, $\frac{1}{\gamma} = 1$ month, $\frac{1}{\delta} = 6$ months. Other parameters are shown in Table 2.1, High R_0 Set.

causalities for pathogen 1 to pathogen 2 (Fig. 2.12, C) is now increasing with the value of the interaction parameter instead of decreasing. Amplitude of all significant causalities (Fig. 2.12, D-F) are slightly increasing with the value of the interaction parameters, and causalities from pathogen 2 to pathogen 1 always are stronger. We still never observe the centred around 1, V-shaped curve that would characterise a good detection of the interaction. With the binning estimator (BIN, Fig.A.4), there is nearly no detection of any causality from pathogen 1 to pathogen 2 (false negative) and a high detection of a causality from pathogen 2 to pathogen 1 (false positive). Thus, even if detection of a causality may happens with BIN NUE, this method appears strongly unable to correctly identify the direction of the interaction.

Parsimonious set: Results of the Transfer Entropy (TE) using linear estimator (LIN) still are quite similar to those of GCA for the last set of parameters (Table 2.1). There is still a 100% detection of the false causality (from path.2 to path.1) but the detection of the real causality (from path.1 to path.2) is slightly inferior (Fig. 2.13, A-C). Especially, the number of detected causalities decrease for facilitating interactions on convalescent and resistant hosts. Amplitudes of the detected causalities are very similar (Fig. 2.13, D-F) except for convalescent individuals. In this case, the amplitude no longer stabilizes around 1 (no interaction) nor increases between 1.25 and 2 (Fig. 2.13, E).

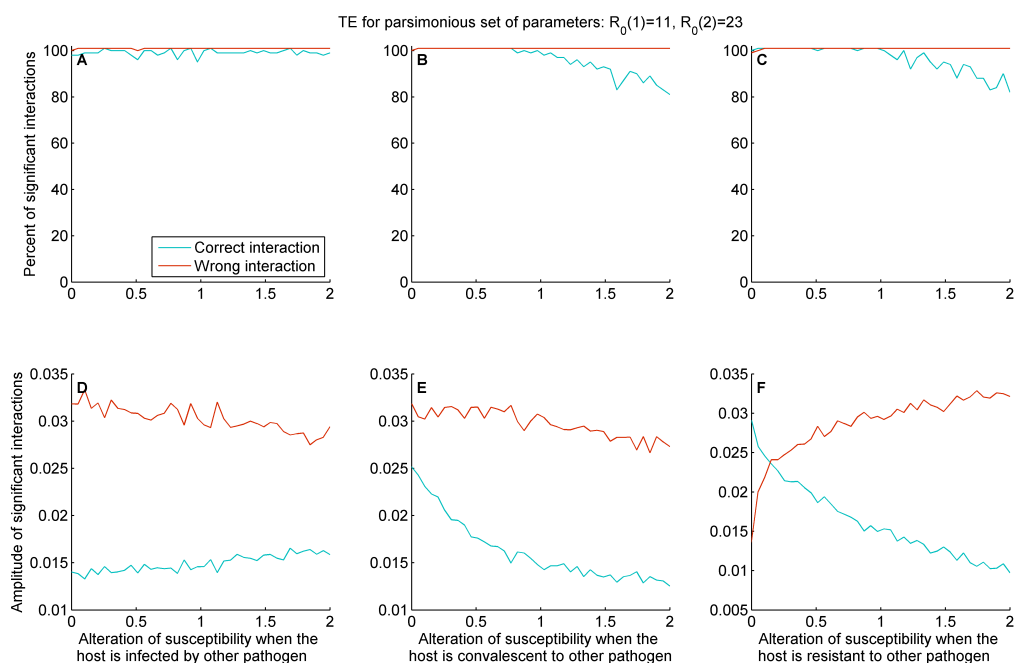


Figure 2.13. Values of LIN NUE Transfer Entropy output according to each type of interaction with the ‘parsimonious’ set of parameters. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for effect of pathogen 1 (resp. 2) on pathogen 2 (resp. 1) are blue (resp. red). $\beta_1 = 100$, $\beta_2 = 200$, $\frac{1}{\gamma} = 6$ months, $\frac{1}{\delta} = 1$ year. Other parameters are shown in Table 2.1, Parsimonious Set.

In all cases, intensities of the causalities identified by Transfer Entropy using a linear estimator are very similar to those identified by GCA. However, the detection of those causalities, in term of significance of the detected links, might be different from GCA according to the parameters of the model. These differences are not improvement though: the repartition of false positives or false negatives changes but is not better. However, with the toolbox used for this chapter, TE is slightly faster than GCA. Using the binning estimator or the nearest neighbours estimator gives worst results than GCA or TE with linear estimator.

		φ : Interaction on infectious			ξ : Interaction on convalescents			χ : Interaction on resistant			
		-	\emptyset	+	-	\emptyset	+	-	\emptyset	+	
Default	GCA	Correct int.	FN	TN	FN	FN	TN	FN	FN	TN	TP-SA
		Wrong int.	TN	TN	TN	TN	TN	TN	TN	TN	TN
	TE	Correct int.	FN	TN	FN	FN	TN	FN	FN	TN	TP-SA
		Wrong int.	TN	TN	TN	TN	TN	TN	TN	TN	TN
High R_0	GCA	Correct int.	FN	nd	TP-WA	TP-WA	nd	TP-WA	TP-SA	nd	nd
		Wrong int.	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA
	TE	Correct int.	FN	nd	TP-WA	TP-WA	FP-WA	TP-WA	FN	FP-WA	TP-WA
		Wrong int.	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA
Parsimonious	GCA	Correct int.	TP-WA	FP-WA	TP-WA	TP-SA	FP-WA	TP-SA	TP-SA	FP-WA	TP-WA
		Wrong int.	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-WA	FP-SA	FP-SA
	TE	Correct int.	TP-WA	FP-WA	TP-WA	TP-SA	FP-WA	TP-WA	TP-SA	FP-WA	TP-WA
		Wrong int.	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-SA	FP-WA	FP-SA	FP-SA

Table 2.2. Summary of the performances of Granger Causality Analysis and Transfer Entropy. **FN**: False Negative, less than 40% detection of a real causality. **TN**: True Negative, less than 40% detection of a non-existing causality. **FP**: False Positive, more than 60% detection of a non-existing causality. **TP**: True Positive, more than 60% detection of a real causality. **WA**: Weak Amplitude of the detected causalities. **SA**: Strong Amplitude of the detected causalities. **nd**: Not Determined, between 40% and 60% detection of a causality. Grey background: visible effect of the interaction at the population scale (Figs 2.3, 2.5, 2.6 Parameters for each set can be found in Table 2.1)

2.4 Discussion

Being able to identify immunological consequences of previous or simultaneous infection with one pathogen on other pathogen circulating in the same population is becoming a major issue for immunological and epidemiological research [118, 291]. Evidences of non-negligible effects on such exposition to several pathogens, either related or not, are growing [35–38, 46, 292–298]. This theoretical study tends to show that such interactions may not always have much impact on epidemics at the population level. For our two-pathogens system, short-term cross-immunity does not have any visible impact on periodicity or number of cases. In this system, only strongly improved susceptibility or longer-term interactions have a notable influence on the dynamics of the epidemics. Short-term partial or perfect cross-immunity does not enough reduce the pool of available susceptible individuals to significantly reduce the transmission of the pathogen. The longer the interaction, the stronger its effect on dynamics at population level. This is consistent with other models [41, 42] that points out the importance of the length of infectious and convalescence period.

Granger Causality analysis is efficient to detect strong positive interactions, that is, interactions that significantly facilitate the infection by a pathogen when the host is or has been infected by another pathogen. For this kind of interactions, GCA is able to properly detect the existence of an interaction, but often fails in determining its direction. Many additional data manipulations have been tested to increase the quality of the detection such as phase filtering, use of sliding windows (overlapping or not), combination of both, without being more successful. These alternative methods give the same or worst results as the one presented in this work.

We also show that using transfer entropy tools with a linear estimator to measure mutual informations between time series for our system is mostly similar to “traditional” GCA. It has been previously shown that for many systems, mainly systems where variables are gaussian, Granger Causality analysis and transfer entropy are strictly equivalent [128, 129]. Thus, it is not surprising that Granger Causality analysis (which uses linear autoregressive models) and transfer entropy using a linear estimator give similar results. However, the proximity of the results of GCA and TE LIN is dependant of the specificities of the pathogens (e.g. contact rate, duration of infectious period). Given that the 2-pathogens SICR model is not linear, it is notable that non-linear estimators (i.e. binning estimator and nearest neighbours estimator) do not achieve a better detection than the linear methods. However, inadequate non-linear methods often performs worst than linear methods when it comes to approximate non-linear dynamics [130].

Detection of causalities is dependant of epidemiological parameters. For the same theoretical interaction, the amplitude of the causalities detected by the Granger Causality Analysis or the Transfer Entropy will be higher if the pathogen which is subject to the interaction has a weaker basic reproductive rate (R_0) than the pathogen inflicting the interaction. Moreover, only the causalities that reflects the actual direction of the interactions are affected. That is, the ‘weaker’ the pathogen subject to the interaction, the better the detection of the direction of the interaction is. Furthermore, key epidemiological characteristics of the disease, as the infectious period or the contact rate, strongly impact the efficacy of the detection.

Here, we showed that GCA method only requires ca. ten years of monthly data (~ 120 data points) to reach its full “effectiveness”. Moreover, Granger Causality Analysis does not benefit from longer time series: results are the same with 15-year long series than with 40-years long ones, but it benefits from more frequent sampling: results are slightly better with weekly data than with monthly data over the same period of time. Long epidemiological time series are uncommon, so robustness of statistical tools to the length of the series is a key issue. Inference method, for example, requires 40-years of monthly data, at the risk of greatly weakening the analysis with

shorter time series [63].

One major issue of using this Granger Causality Analysis for epidemiological time series, and more widely ecological time series, is the non-linearity of the underlying mechanisms. MVAR models inherently are linear models [126, 299], thus lacking performance in predicting time-series resulting from non-linear mechanisms. Several manipulations of the time-series might be done to try to bypass this difficulties. One of them is to use wavelet analysis to extract the phase of the time-series, thus separating the periodical informations and the noise from stochasticity. However this manipulation did not lead to any improvement of our results.

The main purpose of this study was to assess the applicability of exploratory approaches to detect interactions between pathogens in systems where many pathogens co-circulate. It has been previously shown that confirmatory approaches, i.e. approaches that infer that the data can be fitted by a field-specific model [131], are effective in the context of a two-pathogens system, were the exact same model is used to creates the theoretical time series and to fit those series to estimates its parameters [63]. However, confirmatory approaches become more tricky to use as the complexity of the system grows, because of computability limitations: the more complex the model used for fitting is, with many parameters to estimate, the more time the fitting procedure will need. A two-pathogen system with previous knowledge on its dynamic and transmission mechanisms is parsimonious enough to use a confirmatory approach, but with more pathogens and/or unknown mechanisms involved, it becomes less reliable.

Exploratory approaches, on the other hand, does not rely on any preconceived idea about underlying mechanisms, thus being intrinsically more appropriate for complex systems. Unfortunately, this study shows that some of the most-used exploratory approaches, i.e. Granger Causality Analysis and Transfer Entropy, fail to achieve a satisfactory level of interactions' detection using population dynamics and one external measurement (seasonal forcing) alone . Their performances are strongly dependant of the specificities of the system, making them potentially effective for a given set of diseases and totally irrelevant for others. GCA and TE perform better with very specific interactions: long-term facilitation and short-term extremely strong facilitation. Those interactions are not the most biologically plausible, even if they are know to exist, e.g. with AIDS.

Granger Causality, as well as Transfer Entropy and Causation analysis in a broader way, rely on the comprehensiveness of the data used. The original, theoretical formulation of Granger Causality compares the models with 'all the data in the universe' vs. 'all the data except one variable Y' to test the causation of Y on the studied variable. In this work, all available data is limited to the dynamics of both pathogens and one external forcing variable. It is possible that GCA and TE benefit from more complex models, with more measurable variables that could help build better statistical models, such as several external forcing and spatially-explicit data.

Chapter 3

Vaccine Heterogeneity and Serotype Interactions

How should we use candidate Dengue vaccines in endemic areas?

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3.1 Introduction

Dengue is a vector-borne virus transmitted by *Aedes* mosquitoes, *Aedes aegypti* being the primary vector. This infectious disease is widespread throughout the world with about four billions people exposed to this disease in 128 countries [132]. The number of reported cases has tripled in several decades [134] with an average of 390 millions new cases yearly today [133]. Among them, 294 millions cases are mild or asymptomatic infections and about 96 millions apparent cases with around 500,000 severe cases (Dengue Haemorrhagic Fever or Dengue Shock Syndrome) who require hospitalization, resulting in more than 20,000 deaths [134]. It has been suggested that such increase in Dengue incidence could be due to the growing distribution area of mosquito vectors, especially *Aedes aegypti* and *Aedes albopictus* [300–303]. Therefore, Dengue virus is a current Public Health threat in many parts of the World and concerns about this disease will increase significantly during the next years.

Dengue virus exists as four different but closely related serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), genetically homologous up to 70% [135] with some serotypes seeming to be more transmissible than others [61]. Infection by one of these serotypes leads to a life-long immunity against this serotype and a transient protection against the others [136], that can last from two months [136] up to three years [60, 61, 137, 138] according to the different estimations. While the first dengue infection is often asymptomatic, subsequent infections by other serotypes might result in a increased risk of severe form (Dengue Haemorrhagic Fever, DHF, or Dengue Shock Syndrome, DSS). Even though the details of the underlying mechanisms are not well-known and still debated, this might be explained by the presence of antibodies from the first infection. These antibodies form a complex with the virus without disrupting it, thus facilitating the infection of phagocytes [140], yielding an *Antibody Dependant Enhancement* (ADE) [141]. Conversely, recent works tends to show that high concentrations of antibodies are protective while medium concentrations increase the risk of suffering a severe form of the disease [62]. Vertical transmission of antibodies from mother to child might also be responsible for severe form in child [139].

Considerable developments have been made in the last decades in order to design a vaccine against Dengue. Clinical tests have started for several vaccine candidates [142]. One of the most advanced candidate is the *Chimerivax*, or CYD-TDV [143], developed by Sanofi-Pasteur. It is a live-attenuated tetravalent vaccine, recombined from the live-attenuated 17D yellow fever vaccine and genome from pre-membran proteins of every 4 serotypes of dengue [144–146], based on live-attenuated Dengue viruses provided by the Mahidole University group [304, 305]. Phase I trials did not show any side effects or weak immunisation [146], but phase II trial carried out on 4,000 childs in Thailand showed that the vaccine did not provide a significant immunity against DENV-2 [147]. The recent phase III trial is more optimistic, showing a 35% efficacy against DENV-2 over 6,851 children, but still with a high heterogeneity in the protection conferred [148].

Therefore, implementing mass vaccination with such heterogeneous vaccine can interfere strongly with serotype interactions, making extremely challenging to forecast the epidemiological outcomes of such Public Health strategy, especially the possibility of deleterious effects. In this study, we develop a four-serotypes mathematical model to assess epidemiological consequences of the *Chimerivax* vaccine within an endemic area. We especially quantify the influence of vaccine heterogeneity by comparing the expected epidemiological outcomes on a short-term and on a long-term. In the light of these results, we discuss what should be the most appropriate Dengue vaccination policy.

Vaccine	Efficacy				
	DENV-1	DENV-2	DENV-3	DENV-4	Mean
CYD-TDV phase II trial [147]	55.6%	9.2%	75.3%	100%	60.0%
CYD-TDV phase III trial [148]	50.0%	35.0%	78.4%	75.3%	59.7%

Table 3.1. Serotype-specific efficacy of Chimerivax vaccine. This table shows the percentage of vaccinated individuals who will acquire an immunity against each serotype. Based on Sabchaeron *et al.* [147] and Capeding *et al.* [148].

3.2 Methods

Adopting the classic SIR framework [184, 306], the host population is arranged according to their infectious status. For each serotype, Susceptible individuals (S) are immunologically naïve to all serotypes and can become Infectious (I) according serotype-specific transmission rate (λ_i , see Supporting Information S1 Equations). After an infectious period ($\frac{1}{\gamma}$), they become cross-protected against all serotypes (C) during a given period representing the transcending immunity ($\frac{1}{\delta}$). Then, individuals recover from the disease (R) and become susceptible to serotypes that have not infected them yet. Finally, people can be immune against a given serotype by vaccination (V) at birth. Vaccination coverage is 95%, meaning that 95% of the newborns receive the vaccine.

These infectious status are then considered explicitly for all 4 serotypes, leading to a total of 625 (5^4) compartments, represented by a 4-dimensional hyper-matrix of size 5. Each compartment is originally defined by an ordinary differential equation (ODE) describing individual fluxes into and out of those compartments (birth, death, infection, healing and loss of cross-immunity). Fig. 3.1 depicts a simplified version of our model with only two serotypes in order to illustrate how serotype interactions occur as well as how severe forms emerge.

During simulation, we record individuals experiencing severe form of the disease (DHF or DSS). Upon each primary infection, 14% [134, 149] of each individuals will develop such complications, yielding a higher mortality rate (η , see Table B.1 and [134]). Due to Antibody Dependant Enhancement (ADE), this proportion of severe cases is increased to 44% [134, 149] for individuals experiencing a secondary infection. Births exactly compensate deaths to maintain a constant population size. At each time-step, the number of disease-related deaths is counted, and an equal number of supplementary births occurs.

Finally, we introduce vaccination on newborns. A fixed proportion of newborns are immunized against each serotype according to the combination of the vaccine coverage ($n = 95\%$) and the vaccine efficacy against this serotype (n_i). Thus, the proportion of births that are really immune is $n.n_i$ for serotype i . We use a worst-case scenario of the immunological consequences of the vaccine [307] by assuming that vaccine-derived immunity can yield ADE in the same proportions than natural infection.

We therefore simulate the outcomes of the *Chimerivax* vaccine efficiency. We assume serotype-specific efficiencies estimated from the results of the phase II trial of the CYD-TDV vaccine, which shows a very heterogeneous efficacy of the vaccine 28 days after the injection (Table 3.1), for an overall protection against symptomatic dengue of 30.2% [147]. Complementary simulations and sensitivity analysis show that conclusions should remain similar for the results obtained during phase III trials (see Supplementary Material Figs B.4, B.7, B.7 & B.10). We analyze the expected outcomes on a short-term (after 10 years) as well as on a long-term (after 50 years) and quantify the contribution of vaccine heterogeneity in our results.

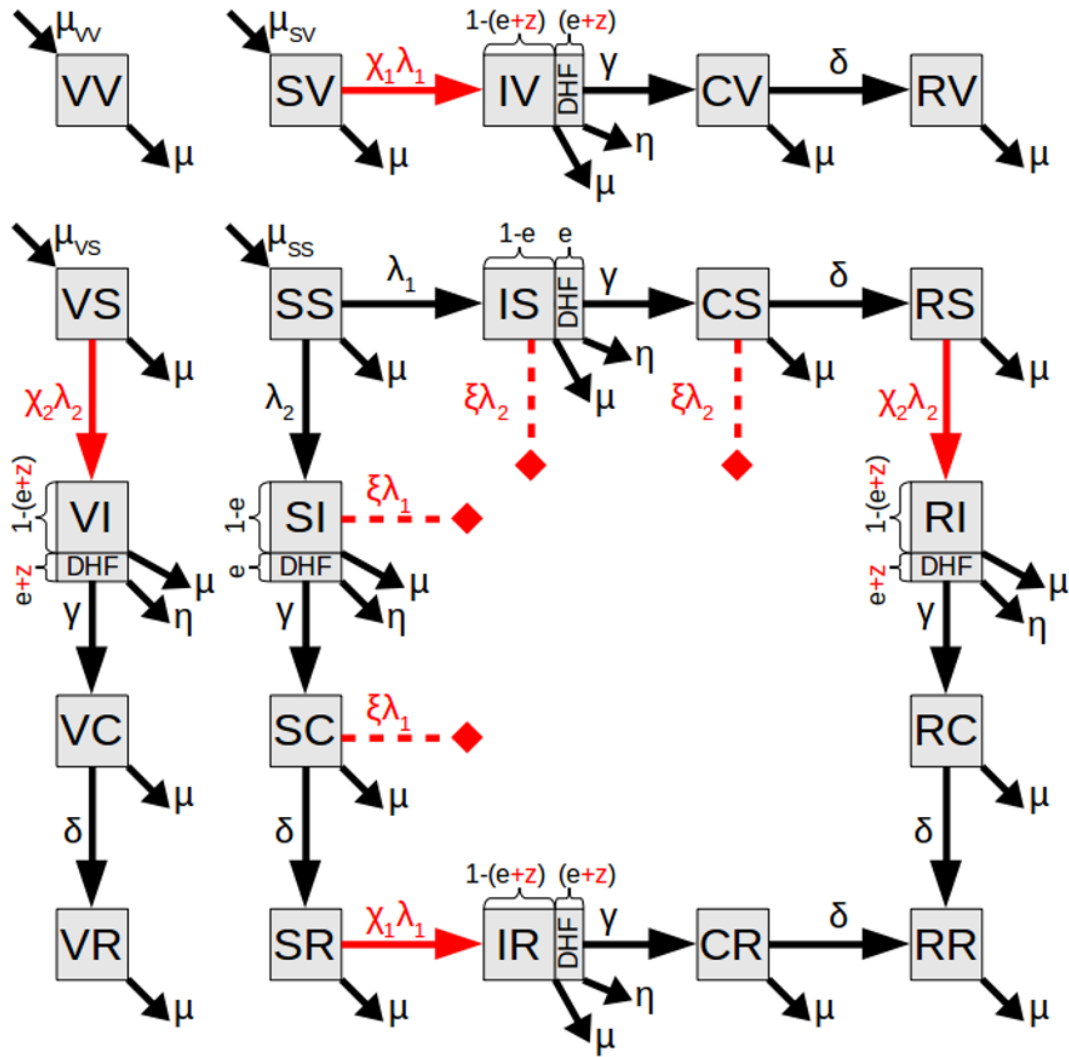


Figure 3.1. Simplified version of our four-serotypes model by illustrating only two serotypes model. Each box is a compartment, each arrow is a flux. Red color highlights interactions between serotype, either by alteration of susceptibility to infection or by an increased risk of DHF/DSS. $\lambda_1 = \beta_1(IV + IS + II + IC + IR + \omega)$, $\lambda_2 = \beta_2(VI + SI + II + CI + RI + \omega)$. $\mu_{VV} = \mu n n_1 n_2$, $\mu_{VS} = \mu n n_1 (1 - n_2)$, $\mu_{SV} = \mu n (1 - n_1) n_2$, $\mu_{SS} = \mu (1 - n) + n (1 - n_1) (1 - n_2)$.

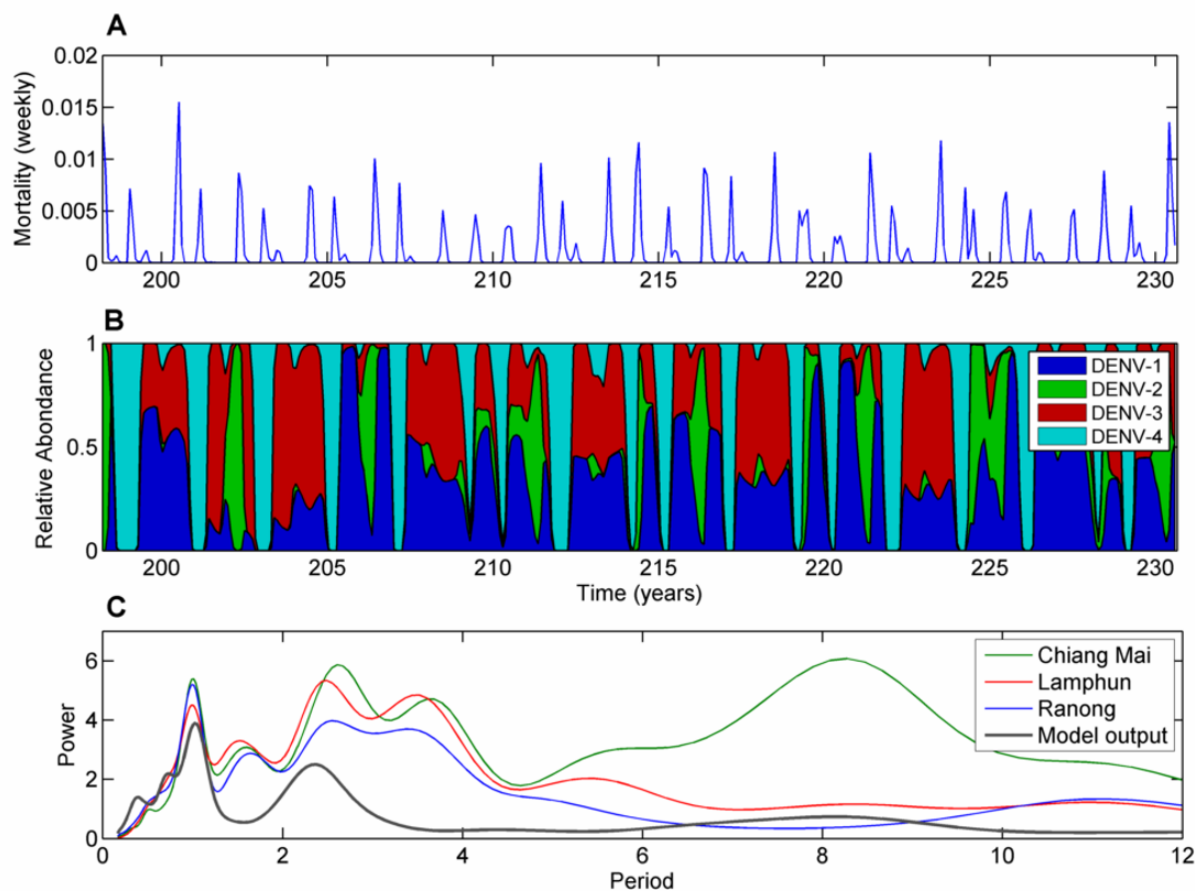


Figure 3.2. Results of a single simulation without vaccination. A: Number of severe cases (DHF or DSS) every week, all serotypes taken together. B: Relative abundance of each serotype. C: Fourier spectrum for 33-years long data. Green, red and blue are (resp.) Chiang Mai, Lamphun and Ranong provinces (Thailand). Black bold is model output. Parameters can be found in Table B.1.

3.3 Results

We first show that our model, without vaccination, is consistent with known epidemiological patterns. In this context, the cumulated number of severe cases predicted by our mathematical framework show annual and 2-3 years periodic behaviour (Fig. 3.2, C), which is coherent with the known dynamics of dengue in Southern Asia where dengue transmission is characterized by marked cyclical pattern associated with both the seasonal change in local climate and modulations by global climate [308, 309]. To illustrate this point we have employed a 33 years long dataset from Thailand with monthly records from each provinces [150]. Most of the provinces have dynamics with a seasonal mode and a 2-3 year component (Fig. 3.2, C and Fig. B.11). Other 4-serotypes models [65] show periodicities of 3.4, 1, 2.1 or 5.2 according to the mechanisms included in the model.

When introducing a vaccine with identical heterogeneity in protection than *Chimerivax* (assuming the results of phase II trial, Table 3.1) with a vaccination coverage of 95%, we do not record a dramatic decrease of the total number of cases during the first ten years (Fig. 3.3, decrease in the mean of total number of cases : 17.83%, $t=-3.5460$, $n=118$, $p\text{-value}<0.1\%$), nei-

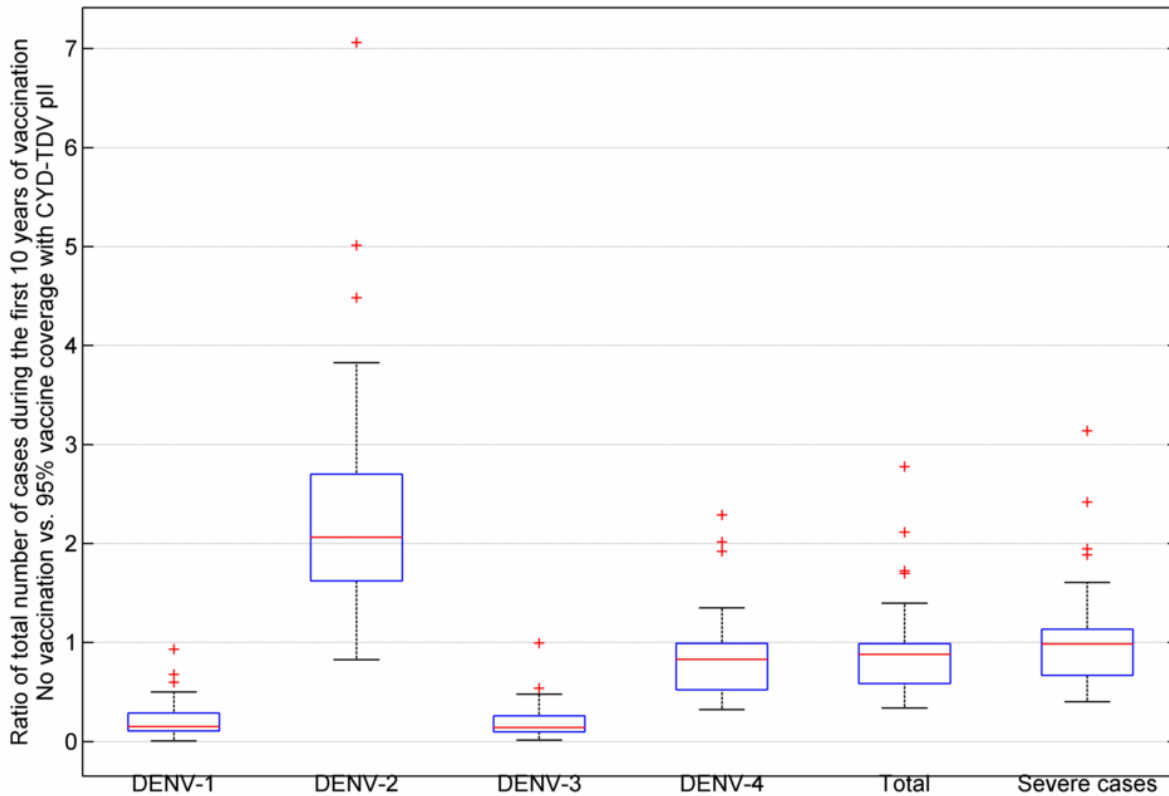


Figure 3.3. Ratio between the total number of cases during the first 10 years of vaccination and during 10 years without vaccination. Vaccination coverage is 95% with a CYD-TDV pII-type vaccine (see Table 3.1 for efficacies). Parameters apart from vaccine efficacy can be found in Table B.1.

ther a reduction of dengue-related deaths (decrease in the mean of mortality : 6.11%, $t=-1.1486$, $n=118$, $p\text{-value}>25\%$, not significant). Instead, DENV-2, the serotype for which the vaccine is the less effective, experiences an increased number of cases compared to the situation without vaccination. This is the result of the alteration in serotypes dynamics that decreases the competitive pressure against DENV-2 and therefore makes more susceptible individuals available for this serotype (Supporting Informations, section S2).

On a long-term (after 40 years of vaccination), the same vaccine only achieves elimination of two serotypes for very high vaccination coverages (90% and 100% for DENV-3 and DENV-4 respectively, Figure B.9). DENV-1 case-count decreases but never reaches negligible level. Furthermore, DENV-2 case-count is increasing (44.1% more infections, 95% CI 25.7-62.4, with 95% vaccination coverage than without vaccination). However, number of severe cases is significantly lower than without vaccination, reaching a reduction of 52.1% (95% CI 43.3-58.0), for a 95% vaccination coverage (Fig. 3.4).

Therefore, on a long-term, such heterogeneous vaccine cannot reach elimination of Dengue. Interestingly, this lack of capacity to trigger high level of herd immunity is due to the heterogeneity of vaccine protection rather than to its overall efficiency. Indeed, an homogeneous one with a 60% efficacy against four serotypes (the average efficiency of the *Chimerivax* vaccine), will decrease the number of severe cases by 97.63% (95% CI 97.28-97.98) with 95% vaccine coverage (Fig. 3.5, A), which is almost twice better than its heterogeneous counterpart. Number of

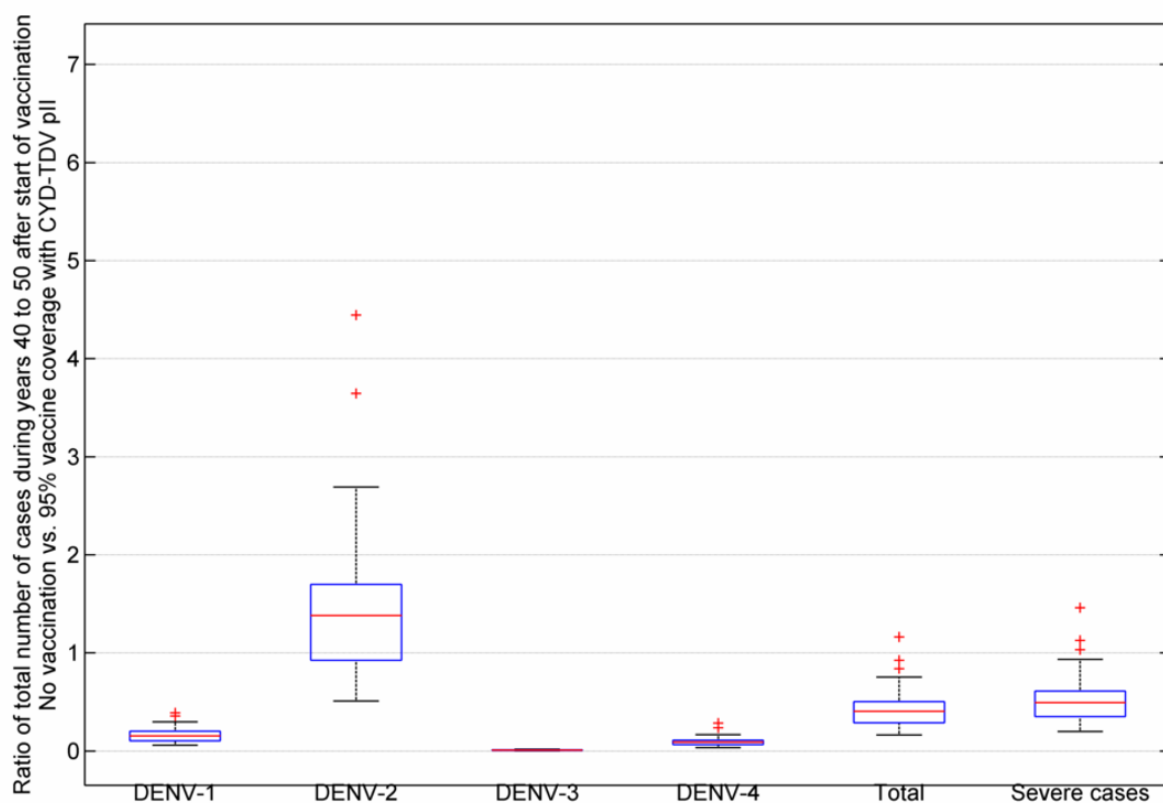


Figure 3.4. Ratio between the total number of cases during the years 40 to 50 after the beginning of the vaccination campaign and during 10 years without vaccination. Vaccination coverage is 95% with a CYD-TDV pII-type vaccine (see Table 3.1 for efficacies). Parameters apart from vaccine efficacy can be found in Table B.1.

DENV-2 infections is also significantly lower in the case of homogeneous vaccine (Fig. 3.5, B), decreasing then the probability of secondary infection and therefore of severe cases from ADE.

3.4 Discussion

Because of more than 500,000 annual hospitalizations and 20,000 deaths every year [134, 310, 311], numerous vaccine candidates have been developed to reduce both mortality and morbidity of Dengue virus [142, 152]. In this study, focusing on a well advanced vaccine candidate (*Chimerivax*, or CYD-TDV [144, 146–148, 151]), we show that vaccine heterogeneity, rather than vaccine overall efficiency, can have contrasted outcomes on a short-term and on a long-term. On a short-term (after 10 years of vaccination), vaccine introduction may appear to have harmful effects because epidemics after the beginning of the vaccination campaign could be stronger than epidemics before the introduction of the vaccine, especially because an increased transmission of DENV-2. In addition, there is no significant decrease in the number of severe cases on this time scale because the heterogeneity of the protection granted by the vaccine scrambles the competition for susceptible between serotypes, leading to a similar number of secondary infections. Nevertheless, these effects disappear on a long-term since the number of immune people for each serotype will have increased enough to trigger a weak herd immunity that reduces this number secondary infections. However, the vaccine heterogeneity avoid the possibility to eliminate the disease by using only vaccination, even on a long-term.

Other vaccine candidates would have been possible to test [152]. One of the most advanced vaccine, based on classically live-attenuated viruses and developed by the Walter Reed Army Institute of Research, has reached phase II trials [153], but phase II trials only provided data about presence of neutralizing antibody in subjects and not about effective protection against the viruses. Moreover, its development is currently on hold [142], making speculative a possible introduction into the population on a short-term. We have also tested the introduction of *Chimerivax* with phase III data. In this case, we show that the increased number of DENV-2 infections is significantly weaker, but DENV-2 stills become the dominant serotype and number of severe cases is still high (reduction in mean number of severe cases: 14.6%, 95% CI 3.90-25.4, see Supporting Informations, Fig. B.4, B.6 & B.8).

While our mathematical framework allows us to consider complex interactions between serotypes, our goal is not to make precise forecasting as individual-based models including all the complexities of host and vector populations. Therefore, it remains a theoretical model and could benefit further improvements to precisely fit local data. Nevertheless, our results are extremely robust to changes in parameters (Supporting Information, Fig. B.10), highlighting that our conclusions about the influence of vaccine heterogeneity should remain valid across a broad range of epidemiological situations.

The short-term effects of vaccination is definitely a serious obstacle to the introduction of current vaccine candidates in populations. Even if long-term consequences of a reasonable vaccination campaign are undeniably positive, such vaccine policy having visible effects only after two human generations could be hard to introduce in the current context of vaccine acceptability issues [154, 155]. It is nevertheless important to say that the discrepancy between short and long-term outcomes could be due to the fact that we have introduced vaccination at birth. Therefore, vaccinating kids, teenagers and adults could reduce this gap despite probably not removing it completely since we have considered a vaccine introduction in a population where Dengue virus is endemic and where a large proportion of individuals would have already experience multiple serotypes infection by the time of vaccine introduction.

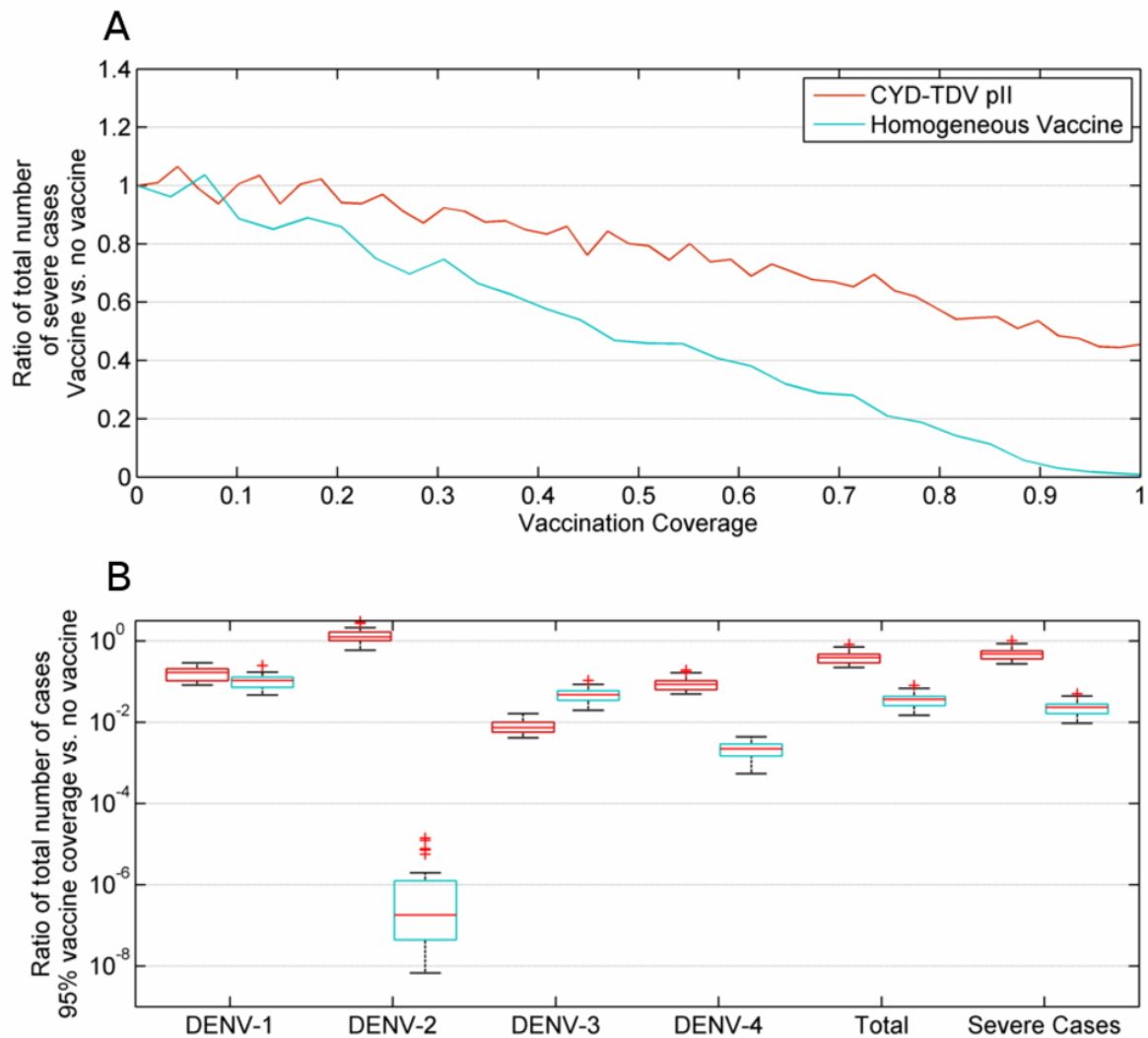


Figure 3.5. Long-term effects of several vaccine. A: total number of severe cases between years 40 and 50 after the beginning of the vaccination campaign, for each vaccine, according to the vaccination coverage. Blue: homogeneous vaccine. Red: CYD-TDV phase II trial. B: ratio of total number of cases recorded between years 40 and 50 after the beginning of the vaccination campaign. Red is ratio between CYD-TDV-like vaccine and no vaccine. Blue is ratio between homogeneous vaccine and no vaccine. Vaccination coverage is 95% in both cases. See Table 3.1 for detailed vaccine efficacies. Parameters apart from vaccine efficacy can be found in Table B.1.

Vaccination could strongly reduce the burden of Dengue in endemic situations. However, the combination of complex interactions between the four serotypes of the virus and the heterogeneity in vaccine efficacy could lead to unexpected, potentially deleterious consequences on short-term. Moreover, the burden decrease on a long-term, i.e., about 50% reduction of severe cases for a vaccine coverage of 95%, is definitely lower than expected and could be potentially not-convincing enough for Public Health authorities. Therefore, one might ask what could be the best strategy with such vaccine. While its potential synergy with vector control remains to be addressed, it would be possible that such vaccine would be used to target in priority individuals under high risk of complications rather than adopting a massive immunization approach. Such approach, already implemented in many countries throughout the World for influenza viruses, have proved its efficiency and can be still improved by identifying key populations to target [156]. Until we will not be able to develop a more homogeneous vaccine, such strategy could represent a relevant backup plan.

Conclusion

Infectious diseases research has long been a matter of studying the system formed by the pathogen, the host we're interested in (often the human), and sometimes its vector, if relevant [312, 313]. Such models may even include, non-exhaustively, climatic factors [314], mobility of hosts and vectors [315], evolution of the pathogen [316].

Nowadays the scope of this research is growing toward more comprehensiveness of the whole community surrounding the pathogen. Multi-host system [221, 317–319] have been studied to explore the effect of host diversity on the spread of a pathogen. Such studies notably showed that the number of intra-specific contacts were lower in more diverse communities, thus slowing the spread of specialist pathogens [319], even if high biodiversity areas could be a source pool for emerging pathogens [221].

Evidences are growing that pathogens interact with each other too [118, 157, 158] and that these interactions could drive the structure of the pathogen community [159, 160] in a so-called 'pathocenosis'. According to the pathocenosis concept, the presence and the incidence of a disease are dependant of those of the others diseases. This could, e.g., link the decrease of bacterial diseases thanks to the progress of hygiene and medicine with the emergence of new viral infections [117, 161].

In this thesis we investigated these pathogen-pathogen interactions. The objectives of this PhD were to review evidences of many different kinds of interactions in order to identify mechanisms behind these interactions and broach the problematic of multiple simultaneous interactions. In a second time, we investigated the potential impact of single pathogen-pathogen interactions at the population scale, and looked for statistical tools able to identify these interactions from population-level data. Finally, we assessed the potential interference between serotypic interactions and Public Health policies in the specific context of dengue and its vaccination.

1 Results of the PhD

1.1 Review of the Literature

The literature review of interactions between pathogens extended our point of view of pathogen-pathogen interactions. Beyond a broad diversity of appearances of such interactions, we realized that they could be sorted by five main categories. We can dissociate intra-host interactions and between-host interactions. Most of those interactions affect the "susceptibility" of the population, either by changing the susceptibility of individuals or the number and availability of susceptible individuals, the effective susceptible pool, but the infectiousness of the pathogen may also be altered. Fundamental mechanisms for pathogen-pathogen interactions are:

- **Cross-immunity.** Cross-immunity is the total or partial protection of the infected host from pathogens genetically closely related to the one(s) that infected him previously.

- **Immune cross-regulation.** Cross-regulation is the result of the trade-off between the two immune pathways, TH₁ and TH₂. The first is related to “cellular immunity” while the second engages “humoral immunity”. Activation of one of these pathways down-regulates the other, weakening the immune reaction to a pathogen who would trigger the regulated pathway.
- **Immunosuppression.** While cross-regulation only weakens a part of the immune system, immunosuppression is the significant decrease of its overall efficiency. Immuno-suppressed hosts are more susceptible to all other pathogens. Both immunosuppression and immune cross-regulation may increase the pathogenic load of the host, leading to more severe infections and possibly higher infectiousness.
- **Decreasing availability of susceptible individuals.** Stepping up from individual level to population level, a decrease of the number of susceptible individuals available for a pathogen can be due to another pathogen. This can be a temporary removal caused by a convalescence period or a quarantine, or a permanent removal caused by pathogen-induced mortality.
- **Increased availability of susceptible individuals or perturbation of behavioural resistance.** Less documented than any other interaction, increased availability of susceptible has nevertheless been proposed to possibly be a consequence of pathogen-pathogen interactions. This can be due to a lack of Public Health involvement, or by the gathering of susceptible and infectious individuals into the same closely related network, thus increasing the number of contact between susceptible and infectious individuals.

Moreover, the perspective of this review highlighted that those interactions rarely occurs alone. Almost every possible combination of two (or possibly more) of them have been described in the literature. These simultaneous interactions might have significant impact on Public Health policies. Non-consideration of them in the design of Public Health strategies may lead to under-optimal or detrimental interventions. Lessons from community ecology avert us of the challenges of predicting community dynamics [320, 321], and make us wanting to design safer and more optimal Public Health policies.

This review gave birth to the concept of “realized susceptibility”. Because of cross-immunity, cross-regulation, immunosuppression and modified availability of susceptible individuals, a population can be more or less vulnerable to a pathogen than it seems from its fundamental susceptibility, i.e. the sole number of susceptible in the population. Realized susceptibility is a population-scale definition of susceptibility that take into account the personal infection history of the individuals and the interaction mechanisms described above in order to better fit the reality of the vulnerability of the population to pathogens.

1.2 Identifying Interactions

To tackle this new problematic raised by the review of the literature, it is necessary to better understand the dynamical impact of pathogen-pathogen interactions. This is where mathematical and computational modelling come in an handy. To estimate the population-scale impact of interactions between pathogens, we went back over a two-pathogen model with multiple kinds of interactions [63]: cross-immunity, immunosuppression and modified availability of susceptible individuals. All these interactions are modulable in intensity and can be temporary or permanent, and occurs at all stages of the infection.

With this model, we saw that many interactions may not have visible consequences on the total number of cases or the periodicity of the diseases. Most short-term interactions, i.e. interac-

tions shorter than one month, will have little or no visible effect at the population scale, whereas life-long interactions, like permanent cross-immunity or immunodepression, will affect the course of the epidemics and their intensity. This is mostly due to the proportion of the population affected by the interactions.

Thus, there are several factors that strongly affect the outcome of an interaction. First, the strength of the interaction is important. A perfect cross-immunity will have more impact than a partial cross-immunity, and a two-fold increase of susceptibility will have less impact than an 100-fold one. The second parameter is the exposure of individuals to the interaction. Two main ways to influence this quantity exist. First is the infectiousness of the pathogen, and ultimately its R_0 . The higher it is, the more people will be infected, and thus, become convalescent and finally resistant. Second is the duration of the interaction. If an individual is, e.g., protected from any other infection while convalescent, this protection will be more significant in the life history of this individual as the convalescent period is longer. Moreover, because of buffer effect, the longer the interaction is, the more individuals at the same time will be subject to it.

Because of this possible lack of visible dynamical effect of interactions, it is particularly tricky to identify interactions from population-scale data using statistical tools. In this PhD, we failed in using exploratory approaches, which do not require any prior knowledge or assumption about the pathogens' dynamics, to achieve such identification. Our approaches of Granger Causality Analysis (GCA) and Transfer Entropy (TE), two of the most promising exploratory tools, are not able to properly identify interactions in data created by our two-pathogens model.

Their performances turn out to be strongly dependant of the parameters of the system. Not surprisingly, GCA and TE perform better with interactions that have more visible effect on the population, such as long-term immunodepression or cross-immunity. GCA and TE rely on the comprehensiveness of data. Here, we used all possibly pertinent data for the analysis, i.e. case-counts of both diseases and seasonality. One can wonder if more complex models, with more explicative variables, would lead to better analysis. This question might be partially answered by considering the result of an analysis using the number of individuals in each sub-compartment of the model instead of only considering the total number of infectious for each pathogen. Such analysis did not improve the identification of interactions. From this we can only conclude that our approach of GCA and TE is not appropriate to identify interactions between pathogens.

1.3 Interactions and Public Health Policies

Despite the previous results, interactions may still have significant impact at the population scale, because they can interfere with Public Health policies. To illustrate this, we took the example of dengue. Dengue is a vector-borne virus that exists as four, strongly interacting serotype. Additionally, vaccines against this disease are currently in development. We used a four-serotype derivative of our model to show that interactions between the four serotypes of dengue could jeopardize the effect of a vaccine at the population scale.

Dengue serotypes are in competition for susceptible individuals because each infection reduces, thanks to a long-lasting transcendental immunity of several months, the effective susceptible pool of all other serotypes. Moreover, serotype are not all equal. Some, namely DENV-1 and DENV-3, appear to be 'pioneer', as they are better at infecting individuals that have never been infected by any serotype, while others, namely DENV-2 and DENV-4, are better at infecting individuals that have been previously exposed to another serotype, this possibly including exposure through vaccination. By conferring an heterogeneous protection, and particularly a very weak protection against DENV-2, the vaccine strongly reduces the incidence of some but not all serotypes, minimizing the competition between them and thus favouring the spread of

serotypes less affected by the vaccine. Such alteration of the competition between serotypes may lead to deleterious short-term effect of the vaccine and very strong epidemics in the first year of vaccination campaigns.

This case-study shows that pathogen should not be considered as independent entities when designing Public Health policies. For dengue, it is necessary to keep working on vaccine efficiency and heterogeneity, and to consider alternative vaccination policies instead of standard mass vaccination. Influenza is another example of such interference between interactions between strains and Public Health. A partial cross-immunity between antigenically similar strains and a fast evolution speed force the vaccine to be redesigned every season with new strains. What happens between serotypes of the same pathogen may happens between different pathogens.

2 Contextualisation of the Findings

In the existing literature, interactions between pathogens have sometimes been described under the term *syndemic*. This term has been introduced recently by medical anthropologists to “label the synergistic interaction of two or more coexistent diseases and resultant excess burden of disease” [322,323]. This definition restrains the study of pathogen interactions to the deleterious ones, neglecting what we called ‘obstructing’ interactions, i.e. interactions that protect the host or the population from pathogens.

Thus, the most recent review about syndemics focuses of what we called ‘facilitating’ interactions, and categorized them according to the level of the interaction: dispersion of the pathogen, contagiousness of infected individuals, virulence of the pathogen, and gene assortment [157]. The potentially dramatic impact of such interactions explains why they receive such interest. Moreover, most of recent works using the term ‘syndemics’ focus on sexually transmitted diseases (especially HIV) and the “confluence of several risk factors” [324–328].

Our review enlarges the view of pathogens interactions to both facilitating and obstructing interactions. It also takes care to form categories broad enough to include all interactions to our knowledge. Most important, it begins to fill the gap in the current literature about the co-occurrence of several interaction at the same time, and stresses out the need for further investigation in this particular field.

Our work on the theoretical model of pathogen interactions apparently tempers the results of other authors. ROHANI *et al.* [42] showed that the removal of hosts from the effective susceptible pool during the convalescence period could strikingly affect the dynamics of pathogens. DE VASCO *et al.* [43] showed that several interactions, including those incorporated in our model, affects the phase correlation between the pathogens’ dynamics.

However, both these works stressed out the importance of the duration of the convalescent period. In this PhD, we showed why this parameter is important. DE VASCO’s works, using a deterministic model, focused on potentially long lasting interactions, i.e., interactions occurring on convalescent — by the way showing the importance of the duration of this convalescence — or resistant individuals. Moreover, they allowed stronger interaction, up to 100-fold increases of susceptibility, while our work restrained to 2-fold increases (but see Fig. A.1). They also omitted the interactions modifying the susceptibility of infectious individuals. We showed that such interactions indeed are the less likely to have a visible impact.

Both works focused on periodicity and phase-correlation of the pathogens. In this PhD, we added the incidence aspect, by monitoring a proxy of the total number of cases. We showed that some interactions might indeed act on the temporality of a disease but without affecting its overall incidence.

Concerning the statistical aspects of this PhD, we tested Granger Causality Analysis and Transfer Entropy with the same mechanistic model than SHRESTHA *et al.* [63] used to test their inference method. Their work showed that inference is able to identify interaction, and they later used the same methods to investigate the interaction between Influenza and Pneumococcal Pneumonia [46]. Our objective here was to stress out the need for more general and easy to set methods. The current literature lack of such method applied for epidemiology. Granger original work was designed for economics [47, 127] and the toolbox we used for neurosciences [119, 122]. The only use, to our knowledge, of Granger Causality in epidemiology was dedicated to the identification of climatic factors on Dengue incidence [329] and not to pathogen interactions. Similarly, Transfer Entropy is a product of Information Theory [278–280] and has been used to detect interactions in neural networks [330] or physiological time series [331]. To our knowledge, Transfer Entropy had never been used in epidemiology.

Lastly, the work on dengue vaccination places itself in a long history of dengue models. Our model is a relatively simple one in term of epidemiological mechanisms. There is no explicit modelling of the vectors (see [332, 333]), and no dispersal or any kind of spatial mechanism (see [334]; for further details on the variety of existing models for dengue, see [335]). However, fewer models explicitly account for serotypic diversity and interactions. Two strains models have been used to discuss the coexistence of several serotypes of dengue [336–338] or the dynamical impact of ADE hypothesis [339]. A four-serotypes model has been developed and used by Wearing and Rohani [65] to examine ecological and immunological mechanisms that generate time series consistent with data. They tested whether seasonal forcing, ADE, asymmetry of virulence (through mortality) and temporary cross-immunity were important to generate time series. They concluded that all of them except asymmetry in virulence were useful to produce dynamics consistent with the data. Thus, asymmetry in virulence has not been included in our model. Yet ADE remains a discussed issue, as the evidences still are debatable and debated [340, 341], and the excess of mortality could have another reason.

At the time this PhD is written, few paper directly concerning the modelling of dengue vaccination has been published (but see [337]). However, many published dengue models give precious insights for vaccination [342] or other kind of control strategies [334]. Moreover, a comparative analysis of how dengue vaccination will affect dengue incidence and disease burden is currently ongoing, leaded by Stefan FLASCHE, who has a large history of vaccination modelling [343–346], together with the WHO. This comparative analysis is bringing together several groups of dengue modellers to compare their simulation results under a commonly specified vaccination scenario. Due to unfortunate timing, our model cannot be included into this ongoing analysis, but will be in the case of a follow-up project.

3 Perspectives for this PhD

This PhD highlighted the lack of literature concerning the co-occurrence of several interactions at the same time between pathogens. Numerous possible combinations have been suggested at least once, tending to show that they are possible, and it would be useful to gather more evidences in order to better understand the mechanisms and the outcome of such interactions. Nevertheless identification of such interactions remains challenging. Nowadays, biological presumptions and evidences from case-study are the main factors that lead to the definitive identification of an interaction between several pathogens.

Our below the initial expectations work on Granger Causality Analysis and Transfer Entropy showed that there is still room for a gold standard, a method that could allow an easy detection

of interactions between pathogens from population-scale data. In our tests, identifying a single causality in a two-pathogen system revealed itself more than tricky. Thus, our approaches of GCA and TE would certainly fail in identifying multiple interactions in a more complex system. A few others candidates may exist, like copula-based test [162, 163] or combining renormalized partial directed coherence with state space modelling [164]. The later has the advantage of taking into account the temporal variability of the causalities.

Even if a successful theoretical approach were found, in order to obtain a method that could be usable with real data, it should be robust to the addition of other parameters, such as spatial heterogeneity, more complete climatic data, dispersal and mobility of individuals and/or vectors. The main point is finding a compromise between the comprehensiveness of the method chosen and its complexity. As stated previously, inference methods are effective but difficult to set up. On the contrary, exploratory approaches lack of precision to satisfactorily catch the dynamics of the system.

As it happens, catching the dynamics of the system might be of vital importance for Public Health. Our model of dengue showed that taking the interactions between serotypes may reveal severe side-effects of *a priori* beneficial vaccine campaigns. This opens two thoughts. First, staying in the specific context of dengue, it is necessary to keep working on the vaccine candidates, focusing on the homogeneity of the protection it confers. Second, it could be useful to generalize awareness of pathogen interactions when designing Public Health policies. Once again, it is a matter of compromise between comprehensiveness and complexity. Choosing which interaction to take into account and which to neglect would be easier with more theoretical studies. Theoretical knowledge would give clues about which interactions are more likely to be important and which are not.

Finally, even if we showed that not every interaction have a dramatical impact at the population scale, this whole PhD tends to stress that studying interactions between pathogens is vital. This thesis documented that a large variety of interactions occurs between pathogens. This is a wide, growing field for Ecology, Medicine and Public Health, and it mostly remains to be explored. Interactions between pathogens are various, complex and challenging, as we still need effective means to identify them. Each interaction is unique and must be studied individually to be fully understood, from intra-host to community scale. Further developments of innovative statistical tools and mathematical or computational models are needed, in order to both identify unknown interactions and understand their consequences on population and Public Health policies.

Interactions happen at several scale and rarely alone or independently from each other. A host-pathogen system is drawn in a wider system, a community of hosts and pathogens, and should be studied in this way. By doing so, we will improve our understanding of diseases dynamics and our ability to fight them. However, this can only be done by starting to better identify these interactions, how they occur and what do they lead to, both at the intra-host and the population scales.

Lessons from this PhD

In an educational point of view, this PhD has improved many of my knowledges and skills. Conducting a large review on a subject I didn't really were aware of (namely interactions between pathogens) learned me to widely explore and filter a broad literature, away from my comfort zone. I was indeed more used to ecological and modelling papers than clinical or medical ones, which made up a large part of the results of the bibliographic investigation. Organizing the outcomes of this research in well-defined categories implies to step back and see the bigger picture. It required to link medical case studies with knowledges from population dynamics and community ecology. Becoming able to do this revealed itself useful for the redaction of this thesis itself.

The adaptation work on the TE and GCA toolboxes increased my technical skill in term of working with other people's code. Both toolboxes needed a large rework to become usable for epidemiology and to fit the specificity of our data. Moreover, to be able to understand both the code and the theoretical methods behind it, I had to reforge and bring my knowledges of time series analysis and causality principles to a new level. To improve those toolboxes and try to get better results from the analyses, I had to learn to try new ways to manipulate and analyse the data, and show initiative at this. And most of all, learn to accept bad results without giving up too soon ... nor too late.

Developing the first version of the model of multi-pathogen dynamics and all its derivative have been an astonishing challenge. It started with a simple two-pathogen deterministic model. Already having in mind the ambition to model more complex system, it rapidly grew up to become the multi-pathogen flexible model it is now, an algorithm that can generate a model for any number of pathogen. To achieve this, I had to push over my skills in term of algorithmic and optimisation of Matlab™ code. Alongside the need for a stochastic version of the two-pathogen model had grown. The translation of the deterministic two-pathogen Matlab model to a stochastic two-pathogens C model has been a good technical exercise, as I wasn't an expert of the C language.

On a less technical, more scientific and human point of view, this PhD has also been a rewarding experience. Its international aspect in a first place. I had the opportunity to go twice to Vietnam, working at the Hanoi School of Public Health and living in Hanoi one and a half month both times. There I discovered how scientific research is done in this country and how to deal with international collaborations. Secondly it was an unfamiliar linguistic experience, and even if my Vietnamese is still pretty poor, it certainly improved both my 'everyday life' and my scientific English, as most of the conversations there were in English.

More broadly, I learned how the researcher life is. The short research experiences that are done during the scholarship of a master student do not credit it enough. During this PhD, I have been confronted to the presentation of my work during seminar and conferences, with a much larger audience than 'simple' lab seminars. I had to pass through the peculiar system of manuscript submission, which I am still not done with. And finally, all those experiences clarified my view of my professional future and ambitions.

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Appendix A

Detecting interactions between pathogens

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A.1 Strong interactions

In order to assess the limit comportment of the model, we then allow the interaction parameters to vary within a wider range, using a logarithmic scale (from 10^{-4} to 10^4 , see Fig. A.1) while using the default parameters (Table 2.1). The interactions can be very strong, so we are more likely to observe an effect of these interactions. The first remarkable result is that obstructing interactions (i.e., interactions that causes a decrease of susceptibility) do not have a measurable effect on the dynamics of the pathogen, except if the interaction applies to resistant individuals. In this case, which is a "partial cross-immunity" case, i.e. an individual who is resistant to a pathogen is partially protected against the other, the number of cases from the second pathogen is strongly reduced, and the dynamics of this pathogen are slowed. This confirms the observations made in section 2.3.1. Moreover, we now see that the periodicity of the second pathogen increases again when the facilitating interaction reaches a sufficient strength.

On the other hand, when the susceptibility is increased (interaction superior to 1), we never observe any significant effect on the total number of cases, even if the interaction strength is significantly larger than in the previous section, but the periodicity of the dynamics is affected: the periods are longer and converge toward the same periodicity as the first pathogen. Total number of cases appear to be intrinsically capped by the model's parameters, independently from susceptibility.

When we run the same analysis for stronger interactions, first visible result is that stronger 'facilitating' interactions are well detected, with a increased rate of detection as the interaction strength increases. However, the detection is symmetrical, and causalities from pathogen 2 to pathogen 1 are (wrongly) detected as much as causalities from pathogen 1 to pathogen 2 (fig A.2). Only for interactions on resistant individuals is the direction of the causality partially observable with the Granger Causality analysis: detection rate is higher for the right direction, even if the intensities of the detected interactions are the same in both directions.

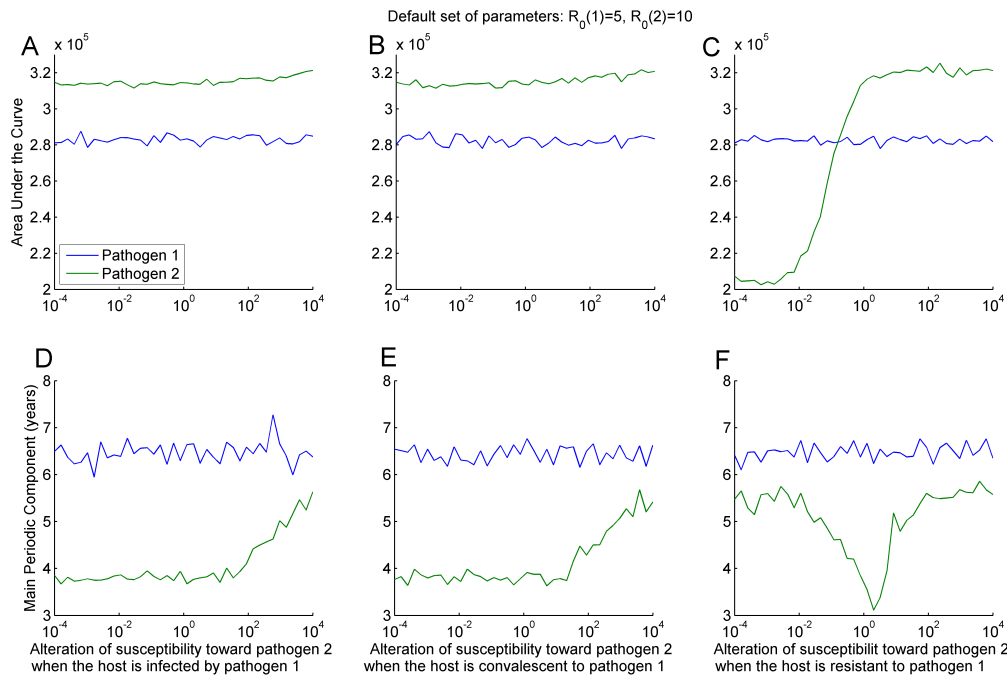


Figure A.1. Values of the generic dynamics indicators according to each type of interaction, with strong interaction strengths. Top: Total number of cases. This is an estimate based on the calculation of the area under the curve. Bottom: Main Periodic Component, determined by the highest peak of the Fourier Spectra of each time series. Left: Indicators values for a range of values of φ . All others interaction parameters set to 1. Center: Indicators values for a range of values of ξ . All others interaction parameters set to 1. Right: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for pathogen 1 (resp. 2) are blue (resp. green). 40-years long examples of simulations for each minima and maxima of interaction strength are shown in side boxes. Parameters can be found in Table 2.1, Default Set.

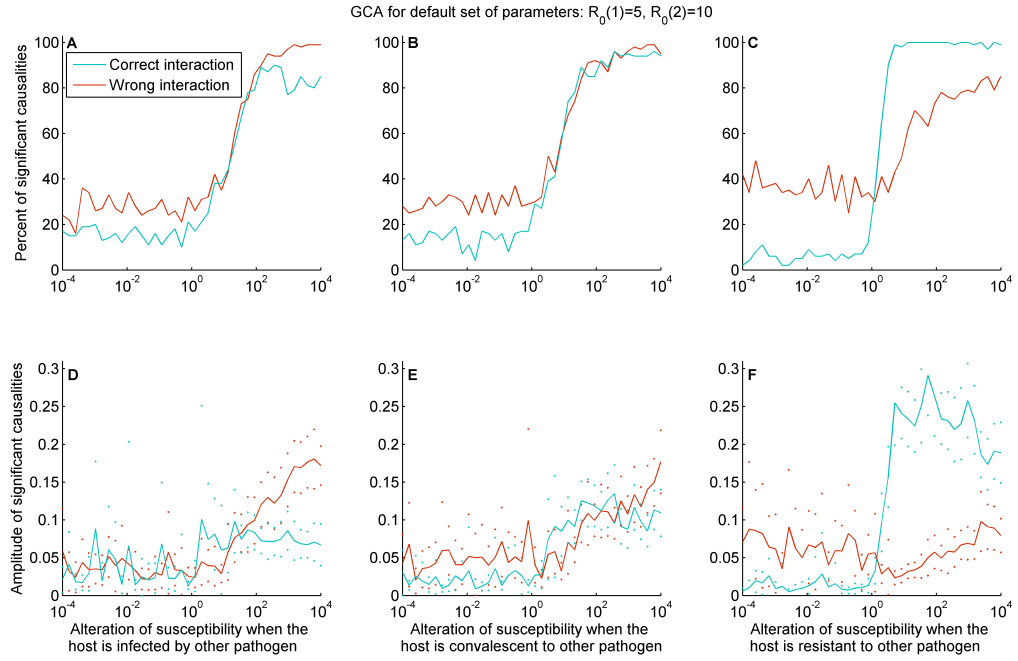


Figure A.2. Values of Granger causality analysis output according to each type of interaction, with high interaction strengths. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. A-D: Indicators values for a range of values of φ_1 . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ_1 . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ_1 . All others interaction parameters set to 1. Values for effect of pathogen 1 on pathogen 2 (resp. 2 on 1) are blue (resp. red). Points delimit 95% confidence intervals. Other parameters are shown in table 2.1, Default Set.

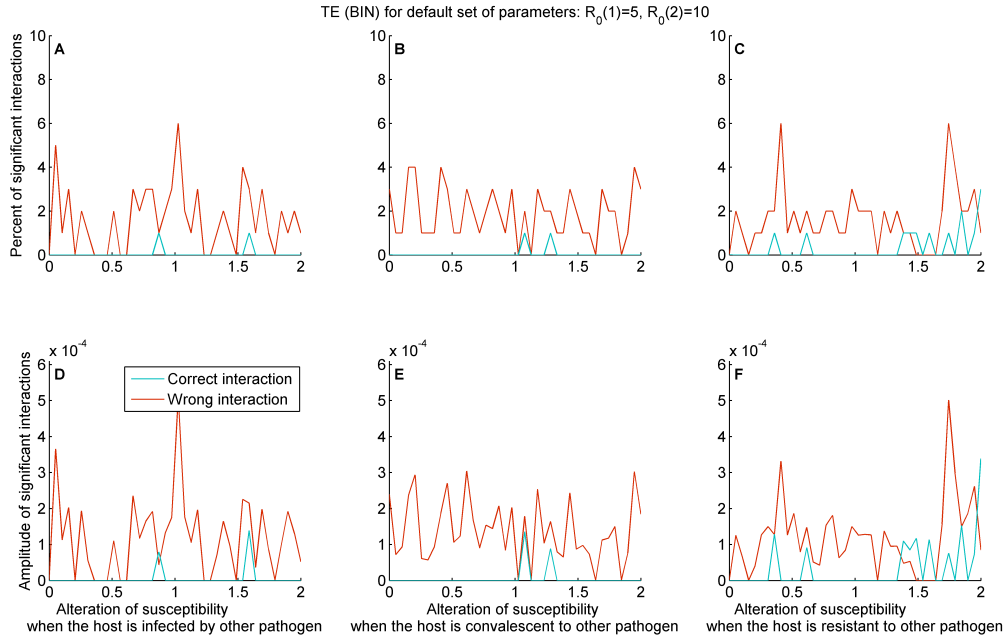


Figure A.3. Values of BIN NUE Transfer Entropy analysis output according to each type of interaction. Top: number of simulations for each point where detected causalities are significant. Bottom: mean amplitude of the significant causalities. Left: Indicators values for a range of values of φ_1 . All others interaction parameters set to 1. Center: Indicators values for a range of values of ξ_1 . All others interaction parameters set to 1. Right: Indicators values for a range of values of χ_1 . All others interaction parameters set to 1. Values for effect of pathogen 1 on pathogen 2 (resp. 2 on 1) are blue (resp. red). Other parameters are shown in table 2.1, Default Set.

'Obstructing' interactions never are well detected. In the case of interactions on resistant individuals, obstructing interactions lead to an increase of the false positive (detection of causalities from path.2 to path.1) and false negative (absence of detection of causalities from path.1 to path.2), while facilitating interactions induce nearly 100% true positive, causalities from pathogen 1 to pathogen 2 being more detected and with a higher intensity (Fig. A.2, C). For the interactions on other compartments, obstructing interactions result in detected causalities similar to causalities detected with no interactions, that is, ca. 20% of false positive in both directions, with low intensities, while facilitating interactions cause higher false and true positives.

A.2 Transfer entropy with binning estimator

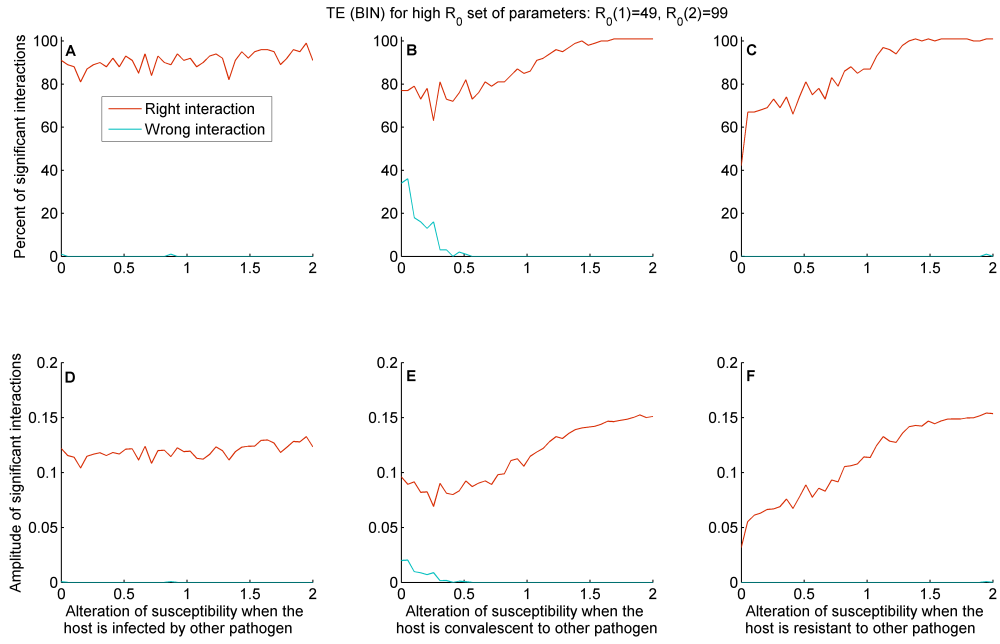


Figure A.4. Values of BIN NUE Transfer Entropy output according to each type of interaction. A-B-C: number of simulations for each point where detected causalities are significant. D-E-F: mean amplitude of the significant causalities. Values of the generic dynamics indicators according to each type of interaction. A-D: Indicators values for a range of values of φ . All others interaction parameters set to 1. B-E: Indicators values for a range of values of ξ . All others interaction parameters set to 1. C-F: Indicators values for a range of values of χ . All others interaction parameters set to 1. Values for pathogen 1 (resp. 2) are blue (resp. green). $\beta_1 = 600, \beta_2 = 1200, \frac{1}{\gamma} = 1month, \frac{1}{\delta} = 6months$. Other parameters are shown in Table 2.1, High R_0 Set.

Appendix B

Vaccine Heterogeneity and Serotype Interactions

How should we use candidate Dengue vaccines in endemic areas?

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B.1 Details of the model

The model is implemented with Matlab™. It is a deterministic continuous time model with fixed time-step. We assume that each flux is an independent process and that over a single time-step, the *per capita* rates are constant. At each time-step, the number of individuals making every possible transition is approximated using an exponential growth function ($X_{...}(t + dT) = X_{...}(t)\exp^{-\lambda dT}$) with λ the rate associated with the transition [63]. Seasonal forcing is a sinus function of amplitude a and period 1 *year*. Model's parameters, shown in Table B.1, are estimated to fit several data from literature, from immunological knowledges (*e.g.* duration of the infection) to empirical data.

B.1.1 Algorithm for the computation of flux.

At each time-step:

1. Births are calculated. Total number of births M is the "natural" birth ($N(1 - \exp^{\mu dT})$) plus the number of disease-induced death at the previous time-step. Those birth are distributed among susceptible and vaccinated according to vaccine coverage (n) and vaccine efficacy for serotype i (n_i). For example, the number of births in the VSSV compartment (vaccinated against serotype 1 and 4, susceptible to serotypes 2 and 3) is $M(nn_1(1 - n_2)(1 - n_3)n_4)$. "Natural" death are computed for every compartment X . Number of death in each compartment X is $X(1 - \exp^{\mu dT})$.

Parameter	Symbol	Value	Unit	Ref
Population size	N	100	<i>individuals</i>	
Birth and death rate	μ	1/65	$year^{-1}$	
Contact rate of serotype i	β_i	260/50.86/231.7/11.13	$year^{-1}.individual^{-1}$	[149]
Duration of infectious period	$1/\gamma$	3.3	<i>days</i>	[134]
Duration of cross-protection	$1/\delta$	6	<i>months</i>	[136–138]
Vaccination coverage (percentage of vaccinated newborns)	n	95	%	
Vaccine efficiency against serotype i	n_i	0 – 100	%	[147, 148]
Amplitude of seasonal forcing	a	50	%	
Alteration of susceptibility against other serotype during infection and cross-protection period	ξ	0	none	[136]
Alteration of susceptibility against other serotype after loss of cross-protection for serotype i	χ_i	1/5.112/1.122/22.99	none	[149]
Risk of DHF/DSS	e	14	%	[134, 149]
Supplementary risk in case of secondary infection	z	30	%	[134, 149]
Mortality rate of DHF/DSS	η	2.800	$year^{-1}$	[134]
Migration rate for infectious individuals	ω	10^{-7}	<i>individus.an</i> ⁻¹	

Table B.1. Model parameters. Values are the same for each serotype unless all four values are explicit. Values always are for DENV-1-2-3-4 in this order.

2. For each serotype/dimension of the model’s matrix, progression of the disease for this serotype is computed.
 - (a) Number of individuals doing each transition from a compartment to another with rate τ are computed. Births, deaths, disease-induced death and severe cases are not computed here, as they are not transition from a compartment to another. Number of individual doing each transition from compartment X to compartment Y with rate τ is $X(1 - \exp^{-\tau \Delta T})$.
 - (b) Two cases:
 - case i. Those flux are removed/added to corresponding compartment in a separated matrix. Thus, their is a matrix for current time-step used to compute the number of individuals doing each transition for each pathogen during the time-step and a different matrix used to apply those transition and computing the new population at the end of the time-step. This method overestimates the number of individuals

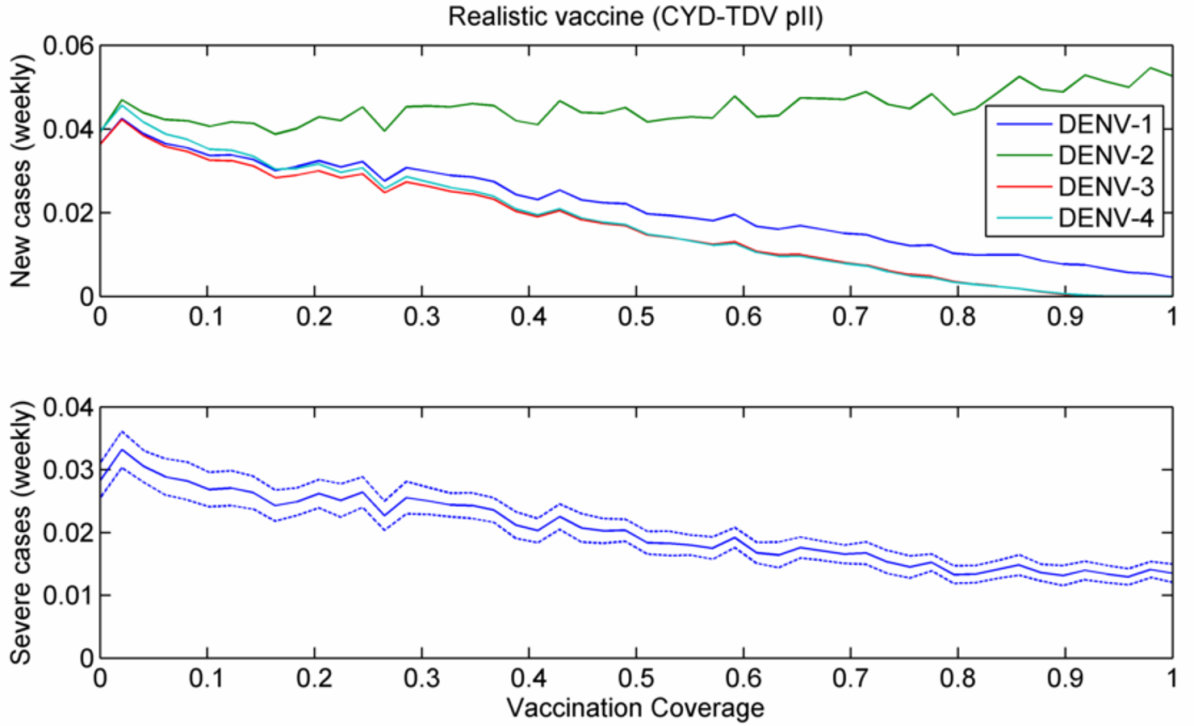


Figure B.1. Long-term effects (after 50 years of vaccination) of several vaccine according to the vaccination coverage. CYD-TDV phase II trial vaccine, see Table 3.1 for detailed vaccine efficacies. Top: Serotype specific case-count. DENV-1, 2, 3 and 4 are resp. blue, green, red and cyan. Bottom: mean number of severe cases per week between year 50 and 60 after the beginning of the vaccination campaign. Dotted lines are 95% confidence interval. Parameters apart from vaccine efficacy can be found in Table B.1. Algorithm used is case ii.

performing each transition but is does not favour transition computed firsts: the order of computation does not matter as the number of individuals in each compartment used for computation of flux does not change within a time-step. This is the method used for the result in this paper.

OR

case ii. Those flux are removed/added to corresponding compartment in the model matrix before the flux for the progression of the disease for the next serotype is computed. This method does not overestimate the total flux but favours progression of the first serotype against progression of the second, second vs third and third vs fourth because the order of the computations matters. See Fig. B.1 for simulation of CYD-TDV pII with this method.

- (c) Number of severe cases in each "infectious" compartment is computed: fixed proportion e (resp. $e + z$) of infected individuals for primary (resp. subsequent) infections.
 - (d) DHF/DSS-related deaths are computed. Number of death in each sub-compartment I_{DHF} is $I_{DHF}(1 - \exp^{-\eta dT})$.
3. (case i only) All previously computed flux are applied to the population now.
 4. Next time-step: $t = t + dT$, go to step 1.

B.1.2 Death rate estimation for DHF/DSS.

We know (from WHO data) that $o = 2.5\%$ of individuals suffering DHF or DSS die within the course of the infection. We know that the infection lasts $\frac{1}{\gamma} = 3.3$ days. Thus, if we consider no new cases, with $D(t)$ the number of individuals suffering DHF/DDS at time t and η the mortality rate of these individuals, we have:

$$\begin{cases} D\left(\frac{1}{\gamma}\right) = (1 - o)D(0) \\ D\left(\frac{1}{\gamma}\right) = D(0) \exp^{-\eta\frac{1}{\gamma}} \end{cases} \quad (\text{B.1})$$

Thus, we have

$$\begin{aligned} D(0) \exp^{-\eta\frac{1}{\gamma}} &= (1 - o)D(0) \\ \Rightarrow \exp^{-\eta\frac{1}{\gamma}} &= (1 - o) \\ \Rightarrow -\eta\frac{1}{\gamma} &= \ln(1 - o) \\ \Rightarrow \eta &= -\gamma \ln(1 - o) \end{aligned}$$

B.1.3 ODE skeleton of the model for two serotypes.

Here we show the complete ODEs of a simplified version of the model, with only two serotypes. The four-serotype model is built on the same skeleton but would be too heavy to be fully transposed here.

$$\begin{aligned} \frac{dX_{SS}}{dT} &= \mu(N(1 - n(n_1 + n_2 - n_1n_2)) - X_{SS}) - \lambda_1X_{SS} - \lambda_2X_{SS} \\ \frac{dX_{IS}}{dT} &= \lambda_1X_{SS} - (\xi\lambda_2 + \mu + \gamma)X_{IS} - \eta X_{IS}^{DHF} \\ \frac{dX_{CS}}{dT} &= \gamma X_{IS} - (\xi\lambda_2 + \mu + \delta)X_{CS} \\ \frac{dX_{RS}}{dT} &= \delta X_{CS} - (\chi_1\lambda_2 + \mu)X_{RS} \\ \frac{dX_{VS}}{dT} &= \mu(n(1 - n_2)(n_1)N - X_{VS}) - \lambda_2X_{VS} \\ \frac{dX_{SI}}{dT} &= \lambda_2X_{SS} - (\xi\lambda_1 + \mu + \gamma)X_{SI} - \eta X_{SI}^{DHF} \\ \frac{dX_{SC}}{dT} &= \gamma X_{SI} - (\xi\lambda_1 + \mu + \delta)X_{SC} \\ \frac{dX_{SR}}{dT} &= \delta X_{SC} - (\chi_2\lambda_1 + \mu)X_{SR} \\ \frac{dX_{SV}}{dT} &= \mu(n(1 - n_1)(n_2)N - X_{SV}) - \lambda_2X_{SV} \\ \frac{dX_{II}}{dT} &= \xi\lambda_2X_{IS} + \xi\lambda_1X_{SI} - (\mu + \gamma + \gamma)X_{II} - \eta X_{II}^{DHF} \\ \frac{dX_{IC}}{dT} &= \gamma X_{II} + \xi\lambda_1X_{SC} - (\mu + \gamma + \delta)X_{IC} - \eta X_{IC}^{DHF} \\ \frac{dX_{IR}}{dT} &= \delta X_{IC} + \chi_2\lambda_1X_{SR} - (\mu + \gamma)X_{IR} - \eta X_{IR}^{DHF} \end{aligned}$$

$$\begin{aligned}
\frac{dX_{IV}}{dt} &= \lambda_1 X_{SV} - (\mu + \gamma) X_{IR} \\
\frac{dX_{CI}}{dT} &= \gamma X_{II} + \xi \lambda_2 X_{IS} - (\mu + \gamma + \delta) X_{CI} - \eta X_{CI}^{DHF} \\
\frac{dX_{CC}}{dT} &= \gamma X_{IC} + \gamma X_{CI} - (\mu + \delta + \delta) X_{CC} \\
\frac{dX_{CR}}{dT} &= \gamma X_{IR} + \delta X_{CC} - (\mu + \delta) X_{CR} \\
\frac{dX_{CV}}{dT} &= \gamma X_{IV} - (\mu + \delta) X_{CV} \\
\frac{dX_{RI}}{dT} &= \delta X_{CI} + \chi_1 \lambda_2 X_{RS} - (\mu + \gamma) X_{RI} - \eta X_{RI}^{DHF} \\
\frac{dX_{RC}}{dT} &= \delta X_{CC} + \gamma X_{RI} - (\mu + \delta) X_{RC} \\
\frac{dX_{RR}}{dT} &= \delta X_{CR} + \delta X_{RC} - \mu X_{RR} \\
\frac{dX_{RV}}{dT} &= \delta X_{CV} - \mu X_{RV} \\
\frac{dX_{VI}}{dT} &= \lambda_2 X_{CV} - (\gamma + \mu) X_{VI} \\
\frac{dX_{VC}}{dT} &= \gamma X_{VI} - (\delta + \mu) X_{VC} \\
\frac{dX_{VV}}{dT} &= \mu (n n_1 n_2 N - X_{VV})
\end{aligned}$$

Additionally, we have:

$$\begin{aligned}
N &= \sum X \\
\lambda_1 &= \beta_1 (X_{IV} + X_{IS} + X_{II} + X_{IC} + X_{IR} + \omega) \\
\lambda_2 &= \beta_2 (X_{VI} + X_{SI} + X_{II} + X_{CI} + X_{RI} + \omega) \\
X_{SI}^{DHF} &= e X_{SI} \\
X_{II}^{DHF} &= e X_{II} \\
X_{CI}^{DHF} &= e X_{CI} \\
X_{RI}^{DHF} &= (e + z) X_{RI} \\
X_{IS}^{DHF} &= e X_{IS} \\
X_{IC}^{DHF} &= e X_{IC} \\
X_{IR}^{DHF} &= (e + z) X_{IR}
\end{aligned}$$

B.2 Other simulations of the model

A broad number of simulations, apart from those presented in the main text, has been made with the model and several vaccine efficacies. Most of significant and informative ones are presented hereafter. Fig. B.2, B.3, B.4 & B.5 show unique simulations without vaccine, with CYD-TDV pII vaccine, CYD-TDV pIII and perfect vaccine, resp. The dominance of DENV-2 with heterogeneous vaccine is striking. We also see from relative abundance that the succession

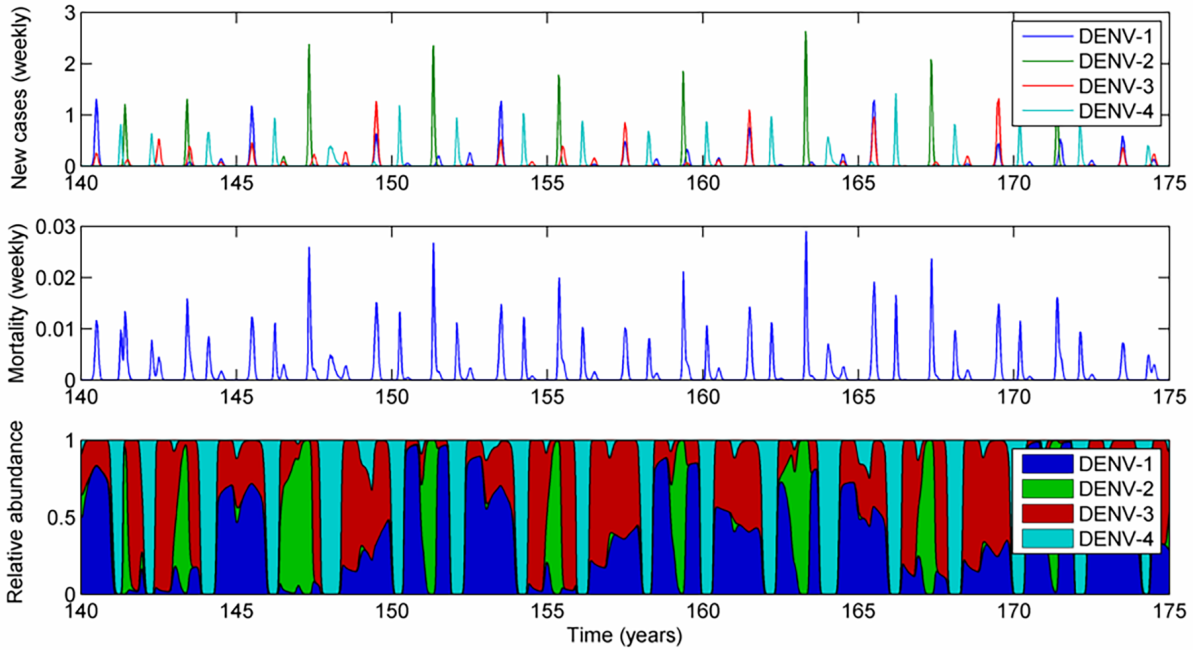


Figure B.2. Single simulation of the model without vaccination. Parameters are shown in Table B.1. Top panel: weekly serotype-specific case-counts (both non-severe and severe). Middle panel: number of deaths due to DHS or DSS every week. Bottom panel: relative abundance of each serotype represented as the fraction of total cases due to each serotype.

of dominant serotype along time become more regular when a vaccine is introduced in the population.

Fig. B.8 & B.9 shows short and long term (resp.) impact of vaccine coverage on serotype-specific cases counts and severe cases counts. Facilitating effect of heterogeneous vaccines on DENV-2 are easily identifiable, particularly on short-term, as well as the lack of effect of these vaccines on severe cases number. On the contrary, homogeneous, 100% effective perfect vaccine always has a positive impact.

B.3 Fourier Spectra

We have proceeded to fourier spectra analysis to compare our simulations to real data (Fig. B.11) and assess the impact of the vaccines on periodicity of the disease (Fig. B.12, B.14 & B.13). The vaccine significantly shorten the dynamics of each serotype, but these has no significant impact on the overall disease periodicity. The comparison to data is for information only, as the simulations does not account for any partial sampling or unidentified asymptomatic cases.

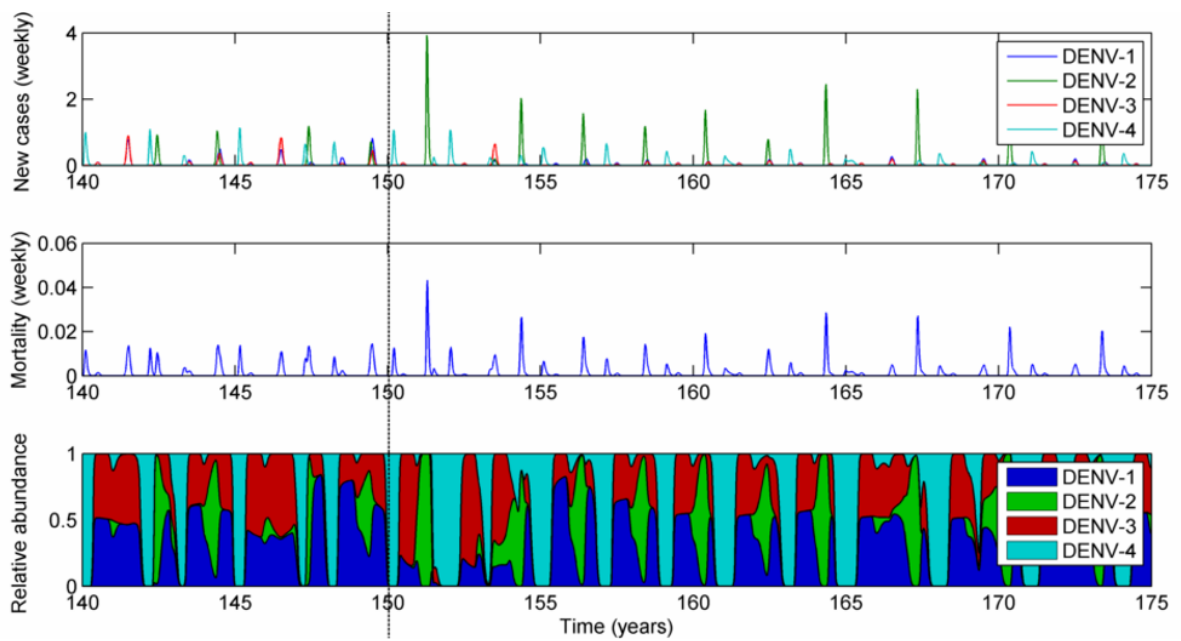


Figure B.3. Single simulation of the model with CYD-TDV II vaccine. Parameters are shown in Table B.1. Vaccination coverage is 66% and vaccine efficacy is based on CYD-TDV phase II trial (see Table B.1). Vaccination starts at $T=150$ years (dashed vertical line). Top panel: weekly serotype-specific case-counts (both non-severe and severe). Middle panel: number of deaths due to DHS or DSS every week. Bottom panel: relative abundance of each serotype represented as the fraction of total cases due to each serotype.

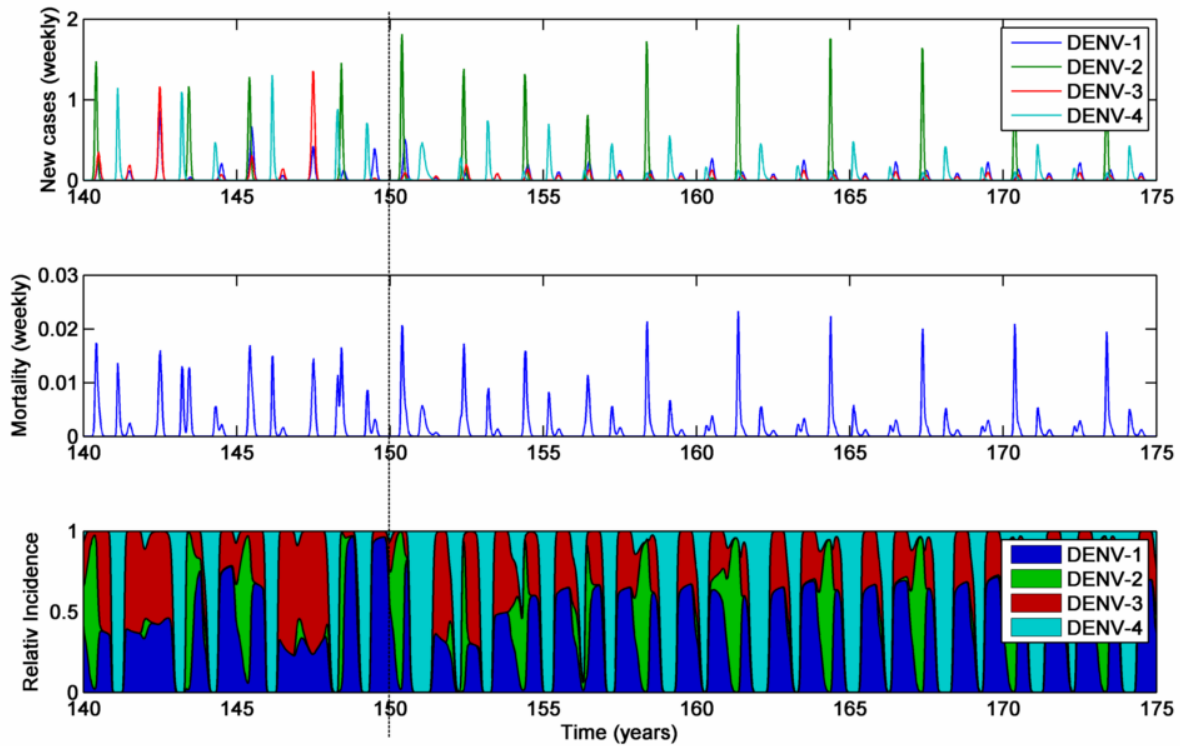


Figure B.4. Single simulation of the model with CYD-TDV III vaccine. Parameters are shown in Table B.1. Vaccination coverage is 66% and vaccine efficacy is based on CYD-TDV phase III trial (see Table B.1). Vaccination starts at $T=150$ years (dashed vertical line). Top panel: weekly serotype-specific case-counts. Middle panel: weekly dengue-related mortality. Bottom panel: relative abundance of each serotype represented as the fraction of total cases due to each serotype.

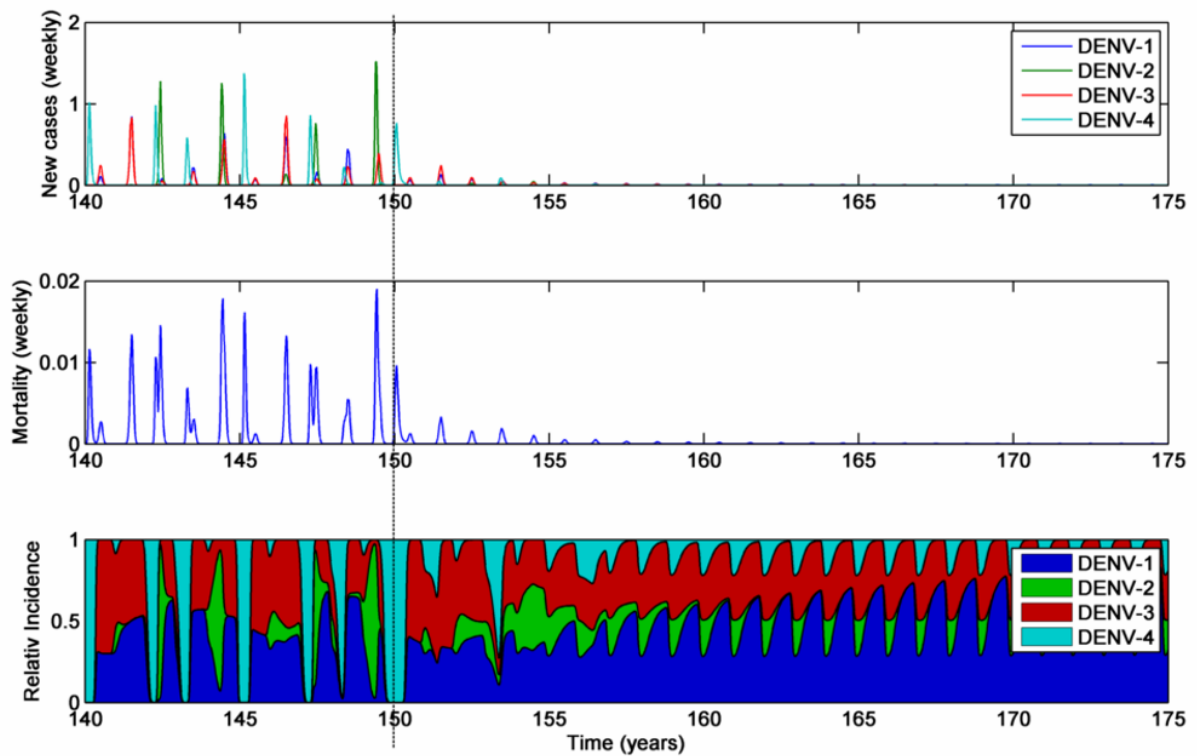


Figure B.5. Single simulation of the model with homogeneous vaccine. Parameters are shown in Table B.1. Vaccination coverage is 66% and vaccine efficacy is "perfect" (see Table B.1). Vaccination starts at $T=150$ years (dashed vertical line). Top panel: weekly serotype-specific case-counts. Middle panel: weekly dengue-related mortality. Bottom panel: relative abundance of each serotype represented as the fraction of total cases due to each serotype.

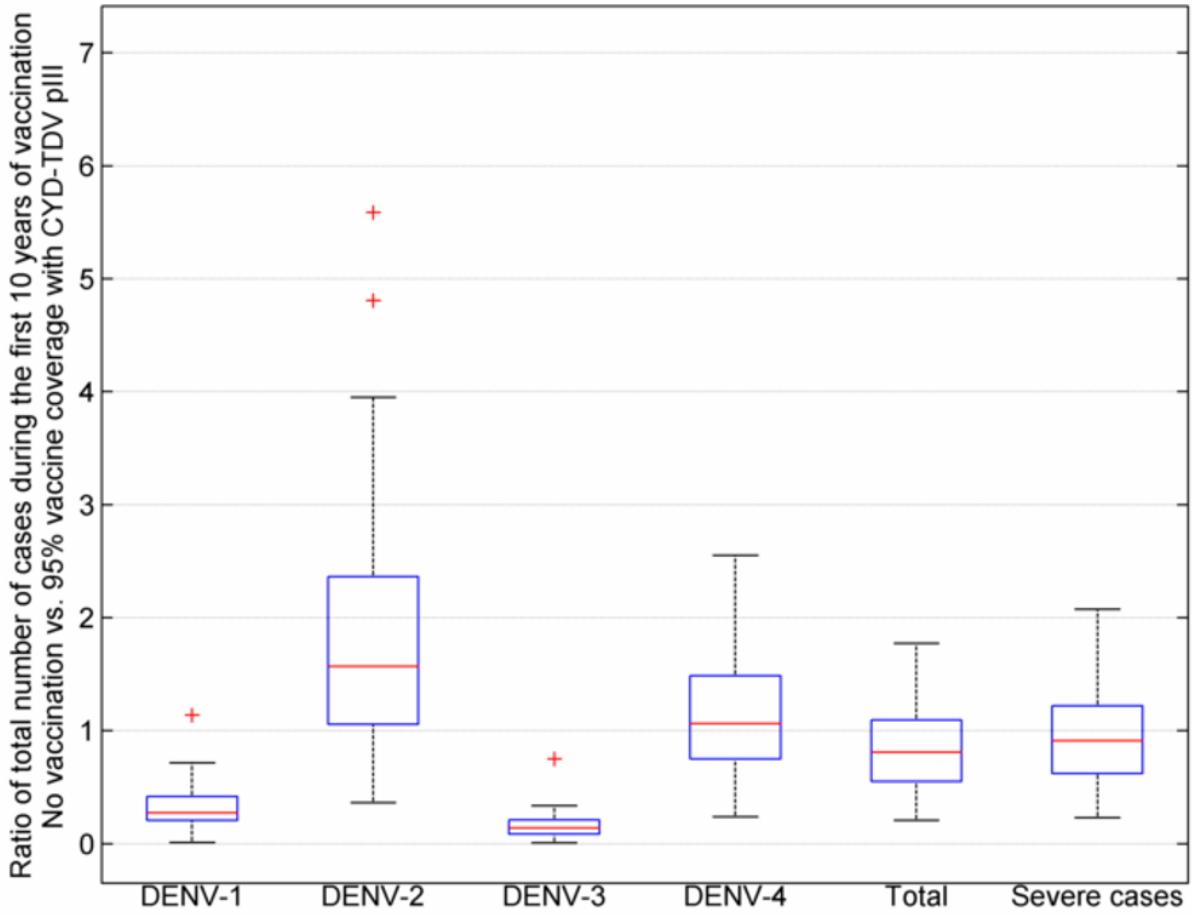


Figure B.6. Ratio between the total number of cases during the first 10 years of vaccination and during 10 years without vaccination. Vaccination coverage is 95% with a CYD-TDV pIII-type vaccine (see Table 3.1 for efficacies). Parameters apart from vaccine efficacy can be found in Table B.1.

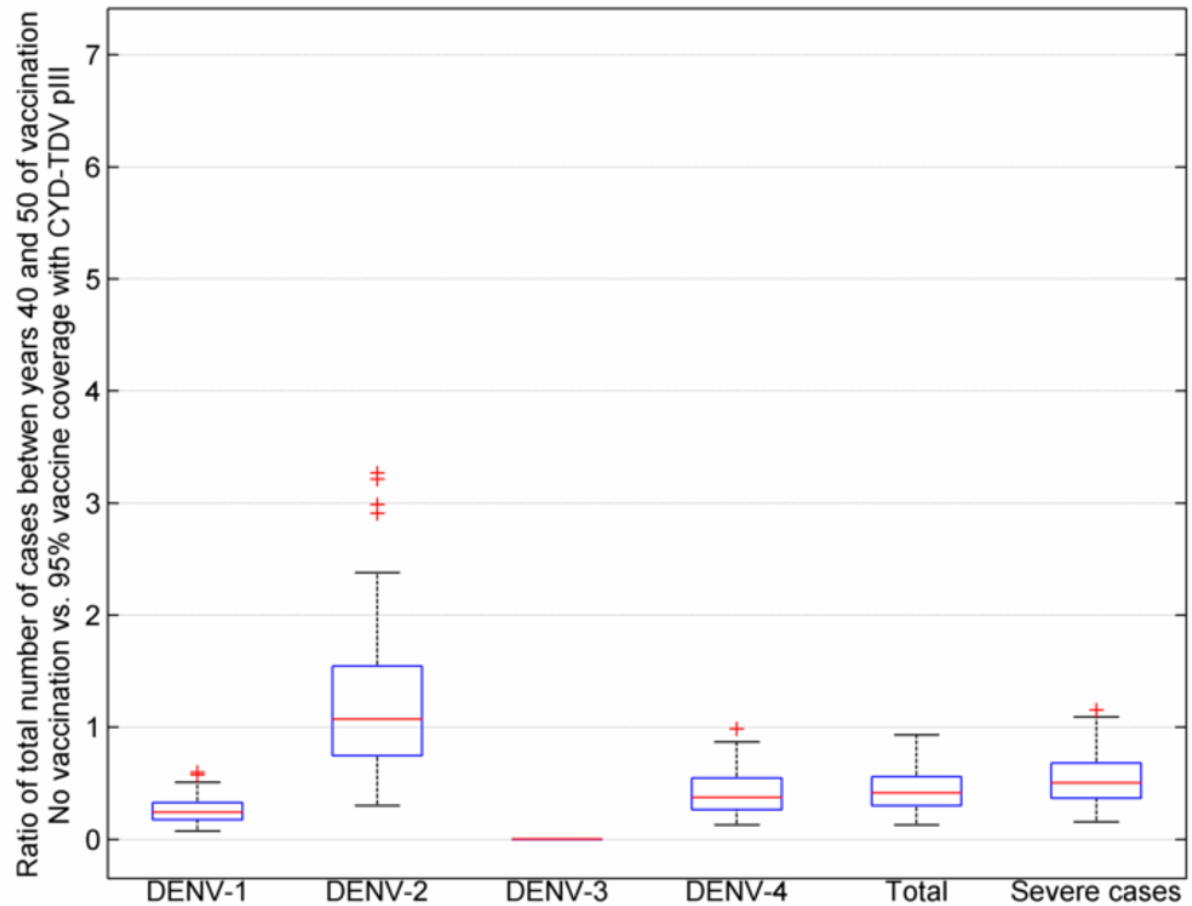


Figure B.7. Ratio between the total number of cases during the years 40 to 50 after the beginning of the vaccination campaign and during 10 years without vaccination. Vaccination coverage is 95% with a CYD-TDV pIII-type vaccine (see Table 3.1 for efficacies). Parameters apart from vaccine efficacy can be found in Table B.1.

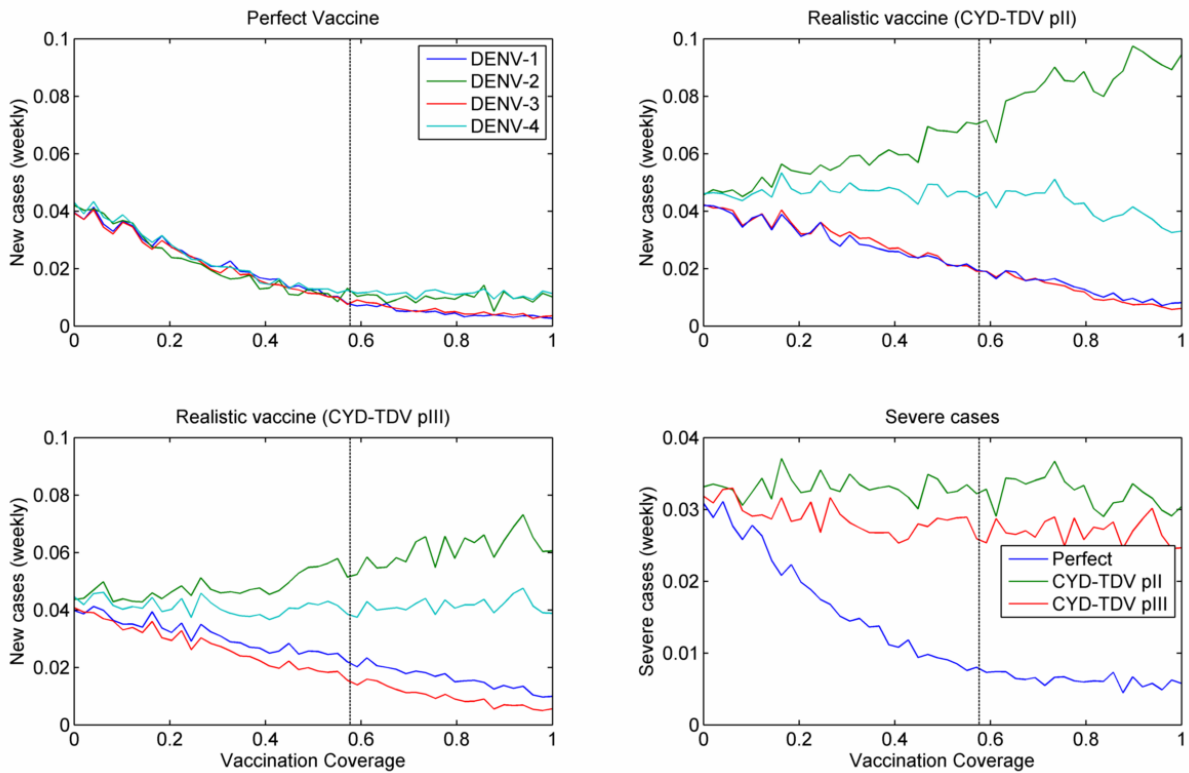


Figure B.8. Short-term effects (first 10 years of vaccination) of several vaccine according to the vaccination coverage. DENV-1, 2, 3 and 4 are resp. blue, green, red and cyan. A, B, C: mean number of serotype-specific new cases per week for various vaccine. A: perfect vaccine. B: CYD-TDV phase II trial vaccine. C: CYD-TDV phase III trial vaccine. See Table 3.1 for detailed vaccine efficacies. D: mean number of severe cases per week between year 1 and 10 after the beginning of the vaccination campaign, for each vaccine. Blue : perfect vaccine, Green: CYD-TDV phase II trial, red: CYD-TDV phase III trial. Parameters apart from vaccine efficacy can be found in Table B.1.

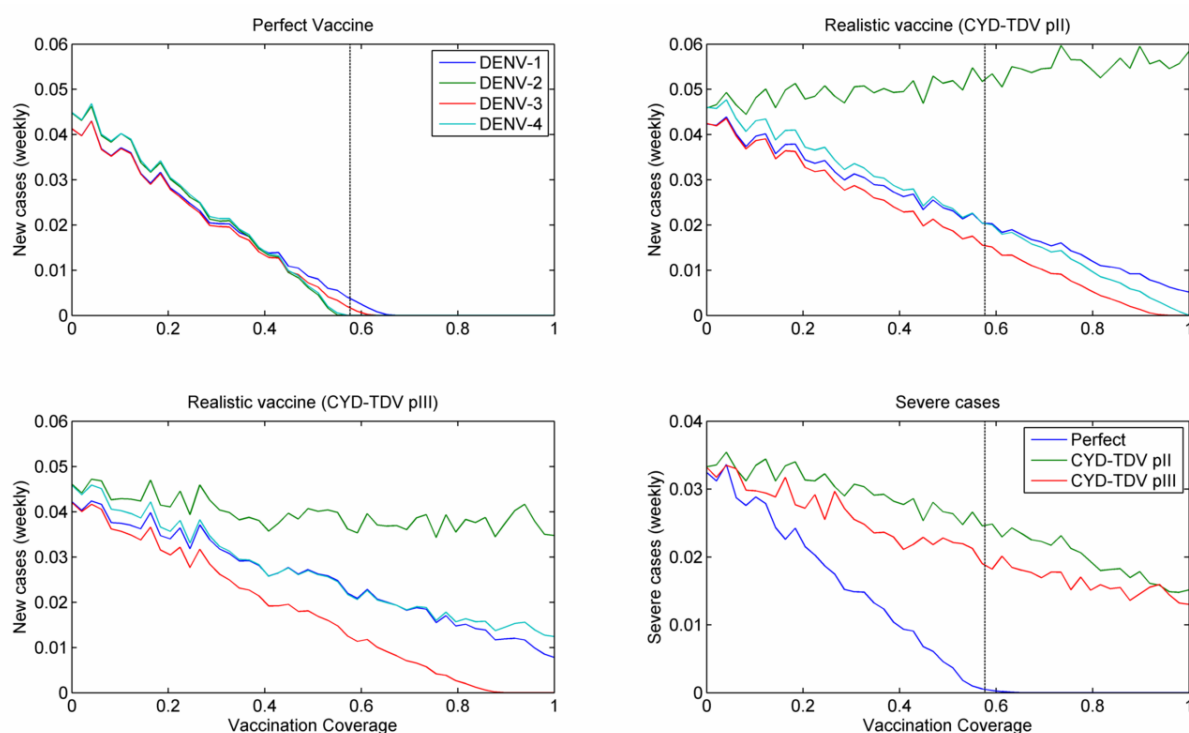


Figure B.9. Long-term effects (after 50 years of vaccination) of several vaccine according to the vaccination coverage. DENV-1, 2, 3 and 4 are resp. blue, green, red and cyan. A, B, C: mean number of serotype-specific new cases per week for various vaccine. A: perfect vaccine. B: CYD-TDV phase II trial vaccine. C: CYD-TDV phase III trial vaccine. See Table 3.1 for detailed vaccine efficacies. D: mean number of severe cases per week between year 50 and 60 after the beginning of the vaccination campaign, for each vaccine. Blue : perfect vaccine, Green: CYD-TDV phase II trial, red: CYD-TDV phase III trial. Parameters apart from vaccine efficacy can be found in Table B.1.

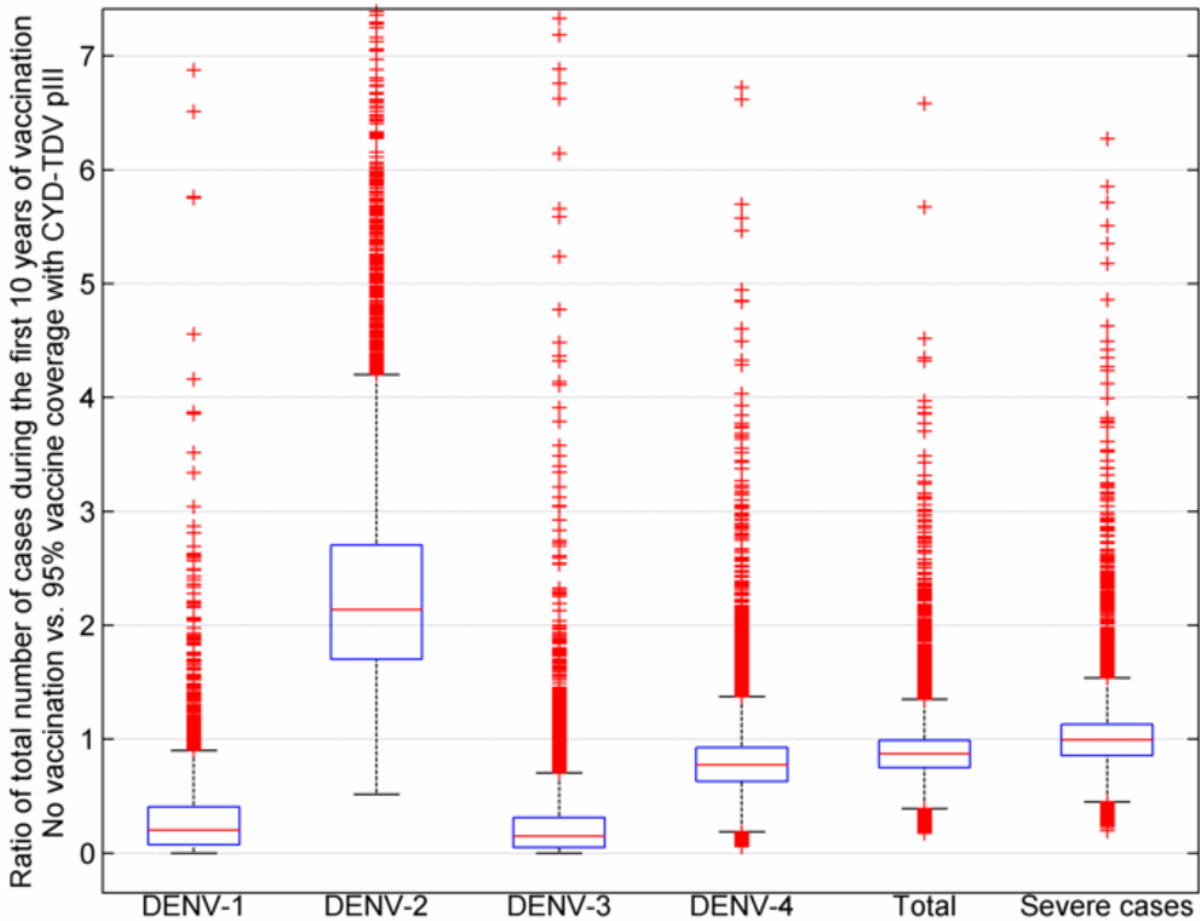


Figure B.10. Ratio between the total number of cases during the first 10 years of vaccination and during 10 years without vaccination. Vaccination coverage is 95% with a CYD-TDV pIII-type vaccine (see Table 3.1 for efficacies). Parameters apart from vaccine efficacy vary of [-20% +20%] from value in Table B.1 according to a Latin Hypercube Sample (LHS) of 10.000 repetitions.

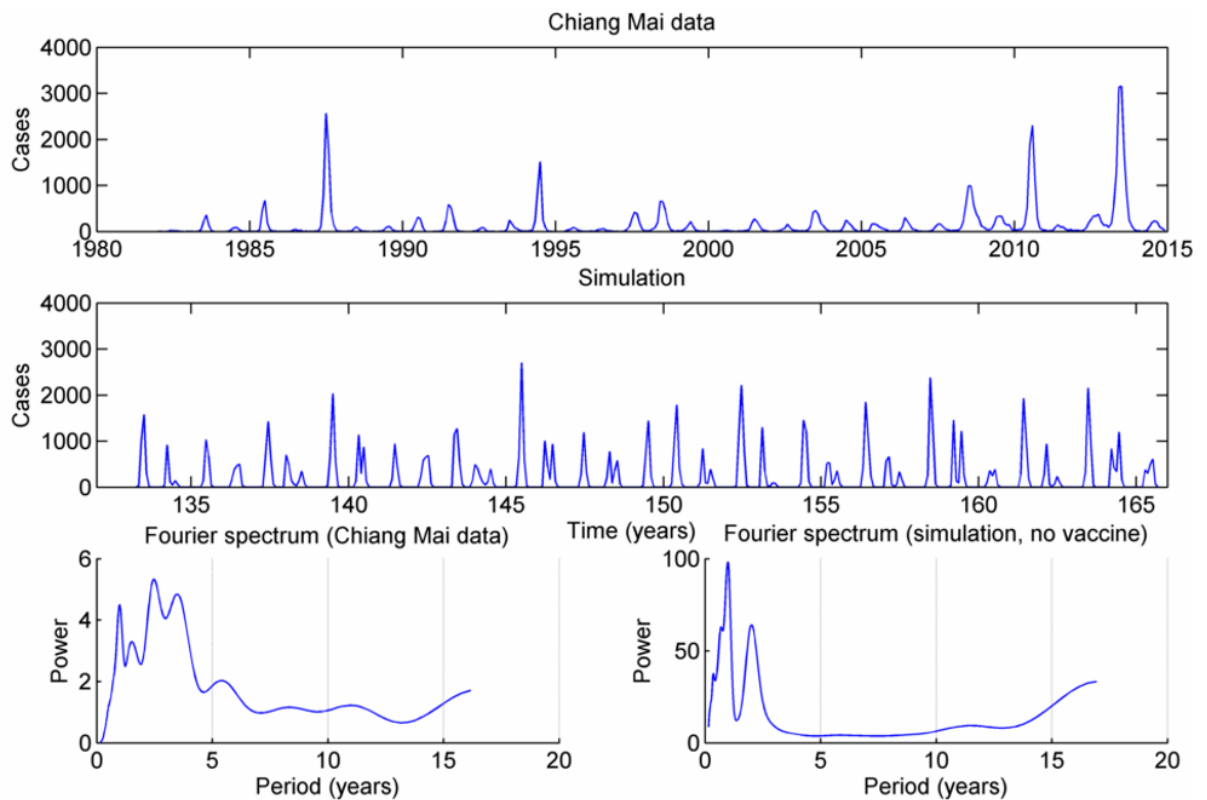


Figure B.11. Comparison between data and simulation. Top: Monthly dengue data from Chiang Mai. Middle: Dengue data from simulation of the model with no vaccination. Bottom: Fourier spectrum of number of cases (all serotype) for Chiang Mai data (left) and simulation (right).

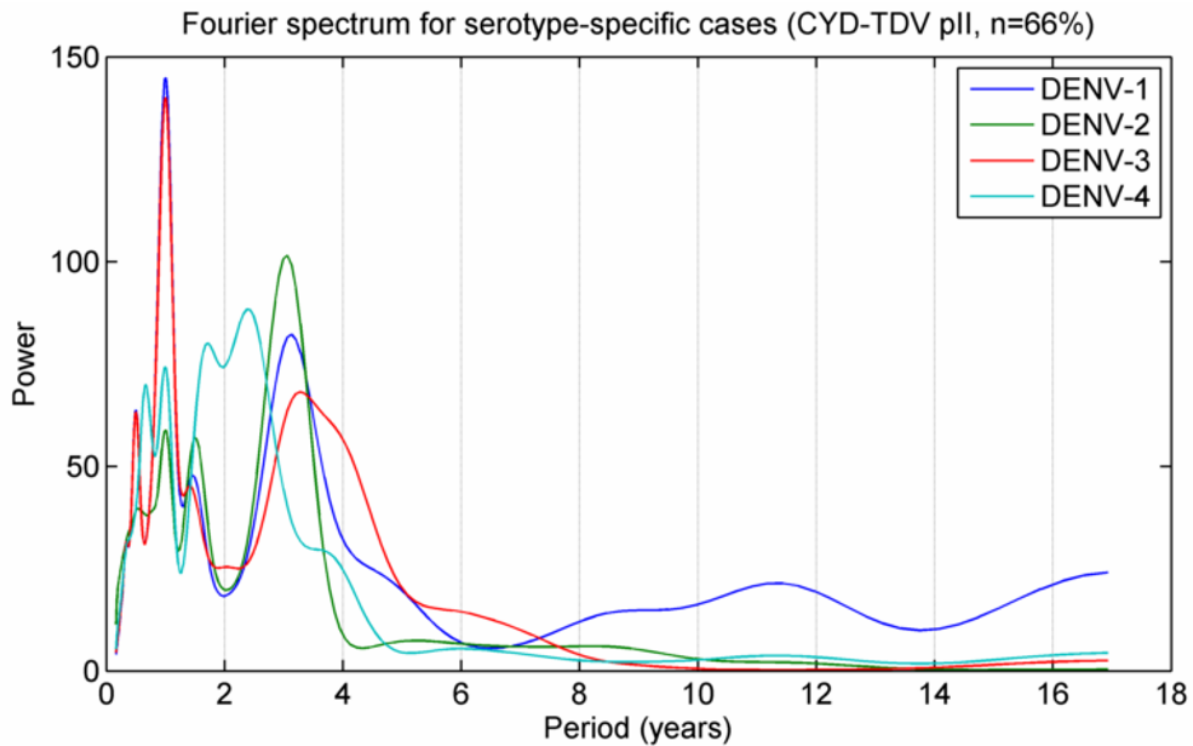


Figure B.12. Fourier spectrum of weekly number of cases (serotype-specific) without vaccination.

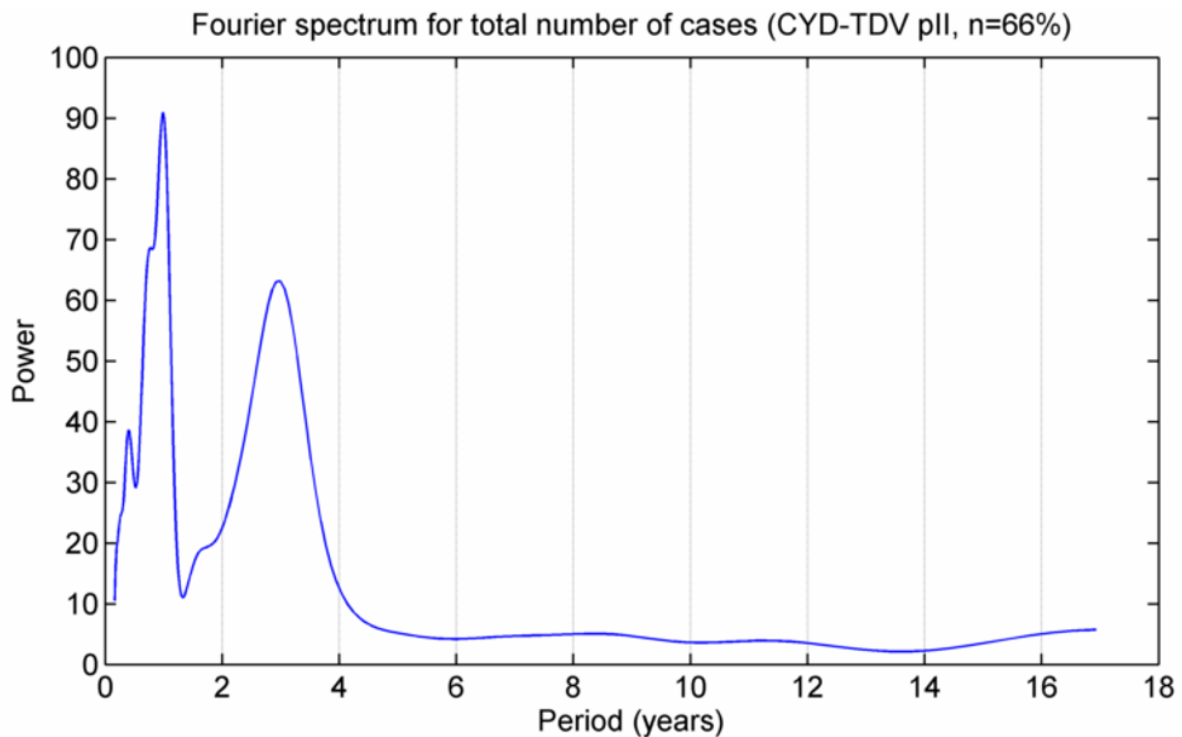


Figure B.13. Fourier spectrum of weekly number of cases (all serotypes) during the first 30 years of vaccination. CYD-TDV phase II trial -like vaccine and a 66% vaccination coverage.

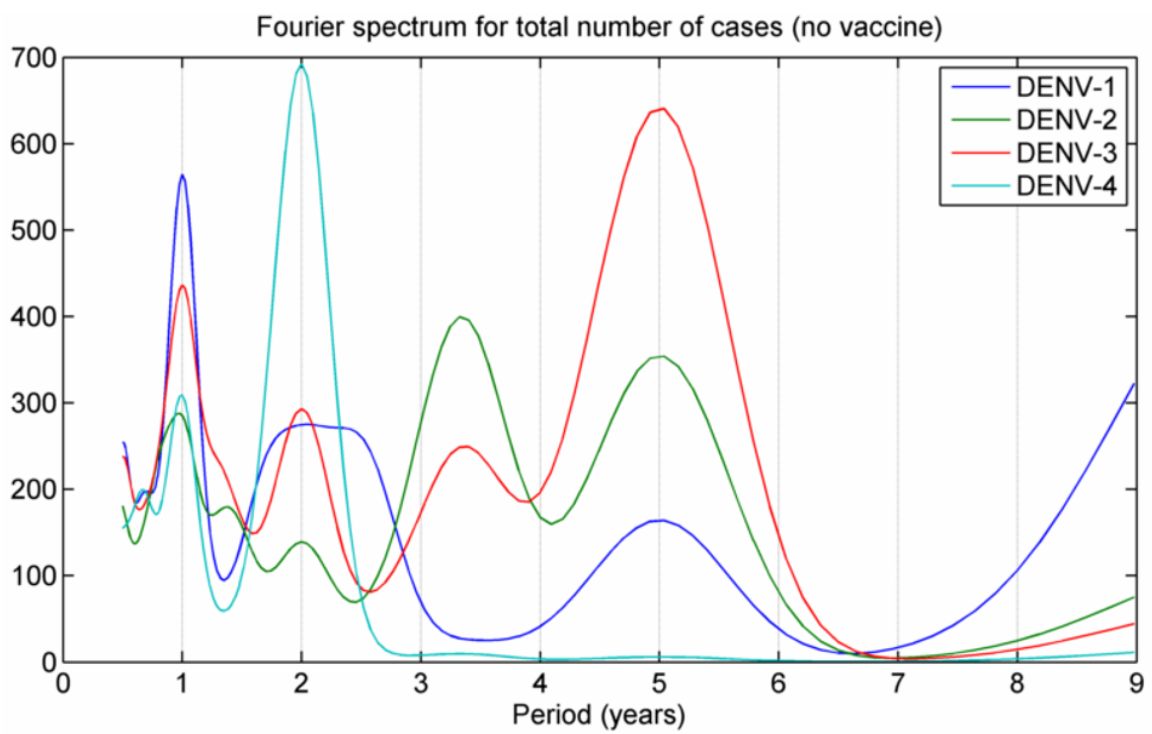


Figure B.14. Fourier spectrum of weekly number of cases (serotype-specific) during the first 30 years of vaccination. CYD-TDV phase II trial -like vaccine and a 66% vaccination coverage.

Résumé

L'étude des pathogènes est un des piliers des progrès en santé publique des dernières décennies. Actuellement, un axe principal qui reste à explorer pour poursuivre ces progrès réside dans l'étude des interactions entre les différents pathogènes qui circulent dans les mêmes populations. En effet, comme n'importe quel être vivant, un pathogène s'inscrit dans un écosystème avec lequel il interagit grandement et qui comporte, entre autres, d'autres pathogènes. Dans cette thèse nous nous sommes intéressés aux implications de ces interactions à différents niveaux. Tout d'abord, un large travail bibliographique a été mené afin d'identifier les interactions déjà connues et référencées, d'en tirer une catégorisation claire et utile, de souligner les manques actuels de la littérature dans ce domaine et d'introduire le concept de susceptibilité réalisée. Dans une seconde partie, il s'agit d'explorer les conséquences dynamiques possibles de certaines interactions identifiées précédemment et de tenter de développer des méthodes largement utilisables de détection d'interactions à partir de données populationnelles. Enfin, la dernière partie se penche sur le cas particulier de la Dengue, dont les quatre sérotypes interagissent fortement entre eux, et des possibles conséquences de ces interactions pour la vaccination contre cette maladie. Cette thèse apporte une nouvelle vision de la dynamique des pathogènes, en les intégrant dans le cadre plus large de la communauté de pathogènes. Elle ouvre sur les possibles progrès des méthodes statistiques et comment les modèles théoriques pourraient aider à la compréhension des communautés de pathogènes.

Mots-clés: Maladies infectieuses, Interactions entre pathogènes, Causalité, Dengue, Vaccination, Modélisation.

Abstract

The study of pathogens is a keystone of considerable progress for Public Health in the last decades. Nowadays, a promising field of study are interactions between pathogens circulating in the same populations. Indeed, just as any living species, a pathogen is part of an ecosystem, and within this ecosystem it interacts with numerous things, including other pathogens. In this PhD thesis we have been interested in the consequences of such interactions at several scales. Firstly a wide bibliographic work has been accomplished in order to identify known and documented interactions. From this work we propose several categories of interactions and point out the gaps in this literature. Then we explored the potential consequences on population of several interactions described in the first part, and tested promising methods to detect such interaction from population-scale data. Lastly we focused on the specific example of dengue, where four strongly interacting serotypes and current vaccine developments rise the issue of the interference between interactions and Public Health policies. A broader vision of pathogens dynamics rises from the embedding of pathogens into a community, and this vision could benefit from progress in statistical methods and theoretical models.

Keywords: Infectious diseases, Interactions between pathogens, Causality, Dengue, Vaccine, Modelling.