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Émergence et contrôle des épidémies dans les populations humaines

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« *Il suivait son idée. C'était une idée fixe et il était surpris de ne pas avancer.* »

Jacques Prévert,
poète

« *Les femmes, je le sais, ne doivent pas écrire. J'écris pourtant.* »

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Introduction

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1.1 Préambule

Depuis la préhistoire, les maladies causées par des agents pathogènes transmissibles ont profondément affecté l'histoire des populations humaines. La paléopathologie, qui est l'étude des maladies dans les populations préhistoriques par l'examen des marques laissées sur les squelettes ou les restes de tissus, a permis de révéler la prévalence et la propagation de certaines maladies infectieuses comme la tuberculose [Raff et al., 2006] et la lèpre [Robbins et al., 2001] et d'en établir des chronologies relatives. Au moyen âge en l'an 1347, les populations européennes ont connu l'une des plus grandes et dévastatrices épidémies de peste de leur histoire décimant entre 30 et 50 % des populations européennes [Lenz and Hybel, 2016]. Plus récemment, une pandémie de grippe particulièrement contagieuse a tué environ 40 millions de personnes entre 1918 et 1919.

Les infections peuvent être causées par différents agents pathogènes tels que les virus, les bactéries, les protozoaires et les champignons. Presque tous ces agents pathogènes sont des organismes microscopiques. La présence des micro-organismes a été révélée grâce à l'invention du microscope il y a environ 350 ans. Ce n'est que très récemment, grâce à l'amélioration technique du microscope, que des formes de micro-organismes plus petites ont été découvertes. La majorité des agents pathogènes qui sont responsables des maladies infectieuses chez les humains sont les virus (ex : Grippe, Variole, certaines infections diarrhéiques, Ebola, etc.) et les bactéries (ex : Choléra, Tuberculose, Infections à Salmonelle, etc.). Le lien entre certains micro-organismes et maladies n'a été prouvé que bien plus tard grâce aux travaux de Pasteur en 1860.

Encore aujourd'hui, malgré les nouvelles technologies médicales comme la vaccination (Edouard Jenner en 1796) et les antibiotiques (Alexander Flemming, 1928), les infections restent l'une des causes majeures de mortalité. En 2016, l'Organisation Mondiale de la Santé (OMS) émet un rapport montrant que trois maladies infectieuses - les maladies respiratoires, les infections diarrhéiques et la tuberculose - sont parmi les dix causes de mortalité les plus importantes tous niveaux socio-économiques confondus. Dans les pays en voie de développement, les maladies infectieuses sont même la première cause de mortalité. De plus, depuis quarante ans, les maladies infectieuses émergentes menacent la santé des populations humaines [Jones et al., 2008]. Elles ont la particularité d'infecter une large gamme d'espèces hôtes et d'être indéfiniment présents dans une population animale qui constitue *le réservoir* du pathogène infectieux. Ces pathogènes sont souvent

la cause d'épidémies imprévisibles et ont un fort taux de létalité.

Au cours de cette thèse, je me suis intéressée à deux aspects majeurs des maladies infectieuses humaines : l'étude de la dynamique épidémique des infections et leur contrôle. Le manuscrit est donc organisé en deux parties ; la première traite de l'étude de la dynamique des maladies infectieuses émergentes (chapitres 2 et 3) qui est peu connu en raison de l'imprévisibilité des émergences ; la seconde est consacrée à l'impact du comportement humain sur le contrôle des infections en prenant deux exemples, (i) l'impact de la prise de décision de vaccination sur la résurgence des infections (chapitre 4) et (ii) l'étude des pratiques culturelles qui limitent la propagation d'une infection dans un groupe social (chapitre 5).

Nous allons tout d'abord introduire le contexte général dans lequel s'inscrit la thèse. Nous nous intéresserons dans un premier temps à l'origine et la distribution géographique des pathogènes responsables des maladies - établies et émergentes - dans les populations humaines (section 1.2). Dans un second temps, nous recenserons quelques facteurs de risque pour l'émergence de nouveaux pathogènes. Nous verrons notamment que le comportement humain est souvent considéré comme la principale cause de l'émergence et de la propagation des agents pathogènes (section 1.3). Dans un troisième temps, nous nous pencherons plus particulièrement sur les principales caractéristiques qui définissent les maladies infectieuses émergentes ainsi que leur capacité de transmission dans les populations humaines (section 1.4). Dans un quatrième temps, l'importance de l'apport de la modélisation mathématique dans l'étude des maladies infectieuse sera présentée avec un bref historique (section 1.5). Enfin, nous énoncerons les stratégies de contrôle possibles (section 1.6).

1.2 Les maladies infectieuses

1.2.1 Origine

Les maladies infectieuses qui menacent les populations humaines sont causées par des agents pathogènes que l'on peut classer en deux catégories : (i) les pathogènes établis, qui sont les pathogènes inféodés aux populations humaines, c'est-à-dire ayant une bonne propagation inter humaine et étant capables de s'y maintenir, et (ii) les pathogènes émergents qui sont inféodés à une ou plusieurs populations animales mais qui en

émergent régulièrement pour infecter les populations humaines.

La plupart des maladies infectieuses, qu'elles soient établies depuis longtemps (rougeole, variole, oreillons, rubéole) ou qu'elles soient nouvellement émergentes (Ebola, Nipah, MERS, SARS), ont une origine animale [Jones et al., 2008; Taylor et al., 2001; Wolfe et al., 2007]. En effet, environ 60% des pathogènes qui infectent l'humain sont des zoonoses [Taylor et al., 2001] - pathogènes qui proviennent des animaux vertébrés mais qui infectent naturellement l'humain. Afin de comprendre le passage d'un pathogène se propageant exclusivement chez l'animal (étape I) à un pathogène se propageant exclusivement chez l'Homme (i.e. infections établies) (étape V), Wolfe et al. [2007] ont proposé un schéma de classification composé de 5 étapes évolutives (voir fig. 1.1). Les étapes intermédiaires (étapes II à IV) correspondent au moment où le pathogène reste présent dans la population animale mais émerge régulièrement dans la population humaine (les maladies émergentes).

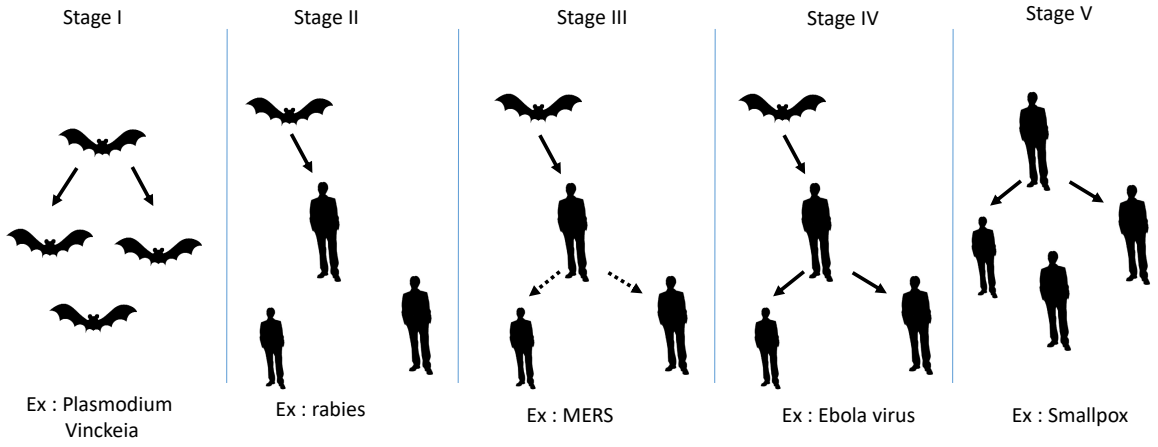

FIGURE 1.1 – Classification des pathogènes proposée par Wolfe et al. (2007). Représentation des étapes évolutives pour passer d'un pathogène qui n'infecte que des animaux (étape I) à un pathogène qui n'infecte que des êtres humains (étape V). Chaque étape correspond à une dynamique épidémiologique particulière chez l'Homme. L'étape II correspond à quelques émergences des populations animales vers les populations humaines sans transmission inter-humaine. L'étape III correspond à l'observation de quelques chaînes de transmission chez l'humain qui s'éteignent rapidement (pas d'épidémies). Enfin, l'étape IV correspond à l'observation de grosses épidémies dans les populations humaines, sans que le pathogène ne puisse se maintenir dans la population sans le réservoir. Figure tirée de Voinson et al. [2018]

Origine des maladies établies. La paléopathologie a permis de révéler des changements dans le patron de distribution des maladies infectieuses qui a accompagné la transition de la chasse et de la cueillette à l'agriculture, passant de quelques individus infectés à un grand nombre [Eshed et al., 2010; Raff et al., 2006]. De plus, l'analyse récente de données génétiques en biologie moléculaire a également permis de dater l'établissement de certains pathogènes dans les populations humaines (p. ex. la rougeole, la variole) au moment de l'essor de l'agriculture, il y a environ 11 000 ans [Furuse et al., 2010; Gubser and Smith, 2002]. Une hypothèse à l'établissement des pathogènes est que celle-ci a pu être possible parce qu'il y a eu un changement de densité des population humaines rendant possible le maintien des agents infectieux [Dobson and Carper, 1996]. Avant l'agriculture, les populations humaines vivaient en petits groupes assez isolés les uns des autres. Elles ont ensuite dû s'établir dans une localité donnée pour cultiver et élever des animaux, augmentant ainsi les contacts avec des animaux sauvages et domestiques. De plus, les populations humaines sont devenues plus denses, permettant le maintien et la propagation des agents pathogènes. L'essor de l'agriculture a ainsi rendu possible l'établissement de certains pathogènes dans l'espèce humaine alors qu'ils n'étaient originellement présents que chez l'animal [Dobson and Carper, 1996; Wolfe et al., 2007].

Origine des maladies émergentes Les pathogènes responsables des maladies émergentes ne sont pas capables de se maintenir dans les populations humaines mais ont la capacité d'y émerger régulièrement. Cela correspond aux étapes II à IV (voir fig. 2.1). Ces pathogènes sont présents indéfiniment dans un réservoir (c.-à-d. une population animale qui ne souffre pas ou peu de la pathogénicité de l'agent infectieux) et sont capables d'infecter une large gamme d'espèces hôtes, notamment les populations humaines. Ces pathogènes ne se maintiennent pas, pour le moment, au sein des populations humaines mais y émergent régulièrement conduisant à d'importantes épidémies. L'un des objets d'étude étant les maladies émergentes, nous y consacrerons une section à part entière Section 1.4.

1.2.2 Distribution géographique

La distribution géographique des pathogènes infectieux demeure un facteur important qui détermine le bien-être différentiel des populations humaines aujourd'hui. En effet, la probabilité d'émergence de nouveaux pathogènes, de même que la diversité en pathogène, ne sont pas homogènes à travers le monde.

La diversité des pathogènes humains dépend de nombreux facteurs environnementaux comme la latitude, la température moyenne ou encore les précipitations. Cashdan [2014] montre que le nombre de pathogènes humains est inversement corrélé à la distance de l'équateur, on observe donc une diversité en pathogènes plus importante lorsqu'on est proche de l'équateur (voir aussi [Dunn et al., 2010]) mais d'autres facteurs peuvent venir s'y ajouter. Plus particulièrement, la diversité des pathogènes en dehors des tropiques augmentent avec la température alors qu'au niveau des tropiques celle-ci augmente principalement avec le taux de précipitation [Cashdan, 2014]. En effet, au niveau des tropiques les pathogènes les plus représentés sont les pathogènes transmis par les moustiques dont le taux de précipitation a un rôle important dans le cycle de vie du moustique.

1.3 Interaction entre populations humaines et pathogènes

Le fait que la cause des maladies infectieuses soit multiple est largement accepté aujourd'hui. S'intéresser aux maladies infectieuses ce n'est pas seulement s'intéresser au micro-organisme pathogène mais c'est aussi s'intéresser aux interactions qu'il forme avec son environnement et ses hôtes potentiels (fig. 1.2). Lorsque l'on étudie les pathogènes humains, l'environnement socioculturel est important à prendre en compte puisque le comportement humain exerce une puissante influence sur l'émergence et le patron de transmission des agents pathogènes [Bauch and Galvani, 2013; Funk et al., 2010, 2014].

1.3.1 Facteurs environnementaux et démographiques

Les contacts entre hôtes constituent une étape importante du transfert de l'agent pathogène vers de nouveaux hôtes. Les changements sociaux et démographiques (p. ex. expansion et déplacement de la population humaine), comportementaux (p. ex. l'utilisation de drogue par voie intraveineuse, les pratiques et contacts sexuels et les pratiques agricoles), ou environnementaux (p. ex. la déforestation et l'expansion agricole)[Murray and Daszak, 2013; Wolfe et al., 2005], peuvent favoriser le passage de l'agent pathogène de l'animal à l'humain et son maintien.

Un exemple frappant et récent d'émergence puis d'établissement d'un agent pathogène dû au changement de comportement humain est le virus de l'immunodéficience humaine (VIH) qui provient du virus de l'immunodéficience simienne (VIS). Les virus de

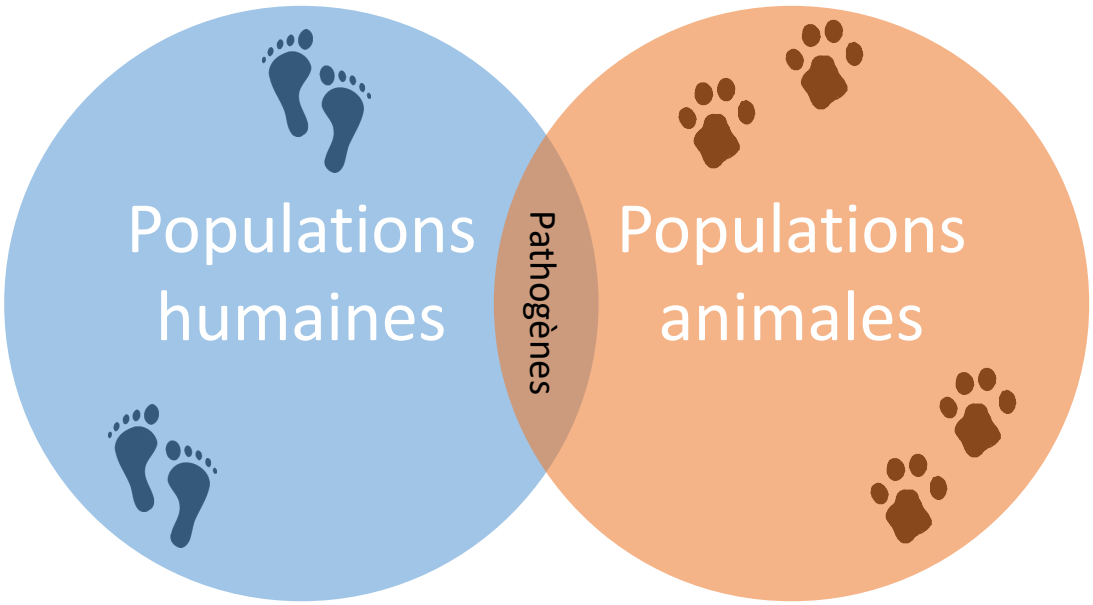

FIGURE 1.2 – Représentation schématique des interactions susceptibles de favoriser l'émergence de pathogènes infectieux émergents dans les populations humaines.

l'immunodéficience simienne (VIS) sont fréquents chez les primates de l'Ancien Monde et ont probablement causé de nombreuses infections zoonotiques dans les populations humaines par le passé, mais l'éloignement géographique des primates dans les forêts d'Afrique centrale par rapport aux populations humaines ont probablement limité l'émergence du virus en infectant un unique individu ou de petits groupes humains isolés [Keele et al., 2006; Van Heuverswyn et al., 2007]. L'urbanisation croissante entre 1884 et 1924 ainsi que la chasse sont deux hypothèses à l'émergence du virus dans les populations humaines [Worobey et al., 2008]. Puis, l'établissement du VIH a probablement été favorisé non seulement par des changements génétiques du pathogène pour conférer une adaptation à la transmission inter humaine (réplication possible du virus dans un hôte humain), préalablement partiellement réalisé chez l'hôte (les chimpanzés), mais aussi de changements dans les comportements humains facilitant la propagation au sein des populations comme les déplacements et les comportements sexuels (p.ex. la prostitution) [Singer, 2015].

1.3.2 Facteurs culturels

Les facteurs que nous appellerons culturels regroupent les croyances et comportements partagés par un groupe spécifique [Hewlett and Hewlett, 2008]. Paul [1955], dans son livre "*Health, Culture and Community*", est le premier à s'intéresser aux réactions

des populations humaines occasionnées par les programmes de santé publique qui leur sont imposés. Il montre, notamment, que lorsqu'une stratégie de contrôle est imposée et qu'elle n'est pas comprise par les populations locales, alors celles-ci l'arrêtent. Par exemple, au Pérou, Wellin [1955] montre que les populations locales arrêtent de faire bouillir leur eau avant de la consommer car ils n'ont pas associé l'action de faire bouillir l'eau à l'élimination des parasites initialement présent. Il est maintenant largement accepté que l'émergence ainsi que le patron de transmission des maladies infectieuses sont affectés par les cultures et le comportement humain. Une des perspectives de l'anthropologie de la santé est de comprendre comment les populations perçoivent, pensent et parlent des maladies afin de comprendre les pratiques culturelles associées.

Les pratiques culturelles qui amplifient les maladies épidémiques sont très étudiées afin de cibler les comportements à l'origine de l'infection et mettre en œuvre de meilleures stratégies de contrôle [Inhorn and Brown, 1997; Logan and Hunt, 1978; Nations, 1986]. Un exemple de pratique culturelle influençant la propagation des maladies infectieuses est la transmission de l'*échinococcose* dans les populations humaines au Turkana (Kenya). L'*échinococcose* est une infection parasitaire transmise à l'Homme par les chiens domestiques eux-mêmes infectés par le bétail. Un lien très fort existe entre les populations humaines et leurs chiens domestiques. Les excréments de chiens sont utilisés comme produits de beauté, afin de se protéger contre les mauvais esprits ou encore pour protéger la peau des femmes. Bien que les populations voient les œufs dans les excréments, aucun lien de causalité n'est établi entre leur présence et l'infection [French et al., 1980]. Cette situation rend l'adaptation culturelle vers des pratiques plus préventives moins probable. Les exemples mettant en évidence un comportement induisant une infection ne sont pas rares. Nations [1986] montre que les pratiques religieuses, le soin parental, les patrons de migration, les relations de parenté, les techniques agricoles ou encore les traitements médicaux traditionnels peuvent augmenter la probabilité d'émergence ou encore augmenter la transmission inter humaine.

1.4 Les maladies infectieuses émergentes

Au cours des 40 dernières années, les maladies infectieuses émergentes ont été reconnues comme l'une des plus importantes menaces pour la santé publique avec 335 événements d'émergence depuis 1940, nombre en augmentation significative entre 1940 et

2008, incluant le SARS, le MERS, le virus Ebola, la grippe aviaire et plus récemment le virus Zika [Jones et al., 2008]. Soixante-quinze pour cent des pathogènes émergents sont zoonotiques c'est-à-dire d'origine animale [Taylor et al., 2001]. Deux principales catégories d'infections émergentes sont généralement définies, les infections nouvellement émergentes et les infections ré-émergentes. Les premières sont des maladies qui apparaissent pour la première fois chez l'hôte humain, tandis que les secondes sont des maladies qui historiquement ont déjà touché les populations humaines, mais qui apparaissent dans une nouvelle région, sous une forme résistante aux antibiotiques ou réapparaissent après une longue période de contrôle ou une disparition [Fauci and Morens, 2012]. L'émergence de ces infections peut être récurrente c'est-à-dire que l'infection émerge sporadiquement pour contaminer la population humaine (voir encadré 1 qui présente l'exemple de la transmission du virus Ebola). La transmission entre humains étant limitée, l'apparition et la dynamique des épidémies humaines sont majoritairement associées à l'introduction récurrente du pathogène dans les populations humaines *via* le réservoir animal.

1.4.1 Le réservoir

L'OMS définit le réservoir d'un agent infectieux comme étant un animal, une personne, une plante, un sol, une substance ou une combinaison de ceux-ci dans lesquels vit normalement l'agent infectieux. L'agent infectieux dépend de ce réservoir pour sa survie et s'y multiplie. C'est à partir du réservoir que l'agent infectieux est transmis à un être humain ou à un autre hôte sensible. Cette définition est générale et implique la notion de persistance de l'hôte dans le réservoir. Un débat afin de savoir quelles sont les espèces à considérer dans le réservoir a débuté avec la première publication de Ashford [1997]. Ashford [1997] voit le réservoir comme un complexe écologique dans lequel le pathogène persiste. Ce complexe écologique prend en compte tous les compartiments dont le pathogène a besoin pour subsister ou terminer son cycle de vie (vecteurs, hôtes secondaires...). Si ce complexe écologique est correctement défini, alors le pathogène devrait survivre indéfiniment. Haydon et al. [2002] reprennent la définition de Ashford mais définissent le complexe écologique du réservoir différemment : ensemble de tous les hôtes qui subissent l'infection en dehors de l'hôte d'intérêt (intérêt du point de vue de l'étude). Tous ces hôtes sont alors impliqués dans le complexe écologique du réservoir. Ce que réfute Ashford [2003] en indiquant que les hôtes n'ayant pas de rôle dans la persistance du pathogène sont des hôtes occasionnels qui ne font pas partie du réservoir.

La définition de Ashford [1997] a l'avantage d'être générale, c'est-à-dire que pour un agent infectieux donné, il n'existe qu'un seul réservoir possible (c'est cette définition que nous utiliserons tout au long de cette thèse). Alors que pour Haydon et al. [2002] pour un agent pathogène donné, le réservoir va dépendre de la population d'intérêt. Par exemple, considérons le virus Nipah responsable de nombreuses épidémies dans les populations humaines d'Asie du Sud Est. Ce virus est maintenu indéfiniment dans les populations de chauve-souris frugivores de la famille des *Ptéropodidés*. Il est également capable d'infecter les populations de porcs, certains animaux domestiques comme les chiens et l'Homme. Si la population d'intérêt est l'Homme, alors d'après Haydon et al. [2002], le réservoir se compose des populations de chauve-souris, de porcs ainsi que des animaux domestiques. Pourtant le virus Nipah n'a besoin que des chauve souris pour survivre indéfiniment même s'il est capable d'infecter un grand nombre d'hôtes. Pour Ashford [1997], le réservoir du virus Nipah est alors seulement composé des chauve-souris frugivores. D'un point de vue empirique, considérer la définition de Haydon et al. [2002] a l'avantage de prendre en compte tous les hôtes et sources d'infection possibles de la population d'intérêt surtout quand on s'intéresse aux stratégies de contrôle à mettre en place pour protéger la population d'intérêt.

Certaines espèces animales sont plus susceptibles d'être le réservoir d'agents pathogènes du fait de leur proximité avec les populations humaines (p. ex. les rongeurs) et/ou du fait de leur biologie (p. ex les chauves souris). Plus particulièrement, les chauves souris sont connues pour être le réservoir d'un très grand nombre d'agents pathogènes responsables de maladies émergentes telles que la rage, le SARS, le MERS, Nipah mais aussi les virus responsables de certaines maladies établies telles que la rougeole, les oreillons ou encore l'hépatite C [Brussow, 2012; Drexler et al., 2012; Han et al., 2015]. Plus de 200 agents pathogènes ont été isolés sur les espèces de chauves souris avec parfois une soixantaine de virus par individu. Pourtant elles ne développent que rarement des symptômes liés à la pathogénicité des agents infectieux. Leur système immunitaire semble avoir évolué pour s'adapter à cette grande et diversifiée charge virale en empêchant les virus de trop se multiplier en leur sein [Moratelli and Calisher, 2015]. Les chauves souris sont également capables de s'adapter très rapidement aux changement écologiques et aux perturbations provoquées par l'Homme comme la déforestation par exemple [Moratelli and Calisher, 2015]. Cela fait d'elles un important réservoir pour l'émergence de nouveaux agents pathogènes chez l'espèce humaine.

Encadré 1 : Exemple du virus Ebola

La maladie à virus Ebola (EVD) appelée aussi fièvre hémorragique d'Ebola (EHF), est une infection émergente qui est causée par le virus Ebola appartenant à la famille des *Filoviridae*. Le virus a été découvert en 1976 lors de deux épidémies simultanées se déroulant en République Démocratique du Congo (RDC) et au Soudan [Suzuki and Gojobori, 1997]. Depuis sa découverte, le virus a ré-émergé et provoqué une vingtaine d'épidémies principalement dans les zones rurales de l'est et du Centre Afrique. Le genre Ebolavirus contient 5 souches distinctes listées ici de la plus virulente à la moins virulente : Zaire Ebola Virus (ZEBOV), Sudan Ebola Virus (SEBOV), Bundibugyo Ebola Virus (BDBV), Taï Forest Ebola Virus (TAFV), Reston Ebola Virus (REBOV) qui n'infecte pas l'Homme mais principalement les primates non-humains [Rajak et al., 2015]. Il a notamment été classé parmi les pathogènes de niveau 4 en biosécurité [Gunther et al., 2011].

Le réservoir du virus Ebola n'est pas encore connu à ce jour [Leendertz et al., 2015]. Il émerge dans la population humaine après un contact avec le réservoir ou une des espèces hôtes telles que les gorilles, les chimpanzés, les céphalophes ou encore les porcs. Jezek et al. [1999] montrent qu'entre 1981 et 1985 dans la région équatoriale de la République démocratique du Congo, le virus a émergé épisodiquement pour infecter l'Homme sans donner lieu à une épidémie. L'émergence récurrente du virus dans les populations humaines ne semble donc pas rare. Une propagation du virus par transmission directe entre individus est possible. Le virus est retrouvé dans une large variété de fluides corporels lors de la phase aiguë de l'infection [Bausch et al., 2007], permettant ainsi sa transmission.

Le virus Ebola, qui a commencé par être un problème localisé en Afrique, est devenu au fil des épidémies une menace globale pour différentes raisons. Le virus est un pathogène zoonotique qui provoque des épidémies récurrentes en Afrique en émergeant et ré-émergeant [Peters et al., 1994]. Une vingtaine d'épidémies ont été répertoriées depuis la découverte du virus en 1976 [De La Vega et al., 2015]. Ce chiffre sous-estime très certainement le nombre total d'émergences car toutes les émergences n'aboutissent pas forcément à la propagation de l'infection dans la population [Jezek et al., 1999].

1.4.2 Transmission du pathogène

Transmission vers les espèces hôtes. Les pathogènes responsables des maladies infectieuses émergentes sont capables d'infecter une large gamme d'espèces hôtes (voir Table 1.1) qui vont souffrir plus ou moins fortement de la pathogénicité de l'agent infectieux. Par exemple dans le cas des Henipavirus (Hendra et Nipah virus), contrairement à la maladie grave que manifestent les chevaux infectés par le virus Hendra, la plupart des porcs infectés par le virus Nipah présentent une maladie bénigne. En effet, 41 % des fermiers qui ont été infectés par le virus n'ont pas reporté d'augmentation du nombre de porcs malades ou morts au sein de leurs fermes [Parashar et al., 2000].

Transmission vers l'espèce humaine. L'influence du réservoir et des espèces hôtes sur les épidémies humaines est difficilement évaluable. Souvent, les épidémies sont détectées une fois qu'un certain nombre d'individus est contaminé. Les petites émergences chez des groupes d'individus isolés peuvent passer inaperçues. De plus, une fois que l'épidémie a débuté, il est difficile d'être sûr de l'origine de l'infection pour l'individu. Un individu peut être infecté par une maladie émergente via deux sources d'infection : soit *primaire*, c'est-à-dire l'infection provient du réservoir ou d'une espèce hôte, soit *secondaire*, dans ce cas l'infection provient d'une contamination par un autre individu infecté. Pour en connaitre l'origine, les individus infectés sont soumis à un questionnaire afin de tracer les contacts pendant la période d'incubation présumée (période durant laquelle l'individu est infecté mais pas contaminant). S'il n'a pas été en contact avec un autre individu infecté alors l'origine de l'infection est considérée comme primaire ; par contre, s'il a eu un contact avec un individu infecté alors l'origine est considérée comme secondaire, même si l'individu a été en contact avec le réservoir ou une espèce animale hôte [Chowell et al., 2014; Luby et al., 2009]. Cette méthode sous estime donc très certainement la proportion du nombre de cas infectés par le réservoir ou les espèces hôtes.

Transmission entre humains. La transmission inter humaine des maladies infectieuses émergentes est faible de manière générale. Dans le tableau 1.1, on remarque que le taux de reproduction de base (R_0), qui représente le nombre moyen d'individus infectés par un individu infectieux, est relativement faible. Le seuil du taux de reproduction de base à partir duquel une infection est considérée comme se propageant dans la population est de 1. Il faut donc qu'en moyenne les individus infectés contaminent au moins 1 individu

Virus	**Réservoir**	**Espèces hôtes**	R_0	**Taux de létalité**	**Références**
Virus Lassa	Rongeurs (*Mastomys Natalensis*)	Humains	–	12 à 23 %	[Bonwitt et al., 2017; Richmond and Baglole, 2003]
Virus Nipah	Chauves souris (*Ptéropodidés*)	Porcs, vaches, chèvres, humains	0.48	40 à 70 %	[Chowdhury et al., 2014; Escaffre et al., 2013; Gurley et al., 2017; Luby et al., 2009]
Virus Hendra	Chauve souris (*Ptéropodidés*)	Chevaux	0	50 %	[Escaffre et al., 2013; Halpin et al., 2000; Hess et al., 2011]
Virus Ebola	?	Céphalophes, porcs, primates non-humains, humains	1.5 – 2.5	50 à 90 %	[Athertone et al., 2017; Ghazanfar et al., 2015; Kuhn and Calisher, 2008]
Virus Marburg	Chauve souris	primates non-humains, humains	1.6	25 à 90 %	[Ajelli and Merler, 2012; Brussow, 2012]
SARS-CoV	Chauve souris frugivores	Raton laveurs (*Nyctereutes procyonoides*), civettes masquées (*Paguma larvata*), humains	2 – 3	6 à 9 %	[Li et al., 2005; Zumla et al., 2015]
MERS-CoV	Chauve souris frugivores, dromadaires (*camelus dromedarius*)	humains	< 1	40 %	[Sabir et al., 2016; Zumla et al., 2015]

TABLE 1.1 – Caractéristiques de certaines maladies infectieuses émergentes. La liste des maladies infectieuses émergentes est non exhaustive et ne représente qu'un petit échantillon. Le taux de létalité ainsi que le taux de reproduction de base (R_0) sont donnés pour l'espèce humaine. Le taux de reproduction de base (R_0) correspond au nombre moyen d'individus infectés par un individu infectieux, en ne considérant que la transmission inter humaine.

au cours de leur période d'infectiosité sinon l'infection s'éteint. La propagation de l'agent pathogène peut occasionnellement être élevée lorsque les conditions sont favorables à la transmission inter humaine telles que dans les hôpitaux ou les centres de soins. Souvent, les personnels soignants possèdent peu de moyens économiques, sont peu formés et la proximité entre soignants et patients est forte. De grosses épidémies y sont alors observées par exemple lors des épidémies d'Ebola, du virus Lassa ou encore du virus Nipah [Fisher-Hoch et al., 1995; Luby and Gurley, 2015].

1.5 L'apport de la modélisation en épidémiologie

Un modèle mathématique est un micro monde imaginaire constitué d'entités se comportant selon des règles précises [Huppert and Katriel, 2013]. La modélisation en épidémiologie sert depuis de nombreuses années. Elle permet de simuler la propagation d'une épidémie dans une population et de tester l'efficacité d'une stratégie de contrôle. Elle permet également de comprendre et de décrire la propagation d'une maladie infectieuse en testant l'effet de différents facteurs comme les contacts entre les individus sains et les individus infectés, le comportement individuel, l'interaction entre les individus, le temps de latence du pathogène, la vaccination, les facteurs écologiques et environnementaux, la diversité des sources d'infection, etc.

1.5.1 Modèle de Bernoulli

La première publication ayant utilisé les mathématiques afin de répondre à une question épidémiologique date de 1760. À cette époque, les épidémies de variole sont nombreuses et la mortalité associée y est assez forte. L'inoculation (ici utilisée pour désigner la variolisation qui consiste en la mise en contact de l'agent pathogène à l'origine de la variole avec un individu sain) est utilisée pour protéger les individus contre la variole. Cependant, ce procédé n'est pas sans risque et un certain taux de mortalité y est associé, même si celui-ci est bien plus faible qu'en cas d'infection lors d'une épidémie. Cette maladie entraîne la mort d'environ un huitième ou un septième de ceux qu'elle attaque alors que le risque de mourir des suites de l'inoculation est de 1/200. Dans l'article "*Essai d'une nouvelle analyse de la mortalité causée par la petite vérole*", traduit en anglais par Blower (2004), Bernoulli a développé un modèle mathématique pour analyser la mortalité due à la variole en Angleterre [Blower and Bernoulli, 2004]. Dans ce modèle, Daniel

Bernoulli compare trois états possibles, (i) population sans variole, (ii) population avec variole mais sans inoculation et (iii) population avec variole et inoculation. Il montre que malgré le coût lié à l'inoculation, généraliser l'inoculation à la naissance permettrait de faire gagner 3 années de vie aux individus. Cette étude est exceptionnelle car elle arrive bien avant la découverte de la théorie des germes. Ce premier modèle de Daniel Bernoulli est le tremplin de l'épidémiologie théorique.

1.5.2 D'autres modèles ayant eu un apport significatif

Les modèles mathématiques récents en épidémiologie prennent leurs racines au $20^{\text{è}me}$ siècle avec les travaux de Hamer, Ross, McDonald, Kermack et Mc Kendrick [Hethcote, 2000]. Hamer établit un modèle pour comprendre les épidémies récurrentes de la rougeole [Hamer, 1906]. Ronald Ross analyse pour la première fois une maladie vectorielle et met en évidence l'importance de la population de moustiques dans la transmission de la malaria dans les populations humaines [Ross, 1916]. Par la suite, il développe avec McDonald un modèle de transmission de la malaria prenant en compte l'interaction entre les populations de moustiques et les populations humaines [Smith et al., 2012]. Kermack et McKendrick ont publié une série d'articles sur ce que l'on appelle maintenant le modèle SIR [Kermack and McKendrick, 1927]. Ils ont adapté leur modèle à la peste de Bombay de 1906 et ont pu conclure que : (1) Il existe un seuil de densité de population qui dépend des taux d'infection, de guérison et de mortalité propres à l'épidémie. Aucune épidémie ne peut se produire si la densité de la population est inférieure à cette valeur seuil. (2) Une légère augmentation du taux d'infection peut entraîner de grandes épidémies. (3) Une épidémie, en général, prend fin avant que la population susceptible ne soit épuisée.

Le modèle de Kermack et McKendrick correspond à un modèle déterministe à trois compartiments Susceptible-Infecté-Rétabli (SIR) où les transitions entre compartiments se font à l'aide des équations différentielles ordinaires ci-dessous :

$$\frac{d\mathrm{S}}{dt} = -\beta \mathrm{SI} \tag{1.1a}$$

$$\frac{d\mathrm{I}}{dt} = \beta \mathrm{SI} - \gamma \mathrm{I} \tag{1.1b}$$

$$\frac{d\mathrm{R}}{dt} = \gamma \mathrm{I} \tag{1.1c}$$

$$\mathrm{N} = \mathrm{S}(t) + \mathrm{I}(t) + \mathrm{R}(t) \tag{1.1d}$$

Ce modèle est un modèle à compartiments où chaque individu hôte (N) peut se trouver dans le compartiment des susceptibles (S), des infectés (I) ou des rétablis (R) à chaque pas de temps. À partir du moment où un individu est infecté, il devient immédiatement infectieux et aucune structure n'est considérée. Le compartiment R comprend tous les individus qui ne participent plus à la chaîne de transmission de l'infection sans distinction de cause (morts, immunisés ou rétablis). Les équations 1.1 décrivent les taux de transitions entre les trois états épidémiologiques possibles. β correspond au taux d'infection par contact et γ est le taux de guérison. Dans le modèle de Kermack-McKendrick, la durée pendant laquelle un individu reste à l'état infecté et infectieux est $1/\gamma$. Ce modèle convient aux épidémies qui se propagent à travers la population à des échelles de temps rapides permettant de négliger des processus écologiques tels que les naissances et les décès.

Le modèle SIR (eq. (1.1)) est un exemple de modèle entièrement mélangé dans lequel un hôte infecté peut infecter tout hôte sensible de la population. Il s'agit d'une hypothèse forte concernant les schémas de contact de l'hôte qui peut ne pas être justifiée pour certaines maladies humaines telles que les maladies sexuellement transmissibles (MST).

À l'aide du système d'équations 1.1, un seuil à partir duquel la propagation est possible est donné par :

$$\frac{\beta S_0}{\gamma} > 1, \tag{1.2}$$

où S_0 correspond à l'état de la population sans maladie. Sans structure, $S_0 = N$ ce qui donne

$$\frac{\beta N}{\gamma} > 1. \tag{1.3}$$

L'eq. (1.3) est connue comme étant le taux de reproduction de base ($R_0 = \beta N/\gamma$) [Diekmann et al., 1990]. Le taux de reproduction de base représente le nombre moyen d'individus infectés par un individu infecté tout au long de sa période d'infectiosité dans une population entièrement constituée d'individus susceptibles. Il détermine si une infection initiale se propage ou disparaît.

Ce modèle a ensuite été enrichi afin de répondre à d'autres questions comme l'effet d'une transmission fréquence dépendante, de la stochasticité, des processus écologiques de mortalité et natalité, etc.

1.5.3 Et aujourd'hui ?

La modélisation mathématique est l'un des outils les plus importants pour l'analyse des caractéristiques épidémiologiques d'une maladie infectieuse et peut fournir des informations utiles sur la dynamique de la maladie. Les organisations de santé publique du monde entier utilisent de tels modèles pour évaluer et mettre au point des politiques d'intervention en cas d'épidémies. La simulation permet une évaluation et une prise de décision rapide, fournissant une compréhension de la dynamique d'une épidémie. L'analyse des modèles mathématiques permet de comprendre les caractéristiques de transmission des maladies infectieuses dans certaines communautés, régions ou pays et peut conduire à développer une approche ciblée afin de réduire l'incidence. Lorsque la modélisation s'intéresse aux maladies établies, ne considérer que la propagation de l'infection dans la population humaine est une hypothèse justifiable dans le sens où la transmission du pathogène ne dépend que de sa capacité à se propager entre individus. Cependant, lorsque le patron de transmission des maladies infectieuses émergentes est analysé alors cette hypothèse n'est plus valable [Lloyd-Smith et al., 2009]. Lloyd-Smith et al. [2009] font la synthèse de 442 modèles mathématiques qui analysent la transmission des pathogènes zoonotiques et concluent que les modèles qui prennent en compte l'émergence du pathogène sont "*dismayingly rare*". Les seuls modèles qui prennent en compte explicitement l'émergence du pathogène sont spécifiques à une maladie c'est-à-dire qu'ils ne permettent pas d'établir un aperçu général du patron de transmission des maladies émergentes. Les chapitres 2 et 3 de cette thèse ont pour objectif de combler cette lacune.

1.6 Les stratégies de contrôle

Les stratégies de contrôle utilisées afin d'empêcher la propagation d'une infection ou de la stopper sont multiples. Elles peuvent être dues à l'innovation médicale (p. ex. les antibiotiques, la vaccination), aux comportements individuels (p. ex. se laver les mains, porter un masque), à l'amélioration des conditions d'hygiène ou encore aux pratiques culturelles (p. ex. soins, isolement). Mais leur efficacité et leur généralisation sont dépendantes d'autres facteurs comme l'acceptation sociale de la pratique et sa compréhension. Par exemple, avant même la découverte des agents pathogènes infectieux, *Ignace Semmelweis* montre que le manque d'hygiène des médecins et étudiants est la cause de la fièvre puerpérale des femmes ayant accouché. En obligeant les médecins à se laver les

mains avant chaque auscultation, il observe une diminution drastique du nombre de morts causés par cette infection. Pourtant, il n'arrive pas à convaincre la communauté médicale et le nombre de décès par fièvre puerpérale reste très élevé [Noskin and Peterson, 2001]. La découverte de stratégies de contrôle n'est donc pas suffisante pour observer un contrôle des infections il faut que cette pratique soit reconnue, acceptée et utilisée par les populations humaines.

1.6.1 Lien entre étiologie et pratiques

Les pratiques de contrôle et de prévention utilisées par les populations dépendent fortement des croyances concernant la cause de l'infection (l'étiologie) [Green, 1999; Murdock, 1980]. Si on prend l'exemple de la peste bubonique au XIV ème Siècle en Europe, les populations pensaient qu'elle se transmettait via la contamination de l'air pollué par les individus infectés (appelé *théorie de miasmes*) [Slack, 1988]. Pour s'en prémunir, les individus infectés étaient donc isolés ensemble dans des quartiers spécifiques. A leur mort, les cadavres étaient retirés dans les six heures maximum puis par souci de rapidité, ils étaient enterrés avec un rituel beaucoup plus court. La vente des biens de personnes mortes dues à la peste bubonique était interdite et leur maison était souvent brûlée pour éviter une contamination [Slack, 1988]. L'utilisation de fumées pour assainir l'air des miasmes était courante. Même si maintenant on sait que cette pratique ne protégeait pas des infections, elle est compréhensible du point de vue de leur croyance.

Toutes les sociétés ont développé une connaissance locale des infections et des pratiques de soins qui peuvent différer du modèle culturel euro-américain, à savoir le modèle biomédical. Le modèle biomédical correspond au modèle de santé pensé et utilisé dans les pays euro-américains. Il reprend la théorie des germes largement établie et reconnue et les pratiques de soins sont tournées vers l'individu [Sobo and Loustaunau, 2010]. Un modèle culturel pour une maladie consiste en l'explication et les prédictions qu'un groupe de personnes fait à propos de cette maladie [Hewlett and Hewlett, 2008].

Hewlett and Hewlett [2008] étudient la perception et la croyance du virus Ebola ainsi que de l'épidémie associée dans les populations Gulu en Ouganda et Congo. L'infection par le virus Ebola est perçue comme une possession du corps de l'individu infecté par un esprit malin. La cause de l'infection est donc perçue comme une cause surnaturelle. Même si les termes employés sont différents du modèle biomédical ("esprit malin" à la place "d'agent pathogène"), les pratiques peuvent permettre de limiter la propagation de

l'infection. En effet, les populations ont des pratiques qui permettent de limiter la propagation de l'agent pathogène dans la population comme la mise en place d'un isolement de la personne infectée (isolement dans la maison la plus éloignée du village). Les individus pouvant prendre soin des individus infectés sont les individus ayant eux mêmes été infectés ou une personne âgée. On peut également observer un arrêt des rapports sexuels pendant l'épidémie, le port d'un bracelet en feuilles de banane censé protéger contre le mauvais esprit, etc [Hewlett and Hewlett, 2008]. Même si toutes les pratiques ne permettent pas de protéger ou de limiter la propagation de l'infection, certaines telles que l'isolement et les soins apportés par des individus immunisés semble adaptatives. Dans le chapitre 4, nous verrons que des pratiques culturelles qui empêchent la propagation des maladies infectieuses peuvent être mises en place par les populations humaines lorsqu'une épidémie est en cours.

1.6.2 La vaccination

Au XVIII ème Siècle, avant l'apparition de la vaccination, les populations se protégeaient de certaines infections notamment de la variole grâce à l'inoculation qui consistait à introduire l'agent pathogène à l'origine de l'infection afin de s'en prémunir. Pour la variole, le risque de décès pouvait varier de 1/50 à 1/250 selon la pratique utilisée.

Il faudra attendre 1796 pour qu'Edward Jenner, médecin de campagne anglais, mette au point le procédé de vaccination en partant de cette observation : les fermières ayant été infectées par la variole de la vache (ou *cow-pox*) - maladie bénigne transmise par les pustules présentes sur les pies des vaches - ne sont pas atteintes par la variole humaine. Il décide donc d'utiliser la variole de vache pour effectuer les inoculations et constate alors que tous les patients ayant été inoculés avec du pus de pustules de vaches sont entièrement immunisés contre la variole humaine. Cette nouvelle pratique connut un succès immédiat. En effet l'inoculation avec un agent bénin plutôt qu'infectieux est beaucoup moins risquée et coûteuse pour les individus. En 1853, la vaccination devient même obligatoire pour les nouveaux-nés en Angleterre. Cette innovation médicale a permis l'éradication mondiale de la variole en 1980.

Encore aujourd'hui, la vaccination est un moyen reconnu comme efficace pour lutter contre les infections [CDC, 1999]. Cependant, aucune autre infection n'a pu être éradiquée. Une protection de la population est néanmoins possible lorsqu'une assez large proportion de la population est vaccinée et a donc atteint l'immunité collective [May and

Silverman, 2003]. Ce seuil est cependant difficile à atteindre mais surtout à maintenir. En effet, empiriquement, une diminution de la couverture vaccinale n'est pas rare lorsque des campagnes de vaccination volontaire sont mises en place, par exemple la rougeole [Jansen et al., 2003] et la coqueluche [Baker, 2003]. Les diminutions sont dues au fait que ces campagnes reposent intégralement sur la prise de décision des individus à accepter la vaccination. Afin d'y pallier, des campagnes de vaccination obligatoire peuvent être mises en place. Pour la protection de la santé publique, ces campagnes de vaccination peuvent être justifiées. Pourtant, du point de vue des libertés civiles, elles en sont des violations [Moran et al., 2008]. Le conflit entre décision individuelle et protection de la population est clair. Comprendre les facteurs influençant la prise de décision semble important surtout dans le cas des campagnes de vaccination volontaire qui restent majoritaires. Pour cela, nous verrons dans le chapitre 5, comment l'intégration d'une prise de décision dépendante de biais cognitifs humains vont façonner la dynamique de la couverture vaccinale.

1.7 Contexte et objectifs de la thèse

Comme nous l'avons vu, les maladies infectieuses ont façonné l'histoire de l'espèce humaine et encore aujourd'hui, malgré les innovations médicales telles que la vaccination, elles restent une des principales causes de mortalité. Depuis quarante ans, une des menaces majeures est l'émergence de nouveaux pathogènes et cela pour plusieurs raisons : l'émergence de l'infection est imprévisible, les épidémies sont difficilement contrôlables, l'effet du réservoir et des populations animales intermédiaires est mal connu. Les maladies infectieuses émergentes peuvent s'adapter à la transmission inter humaine et devenir une maladie établie que même par vaccination, nous ne contrôlons pas toujours. C'est dans ce contexte que s'inscrit ma thèse. En épidémiologie, deux objectifs principaux dominent les études. L'étude du patron de transmission des infections et le contrôle de ces infections. La thèse se découpe donc en deux parties, l'étude du patron de distribution des maladies infectieuses émergentes (chapitres 2 et 3) et l'étude de deux types de stratégies de contrôle, (i) l'efficacité de la vaccination (chapitre 4) et (ii) l'étude des pratiques culturelles qui limitent la propagation d'une infection dans un groupe social (chapitre 5).

Patron de transmission des maladies infectieuses émergentes. La caractéristique principale des maladies émergentes est la persistance du pathogène dans une espèce animale hôte que l'on définit comme étant *le réservoir*. L'essentiel des modèles mathématiques concernant les maladies infectieuses émergentes font l'hypothèse que l'émergence du pathogène du réservoir est négligeable et que la transmission inter humaine suffit à prédire la prévalence de l'infection. Or, les épidémies causées par les pathogènes émergents peuvent être grandes sans pour autant que la transmission inter humaine le soit. Nous nous intéresserons dans le premier chapitre intitulé "*Stochastic dynamics of an epidemic with recurrent spillovers from an endemic reservoir*", à l'effet de l'émergence récurrente du pathogène *via* le réservoir sur la dynamique épidémiologique dans la population humaine.

En plus du réservoir, les pathogènes responsables des maladies émergentes sont capables d'infecter un large éventail d'espèces hôtes qui vont eux-mêmes avoir un impact sur la dynamique épidémiologique humaine. Ces espèces seront définies comme des hôtes intermédiaires. Elles peuvent agir de deux manières : soit comme une seconde source d'infection en plus du réservoir, par exemple, la transmission du virus du Nipah

à l'espèce humaine peut se faire *via* le réservoir et *la population intermédiaire*; soit permettre au pathogène d'infecter la population humaine quand aucune émergence n'a été associée au réservoir, par exemple, dans le cas du virus Hendra, toutes les émergences ont été associées aux contacts avec l'hôte intermédiaire c'est-à-dire les chevaux. Dans le chapitre intitulé "*Impact of an intermediate host on the epidemiological dynamics of emerging infectious diseases*", nous étudierons les effets d'amplification ou de dilution de l'ajout de l'espèce intermédiaire sur la dynamique épidémique.

Stratégies de contrôle. Le contrôle des maladies infectieuses a été le premier sujet d'étude en modélisation mathématique. Cela permet de tester l'efficacité d'une stratégie avant de l'implémenter. Pour les maladies établies, l'un des moyens reconnus comme efficaces est la vaccination. Elle a permis d'éradiquer la variole en 1980. Pourtant depuis aucune éradication supplémentaire n'a été réalisée. La vaccination permet cependant de protéger les populations lorsqu'un certain nombre d'individus de la population est vacciné (couverture vaccinale). Or, on observe des résurgences de maladies infectieuses pourtant auparavant contrôlées par la vaccination (p. ex. rougeole, rubéole, etc.) certainement dues au fait que les campagnes de vaccination sont volontaires. Le chapitre 3 intitulé "*Beyond rational decision-making : modelling the influence of cognitive biases on the dynamics of vaccination coverage*", nous permet de comprendre les fluctuations de la couverture vaccinale observées dans les populations humaines lorsque la prise de décision concernant la vaccination est modélisée en prenant compte des biais cognitifs tels que le conformisme (le fait d'adopter l'opinion la plus commune dans la population) et le biais de confirmation (le fait de mettre plus de poids sur les informations qui confirment l'opinion).

Lorsqu'aucune innovation médicale n'est possible, c'est-à-dire lorsqu'aucun traitement n'existe pour contrôler ou soigner l'infection, la seule stratégie possible est d'éviter ou de limiter la propagation de l'infection dans les populations humaines. Dans le cas des maladies infectieuses émergentes, peu de traitements efficaces sont disponibles. Néanmoins, on sait que les populations humaines sont en contact avec les agents pathogènes depuis très longtemps. Les pathogènes étant de puissants agents de sélection naturelle, ce contact aurait pu permettre aux populations humaines d'acquérir des pratiques culturelles adaptées au contrôle des infections. Pourtant, puisque les populations ont souvent des croyances surnaturelles concernant la cause de l'infection, il est considéré que leurs pratiques culturelles associées sont mal adaptatives. Dans le chapitre 4 intitulé "*Cultural*

adaptations to infectious diseases transmission", nous établirons une synthèse des pratiques culturelles qui, contrairement à ce qui est généralement supposé, les populations humaines ont également adopté des comportement empêchant ou limitant la propagation de l'infection dans les populations.

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Chapitre 2

Stochastic dynamics of an epidemic with recurrent spillovers from an endemic reservoir

MARINA VOINSON, SYLVAIN BILLIARD, ALEXANDRA ALVERGNE, CHARLINE SMADI

Sommaire

L'émergence de nouveaux pathogènes menacent la santé et le bien-être des populations humaines. Les pathogènes infectieux sont maintenus dans des populations animales qui en sont le *réservoir*. Le réservoir est défini comme étant le complexe écologique dans lequel le pathogène est indéfiniment maintenu, il y est donc endémique [Ashford, 1997]. L'émergence de ces nouveaux pathogènes est en augmentation en raison de la croissance démographique des populations humaines, de la déforestation et de l'intensification de l'agriculture [Jones et al., 2008; Keesing et al., 2010]. Les maladies causées par les pathogènes émergents sont souvent mortelles mais se propagent peu au sein des populations humaines. Une des raisons qui expliqueraient l'observation d'épidémies dans les populations humaines est l'émergence récurrente du pathogène du réservoir vers les populations humaines.

L'objectif de ce chapitre est de comprendre l'effet de cette émergence récurrente du pathogène sur la dynamique épidémiologique observée dans une population humaine et d'en établir un aperçu général. Peu d'études théoriques ont étudié l'effet de la transmission des agents pathogènes à partir d'une population animale et aucune n'a considéré d'émergence récurrente d'un réservoir où le pathogène y est endémique. En effet, l'écologie des maladies infectieuses chez l'homme s'explique généralement par la capacité des agents infectieux à se propager entre individus [Lloyd-Smith et al., 2009]. Nous proposons ici une nouvelle approche utilisant la modélisation stochastique pour évaluer l'importance de la transmission récurrente d'un agent pathogène depuis un réservoir animal par rapport à la transmission inter humaine pour prédire la dynamique épidémiologique de l'hôte.

Un modèle stochastique en temps continu de type Susceptible-Infecté-Rétabli (SIR) avec émergence récurrente du pathogène *via* un réservoir est considéré. Un compartiment "*réservoir*" a donc été ajouté au modèle classique SIR. Les taux de transmission inter humaine et de transmission récurrente du pathogène *via* le réservoir sont les deux paramètres du modèle. Notre objectif est donc d'étudier comment ces deux paramètres affectent la dynamique épidémiologique dans la population humaine, plus particulièrement le nombre moyen d'épidémies, la taille moyenne des épidémies ainsi que la taille de la plus grande épidémie.

Les résultats montrent que la dynamique épidémiologique communément observée des maladies infectieuses émergentes peut être regroupée en trois catégories : (i) quelques chaînes de transmission d'individus infectés qui s'éteignent rapidement, (ii) un foyer im-

portant et peu de chaînes de transmission et (iii) une seule grande épidémie. Nous montrons notamment que la dynamique dépend non seulement de la capacité de l'agent pathogène à se propager entre les individus humains, mais également du nombre moyen de transmissions par *spillover* (c.-à-d. émergence *via* le réservoir) pendant une épidémie. Dans le cas des maladies infectieuses émergentes et des agents pathogènes zoonotiques, les résultats suggèrent fortement que le taux de transmission de l'agent pathogène par le réservoir est aussi important que le taux de transmission directe pour prédire la dynamique de la maladie.

Ce chapitre a fait l'objet d'un article publié à *Journal of Theoretical Biology* [Voinson et al., 2018].

abstract

Most emerging human infectious diseases have an animal origin. While zoonotic diseases originate from a reservoir, most theoretical studies have principally focused on single-host processes, either exclusively humans or exclusively animals, without considering the importance of animal to human transmission (i.e. spillover transmission) for understanding the dynamics of emerging infectious diseases. Here we aim to investigate the importance of spillover transmission for explaining the number and the size of outbreaks. We propose a simple continuous time stochastic Susceptible-Infected-Recovered model with a recurrent infection of an incidental host from a reservoir (e.g. humans by a zoonotic species), considering two modes of transmission, (1) animal-to-human and (2) human-to-human. The model assumes that (i) epidemiological processes are faster than other processes such as demographics or pathogen evolution and that (ii) an epidemic occurs until there are no susceptible individuals left. The results show that during an epidemic, even when the pathogens are barely contagious, multiple outbreaks are observed due to spillover transmission. Overall, the findings demonstrate that the only consideration of direct transmission between individuals is not sufficient to explain the dynamics of zoonotic pathogens in an incidental host.

2.1 Introduction

Recent decades have seen a surge of emerging infectious diseases (EIDs), with up to forty new diseases recorded since the 1970s [Jones et al., 2008]. Sixty percent of emerging human infectious diseases are zoonotic, i.e. are caused by pathogens that have an animal origin [Jones et al., 2008; Taylor et al., 2001]. The World Health Organization defines zoonotic pathogens as "pathogens that are naturally transmitted to humans via vertebrate animals". The epidemics caused by EIDs impact the societal and economical equilibria of countries by causing unexpected deaths and illnesses thereby increasing the need for health care infrastructures and by interfering with travel [Morens and Fauci, 2013]. Moreover, the risk of EIDs being transmitted to humans from wildlife is increasing because of the recent growth and geographic expansion of human populations, climate change and deforestation, which all increase the number of contacts between humans and potential new pathogens [Jones et al., 2008; Keesing et al., 2010; Murray and Daszak, 2013]. Given most EIDs have an animal origin, it is crucially important to understand how infections spread from animal to human populations, i.e. by spillover transmission.

There is numerous empirical evidence that the epidemiological dynamics of infectious diseases is highly dependent on the transmission from the reservoir (the reservoir will be defined following Ashford's definition (1997), i.e. a pathogen is persistent in the environment of the incidental host, see Table 2.1 for details). The start of an outbreak is promoted by a primary contact between the reservoir and the incidental host (i.e. host that becomes infected but is not part of the reservoir) leading to the potential transmission of the infection to the host population. Moreover, multiple outbreaks are commonly observed during an epidemic of zoonotic pathogens in human populations, for instance in the case of the epidemic of the Nipah Virus between 2001 and 2007 [Luby et al., 2009]. With regards to the Ebola virus, some twenty outbreaks have been recorded since the discovery of the virus in 1976 [De La Vega et al., 2015]. This number of outbreaks undoubtedly underestimates the total number of emergences because not all emergences necessarily lead to the spread of the infection from an animal reservoir to the host population [Jezek et al., 1999]. While the reservoir has an important role for causing the emergence of outbreaks, the role of spillover transmission on the incidental epidemiological dynamics is rarely discussed.

Empirically, it is generally difficult to distinguish between direct transmission and

transmission from the reservoir. Only in the case of non-communicable diseases it is easily possible to measure the importance of the recurrent transmission from the reservoir, since all infected individuals originate from a contact with the reservoir. For instance, the H7N9 virus, for which most human cases are due to a contact with an infected poultry, approximately 132 spillovers have been listed during the epidemic of 2013 [Zhou et al., 2013]. For pathogens that are able to propagate from one individual to another, the origin of the infection can be established according to patterns of contacts during the incubation period [Chowell et al., 2014; Luby et al., 2009]. Most often, if an infected individual has been in contact with another infected individual in his recent past, direct transmission is considered as the likeliest origin of the infection. However, both individuals might have shared the same environment and thus might have been independently infected by the reservoir. This leads to overestimating the proportion of cases that result from person-to-person transmission. Moreover, when the pathogen infects an individual and the latter does not produce secondary cases then the detection of emergence is unlikely.

Definitions of a reservoir	**Authors**	**Refs**
"any animal, person, plant, soil, substance or combination of any of these in which the infectious agent normally lives"	CDC	[CDC, 1999]
"all hosts, incidental or not, that contribute to the transmission to the target host (i.e. the population of interest) in which the pathogen can be permanently maintained"	Haydon et al.	[Haydon et al., 2002]
"an ecologic system in which an infectious agent survives indefinitely"	Ashford	[Ashford, 1997, 2003]

TABLE 2.1 – Definitions of a reservoir from the literature. The reservoir is mostly used as defined by the Centre for Disease Control and prevention (CDC). Two other definitions have been proposed to clarify and complete the notion of reservoir in the case of zoonotic pathogens. On the one hand, Haydon et al. (2002) define the reservoir from a practical point of view in order to take into account all hosts epidemiologically connected to the host of interest (i.e. target host), to implement better control strategies. On the other hand, Ashford (1997) establishes a more generalizable definition : for a given pathogen there is a single reservoir.

Pathogen spillover is often neglected in epidemiological theoretical models. It is generally assumed that the epidemiological dynamics of outbreaks is driven by the ability of the pathogen to propagate within hosts. For instance, a classification scheme for pathogens has been proposed by Wolfe et al. (2007), including five evolutionary stages in which the pathogen may evolve ranging from an exclusive animal infection (Stage I) to an exclusive human infection (Stage V) (Figure 2.1) [Wolfe et al., 2007]. The intermediate stages are

those found for the zoonotic pathogens (Stages II-IV). Lloyd-Smith et al. (2009), proposed to enhance the classification scheme by differentiating the Stages II-IV by the ability of pathogens to propagate between individuals in the incidental host (i.e. as a function of the basic reproductive ratio R_0) : the non-contagious pathogens ($R_0 = 0$, Stage II), pathogens barely contagious inducing stuttering chains of transmission ($0 < R_0 < 1$, Stage III) and contagious pathogens inducing large outbreaks ($R_0 > 1$, Stage IV) [Lloyd-Smith et al., 2009]. However, the role of the reservoir is not clearly defined, and spillover effects on the epidemiological dynamics are not discussed.

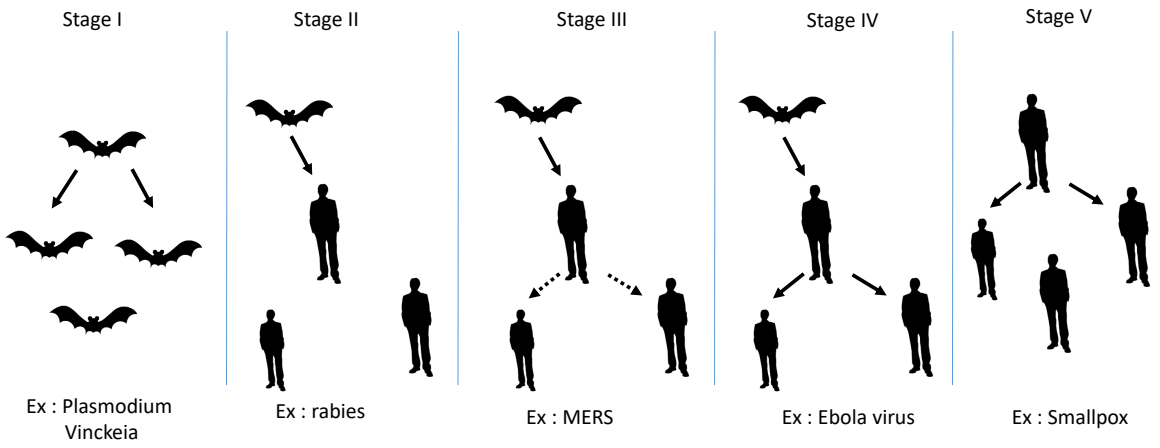


FIGURE 2.1 – Representation of the classification scheme of pathogens proposed by Wolfe et al. (2007). A pathogen may evolve from infecting only animals (Stage I) to infecting only humans (Stage V). Each stage corresponds to a specific epidemiological dynamics in the incidental host. Stage II corresponds to few spillovers from animals (e.g. bats) to humans with no possible transmission between humans. Stage III corresponds to few stuttering chains of transmission between humans that go extinct (no outbreaks). Stage IV corresponds to large outbreaks in human population but the pathogen cannot be maintained without the reservoir.

Only a few models have investigated the dynamics of EIDs by taking into account explicitly the transmission from the reservoir to the incidental host. Lloyd-Smith et al. (2009) have analysed 442 modelling studies of zoonotic pathogens and concluded that "models incorporating spillover transmission are dismayingly rare" [Lloyd-Smith et al., 2009]. More recent models aimed at investigating the dynamics of EIDs by taking into account the spread of the pathogen using multi-host processes but disregarding the persistence of the pathogen in the reservoir [Singh et al., 2013], or by focusing on the dynamics and conditions of persistence of the pathogen between two populations [Fenton and

Pedersen, 2005]. Models that have considered an endemic reservoir are disease-specific and do not generate generalizable dynamics [Chowell et al., 2014; Nieddu et al., 2017]. More recently, Singh and Myers (2014) developed a Susceptible-Infected-Recovered (SIR) stochastic model coupled with a constant force of infection. The authors are mostly interested in the effect of population size and its impact on the size of an outbreak [Singh and Myers, 2014]. However, this approach does not allow teasing apart the contribution of the incidental host transmission from that of the transmission from the reservoir in modulating the dynamics of zoonotic pathogens.

In this paper, we aim to provide general insights into the dynamics of a zoonotic pathogen (i.e. pathogens classified in stages II-IV) emerging from a reservoir and its ability to propagate in an incidental host. To do so, we developed a continuous time stochastic model that can dissociate the effect of between-host (i.e. direct) transmission from the effect of spillover (i.e. reservoir) transmission. A multi-host process with a reservoir and an incidental host is considered. The epidemiological processes are stochastic, which is particularly relevant in the case of transmission from the reservoir and more realistic because only a small number of individuals are expected to be infected at the beginning of an outbreak. The model makes a number of assumptions. First, the epidemiological processes are much faster than the demographic processes. Second, the pathogen in the reservoir is considered as endemic and might contaminate recurrently the incidental host. Third, an individual cannot become susceptible after having been infected. As a consequence, the total number of susceptible individuals in the incidental host decreases during the epidemic. This is what is expected for an epidemic spreading locally during a short period of time (at the scale of a few thousands individuals during weeks or months, depending on the disease and populations considered). We then harness the model to predict the effects of both spillover transmission and direct transmission on the number and the size of outbreaks. Outbreaks occur when the number of cases of disease increases above the epidemiological threshold. In the case of non emerging infectious diseases, an epidemiological threshold is used to gauge the start of outbreaks. For instance for the seasonnal influenza the epidemiological threshold is calculated depending on the incidence of the disease during the previous years [Tay et al., 2013]. In the case of emerging infectious diseases, no incidence is normally expected in the population so from a small number of infected individuals, the outbreak can be considered to spread. We show that, regarding the epidemiological dynamics, the recurrent emergence of the pathogen from the reser-

voir in the incidental host is as important as the transmission between individuals of the incidental host. We conclude by discussing the implications of these results for the classification of pathogens proposed by Lloyd-Smith et al. (2009).

2.2 Model

A continuous time stochastic Susceptible-Infected-Recovered (SIR) compartmental transmission model [Kermack and McKendrick, 1927] with recurrent introduction of the infection into an incidental host by a reservoir is considered (Figure 2.2). Our goal here is not to study a disease in particular but to provide general insights of the reservoir effect on the epidemiological dynamics of the incidental host. The infection is assumed to propagate quickly relatively to other processes such as pathogen evolution and demographic processes. The reservoir is defined as a compartment where the pathogen is persistently maintained, this pathogen is then considered as endemic. The population is fully mixed. An individual can be infected through two types of transmission, from the reservoir by the spillover transmission and by direct contact between individuals. We neglect the possibility for reverse infection from the incidental host to the reservoir.

Transitions		Effects	Transition rates
1	$(S,I,R) \to (S-1, I+1, R)$	Direct transmission	βSI
2	$(S,I,R) \to (S-1, I+1, R)$	Spillover	τS
3	$(S,I,R) \to (S, I-1, R+1)$	Recovery	γI

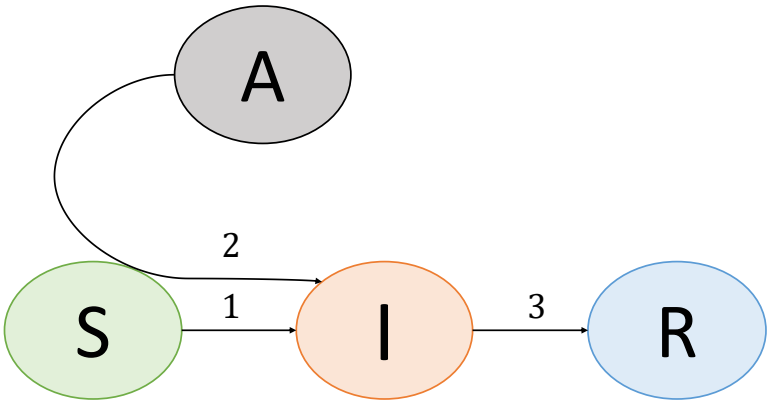


FIGURE 2.2 – Representation of the stochastic model with transitions. A reservoir (A) has been added to a classical SIR model where the pathogen is persistent. Individuals are characterized by their epidemiological status in the incidental host (S : suceptible; I : infected; R : recovered). S, I and R are measured in numbers of individuals. All stochastic transitions with assiociated rates are listed in the table. A susceptible individual becomes infected through the transmission by contact at rate βSI or through the reservoir at rate τS. An infected individual recovers at rate γ.

The incidental host is composed of N individuals. The infection can spillover by contact

between the reservoir and the incidental host at rate τS where S is the number of susceptible individuals and τ is the rate at which an individual becomes infected from the reservoir. In the incidental host, the infection can propagate by direct contact at rate βSI where I is the number of infected individuals and β is the individual rate of infection transmission. An infected individual can recover at rate γ. The propensity of the pathogen to be transmitted between individuals within host is expressed in terms of the basic reproductive ratio of the pathogen, R_0, which is widely used in epidemiology. R_0 corresponds to the average number of secondary infections produced by an infected individual in an otherwise susceptible population. In a deterministic model, for a pathogen to invade the population, R_0 must be larger than 1 in the absence of reservoir. In a stochastic model, the higher the R_0 the higher the probability for the pathogen to invade the population. In a SIR model, the basic reproductive ratio R_0 equals to $\beta N/\gamma$. Individuals in the recovered compartment do not contribute anymore to the transmission process. Since we assume that demographic processes are slower than epidemic processes, the number of susceptible individuals decreases during the epidemic due to the consumption of susceptibles by the infection until the extinction of the susceptible population. In other words, in our model, R_0 will decrease because of the successive spillovers from the reservoir. We expect this to occur especially at short space and time scales (a local population during the course of weeks or months).

To analyse the dynamics in the incidental host, three statistics will be studied (i) the mean number of outbreaks, (ii) the mean size of the recurrent outbreaks during an epidemic and (iii) the mean size of the largest outbreak occurring during an epidemic. We consider the appearance of an outbreak when the incidence of the infection exceeds the threshold c and define the maximum size of an outbreak as the largest number of infected individuals during the largest outbreak.

2.2.1 Analysis of the model

Stochastic simulations The epidemiological dynamics described previously can be simulated with the following algorithm (simulations were run in C++). The population state is assumed to be known at time t. A total event rate (Ω), only depending of the state of the population at time t, is calculated for each iteration.

A) The total event rate Ω of the continuous time stochastic SIR model is given by :

$$\Omega = \beta SI + \tau S + \gamma I.$$

B) The next event time is $t' = t + \delta$ where δ is exponentially distributed with parameter Ω.

C) The next event to occur is randomly chosen : direct transmission, spillover transmission or recover with respective probabilities $\beta SI/\Omega$, $\tau S/\Omega$ and $\gamma I/\Omega$.

We performed stochastic individual-based simulations of the epidemics with spillover transmission, using rates as presented in Figure 2.2. The incidental host is initially ($t = 0$) composed of 1000 susceptible individuals (N = S = 1000). The infection is considered as endemic in the reservoir. Simulations are stopped when there are no susceptible individuals anymore. An outbreak begins when the number of infected individuals reaches the epidemiological threshold c ($c = 5$ infected individuals in the simulations) and ends when there is no infected individuals anymore (I = 0). Stochastic simulations were run for values of the basic reproductive ratio (R_0) ranging from 0 to 10 and of the spillover transmission (τ) ranging from 10^{-10} to 10^{-1}, 10 000 simulations are performed for each parameter set. All other parameter values are detailed in Table 3.1.

Parameters	**Values**
R_0	variable
γ	0.1 UT^{-1}
τ	variable (UT^{-1})
c	5 infected individuals
N	1000 individuals

TABLE 2.2 – Parameters used and their values. UT denotes the unit of time which can be expressed in days or weeks.

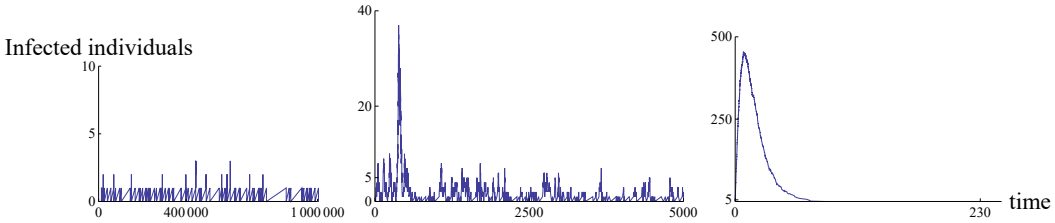
Approximation by a branching process The epidemiological model with recurrent introduction of the infection into an incidental host by a reservoir can be approximated by a branching process with immigration from the reservoir to the incidental host at the beginning of the infectious process (thus assuming that individual "birth" and "death" rates of infected individuals are constant during the starting phase of an outbreak). The individual birth and death rates are respectively βN, the transmission rate and γ, the recovery rate. The immigration rate corresponds to the spillover rate, τN, at the beginning of the

infection. In other words, we assume that the number of susceptibles is N to study the beginning of the infection, which is a good approximation as long as few individuals have been infected. We distinguish between two regimes in the incidental host, the subcritical regime when $R_0 < 1$ and the supercritical regime when $R_0 > 1$. We suppose that at time $t = 0$ a single individual is infected by the spillover transmission.

2.3 Results

2.3.1 The epidemiological dynamics in the incidental host

As illustrated in Figure 2.3, three patterns are observed (i) a stuttering chain of transmission that goes extinct, i.e. infection spreads inefficiently, (corresponding to Stage II in Wolfe's classification, see Figure 2.1), (ii) a large outbreak and few stuttering chains of transmission (corresponding to Stage III, see Figure 2.1) and (iii) a single large outbreak consuming a large number of susceptible individuals (corresponding to Stage IV see Figure 2.1).



(a) Stage II
Low values of τ and R_0

(b) Stage III
Intermediate values of τ or R_0

(c) Stage IV
High values of τ or R_0

FIGURE 2.3 – Examples of stochastic simulations. Three examples of epidemiological dynamics corresponding to the three Stages II, III and IV (see Figure 2.1) respectively with low values of both direct and spillover transmissions ($R_0 = 0.2$ and $\tau = 10^{-7}$), intermediate values of direct or spillover transmission ($R_0 = 1.5$ and $\tau = 10^{-4}$), high value of direct or spillover transmission ($R_0 = 2$ and $\tau = 10^{-1}$).

Figure 2.4 shows the roles of the direct transmission, R_0, and the spillover transmission, τ, in the occurrence of the three patterns depicted in Figure 2.3, in the case of a threshold $c = 5$ and $c = 10$. Stuttering chains of transmission occur when the pathogen is barely contagious between individuals (small R_0) and when the recurrent emergence of the pathogen (τ) is low. At the opposite, when the pathogen is highly contagious (large R_0) or when the spillover transmission is high (τ), only one large outbreak is observed. Finally, both dynamics (a large outbreak and stuttering chains of transmission) are observed for

intermediate value of both direct and spillover transmission. The dynamics observed in the three stages depend both of the value on the direct transmission (R_0) and the effect of the reservoir (τ).

The three stages are observed when spillover transmission (τ) or the direct transmission (R_0) is low, two stages appear when direct or spillover transmission is intermediate and only one stage is observed when at least one of the two transmission is high. Hence, both types of transmission are important in the emergence of epidemiological dynamics.

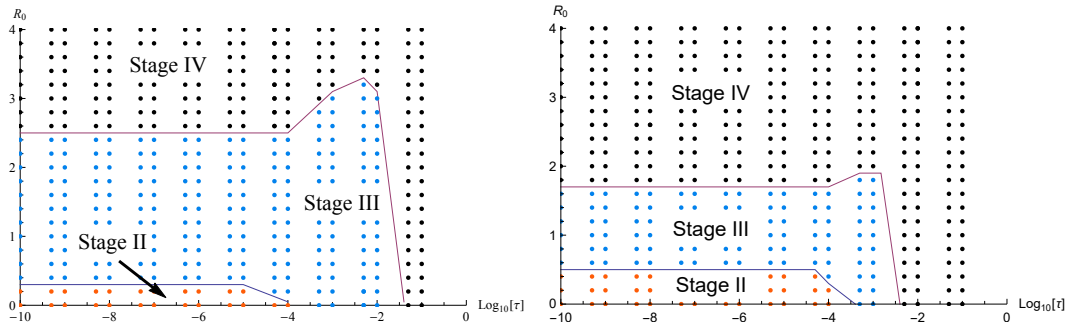
Figure 2.4 shows that the epidemiological threshold c little affects the observed dynamics. For both values $c = 5$ and $c = 10$, the three patterns are observed. However, the values of both transmissions (τ and R_0) on the frontiers between stages are different. The parameter range for which the patterns of the stages II and IV are observed are wider for a higher threshold value (compare Fig. 4a and 4b), whereas stage III is narrower. When the direct and the spillover transmissions are low, it is more difficult for the infection to reach a higher threshold. Thus, there are more stuttering chains of transmission. In the same way, when the direct or the spillover transmission is high, a large outbreak is observed then some stuttering chains of transmission occur but do not reach the epidemiological threshold.

For both values of epidemiological threshold (Figure 2.4a and 2.4b), a "bulb" is observed in the Stage III where the direct transmission is high. After the occurence of a large outbreak, the susceptible population becames small. Hence the next excursion is very unlikely to reach the epidemiological threshold. However, a high enough spillover transmission rate is able to counterbalance the small effective R_0 and to produce other outbreaks after the large one. The "bulb" is less pronounced in the case of a higher threshold (Figure 2.4b) because the susceptible population consumed during the large outbreak is important leading to the failure for the next excursion to reach a high epidemiological threshold.

2.3.2 Number of outbreaks when the effect of the reservoir is low

Case of a barely contagious pathogen ($R_0 < 1$) **:**

We aim at approximating the mean number of outbreaks in the case where the spillover transmission rate τ and the reproductive number R_0 are small (subcritical case corresponding to $R_0 < 1$). The method of approximation is the following : let us denote by S_i the



(a) Epidemiological threshold $c = 5$ (b) Epidemiological threshold $c = 10$

FIGURE 2.4 – Classification scheme of the epidemiological dynamics observed in simulations. The general epidemiological dynamics is depicted as a function of the direct transmission (R_0) and the spillover transmission (τ). The epidemiological dynamics of stochastic simulations are classified following the stages described by Wolfe et al. (2007), Stage II : stuttering chains of transmission (i.e. less than one outbreak), Stage III : one large outbreak and stuttering chains of transmission (i.e. more than one outbreak) and Stage IV : a single large outbreak.

number of susceptible individuals at the beginning of the i-th excursion. During the i-th excursion, we set this number of susceptibles to its initial value S_i, and consider that the rate of new infections is $\beta I S_i$. We thus obtain a branching process with individual birth (infection) rate βS_i and individual death (recovery) rate γ. When there is no more infected individuals, we compute the mean number of recovered individuals produced by this branching process excursion, denoted by $\mathbb{E}[K(S_i, \beta, \gamma)]$, and make the approximation that

$$S_{i+1} = S_i - \mathbb{E}[K(S_i, \beta, \gamma)], \tag{2.1}$$

where $\mathbb{E}[K(S_i, \beta, \gamma)]$ can be computed and equals (see Appendix 2.5.1) :

$$\mathbb{E}[K(S_i, \beta, \gamma)] = \frac{\gamma}{\gamma + \beta S_i} \sum_{k=0}^{\infty} \frac{(2k)!}{(k!)^2} \left(\frac{\gamma \beta S_i}{(\gamma + \beta S_i)^2} \right)^k. \tag{2.2}$$

In other words, the initial number of susceptible individuals for the $i+1$-th excursion is the initial number of susceptible individuals for the i-th excursion minus the mean number of recovered individuals produced during the i-th excursion under our branching process approximation. We repeat the procedure for the $i+1$-th excursion, and so on, until k satisfies $S_k > 0$ and $S_{k+1} \leq 0$ (no susceptible anymore). In order to be considered as an outbreak, an excursion has to exceed c individuals, where we recall that c is the epidemiological threshold. Under our branching process approximation, the probability

for the i-th excursion to reach the epidemiological threshold (see Appendix 2.5.1) is :

$$P(S_i, \beta, \gamma) = \frac{(\gamma/\beta S_i) - 1}{(\gamma/\beta S_i)^c - 1}. \tag{2.3}$$

As a consequence, our approximation of the mean number of outbreaks ($\mathbb{E}[O(N, \beta, \gamma)]$) reads :

$$\mathbb{E}[O(N, \beta, \gamma)] = \sum_{i=0}^{k} P(S_i, \beta, \gamma), \tag{2.4}$$

where $S_1 = N$, and the S_i's are computed as described in (2.1).

The mean number of outbreaks computed with the branching process is a good approximation compared to numerical simulations for a small spillover transmission ($10^{-10} \leq \tau \leq 10^{-6}$) (Figure 2.5). The spillover transmission added in our model introduces the infection recurrently and allows the infection to spread even for a pathogen barely contagious (R0 < 1). According to Figure 2.5 when $R_0 < 1$ the number of outbreaks increases when the direct transmission between individuals increases. Indeed, the higher the direct transmission, the higher the probability for the excursions to reach the epidemiological threshold (c). The number of outbreaks can be high because when the direct transmission is smaller than 1, the infection spreads inefficiently and does not consume a large number of susceptibles allowing the next excursion to exceed the epidemiogical threshold.

Figure 2.6 shows that the average number of outbreaks is a non-monotonic function of the direct transmission (R_0) and the spillover transmission (τ). More precisely, figure 2.6b shows that for intermediate and low values of spillover transmission ($10^{-6} \leq \tau \leq 10^{-4}$), the average number of outbreaks increases until R0 ~ 1 then decreases until it reaches one outbreak when the direct transmission is high ($R_0 > 2.5$). Moreover, we observed an increasing number of outbreaks with τ when the pathogen is barely contagious. By contrast, in figure 2.6a, we show that the average number of outbreaks decreases when τ becomes large ($\tau \geqslant 5.10^{-4}$).

Case of a contagious pathogen $R_0 > 1$:

The supercritical case ($R_0 > 1$) is now considered and the spillover transmission rate (τ) is still supposed small.

In this case, two different types of excursions occur in the incidental host : (i) a large outbreak which consumes, with a probability close to one, a large proportion of susceptible individuals and (ii) multiple excursions before and after a large outbreak which each

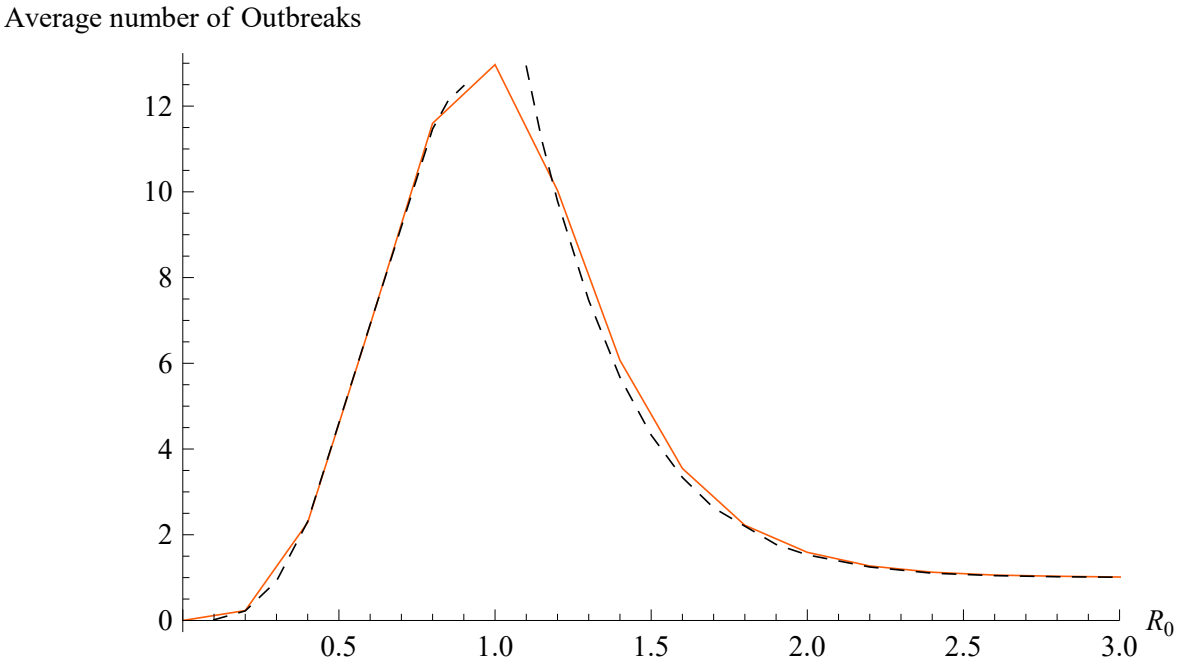
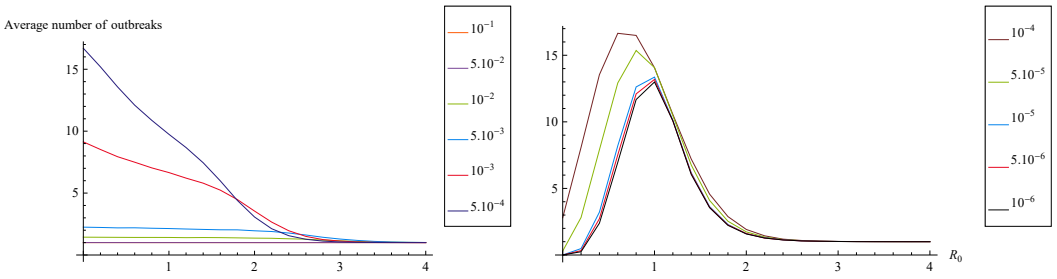


FIGURE 2.5 – Average number of outbreaks for a low spillover transmission. The orange and black dotted curves represent the results, from numerical simulations and branching process approximation, respectively. The average number of outbreaks approximated is evaluated when the spillover transmission τ is small. For the numerical simulations, $\tau = 10^{-10}$ has been chosen. There is a break in the dotted curve (branching process) because our approximation is not valid in the critical regime (when R_0 is close to 1).



(a) (b)

FIGURE 2.6 – Average number of outbreaks obtained from stochastic simulations. The average number of outbreaks is depicted as a function of the direct transmission $0 < R_0 < 4$ and the spillover transmission (a) $5.10^{-4} \leq \tau \leq 10^{-1}$ and (b) $10^{-6} \leq \tau \leq 10^{-4}$ and for an epidemiological threshold $c = 5$.

consumes few susceptible individuals. We let $O_{before}(N,\beta,\gamma)$ and $O_{after}(N,\beta,\gamma)$ denote the number of outbreaks occurring respectively before and after the large outbreak. Because $R_0 > 1$, the probability to have one large outbreak is close to one. Hence we make the approximation that one large outbreak occurs during the epidemic, and the total number of outbreaks ($O_{total}(N,\beta,\gamma)$) can be approximated by :

$$O_{total}(N,\beta,\gamma) = O_{before}(N,\beta,\gamma) + 1 + O_{after}(N,\beta,\gamma). \tag{2.5}$$

To be part of outbreaks occurring before the large one, an excursion has to satisfy two conditions (i) to have a size higher than the epidemiological threshold c, and (ii) to be of a size not too large otherwise it would correspond to the large outbreak. To be more precise, this condition will correspond to the fact that the supercritical branching process used to approximate this excursion does not go to infinity. As a consequence, $O_{before}(N,\beta,\gamma)$ can be approximated by (See Appendix 2.5.2) :

$$O_{before}(N,\beta,\gamma) = \frac{1}{(\beta N/\gamma)^c - 1}. \tag{2.6}$$

To approximate the number of outbreaks after the large outbreak ($O_{after}(N,\beta,\gamma)$), we need to know how many susceptible individuals remain in the population. The number of susceptibles consumed before the large outbreak is negligible with respect to the number of susceptibles consumed during the large outbreak. Hence we can consider that the initial state of the large outbreak is N susceptibles, one infected individual and no recovered individual. The number of susceptibles remaining after the large outbreak can be approximated with the deterministic SIR model.

The large outbreak stops when there is no infected individual anymore in the incidental host. Using that $\frac{\dot{S}}{S} = -\beta I = \frac{-\beta}{\gamma}\dot{R}$, we get :

$$(N - \frac{\gamma}{\beta}\log N) - (S - \frac{\gamma}{\beta}\log S) = 0 \tag{2.7}$$

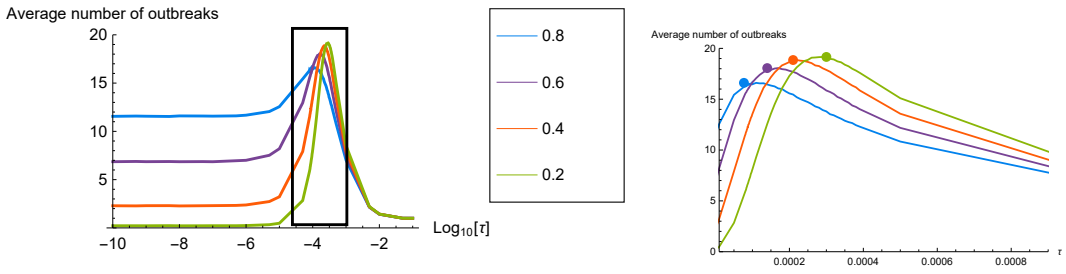
which has one trivial solution ($S = N$) and a non-trivial solution with no explicit expression denoted $N_{after}(N,\beta,\gamma)$. After the large outbreak, the reproductive ratio for the next excursions, denoted $R_{0_{after}}$, is subcritical ($R_{0_{after}} < 1$) (see Appendix 2.5.2) and the number of outbreaks after the large one, denoted O_{after}, can be approximated using Equations **??**.

The branching process approximations of the mean number of outbreaks in the super-

critical regime, depicted in Figure 2.5, are close to the mean number of outbreaks computed by numerical simulations when the recurrent infection from the reservoir is small. The number of outbreaks decreases when the pathogen becomes highly contagious to reach one outbreak when $R_0 > 2.5$. When the infection is introduced in the incidental host by the spillover transmission, the probability to reach the epidemiological threshold depends on the direct transmission between individuals. When the direct transmission increases the infection spreads more efficiently consuming a large number of susceptible individuals allowing few or no other excursion to reach the epidemiological threshold and producing only one outbreak when $R_0 > 2.5$.

2.3.3 What is the effect of the reservoir on the number of outbreaks?

We now focus on the effect of the spillover transmission with a pathogen barely contagious ($R_0 < 1$) on the number of outbreaks. We exclude for the sake of simplicity the cases very close to the critical case, that is to say, $1 - R_0$ is not too close to 0. Because we consider the subcritical case ($R_0 < 1$), the excursions are small and at the beginning of the epidemiological dynamics, we make the approximation that the spillover transmission rate is constant equal to τN, and the direct transmission rate is equal to βNI. We thus consider a birth and death process with constant immigration rate τN, individual birth rate βN and individual death rate γ. We are interested in the effect of the parameter τ on the mean number of outbreaks. In particular we aim at estimating the value of τ maximising the mean number of outbreaks, denoted τ_{opt}.



(a) (b)

FIGURE 2.7 – Average number of outbreaks as a function of the spillover transmission. The average number of outbreaks is represented as a function of the basic reproductive ratio ($0.2 < R_0 < 0.8$) and the spillover transmission rate of a pathogen ($Log_{10}[10^{-10}] \leq \tau \leq Log_{10}[10^{-1}]$). The rectangle in figure (a) represents the results enlarged in figure (b). In figure (b) the dots represent the estimation of the value of the spillover transmission (τ_{opt}) for each basic reproductive ratio where the number of outbreaks is maximal.

A first quantity which will help giving us an idea of the order of magnitude of the values of τ to be considered is the mean number of infected individuals at large times. This quantity, denoted m_I, equals (see for instance Equation (8.74) in [Bailey, 1990]) :

$$m_I = \frac{\tau N}{\gamma - \beta N} = \frac{\tau N/\gamma}{1 - R_0}.$$

In particular, when

$$m_I \gg c \iff \frac{\tau N}{\gamma} \gg c(1 - R_0), \tag{2.8}$$

the mean number of infected individuals is much larger than c, and when on the contrary

$$m_I \ll c \iff \frac{\tau N}{\gamma} \ll c(1 - R_0), \tag{2.9}$$

the mean number of infected individuals is negligible with respect to c.

Let us first consider the first case (equation (2.8)), and choose $\alpha > 1$ such that

$$\frac{\tau N}{\gamma} \geq \alpha(c-1)(1 - R_0).$$

Then we can show (see Appendix 2.5.3), that the probability p_c that a first infection by the reservoir gives rise to an outbreak (that is to say the number of infected individuals reaches c before 0) is larger than :

$$p_c \geq \frac{(\alpha - 1)(1 - R_0)}{1 + \alpha(1 - R_0)} \underset{\alpha \to \infty}{\to} 1. \tag{2.10}$$

Moreover, we can show that if an excursion reaches the level c, it has a probability close to one to lead to a large outbreak consuming a large number of susceptible individuals. Thus only few stuttering chains of transmission will emerge. In Figure 2.7a, when τ is large ($\tau > 10^{-2}$ thus $\tau N/(c\gamma(1-R_0)) \geq 25$), only one outbreak is observed because the large number of spillovers prevents the outbreak from dying out.

Let us now consider the second case (equation (2.9)). Recall that in the case of emerging infectious diseases, the threshold c can be considered as small. Hence we may consider without loss of generality that (2.9) implies :

$$\frac{\tau N}{\gamma} \leq \frac{1 - R_0}{2}. \tag{2.11}$$

In this case, we can prove (see Appendix 2.5.3) that the probability that the number of infected individuals is higher than the threshold c is :

$$\mathbb{P}(\mathrm{I} > c) \leq \frac{\tau \mathrm{N}}{c\gamma(1-\mathrm{R}_0)} \left(\frac{1+\mathrm{R}_0}{1-\mathrm{R}_0}\right) \left(\frac{1+\mathrm{R}_0}{2}\right)^{1/\ln(2/(1+\mathrm{R}_0))-1}.$$

Thus the probability for the number of infected individuals to reach the epidemiological threshold c is small under condition (2.9). As a consequence, few outbreaks will occur. Indeed, the successive spillovers by the reservoir will produce outbreaks with a small probability, but will nevertheless consume susceptible individuals, until there is no more susceptible in the population. According to Figure 2.7a, when a small effect of spillover transmission ($\tau < 10^{-6}$) and a small reproductive ratio ($\mathrm{R}_0 \leq 0.6$) are considered ($\tau \mathrm{N}/(c\gamma(1-\mathrm{R}_0)) < 2.10^{-2}$) then the number of outbreaks is small. In the case of a slightly higher direct transmission rate ($\mathrm{R}_0 = 0.8$), each spillover has a non negligible probability to become an outbreak (more precisely 0.12 when $c = 5$) and the number of outbreaks is higher.

We thus predict that the number of outbreaks will tend to be large when the average size of an excursion is close to the epidemiological threshold ($m_{\mathrm{I}} \simeq c$). These observations allow us to give a first rough upper bound of the optimal value τ_{opt}. Indeed, if the mean number of infected individuals ($\mathrm{E}[\mathrm{I}]$) is equal to c, the ratio $\mathrm{V}ar(\mathrm{I})/\mathbb{E}^2[\mathrm{I}]$ equals $1/(c(1-\mathrm{R}_0))$ (where $\mathrm{V}ar[\mathrm{I}]$ represents the variance of the number of infected individuals, see Appendix 2.5.3) and whose value belongs to $[0.25, 1]$ when $c = 5$ for the values of R_0 considered, which is large. Moreover in this case the distribution of I is skewed to the right (see Figure 2.10). This implies that the number of infected individuals will be larger than c a large fraction of the time producing outbreaks which do not go extinct before a new infection by the reservoir, and thus producing few outbreaks. Hence we may conclude that τ_{opt} is smaller than the τ leading to a mean number of infected individuals c. For instance for the parameters considered in Figure 2.7a, this gives that τ_{opt} is smaller than :

— 10^{-4} when $\mathrm{R}_0 = 0.8$,

— 2.10^{-4} when $\mathrm{R}_0 = 0.6$,

— 3.10^{-4} when $\mathrm{R}_0 = 0.4$,

— 4.10^{-4} when $\mathrm{R}_0 = 0.2$,

Let us now be more precise on the estimation of τ_{opt}. To this aim, we will apply two

results of the theory of branching processes with immigration. The first one, which can be found in [Bailey, 1990] (Equation (8.74)) describes the total infectious lines over the course of the infection, denoted by m :

$$m = (1 - R_0)^{-\frac{\tau}{\beta}} = (1 - R_0)^{-\frac{\tau N}{\gamma R_0}}. \tag{2.12}$$

Notice that m is necessarily larger than 1 as an infection from the reservoir is needed to generate the first infectious line.

The second result is the mean number of infectious lines expected to be present at any time, that is to say in the theory of branching processes the number of distinct immigrants which have descendants alive at a given moment. For large times, this mean number (M_I) is equal to :

$$M_I = \tau N \mathbb{E}[T_0]$$

(see Chapter 8.7 in [Pardoux, 2007]), where $\mathbb{E}[T_0]$ denotes the mean lifetime of a branching process without immigration, with individual birth rate βN, individual death rate γ, and initial state 1. This expression can be computed explicitly (see Appendix 2.5.3) and equals :

$$\mathbb{E}[T_0] = \frac{1}{\beta N} \log\left(\frac{1}{1 - R_0}\right),$$

thus leading to the expression :

$$M_I = \frac{\tau N}{\gamma R_0} \log\left(\frac{1}{1 - R_0}\right). \tag{2.13}$$

We will divide an excursion into m/M_I blocks of M_I simultaneous infectious lines (thus without immigration). The idea for such an estimation is the following : it is known that if a Poisson process has k jumps during a time interval, the jumps are uniformly distributed during this time interval. As the infections by the reservoir follow approximately a Poisson process with parameter τN, and we know that in expectation m infections by the reservoir occur before all infected individuals are removed, we divide the epidemic in homogeneous blocks. We choose these blocks to have an initial number of M_I infected individuals to allow the use of results on branching processes with immigration. The initial number of infected individuals in each block is thus M_I, and as a consequence the

infection has a probability

$$\frac{R_0^{-M_I}-1}{R_0^{-c}-1}$$

to reach the threshold c (see Appendix 2.5.3). Hence the probability for the whole excursion to reach the threshold c can be approximated by

$$1-\left(1-\frac{R_0^{-M_I}-1}{R_0^{-c}-1}\right)^{m/M_I}.$$

We want this probability to be not too close to 0, otherwise most susceptible individuals would be consumed without giving rise to an outbreak. We also want this probability to be not too close to 1. Indeed, as we have shown in the beginning of this section, this would correspond to a case where $\tau N/\gamma$ is much larger than $c(1-R_0)$ and once the infected number of individuals has reached the value c it would be very likely to reach a large value and consume a large number of susceptible individuals. As a consequence, we would have at the limit only one large outbreak. We thus choose to equalize this probability to one half to get an estimation of τ_{opt}. Notice that this choice is arbitrary but has only a small effect on the final results. For instance, a choice of 0.3 or 0.7 would give very close results. The most important is to stay away from 0 and 1. As a conclusion, τ_{opt} is estimated as the unique solution to :

$$\left(1-\frac{R_0^{-M_I}-1}{R_0^{-c}-1}\right)^{\frac{m}{M_I}}=\left(1-\frac{R_0^{\frac{\tau_{opt}N\log(1-R_0)}{\gamma R_0}}-1}{R_0^{-c}-1}\right)^{-\frac{\gamma R_0(1-R_0)^{-\tau_{opt}N/(\gamma R_0)}}{\tau_{opt}N\log(1-R_0)}}=\frac{1}{2}. \tag{2.14}$$

The unicity of the solution is proved in Appendix 2.5.3.

Figure 2.7b presents the values of τ maximising the number of outbreaks and their estimations (dots) obtained by the branching process approximations. The estimates derived under the branching process approximation give good results, with error ranging from 3 to 33 % regardless the value of the epidemiological threshold (Table 2.3).

To get the estimation of τ_{opt} we have made several approximations. First we have considered that the spillover rate by the reservoir is constant equal to τN, whereas it is decreasing and equals to τS, and that the rate of direct transmission due to infected individuals in the population is βNI and not βSI. We believe that these approximations are

R_0	c	τ_{opt} esti	τ_{opt} simu	error
0.8	5	$7.7\ 10^{-5}$	$1.1\ 10^{-4}$	30
0.8	10	$1.4\ 10^{-4}$	$2.1\ 10^{-4}$	33
0.6	5	$1.4\ 10^{-4}$	$1.7\ 10^{-4}$	18
0.6	10	$2.7\ 10^{-4}$	$2.8\ 10^{-4}$	4
0.4	5	$2.1\ 10^{-4}$	$2.2\ 10^{-4}$	5
0.4	10	$4.3\ 10^{-4}$	$4.1\ 10^{-4}$	5
0.2	5	$3.0\ 10^{-4}$	$2.9\ 10^{-4}$	3
0.2	10	$6\ 10^{-4}$	$4.9\ 10^{-4}$	22

TABLE 2.3 – Values of the optimal spillover transmission from numerical simulations and estimations. The optimal spillover transmission is calculated for R_0 being equal to 0.2, 0.4, 0.6, and 0.8. We present the values of the optimal spillover for two values of epidemiological threshold $c = 5$ (blue lines) and $c = 10$ (white lines). The errors are ranging from 3 to 33 % with a mean error of 15 %.

reasonable because the probability for an excursion to reach the threshold decreases with the consumption of susceptible individuals, and as a consequence, most of the outbreaks will occur at the beginning of the process. However, the real τ_{opt} should be a little bit higher than the one we estimate, to counterbalance the fact that the real infection rates (by the reservoir and the infected individuals) are smaller than the one we use in our calculations. This may explain why in most of the cases we underestimate the real τ_{opt} (see Table 2.3).

The following approximation we made is the decomposition of the excursions into blocks with an initial number of individuals M_I. In the real process there are no simultaneous infections by the reservoir. However this approximation allows to take into account previous infections by the reservoir whose infectious lines are still present.

When the ratio, $Var[I]/\mathbb{E}^2[I] = \tau N/\gamma$, is small (see Appendix 2.5.3), the value of I stays close to its expectation and few outbreaks occur, as the number of infected individuals rarely reaches 0. For instance, for $R_0 = 0.2$ and $\tau = 4.9.10^{-4}$, $\tau N/\gamma \sim 0.2$. As decreasing τ increases this ratio, this could explain why we overestimate τ_{opt} for small values of R_0 (because smaller values of R_0 necessitate higher values of τ to get the same probability to reach the threshold c).

2.3.4 What is the effect of the reservoir on the expected size of the largest outbreak?

During the epidemic, a large outbreak can occur depending on the value of the direct transmission (R_0) and the spillover transmission (τ) and corresponds to the largest number of infected individuals. To analyse the effect of the recurrent emergence of the pathogen on the size of the largest outbreak, we model the largest outbreak by a SIR deterministic model with a spillover transmission :

$$\begin{cases} \dot{S} = -\beta SI - \tau S \\ \dot{I} = \beta SI + \tau S - \gamma I \\ \dot{R} = \gamma I. \end{cases} \tag{2.15}$$

Since no explicit expression of the size of the outbreak can be obtained with the deterministic model, we estimated it using numerical analyses.

Figure 2.8 shows that the maximal number of infected individuals during the largest outbreak increases with the direct transmission (R_0) and the spillover transmission (τ). When the direct transmission (R_0) is small, the size of the largest outbreak can differ by orders of magnitude with varying spillover transmission (τ). Furthermore, a large outbreak can be observed for a pathogen barely contagious ($R_0 < 1$) when the recurrent emergence of the pathogen is high ($\tau \geqslant 10^{-3}$).

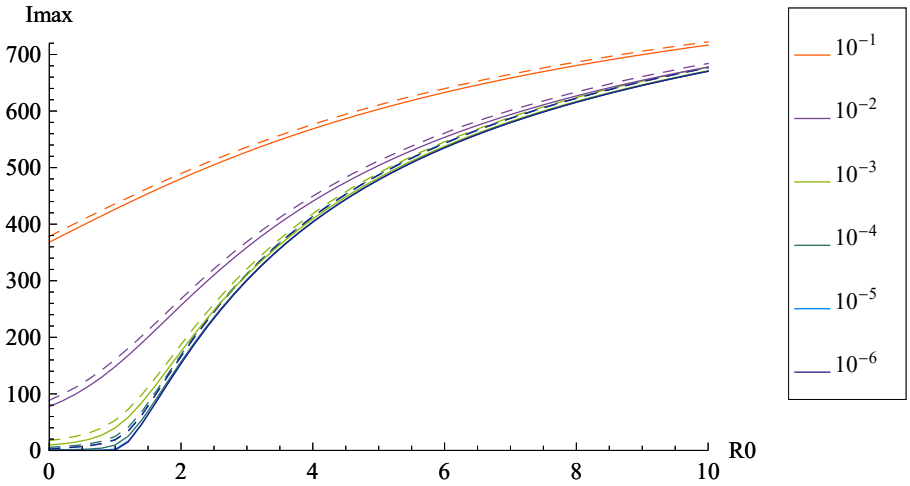


FIGURE 2.8 – The average maximum number of infected individuals during the largest outbreak. The number of infected individuals during the largest outbreak (I_{max}) is numerically found with the deterministic model (line) and the numerical simulations of the continuous time stochastic model (dashed line). The situation is indicated for a reproductive ratio (R_0) varying from 0 to 10 and with the recurrent emergence rate of the pathogen (τ) varying from 10^{-6} to 10^{-1}.

2.4 Discussion

Zoonotic pathogens constitute one of the most pressing concerns with regards to future emerging diseases, but studies investigating the importance of the role of animal reservoirs for the epidemiological dynamics of infectious diseases are lacking. Indeed, most theoretical works only consider pathogen transmission between conspecifics for predicting disease epidemiology. Here, we build a continuous time stochastic SIR model to consider the statistical process underlying a spillover transmission, i.e transmission from an animal reservoir to a host. We analyse the model to predict the number and the size of outbreaks as a function of both the spillover transmission and within host. The model shows that spillover transmission influences the epidemiological dynamics as much as the transmission by direct contact between individuals. Three different dynamics are observed, ranging from the absence of oubreaks to a single large outbreak. The findings have implications for (1) modelling the dynamics of EIDs, (2) understanding the occurrence of outbreaks in the case of pathogens that are barely contagious and (3) control strategies.

In our results, the appearance of outbreaks depends on both the transmission from the reservoir and the direct transmission between individuals. Generally, the occurrence of epidemics in humans is attributed to the ability of the pathogen to propagate between individuals. In the case of a single-host process, the notion of the basic reproductive ratio

R_0 seems sufficient to evaluate the spread of the pathogen in a population entirely composed of susceptible individuals. In EIDs, R_0 is also used to gauge the risk of pandemics. In this way, Lloyd-Smith et al. (2009) delineate the three stages identified for a zoonotic pathogen [Wolfe et al., 2007] by using the ability of the pathogen to spread between individuals. Each stage corresponds to a specific epidemiological dynamics ranging from a non-contagious pathogen making an outbreak impossible (Stage II, $R_0 = 0$) to a barely contagious pathogen with few outbreaks and stuttering chains of transmission (Stage III, $R_0 < 1$) to a contagious pathogen making a large outbreak possible (Stage IV, $R_0 > 1$). The aim of the Wolfe's classification is to establish each stage at which a zoonotic pathogen may evolve to be adapted to human transmission only, in order to identify pathogens at potential risk of pandemics. However, in our model, by taking into account the recurrent emergence of the pathogen from the reservoir, the three dynamics that define the three stages will depend on both the spillover transmission and the direct transmission of the pathogen between individuals. The results suggest that in the case of pathogen spilling recurrently over an incidental host, the direct transmission should not be the only parameter to consider.

The presence of a reservoir and its associated recurrent spillovers dramatically impact the epidemiological dynamics of infectious diseases in the incidental host. Without transmission from the reservoir, the probability to have an outbreak when the pathogen is barely contagious only depends on the direct transmission between individuals, and the outbreak rapidly goes extinct. By contrast, the results show that the recurrent emergence of the pathogen from a reservoir increases the probability to observe an outbreak. Spillover transmission enhances the probability to both observe longer chains of transmission and reach the epidemiological threshold (i.e. threshold from which an outbreak is considered) even for a pathogen barely contagious. Moreover, this coupling model (reservoir-human transmission) allows the appearance of multiple outbreaks depending on both the ability of the pathogen to propagate in the population and the transmission from the reservoir. Zoonotic pathogens such as MERS, Ebola or Nipah are poorly transmitted between individuals (R_0 estimated to be less than 1) [Althaus, 2014; Chowell et al., 2014; Luby et al., 2009; Zumla et al., 2015] yet outbreaks of dozens/hundreds/thousands of infected individuals are observed. We argue that, as suggested by our model, the human epidemic caused by EIDs could be due to a recurrent spillover from an animal reservoir.

In the case of zoonotic pathogens, it is of primary importance to distinguish between

primary cases (i.e. individuals infected from the reservoir) and secondary cases (i.e. individuals infected from another infected individual) to specify which control strategies to implement and how to optimize public health resources. According to the stochastic SIR model coupled with a reservoir analysed here, the same dynamics can be observed depending on the relative contribution of the transmission from the reservoir and the direct transmission by contact with an infected individual (see Figure 2.4). For example, a large outbreak is observed either for a high spillover transmission or for a high direct transmission. The proposed stochastic model makes it possible to understand the effects of the infection from the reservoir or from direct transmission on the epidemiological dynamics in an incidental host when empirically this distinction is difficult. Empirically, the origin of the infection is established by determining the contact patterns of infected individuals during the incubation period. Thereafter, the role of control programs implemented could be evaluated in order to determine better strategies.

We have considered that the reservoir is a unique population in which the pathogen can persist, which is a simplifying assumption. The pathogen is then endemic in the reservoir and the reservoir has a constant force of infection on the incidental host. The reservoir can be seen as an ecological system comprising several species or populations in order to maintain the pathogen indefinitely [Haydon et al., 2002]. For example, bat and dromedary camel (*Camelus Dromedarius*) populations are involved in the persistence of MERS-CoV and in the transmission to human populations [Sabir et al., 2016]. In these cases, the assumptions of a constant force of infection can be valid because the pathogen is endemic. However, zoonotic pathogens can spill over multiple incidental hosts and they can infect each other. In the case of the Ebola virus, which infects multiple incidental hosts such as apes, gorillas and monkeys [Ghazanfar et al., 2015], the principal mode of contamination of the human population is the transmission from non-human primate populations. Moreover, the contact patterns between animals and humans is one of the most important risk factors in the emergence of avian influenza outbreaks [Meyer et al., 2017]. These different epidemiological dynamics with transmission either from the reservoir or from other incidental hosts can largely impact the dynamics of infection observed in the human population, and the investigations of those effects can enhance our understanding of zoonotic pathogens dynamics.

In our model, we make a second simplifying assumption by considering that the infection propagates quickly relatively to other processes such as pathogen evolution and

demographic processes. This assumption can be not valid in the case of low emergence of the pathogen from the reservoir. Indeed, the time between two spillovers can be long and makes the evolution of the pathogen possible inside the reservoir. Moreover, during the time between two spillovers, the demography in the incidental host can vary and impact the propagation of the pathogen. In the case of low spillover transmission in the incidental host, the effect of both pathogen evolution and demograhic processes can be a topic for future research on the epidemiological dynamics of emerging infectious diseases.

In this paper, we have argued that the conventional way for modelling the epidemiological dynamics of endemic pathogens in an incidental host should be enhanced to account for spillover transmission in addition to conspecifics transmission. We have shown that our continuous time stochastic SIR model with a reservoir produces similar dynamics to those found empirically (see the classification scheme for pathogens from [Wolfe et al., 2007]). This model can be used to better understand the ways in which EIDs transmission routes impact disease dynamics.

2.5 Appendices

In this appendix, we derive results on the branching process approximation stated in Section 2.3. The main idea of this approximation is the following : when the epidemiological process is subcritical ($R_0 < 1$), an excursion will modifiy the state of a small number of individuals with respect to the total population size. During the i-th excursions, the direct transmission rate βSI will stay close to $\beta S_i I$ where S_i denotes the number of susceptibles at the beginning of the i-th excursion. Hence, if we are interested in the infected population, the rate $\beta S_i I$ can be seen as a constant individual birth rate βS_i. Similarly, γI, which is the rate at which an individual in the population recovers, can be interpreted as a constant individual death rate γ in the population of infected individuals.

2.5.1 Number of outbreaks in the subcritical case ($R_0 < 1$)

In this section, we focus on the number of outbreaks when $R_0 < 1$ and when the rate of introduction of the infection by the reservoir is small ($\tau \ll 1$). That is to say, we consider that each introduction of the infection by the reservoir occurs after the end of the previous excursion created by the previous introduction of the infection by the reservoir. According to Equation (2.12), this approximation is valid as long as the ratio τ/β is small.

We first approximate the mean number of susceptible individuals consumed by an excursion. Let us consider a subcritical branching process with individual birth rate βN and individual death rate γ. As this process is subcritical, we know that the excursion will die out in a finite time and produce a finite number of individuals. Then from Britton and Pardoux [in preparation] or Van Der Hofstad [2016], if we denote by $K[N,\beta,\gamma]$ the total number of individuals born during the lifetime of this branching process (counting the initial individual), we know that :

$$\mathbb{P}(K(N,\beta,\gamma)=k)=\frac{(2k-2)!}{k!(k-1)!}\left(\frac{\beta N}{\gamma+\beta N}\right)^k\left(\frac{\gamma}{\gamma+\beta N}\right)^{k-1},$$

where $\mathbb{P}$ denotes a probability, and hence

$$\mathbb{E}[K(N,\beta,\gamma)]=\frac{\beta N}{\gamma+\beta N}\sum_{k=0}^{\infty}\frac{(2k)!}{(k!)^2}\left(\frac{\gamma\beta N}{(\gamma+\beta N)^2}\right)^k,$$

where $\mathbb{E}$ is the expectation.

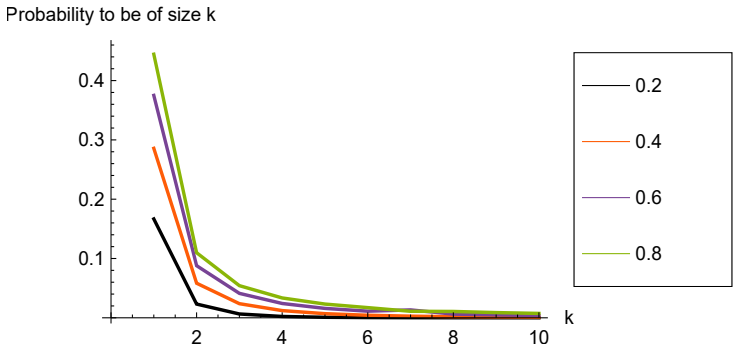


FIGURE 2.9 – Probability for an excursion to be of size k. The situation is indicated for a reproductive ratio (R_0) varying from 0.2 to 0.8.

By definition, an excursion is considered as an outbreak only if the maximal number of individuals infected at the same time during this excursion is larger than an epidemiological threshold that we have denoted by c. Hence in order to approximate the number of outbreaks we still have to compute the probability for an excursion to be an outbreak. This is a classical result in branching process theory which can be found in Athreya and Ney [1972] for instance.

$$P(N,\beta,\gamma):=\mathbb{P}(\text{more than c individuals infected at a given time})=\frac{\gamma/\beta N-1}{(\gamma/\beta N)^c-1}. \quad (2.16)$$

With these results in hands, the method to approximate the mean number of outbreaks is

the following : the probability that the first excursion is an outbreak is

$$\frac{\gamma/\beta N - 1}{(\gamma/\beta N)^c - 1}.$$

The number of susceptibles at the beginning of the second excursion is approximated by

$$S_2 = N - \mathbb{E}[K(N, \beta, \gamma)].$$

The second excursion has a probability

$$\frac{\gamma/\beta S_2 - 1}{(\gamma/\beta S_2)^c - 1}$$

to be an outbreak. The number of susceptibles at the beginning of the third excursion is approximated by

$$S_3 = S_2 - \mathbb{E}[K(S_2, \beta, \gamma)],$$

and the third excursion has a probability

$$\frac{\gamma/\beta S_3 - 1}{(\gamma/\beta S_3)^c - 1}$$

to be an outbreak. The procedure is iterated as long as there is still a positive number of susceptible individuals. This gives 2.4.

2.5.2 Number of outbreaks in the supercritical case ($R_0 > 1$)

We now focus on the case $R_0 = \beta N/\gamma > 1$. In this case the approximating branching process is supercritical and go to infinity with a positive probability. In the case where the epidemic process describes small excursions, the branching process approximation is still valid, but in the case where it describes a large excursion, then a large fraction of susceptible individuals is consumed and the branching approximation is not valid anymore. However, as all the quantities (susceptible, infected and recovered individuals) are large, a mean field approximation is a good approximation of the process. Here the mean

field approximation is the deterministic SIR process, whose dynamics is given by :

$$\begin{cases} \dot{S} = -\beta SI \\ \dot{I} = \beta SI - \gamma I \\ \dot{R} = \gamma I. \end{cases} \tag{2.17}$$

Let us first focus on the small excursions occurring before the large one.

As they are small, they can be approximated by a branching process. Here, unlike in the previous section, the approximating branching process Z is supercritical, as $\beta N > \gamma$. We compute its probability to drift to infinity :

$$p_G := \mathbb{P}(Z_\infty = \infty) = \frac{\beta N - \gamma}{\beta N}.$$

As we will see, a supercritical branching process with individual birth rate βN and individual death rate γ conditionned to go extinct has the same law as a subcritical branching process with individual birth rate γ and individual death rate βN. Indeed, if we denote by Z_n the successive values of this branching process, we get for every couple of natural numbers (n,k) :

$$\begin{aligned} \mathbb{P}(Z_{n+1} = k+1 | Z_n = k, Z_\infty = 0) &= \frac{\mathbb{P}(Z_{n+1} = k+1, Z_n = k, Z_\infty = 0)}{\mathbb{P}(Z_n = k, Z_\infty = 0)} \\ &= \frac{\mathbb{P}(Z_\infty = 0 | Z_{n+1} = k+1, Z_n = k)\mathbb{P}(Z_{n+1} = k+1 | Z_n = k)}{\mathbb{P}(Z_\infty = 0 | Z_n = k)} \\ &= \frac{\mathbb{P}(Z_\infty = 0 | Z_{n+1} = k+1)}{\mathbb{P}(Z_\infty = 0 | Z_n = k)} \frac{\beta N}{\beta N + \gamma} = \left(\frac{\gamma}{\beta N}\right)^{k+1} \left(\frac{\gamma}{\beta N}\right)^{-k} \frac{\beta N}{\beta N + \gamma} = \frac{\gamma}{\beta N + \gamma}. \end{aligned}$$

where $\mathbb{P}(A|B)$ denotes the probability of the event A when B is realised. We used again in this series of equalities classical results on branching processes that can be found in Athreya and Ney [1972]. As a consequence, if we denote by $G[N,\beta,\gamma]$ the number of susceptible individuals consumed by the excursion of a supercritical branching process with individual birth rate βN and individual death rate γ conditionned to go extinct, we get :

$$\mathbb{E}[G(N,\beta,\gamma)] = \frac{\gamma}{\gamma + \beta N} \sum_{k=0}^{\infty} \frac{(2k)!}{(k!)^2} \left(\frac{\gamma \beta N}{(\gamma + \beta N)^2}\right)^k,$$

and the probability for this excursion to have a size bigger than the epidemiological thre-

shold c is

$$\frac{\beta N/\gamma - 1}{(\beta N/\gamma)^c - 1}.$$

As the number of susceptible individuals stays large until the large excursion occurs, we may keep N as the initial number of susceptibles at the beginning of the excursions instead of replacing it by their mean value, as we have done in the previous section.

The different quantities we have just computed allow us to approximate the number of small excursions before the large excursion : in expectation, we have

$$\sum_{k=1}^{\infty} (k-1) p_G (1-p_G)^{k-1} = \frac{1-p_G}{p_G} = \frac{\gamma}{\beta N - \gamma}$$

small excursions, which consume

$$\frac{\gamma^2}{(\beta N)^2 - \gamma^2} \sum_{k=0}^{\infty} \frac{(2k)!}{(k!)^2} \left(\frac{\gamma \beta N}{(\gamma + \beta N)^2} \right)^k$$

susceptibles and produce

$$\frac{\gamma}{\beta N - \gamma} \frac{\beta N/\gamma - 1}{(\beta N/\gamma)^c - 1} = \frac{1}{(\beta N/\gamma)^c - 1}$$

outbreaks.

Now we focus on the large excursion. We use Equation (2.17) to approximate its dynamics. This equation is well known, and it is easy to obtain the equation satisfied by the final number of susceptible individuals : from (2.17)

$$\frac{\dot{S}}{S} = -\beta I = -\frac{\beta}{\gamma} \dot{R}.$$

Hence

$$\ln(S(t)) - \ln(S(0)) = -\frac{\beta}{\gamma}(R(t) - R(0)) = -\frac{\beta}{\gamma}(N - I(t) - S(t)).$$

In particular, if we are interested in the time T_f when there is no more infected individual and we suppose that at time 0 there is only one infected individual we get

$$\ln(S(T_f)) - \ln(S(0)) = \frac{\beta}{\gamma}(S(T_f) - S(0)).$$

That is to say, $S(T_f)$ and $S(0)$ are related by the equation

$$S(T_f) - \frac{\gamma}{\beta}\ln(S(T_f)) = S(0) - \frac{\gamma}{\beta}\ln(S(0)).$$

Rigorously, the value of $S(0)$ depends on the number of susceptible individuals consumed by the small excursions before the large excursion, but we have seen that this number is small compared to the population size, N. Hence the number of susceptible individuals remaining after the large excursion can be approximated by the smallest solution of :

$$S(T_f) - \frac{\gamma}{\beta}\ln(S(T_f)) = N - \frac{\gamma}{\beta}\ln(N). \tag{2.18}$$

(as the largest solution is $S(T_f) = N$).

Notice that it is easy to have an idea of the error caused by a small variation of the initial state. Indeed, if we denote by S_f the smallest solution of (2.18) and by $S_f - l(k)$ the solution when $S(0) = N - k$ for a k small with respect to N, we get :

$$(S_f - \frac{\gamma}{\beta}\ln(S_f)) - (S_f - l(k) - \frac{\gamma}{\beta}\ln(S_f - l(k))) = (N - \frac{\gamma}{\beta}\ln(N)) - (N - k - \frac{\gamma}{\beta}\ln(N-k)),$$

or in other terms

$$l(k) + \frac{\gamma}{\beta}\ln(1 - l(k)/S_f) = k + \frac{\gamma}{\beta}\ln(1 - k/N).$$

As k and $l(k)$ are small with respect to N, this can be approximated by

$$l(k) \sim k\left(1 - \frac{\gamma}{\beta N}\right) / \left(1 - \frac{\gamma}{\beta S_f}\right).$$

Finally, notice that in (2.17), S is a decreasing quantity, and I is a non-negative quantity, which varies continuously. Hence $\dot{I} = I(\beta S - \gamma)$ has to be negative before I hits 0. As a consequence,

$$\frac{\beta S_f}{\gamma} < 1.$$

This ensures that the epidemic is subcritical after the large outbreak.

2.5.3 Effect of the reservoir on the number of outbreaks

In this section, we focus on the effect of the reservoir transmission rate (parameter τ) on the number of outbreaks when the infection is subcritical ($R_0 < 1$). The idea is the

following : first, as excursions of subcritical branching processes are small, we can make the approximation that, at the beginning, the infection rate by the reservoir is constant equal to τN, and that the direct transmission rate is equal to βNI. Making this approximation allows us to handle the two processes of infection (by contact and by the reservoir) independently, and to use known results on branching processes with immigration.

Large τ

Recall that I denotes the number of infected individuals. We first assume (2.8) and prove inequality (2.10). Let us choose $\alpha > 1$ such that

$$\frac{\tau N}{\gamma} \geq \alpha(c-1)(1-R_0).$$

Then for any $1 \leq k \leq c-1$, the jump rates of the process I are :

$$\tau(k \to k+1) = \tau N + \beta N k = \gamma\left(\frac{\tau N}{\gamma} + R_0 k\right) \geq \gamma k((1-R_0)\alpha + R_0)$$
$$\tau(k \to k-1) = \gamma k.$$

Hence

$$\frac{\tau(k \to k+1)}{\tau(k \to k-1)} \geq 1 + (\alpha-1)(1-R_0).$$

This implies that once one individual is infected, the probability for the number of simultaneously infected individuals to reach c before the recovery of all infected individuals is larger than the probability that a birth and death process with initial state 1 and birth (b) and death (d) rates satisfying

$$\frac{b}{d} = 1 + (\alpha-1)(1-R_0)$$

reaches the state c. Applying (2.16), we deduce that this probability p_c2.5.3 satisfies :

$$p_c = \frac{1-(1+(1-R_0)\alpha+R_0)^{-1}}{1-(1+(1-R_0)\alpha+R_0)^{-c}} \geq 1-(1+(1-R_0)\alpha+R_0)^{-1}$$
$$= \frac{(\alpha-1)(1-R_0)}{1+(\alpha-1)(1-R_0)}.$$

This proves (2.10).

Moreover, as α has been taken large, the infectious process stays supercritical (in the sense that the next event is more likely to be an infection than a recovery) until a size k

satisfying

$$\gamma k = \tau N + \beta N k \geq \gamma(\alpha(c-1)(1-R_0) + R_0),$$

and thus if the number of infected individuals reaches c it is likely to reach a large value and consume a large number of susceptible individuals.

Small τ

As we approximate the infection process by a branching process with constant immigration, the law of I under this approximation converges to a well known law, provided by Equation (8.75) in Bailey [1990] :

$$\mathbb{E}[x^I] = \left(\frac{1-R_0 x}{1-R_0}\right)^{-\frac{\tau N}{\gamma R_0}}, \quad 0 \leq x \leq 1. \tag{2.19}$$

From this law, we can deduce the probability for I to be equal to any integer k :

$$\mathbb{P}(I = k) = (1-R_0)^{\frac{\tau N}{\gamma R_0}} \frac{1}{k!} \prod_{i=0}^{k-1} \left(\frac{\tau N}{\gamma} + iR_0\right),$$

and thus, the probability for I to be larger than c is

$$\mathbb{P}(I > c) = (1-R_0)^{\frac{\tau N}{\gamma R_0}} \sum_{k=c+1}^{\infty} \frac{1}{k!} \prod_{i=0}^{k-1} \left(\frac{\tau N}{\gamma} + iR_0\right).$$

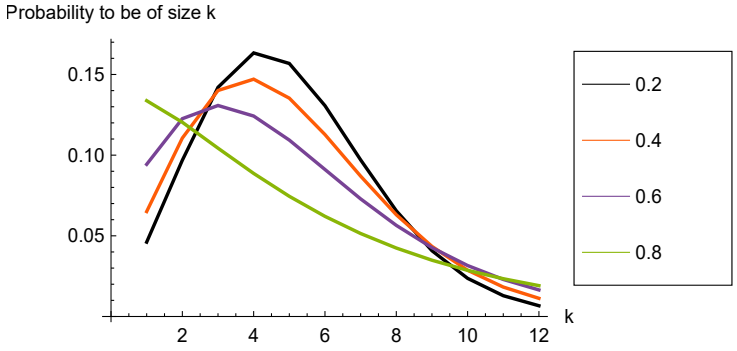


FIGURE 2.10 – Distribution of the number of infected individuals in a branching process with immigration for large times. The legend corresponds to the values of R_0 considered.

Recall that we assumed that

$$\frac{\tau N}{\gamma} \leq \frac{1-R_0}{2}.$$

We thus get the following inequality

$$\mathbb{P}(\mathrm{I} > c) \leq \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)} \sum_{k=c+1}^{\infty} \frac{1}{k!} \prod_{i=1}^{k-1} \left(\frac{1-\mathrm{R}_0}{2} + i\mathrm{R}_0 \right).$$

Now let us notice that for any $i \geq 1$:

$$\frac{1-\mathrm{R}_0}{2} + (i-1)\mathrm{R}_0 < i\frac{1+\mathrm{R}_0}{2}.$$

We thus get

$$\begin{aligned}
\mathbb{P}(\mathrm{I} > c) &\leq \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)} \sum_{k=c+1}^{\infty} \prod_{i=2}^{k} \frac{(1-\mathrm{R}_0)/2 + (i-1)\mathrm{R}_0}{i} \\
&\leq \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)} \sum_{k=c+1}^{\infty} \left(\frac{1+\mathrm{R}_0}{2} \right)^{k-1} \\
&= \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)} \left(\frac{1+\mathrm{R}_0}{2} \right)^{c-1} \frac{2}{1-\mathrm{R}_0} \\
&\leq \frac{\tau \mathrm{N}}{c\gamma(1-\mathrm{R}_0)} \left(\frac{1+\mathrm{R}_0}{1-\mathrm{R}_0} \right) \left(\frac{1+\mathrm{R}_0}{2} \right)^{1/\ln(2/(1+\mathrm{R}_0))-1},
\end{aligned}$$

where to get the last inequality we computed the maximum of the function $x \mapsto x a^{x-1}$ for $a = (1+\mathrm{R}_0)/2$. As a conclusion, for a fixed $\mathrm{R}_0 < 1$ and a small enough τ, the probability for the number of infected individuals at a given time to be higher than c is bounded by a function of R_0 time $\tau\mathrm{N}/(c\gamma(1-\mathrm{R}_0))$. This probability is thus small when the last term is small.

Variance of the process

Recall Equation (2.19). It allows us to compute the variance of I, as follows :

$$\mathbb{E}[\mathrm{I}] = \partial_x \mathbb{E}[x^{\mathrm{I}}]_{|x=1} = \frac{\tau \mathrm{N}}{\gamma \mathrm{R}_0} \frac{\mathrm{R}_0}{1-\mathrm{R}_0} = \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)},$$

and

$$\mathbb{E}[\mathrm{I}(\mathrm{I}-1)] = \partial_{xx} \mathbb{E}[x^{\mathrm{I}}]_{|x=1} = \frac{\tau \mathrm{N}}{\gamma \mathrm{R}_0} \left(\frac{\tau \mathrm{N}}{\gamma \mathrm{R}_0} + 1 \right) \left(\frac{\mathrm{R}_0}{1-\mathrm{R}_0} \right)^2 = \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)^2} \left(\frac{\tau \mathrm{N}}{\gamma} + \mathrm{R}_0 \right).$$

Thus

$$\begin{aligned}\mathrm{Var}[\mathrm{I}] &= \mathbb{E}[\mathrm{I}(\mathrm{I}-1)] + \mathbb{E}[\mathrm{I}] - \mathbb{E}^2[\mathrm{I}] \\ &= \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)^2}\left(\frac{\tau \mathrm{N}}{\gamma} + \mathrm{R}_0 + 1 - \mathrm{R}_0 - \frac{\tau \mathrm{N}}{\gamma}\right) = \frac{\tau \mathrm{N}}{\gamma(1-\mathrm{R}_0)^2}.\end{aligned}$$

In particular,

$$\frac{\mathrm{V}ar[\mathrm{I}]}{\mathbb{E}^2[\mathrm{I}]} = \frac{\tau \mathrm{N}}{\gamma}.$$

Duration of the excursion of a subcritical branching process

In this section we provide an expression for the term $\mathbb{E}[\mathrm{T}_0]$ which appears in the definition of M_I (see Equation (2.13)). This expression derives from the following equality, which can be found in Athreya and Ney [1972]. Let $t \geq 0$ and T_0 denotes the extinction time of the excursion of a branching process, with one individual at time 0. Then we have

$$\mathbb{P}(\mathrm{T}_0 > t) = \frac{\gamma - \beta \mathrm{N}}{\gamma e^{(\gamma-\beta \mathrm{N})t} - \beta \mathrm{N}}.$$

This allows one to compute the expectation of T_0 as follows :

$$\mathbb{E}_1[\mathrm{T}_0] = \int_0^\infty t\mathbb{P}(t < \mathrm{T}_0 \leq t + dt) = -\int_0^\infty t\partial_t \mathbb{P}(\mathrm{T}_0 > t)dt = \int_0^\infty \mathbb{P}(\mathrm{T}_0 > t)dt,$$

where we made an integration by parts. Thus

$$\mathbb{E}_1[\mathrm{T}_0] = \int_0^\infty \frac{\gamma - \beta \mathrm{N}}{\gamma e^{(\gamma-\beta \mathrm{N})t} - \beta \mathrm{N}} = \lim_{t\to\infty} \frac{1}{\beta \mathrm{N}} \log\left(\frac{\gamma - \beta \mathrm{N} e^{-(\gamma-\beta \mathrm{N})t}}{\gamma - \beta \mathrm{N}}\right) = \frac{1}{\beta \mathrm{N}} \log\left(\frac{\gamma}{\gamma - \beta \mathrm{N}}\right).$$

Approximating blocks

Recall that if we consider a branching process with individual birth rate $\beta \mathrm{N}$, individual death rate γ, and initial state $k \leq c$, the probability for this process to reach the size c is

$$\frac{\mathrm{R}_0^{-k} - 1}{\mathrm{R}_0^{-c} - 1}$$

(see Athreya and Ney [1972] for instance). We use this result to approximate the probability for a block of the excursion to reach the threshold c by

$$\frac{\mathrm{R}_0^{-\mathrm{M}_\mathrm{I}} - 1}{\mathrm{R}_0^{-c} - 1},$$

where we recall that M_I is the mean number of simultaneous excursions generated by different infections from the reservoir. Notice that this is an approximation, as M_I is not necessarily an integer.

Unicity of the solution

We end this appendix with the proof of the unicity of the solution to (2.14). To simplify the notations, we introduce the function F, which at x associates :

$$F(x) := \left(1 - \frac{R_0^{-x} - 1}{R_0^{-c} - 1}\right)^{e^x/x}.$$

τ_{opt} is thus a solution to

$$F\left(\frac{\tau N}{\gamma R_0} \log\left(\frac{1}{1 - R_0}\right)\right) = \frac{1}{2}. \tag{2.20}$$

First we notice that F is only defined for $x \leq c$. Otherwise the term in brackets would be negative. Second, notice that if $x \leq 1$ and for any $c \geq 2$ and $R_0 < 1$,

$$\frac{R_0^{-x} - 1}{R_0^{-c} - 1} \leq \frac{R_0^{-1} - 1}{R_0^{-c} - 1} \leq \frac{R_0^{-1} - 1}{R_0^{-2} - 1} = \frac{1}{1 + R_0^{-1}} < \frac{1}{2}.$$

This shows that if $x \leq 1$, $F(x) > 1/2$. We now determine the sign of $F'(x)$ for x belonging to the interval $[1, c]$. A direct computation gives :

$$F'(x) = F(x)\left(\frac{e^x R_0^{-x} \log R_0}{(R_0^{-c} - 1)x\left(1 - \frac{R_0^{-x}-1}{R_0^{-c}-1}\right)} + \frac{e^x}{x}\left(1 - \frac{1}{x}\right)\log\left(1 - \frac{R_0^{-x} - 1}{R_0^{-c} - 1}\right)\right).$$

As the two logarithms are negative for x belonging to $(1, c)$, we deduce that $F'(x) < 0$ for x belonging to $(1, c)$. As $F(1) > 1/2$ and $F(c) = 0$, we conclude that $F(x) = 1/2$ has a unique solution on the interval $(1, c)$. This is equivalent to the fact that (2.20) has a unique solution τ_{opt} which belongs to

$$\left(\frac{\gamma R_0}{N} \log^{-1}\left(\frac{1}{1 - R_0}\right), c\frac{\gamma R_0}{N} \log^{-1}\left(\frac{1}{1 - R_0}\right)\right).$$

This ends the proof.

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Chapitre 3

Impact of an intermediate host on the epidemiological dynamics of emerging infectious diseases

MARINA VOINSON, CHARLINE SMADI, SYLVAIN BILLIARD

Sommaire

Nous venons de voir dans le chapitre précédent que le réservoir du pathogène était aussi important à considérer que la transmission inter humaine dans le cas des maladies infectieuses émergentes. En plus d'être indéfiniment maintenus dans un réservoir, les pathogènes responsables des maladies infectieuses émergentes ont la capacité d'infecter une large gamme d'espèces hôtes. Les populations humaines pourront être infectées soit par l'émergence du pathogène *via* le réservoir, soit *via* une population intermédiaire. Empiriquement, trois types d'émergence sont observées soit exclusivement *via* le réservoir (p.ex. le virus Lassa) [Bonwitt et al., 2017], soit exclusivement *via* la population intermédiaire (p.ex. le virus Hendra) [Middleton et al., 2014], soit *via* les deux sources d'infection, réservoir et population intermédiaire (p.ex. le virus Nipah) [Woolhouse and Gowtage-Sequeria, 2005].

L'objectif de ce chapitre est d'étudier le rôle de la transmission du pathogène *via* l'hôte intermédiaire en plus du réservoir sur la dynamique épidémiologique de la population d'intérêt, par exemple une population humaine. Pour cela, le modèle stochastique en temps continu de type Susceptible-Infecté-Rétabli (SIR) avec le réservoir est réutilisé mais nous ajoutons une population intermédiaire entre le réservoir et la population d'intérêt en utilisant un second modèle SIR. Dans ce modèle impliquant plusieurs hôtes (le réservoir, une population intermédiaire et une population d'intérêt), cinq mécanismes de transmission vont influencer la dynamique épidémiologique : (1-2) l'émergence *via* le réservoir dans les deux populations incidentes, (3-4) la transmission entre individus dans chaque population incidente et (5) la transmission entre les deux populations incidentes. Pour cette dernière, nous faisons l'hypothèse que la transmission est unidirectionnelle, c'est-à-dire uniquement de la population intermédiaire vers la population d'intérêt.

Nous montrons que lorsque la population intermédiaire, qui empêche la transmission directe entre le réservoir et la population d'intérêt, est la seule source d'infection pour la population d'intérêt, alors elle permet de réduire la prévalence dans la population d'intérêt. Cependant, une amplification de la prévalence est observée lorsque les deux sources d'infection (le réservoir et la population intermédiaire) sont considérées.

Abstract

Emerging infectious diseases have a low host specifity and can emerge in a broad range of hosts. The studies about the effect of multi-host diversity on the prevalence show an amplifying effect of the epidemic disease. However, in addition to the cross-species transmission, the emerging infectious diseases are indefinitely maintained in a reservoir. Yet the dynamics of pathogens in a multi-host model is studied apart from this specificity. Here, we aim to investigate the effect of multi-host diversity on the epidemiological dynamics observed in the interest population (e.g. humans). We compare two types of diversity on the epidemiological dynamics of the interest population : (i) a single source of infection, i.e. either the reservoir or the intermediate host and (ii) both sources of infection. The results show two opposite effects on epidemiological dynamics. Firstly, the intermediate host can prevent the direct transmission from the reservoir to the interest population and thus reduce the infection prevalence. Secondly, an amplifying effect on the disease prevalence is observed when both sources of infection are possible, the between-populations transmission and the spillover from the reservoir.

3.1 Introduction

Zoonotic pathogens have a serious impact on socio-economic life in humans. More than 60% of human pathogens are classified as zoonoses [Cleaveland et al., 2001; Taylor et al., 2001] i.e. pathogens coming from vertebrate animals. The pathogen either spreads efficiently in human populations once introduced from animals (e.g. influenza or human immunodeficiency virus), or spills over recurrently from an animal reservoir causing smaller outbreaks with high fatality rates (e.g. Nipah virus or Ebola virus). Emerging infectious diseases (EID's) fall into the latter category of zoonoses. The pathogens responsible of the EID's are naturally present in a reservoir in which they can live indefinitely [Ashford, 1997] and emerge recurrently in human populations. More than 335 EID's were recorded since the 1940's [Jones et al., 2008].

Many factors have been proposed to explain disease emergence including pathogen characteristics (e.g. mutation), host populations characteristics (e.g. population size, migration) and ecological factors (e.g. land use, agriculture) [Cleaveland et al., 2001; Morens and Fauci, 2013]. Several authors noticed that human encroachment on wildlife habitats may result in increased transmission at the wildlife-human interface [Keesing et al., 2010; Murray and Daszak, 2013; Olival et al., 2017]. Indeed, pressures of human encroachment on shrinking wildlife habitat also cause increased wildlife population densities and the emergence of EID's [Daszak et al., 2000]. Moreover, the agriculture expansion and the increasing number of livestock's can indirectly lead to an increasing disease emergence by acting as a bridge between human and reservoir hosts. By changing their environment, human populations modify the contact rate between humans and potential reservoir hosts. Recent anthropogenic ecological change is likely to cause major changes to the geographic range leading to change in incidence of diseases by increasing the contact rate with the principal source of infection - animal populations [Shrag and Wiener, 1995].

Pathogens that can infect a broad range of hosts are ubiquitous and determining the source of infection may be of primary interest to implement effective strategy of control [Morse et al., 2012]. A pathogen responsible of emerging infectious disease is indefinitely maintained in an ecological system, which defines the reservoir [Ashford, 1997, 2003]. Human populations can be infected by (i) a reservoir, i.e. the reservoir can be the only source of infection for the human populations. For instance, the emergence of the lassa virus can be attributed to contacts with *Mastomys natalensis*, a common mouse in hu-

man households [Bonwitt et al., 2017]. (ii) An intermediate host, i.e. in addition to the reservoir host, the emerging infectious disease can infect a broad range of incidental hosts that are irrelevant for the long-term persistence of the pathogen. Then, the pathogen can spill over to the human population from those incidental populations and be the only source of infection. For instance, the infection by the hendra virus is due to a contact with a single intermediate host, the horses which are themselves infected by fruit bats, the reservoir [Middleton et al., 2014]. (iii) Both ways of infection, i.e. a reservoir and one or several intermediate hosts. This is the case for the major part of pathogens responsible of EID's such as Ebola virus, Marburg virus, Nipah and Middle East respiratory syndrom coronavirus (MERS). Understanding the contact processes between wildlife and humans is especially important in the case of EID's that have a low host specificity [Woolhouse and Gowtage-Sequeria, 2005].

The effect of the cross-species transmission in the case of zoonotic disease remains poorly understood. Mathematical models taking into account the effect of the cross-species spillover while studying zoonotic diseases are rare [Lloyd-Smith et al., 2009]. In a previous work, we have shown the importance of the reservoir on epidemiological dynamics of EID's with the use of a simple stochastic Susceptible-Infected-Recovered (SIR) model with a reservoir [Voinson et al., 2018]. In this model, the reservoir, where the pathogen is endemic, was considered as the only source of infection. However, as we mentioned previously, the major part of EID's in addition to the reservoir features one or several intermediate host species. Some authors have explored the effect of host-pathogen community assemblages (i.e. multi-host diversity) on epidemiological dynamics [Dobson, 2004; Roche et al., 2012; Rudolf and Antonovics, 2005]. Two possible effects have been found, an amplifying effect in the case of density-dependent transmission and a buffering effect or dilution effect in the case of frequency-dependent transmission. In order to study the amplifiying and dilution effect of the epidemic disease in the case of multi-host species, it seems important to define what is generally called an amplifying or a dilution effect and how it is measured. Classically, the term "dilution effect" (resp. "amplifying effect") is used in a phenomenological sense to describe the situation when there is a decrease (resp. an increase) in disease frequency (i.e. the prevalence) [Rudolf and Antonovics, 2005]. To do so, a reference model is needed in order to see if a decrease or an increase in disease frequency is observed. In previous works, the effect of the multi-host diversity was explored and compared with the expectations of the single-host model with a single introduction

of infection [Dobson, 2004; Roche et al., 2012; Rudolf and Antonovics, 2005]. In particular, these studies did not consider the long-term persitence of the pathogen in a reservoir while studying the dynamics of emerging diseases.

In this paper, we propose to address the effect of the multi-host diversity by analysing a stochastic model with a reservoir and two incidental populations. The pathogen is indefinitely maintained in the reservoir and can spillover to both incidental populations, the intermediate host and the interest population. The aim is to study the role of the intermediate host in addition to the reservoir on the epidemiological dynamics of the interest population (e.g. the human population). In this multi-hosts process, five mechanisms can have an impact on the epidemiological dynamics of the interest population, (1-2) the spillover transmission from the reservoir to both incidental populations (i.e. the intermediate host and the interest population), (3-4) the transmission between individuals within each incidental population and (5) the inter-incidental transmission, i.e. the transmission of the pathogen from the intermediate host to the interest population. The model is harnessed to predict the number of outbreaks and the size of the largest outbreak. Outbreaks occur when the number of cases reaches the epidemiological threshold. In the case of EID's the epidemiological threshold is generally low because no cases is normally expected. The effect of the multi-host diversity on the epidemiological dynamics of the interest population will be analysed by comparing two types of diversity : a single source of infection (either the reservoir or the intermediate host) and both sources of infection. We are interested in two main questions. What is the effect of the intermediate host on the epidemic disease observed in the interest population? In the intermediate host, the pathogen is epidemic and the outbreaks observed in the intermediate host are seen as amplifiers of the epidemic disease in human populations. What is the effect of the addition of a second source of infection either the inter-incidental transmission or the reservoir? We show that adding the intermediate host can dilute the epidemic disease when it is the only source of infection while adding the intermediate host as a second source of infection in addition to the reservoir, amplifies the epidemic disease.

3.2 Methods

3.2.1 Model

A model with a reservoir and two incidental populations, the intermediate host and the interest population, is considered. The demographic processes such as birth and death are assumed to be much slower than the epidemiological processes. This is what is expected for an epidemic spreading locally during a short period of time. The pathogen in the reservoir is assumed to live indefinitely and spills over recurrently into one or both incidental populations. We assume that the epidemic follows a stochastic SIR model Kermack and McKendrick [1927] in both incidental populations (see Figure 3.1). Each incidental population x is divided into three compartments : susceptible individuals (S_x), infected individuals (I_x) and recovered or dead individuals (R_x). Individuals in the compartment R_x are not involved anymore in the transmission chains. The incidental populations (subscript x) correspond to either the intermediate host (subscript h) or the interest population (subscript p). Two routes of transmission are considered : the within-populations transmission and the between-populations transmission. The total number of susceptible individuals decreases during the epidemic since an individual cannot become susceptible after infection. We assume no reverse infections from the incidental populations to the reservoir and between incidental populations, which corresponds to many documented EID's. For instance Nipah virus : a fruit bat species is a reservoir host that maintains the pathogen indefinitely and transmits the pathogen to pigs [Chua, 2010]. While transmission may occur from bats to pigs and pigs to humans, there is no reciprocal transmissions from pigs to bats and from humans to pigs.

The within-populations transmission The pathogen is able to spread between individuals in both incidental populations as follows : a susceptible individual is infected by direct contact with an infected individual at rate β_x and recovers or dies at rate γ_x. The basic reproductive ratio R_{0_x} is equal to $\beta_x S_x/\gamma_x$ and represents the mean number of infected individuals that one infected individual generates during its infectious period in a whole susceptible population.

The between-populations transmission The incidental populations are connected to each other by the inter-incidental transmission which occurs at rate π. The pathogen from

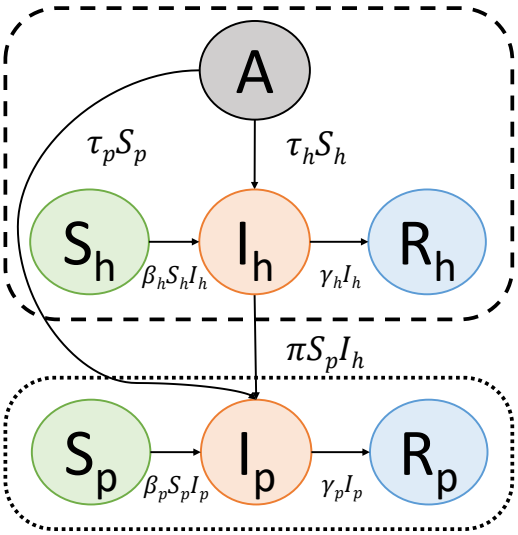


FIGURE 3.1 – Structure of the full model. The pathogen is persistent in the reservoir (A) and emerges recurrently in incidental populations at rate τ_x. Two incidental populations are considered, the intermediate host and the interest population (respectively subscript h and p). In both incidental populations, the individuals are divided into three compartments depending on their epidemiological status (S_x : susceptible, I_x : infected and R_x : recovered or dead individuals). A susceptible individual is infected by direct contact with an infected individual at rate $\beta_x I_x$ and an infected individual dies or recovers at rate γ_x. A third way of infection is possible for the interest population by a contact with an infected individual from the intermediate host (I_h) at rate $\pi S_p I_h$. The interest population is surrounded by a dotted line and the sources of infection for the interest population are surrounded by a dashed line.

the intermediate host emerges to the interest population by direct contact between an infected individual from the intermediate host (I_h) and a susceptible individual from the interest population (S_p) at rate $\pi I_h S_p$. Moreover, the pathogen can emerge from the reservoir and spills over from the intermediate host at rate τ_h and over the interest population at rate τ_p.

We are interested in the effect of the multi-host diversity on the epidemiological dynamics of the interest population. In the case of EID's, two statistics are important to analyse the epidemiological dynamics (i) the number of outbreaks and (ii) the size of the largest outbreak, i.e. the peak of infected individuals. This stochastic model and the interest variables are too complexe to be studied mathematically, then simulations will be used. However, the effect of the reservoir on the epidemiological dynamics of the interest population has been studied mathematically in a previous paper Voinson et al. [2018].

3.2.2 Simulations

The stochastic continuous time model presented in Figure 3.1 is analysed by simulations following the algorithm described in Section 3.5.1. The intermediate host and the

interest population are initially ($t = 0$) composed of 1000 susceptible individuals ($N_x = S_x = 1000$). Stochastic simulations were run for a basic reproductive ratio (R_{0_x}) ranging from 0 to 4 and for a spillover rate (τ_x) and an inter-incidental transmission (π) ranging from 10^{-6} to 10^{-1}. The average number of outbreaks and the size of the largest outbreak are measured in the interest population. An outbreak occurs when the number of infected individuals reaches the epidemiological threshold ($I_p \geq c$) and ends when there are no infected individuals anymore ($I_p = 0$). Simulations are stopped when there are no susceptible individuals anymore in the incidental populations.

Parameters	**Values**
R_{0_x}	variable
γ_x	0.1 UT^{-1}
τ_x	variable (UT^{-1})
π	variable (UT^{-1})
S_x	1000 individuals
c_x	5 infected individuals

TABLE 3.1 – Parameters used and their values. UT denotes the unit of time which can be expressed in days or weeks.

The combination of five mechanisms can affect the epidemiological dynamics observed in the interest population : (1) the spillover from the reservoir to the intermediate host, (2) the spillover toward the interest population, (3) the between individuals transmission in the intermediate host, (4) the between individuals transmission in the interest population and (5) the inter-incidental transmission. In order to evaluate the significance of each mechanism and both sources of infection, we split the full model into two simpler models to have only one source of infection for the interest population in each model. In the first and second models, the only source of infection considered is respectively the reservoir and the intermediate host (see Figure 3.2).

The relative number of outbreaks and the relative size of the largest outbreak are presented in the results. The aim is to study the effect of the multi-host diversity on the epidemiological dynamics of the interest population. To do so, we compare two models with one host of difference between them and make the ratio of both statistics of the more complex model to the less complex model (see Table 3.2). Firstly, to study the effect of the intermediate host acting as a bridge between the interest population and the reservoir, we compared the intermediate host model with the reservoir model. That allowed us to

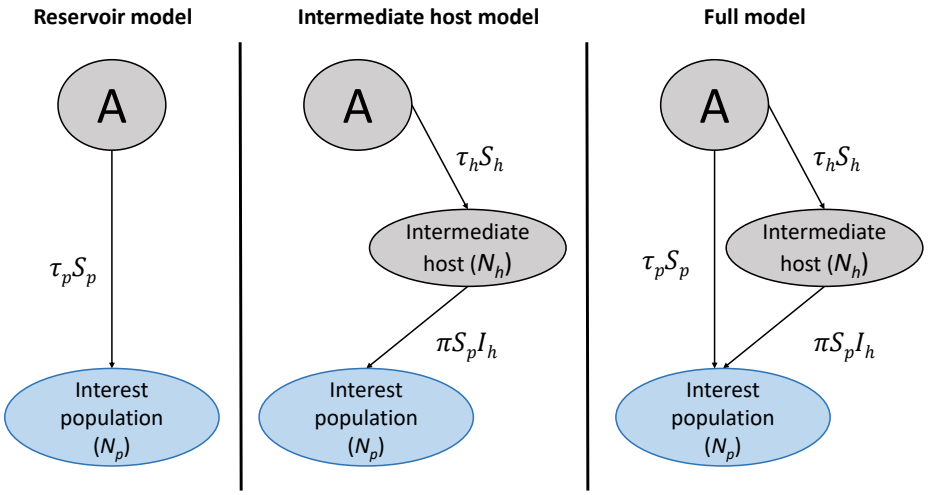


FIGURE 3.2 – Structure of the nested models. The models are presented from left to right depending on their complexity level, from the less complex to the most complex respectively. The model in the left represents the model where the only source of infection for the interest population is the reservoir, the pathogen spills over to the population at rate $\tau_p S_p$. In the middle, the only source of infection is the intermediate host who is suffering from the infection by the reservoir at rate $\tau_h S_h$ and contaminates the interest population at rate $\pi S_p I_h$. Finally, the model on the right represents the full model where the intermediate host and the reservoir infect the interest population.

determine the effect of a population that prevents direct spillover from the reservoir to the interest population. Secondly, to study the effect of the addition of a second source of infection (either the intermediate host or the reservoir) on the epidemic disease of the interest population, we respectively compared the full model with the reservoir model and the full model with the intermediate host model.

We generated the results as follow. Consider that we want to study the effect of the intermediate host as a second source of infection. We calculate the ratio of both statistics, i.e. the number of outbreaks and the size of the largest outbreak, of the full model to the reservoir model in order to have the intermediate host as the only difference between both models. We start by checking that by removing the mechanism of difference between the two models in the more complex model (here the intermediate host model) we find the same values for both statistics thus the relative number equals to 1 (orange curve in all figures), we will use it as reference. Finally, to observe the dilution and the amplifying effect, we observe if the relative number of outbreaks or size of the largest outbreak is respectively lower or higher than one, the reference.

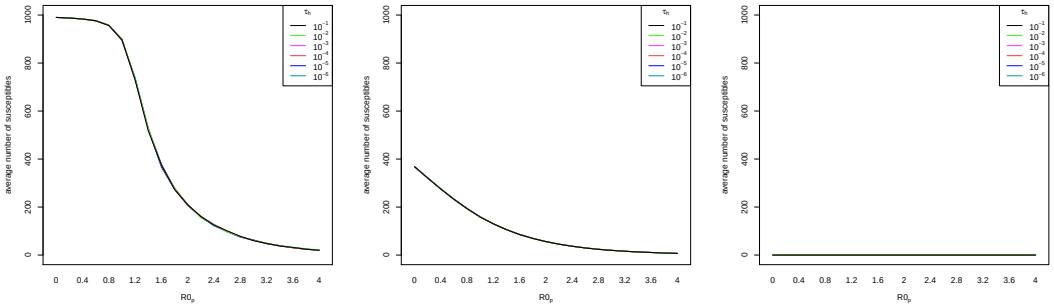
For each comparison model (see Table 3.2), we chose three figures representing three qualitatively different dynamics for different parameters values. The other values of parameters are showed in Sections 3.5.2 to 3.5.4.

↶	Reservoir model	Intermediate host model	Full model
Reservoir model		Bridge effect	Intermediate host effect
Intermediate host model			Reservoir effect

TABLE 3.2 – Comparison models. This Table represents the three comparison choices and the effects studied for each comparison model. The arrow represents the sense of the ratio. The ratio is always of the more complex model on the simpler model.

3.3 Results

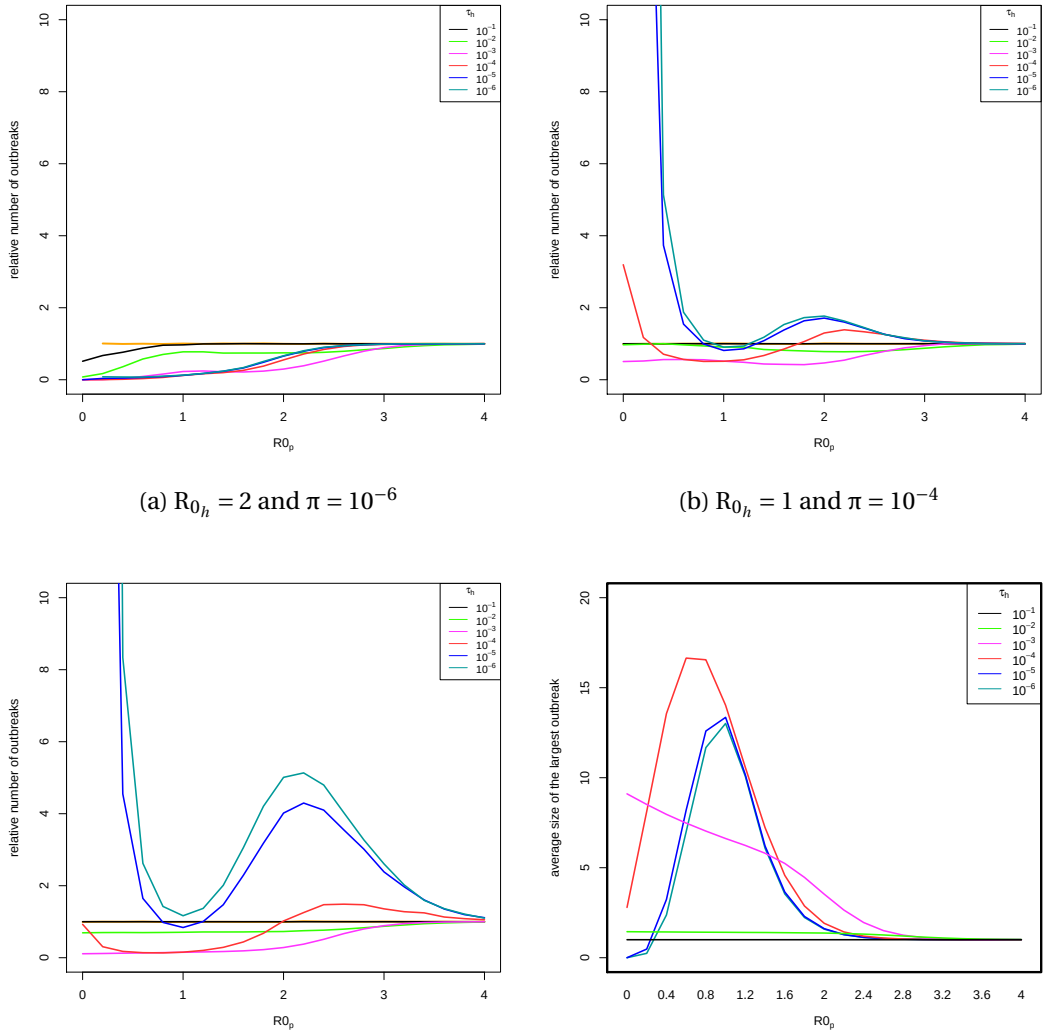
3.3.1 Relative number of outbreaks



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

FIGURE 3.3 – Average number of susceptibles remaining in the interest population after the extinction of the epidemic disease in the intermediate host. The average number of susceptibles remaining in the interest population is presented for the intermediate host model and is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Different values of parameters have been used : a spillover rate ranging from 10^{-6} to 10^{-1} and an inter-incidental transmission equals to 10^{-6}, 10^{-4} and 10^{-2}.

Dilution effect A dilution effect of the number of outbreaks can be observed through two mechanisms : (i) the number of outbreaks is lower because the number of spillovers from the sources of infection is lower or (ii) the number of spillovers is higher causing a higher consumption of susceptible population and leading to a lower probability for



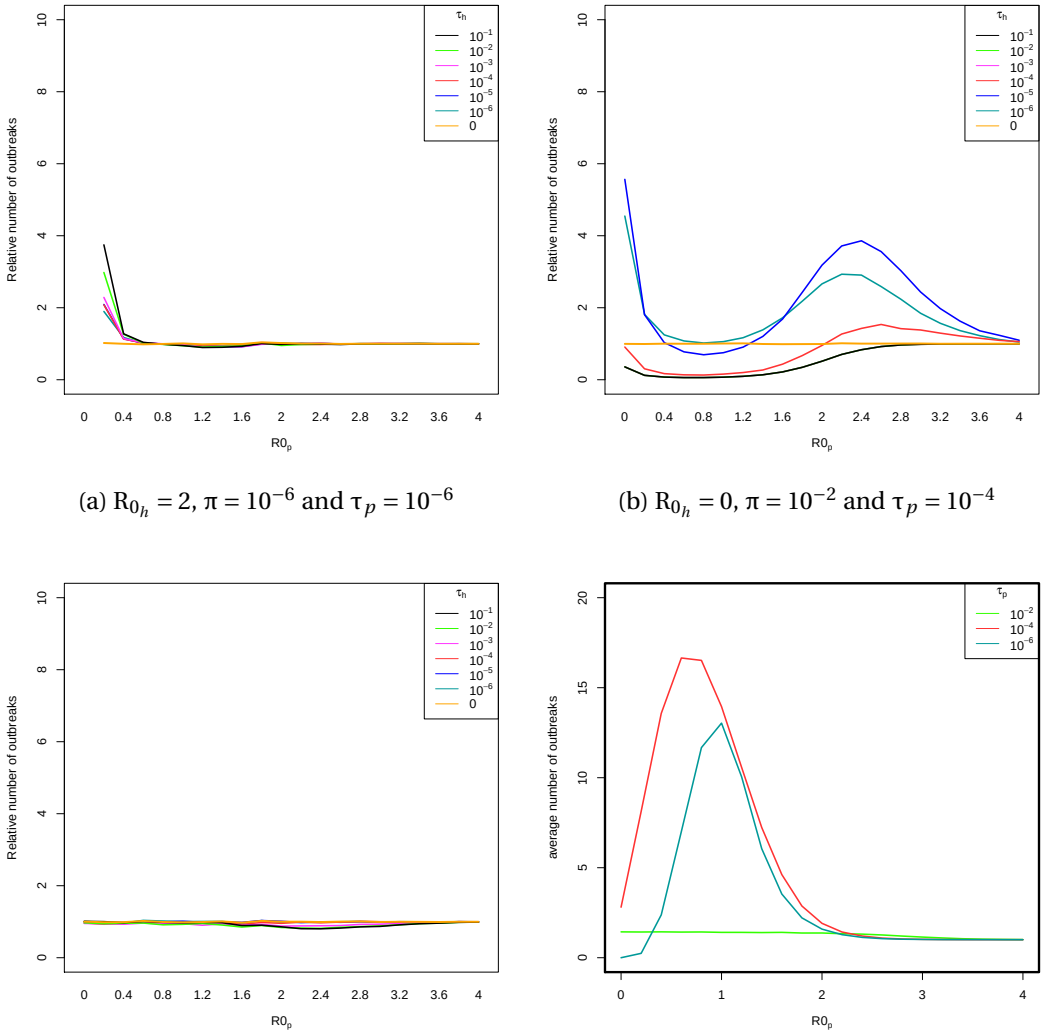
(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$

(b) $R_{0_h} = 1$ and $\pi = 10^{-4}$

(c) $R_{0_h} = 0$ and $\pi = 10^{-2}$

(d) Average number of outbreaks

FIGURE 3.4 – Relative number of outbreaks between the intermediate host model and the reservoir model. Figures 3.4a to 3.4c represent the relative number of outbreaks calculated as the ratio of the average number of outbreaks of the intermediate host model on the reservoir model. The average number of outbreaks for the reservoir model is depicted as a function of the direct transmission between individuals (R_{0_p}) (d). Each curves represent a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.



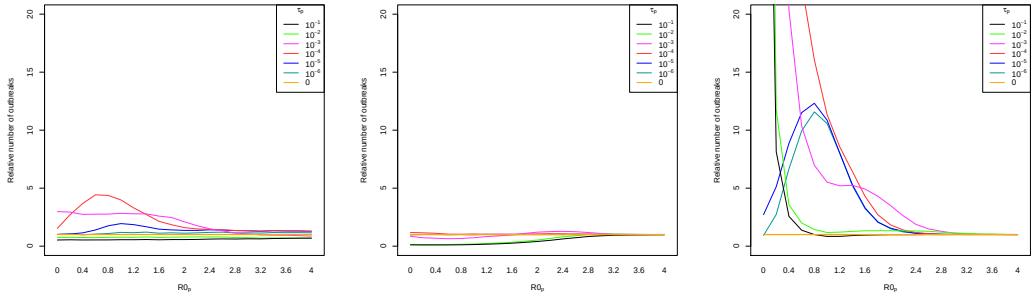
(a) $R_{0_h} = 2$, $\pi = 10^{-6}$ and $\tau_p = 10^{-6}$

(b) $R_{0_h} = 0$, $\pi = 10^{-2}$ and $\tau_p = 10^{-4}$

(c) $R_{0_h} = 1$, $\pi = 10^{-2}$ and $\tau_p = 10^{-2}$

(d) Average number of outbreaks

FIGURE 3.5 – Relative number of outbreaks between the full model and the reservoir model. Figures 3.5a to 3.5c represent the relative number of outbreaks calculated as the ratio of the average number of outbreaks of the full model on the reservoir model. The average number of outbreaks for the reservoir model is depicted as a function of the direct transmission between individuals (R_{0_p}) (d). Each curves represent a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.



(a) $R_{0_h} = 2$, $\pi = 10^{-2}$ and $\tau_h = 10^{-6}$ (b) $R_{0_h} = 1$, $\pi = 10^{-4}$ and $\tau_h = 10^{-4}$ (c) $R_{0_h} = 0$, $\pi = 10^{-6}$ and $\tau_h = 10^{-2}$

FIGURE 3.6 – Relative number of outbreaks between the full model and the intermediate host model. Figures 3.6a to 3.6c represent the relative number of outbreaks calculated as the ratio of the average number of outbreaks of the full model on the intermediate host model. Each curves represent a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}.

the next excursion to reach the epidemiological threshold in order to be considered as an outbreak.

More precisely, a dilution effect is observed when the bridge effect is analysed that is to say when the intermediate host acts as a bridge between the reservoir and the interest population (intermediate host model) compared to the reservoir model where the reservoir is the only source of infection. In Figure 3.4a, when the inter-incidental transmission in the intermediate host is low ($\pi = 10^{-6}$), the average number of outbreaks in the interest population is always lower in the intermediate host model than in the reservoir model independently of the within-populations transmission in the intermediate host (R_{0_h}) (see fig. 3.10). Indeed, in the intermediate host model, the intermediate host is the only source of infection and the disease spreads between individuals and consumes the susceptible population by contrast with an endemic reservoir. When the inter-incidental transmission is low, the intermediate host consumes only few susceptible individuals in the interest population (see fig. 3.3). The ending of the disease epidemic in the intermediate host prevents the occurrence of outbreaks in the interest population.

The second mechanism of dilution effect is widely present when a second source of infection is added either the intermediate host or the reservoir or when the mechanisms of transmission are high. Indeed in those cases, because of the higher spillovers from the source of infection (either the intermediate host or the reservoir or both), a higher emergence of the pathogen is observed in the interest population, limiting the extinction of the occuring outbreak and consuming a higher proportion of the susceptible population.

The next excursion will be then less likely to reach the epidemiological threshold (c).

Amplifying effect An amplifying effect is observed when a higher transmission of infection or the addition of a second source of infection allows the small excursions to reach the epidemiological threshold.

When the bridge effect is analysed, a higher average number of outbreaks is observed in the intermediate host model by comparison with the reservoir model (see figs. 3.4b and 3.4c). Because the spillover rate (τ_h) is low, the consumption of the susceptible population in the intermediate host is low. Moreover, since the inter-incidental transmission is intermediate or high ($\pi \geqslant 10^{-4}$), the emergence of the pathogen from the intermediate host to the interest population allows the excursions to reach the epidemiological threshold (c) more frequently in the interest population.

When the transmission mechanisms are low, the addition of a second source of infection (either the intermediate host or the reservoir) allows the small excursions in the interest population to reach the epidemiological threshold c in order to be considered as outbreaks (see figs. 3.5b, 3.6a and 3.6c).

3.3.2 Relative size of the largest outbreak

Dilution effect A dilution of the size of the largest outbreak is observed in the interest population through two mechanisms : (i) because the disease consumes susceptible individuals in the intermediate hosts and (ii) because the addition of a second source of infection leads to a higher size of outbreaks.

When the bridge effect is analysed (see figs. 3.7a and 3.7b), the average size of the largest outbreak is always smaller when the inter-incidental transmission is intermediate or low ($\pi \leqslant 10^{-4}$). Indeed, the infection is epidemic in the intermediate host and consumes a large proportion of the susceptible population of the intermediate host. Because the inter-incidental transmission depends on the number of infected individuals in the intermediate host, the size of the largest outbreak is lower by contrast with an endemic reservoir where the pathogen is indefinitly maintained and contaminates recurrently the interest population.

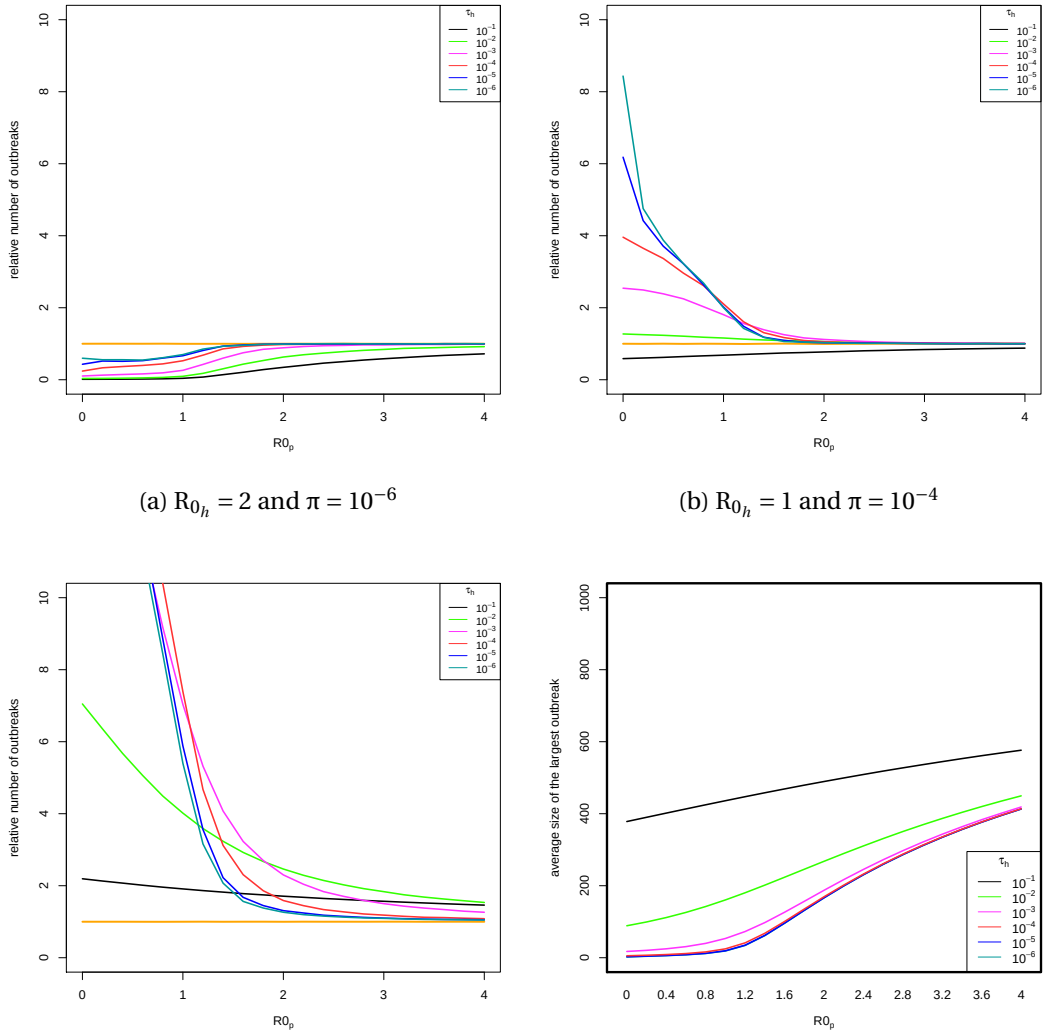
The addition of the reservoir as a second source of infection allows outbreaks to be higher and the infection consumes a larger proportion of susceptible individuals. The number of susceptibles in the interest population is then lower in the full model compared to

the intermediate host model when the large outbreak appears leading to a lower size of the largest outbreak.

Amplifying effect An amplifying effect of the average size of the largest outbreak is observed due to the high spillover from the source of infection to the interest population.

In the case of the analyse of the bridge effect (see figs. 3.7b and 3.7c), an higher average size of the peak of infected individuals is observed due to the epidemiological dynamics observed in the intermediate host which increases the number of spillovers.

When a second source of infection is added, either the intermediate host or the reservoir, this effect is widely observed (see figs. 3.8 and 3.9). Indeed, the second source of infection reinfects recurrently the interest population through the inter-incidental transmission or the spillover rate preventing the extinction of outbreaks and causing largest outbreaks.



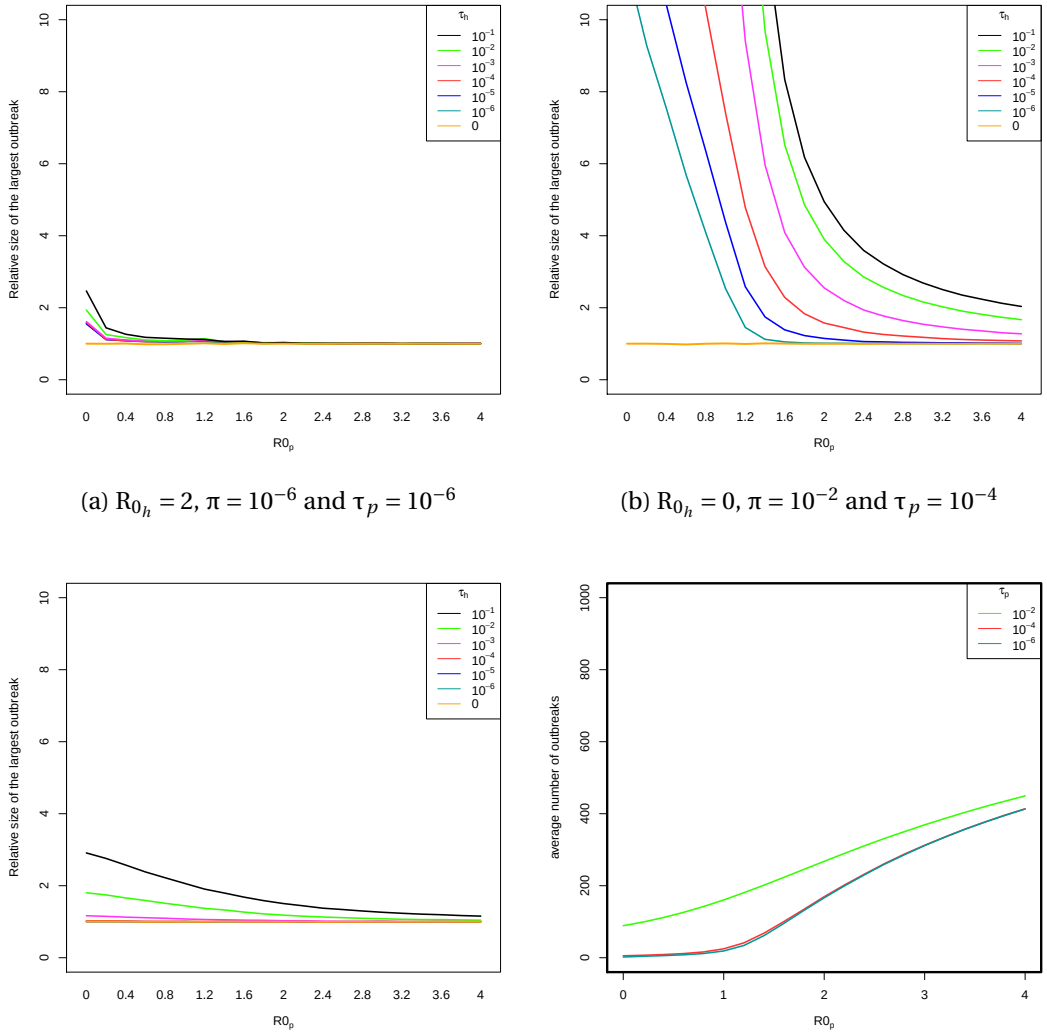
(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$

(b) $R_{0_h} = 1$ and $\pi = 10^{-4}$

(c) $R_{0_h} = 0$ and $\pi = 10^{-2}$

(d) Average size of the largest outbreak

FIGURE 3.7 – Effect of the intermediate host acting as a bridge on the relative size of the largest outbreak. Figures 3.7a to 3.7c represent the relative size of the largest outbreak calculated as the ratio of the average size of the largest outbreak of the intermediate host model on the reservoir model. The average size of the largest outbreak for the reservoir model is depicted as a function of the direct transmission between individuals (R_{0_p}) (d). Each curves represent a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.



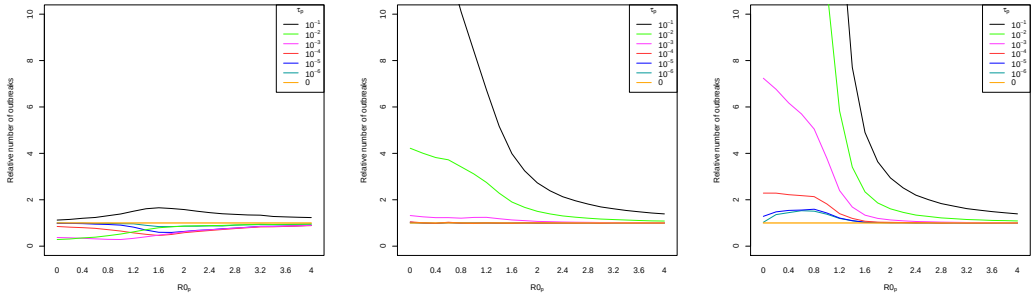
(a) $R_{0_h} = 2$, $\pi = 10^{-6}$ and $\tau_p = 10^{-6}$

(b) $R_{0_h} = 0$, $\pi = 10^{-2}$ and $\tau_p = 10^{-4}$

(c) $R_{0_h} = 1$, $\pi = 10^{-2}$ and $\tau_p = 10^{-2}$

(d) Average size of the largest outbreak

FIGURE 3.8 – Effect of the intermediate host as the second source of infection on the relative size of the largest outbreak. Figures 3.8a to 3.8c represent the relative size of the largest outbreak calculated as the ratio of the average size of the largest outbreak of the full model on the reservoir model. The average size of the largest outbreak for the reservoir model is depicted as a function of the direct transmission between individuals (R_{0_p}) (d). Each curves represent a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.



(a) $R_{0_h} = 2$, $\pi = 10^{-2}$ and $\tau_h = 10^{-6}$ (b) $R_{0_h} = 0$, $\pi = 10^{-2}$ and $\tau_h = 10^{-4}$ (c) $R_{0_h} = 0$, $\pi = 10^{-6}$ and $\tau_h = 10^{-2}$

FIGURE 3.9 – Effect of the reservoir as the second source of infection on the relative size of the largest outbreak. Figures 3.9a to 3.9c represent the relative size of the largest outbreak calculated as the ratio of the average size of the largest outbreak of the full model on the intermediate host model. Each curves represent a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}.

3.4 Discussion

Cross-species transmission is often associated with the emergence of pathogens in a broad range of hosts species and can have a serious impact on socio-economic human life. Emerging infectious diseases have a low host specificity (Woolhouse2005) and are maintained indefinitely in a reservoir population which does not show pathogenicity effects. In this paper, a continuous time stochastic model with a reservoir and two incidental populations, an intermediate host and an interest population, is analysed. We study the number of outbreaks and the size of the largest outbreak in the interest population (i.e. human population) as a function of between- and within-populations transmission rates. Two levels of diversity are analysed : a single source of infection (either the reservoir or the intermediate host) or both sources of infection. This framework has allowed us to study the amplifying or dilution effect of the epidemiological dynamics of the interest population.

We are first interested in the effect of the addition of a second source of infection on the epidemiological dynamics of the interest population. The analysis suggests that the addition of a second source of infection either amplifies or dilutes the epidemic disease depending on the statistic observed. In the comparison models where the intermediate host has been added (full model compared with the reservoir model), a dilution effect can be observed in the number of outbreaks while an amplifying effect on the size of the largest outbreak is always observed. In the case of emerging infectious diseases when human populations are already in contact with the reservoir, the addition of a second

source of infection that suffers from the infection amplifies the gravity of the epidemic disease. Indeed, even if we observed less outbreaks, the outbreaks are larger and consume a larger proportion of susceptible individuals. A recent example has been observed during the 2013-2015 Ebola outbreak which is the larger Ebola outbreak to date. Several factors have been proposed to explain this amplification of the epidemic disease such as a change in virulence, in capacity of transmission between individuals, the increase contact between individuals [Brown et al., 2016; Park et al., 2015]. We show here that the higher size of the outbreak could be explain by a higher contact rate with the intermediate host which are numerous in the case of Ebola virus (chimpanzees, gorillas, antelope and bats) [Muyembe Tamfum et al., 2012]. Targeting the factors that amplify the epidemic disease can help the control and the preventing of the infectious diseases.

Broadly, a buffering effect of the number of outbreaks and the size of the largest outbreak is observed when the intermediate host acts as a bridge between the reservoir and the interest population but only when the between-populations transmission is low. The number of outbreaks and the size of the largest outbreak are compared with the model with the reservoir as the only source of infection. This suggests that the within-host transmission in the intermediate host allows to dilute the between-host transmission but only when this transmission is low. The effect of the cross-species transmission has been studied and it has been shown that in the case of a density-dependent transmission, the addition of species amplifies the disease in the interest population [Dobson, 2004; Rudolf and Antonovics, 2005]. In those models, the epidemiological dynamics is compared with a single introduction in a SIR model and it is shown that the increasing host species diversity amplifies the frequency of the disease. In our case, the reference model used is the model with the reservoir acting as a source of infection. The pathogen spills over from the incidental population recurrently causing number of outbreaks and leading to a higher peak of infected individuals. The insertion of the intermediate host between the reservoir and the interest host allows to a lower number of outbreaks and lower size of the largest outbreak.

By analysing the source of infection of an interest population, a strategy of control can be implemented. In particular, when no drugs or other traitements are possible, zooprophylaxis can allow to decrease human exposure to any given pathogen by using an animal population to divert the source of infection. This strategy of control has been implemented for malaria in order to divert insect blood feeding from humans to other animals, of-

ten cattle [Asale et al., 2017; Saul, 2003]. Presence of multiple species can, in theory, have both a dilution effect, where the feeding on other species decreases the proportion of vectors feeding on the target species for a disease, and an amplifying effect where the access to multiple feeding hosts causes an increased abundance of vectors. The dilution effect is used in zooprophylaxis. In our model, a dilution effect is observed only when instead of having a pathogen that spills over recurrently from an endemic reservoir, an intermediate host is placed between the endemic reservoir and the interest population and acts as a bridge receiving the infection. When the contact between the intermediate host and human populations is low and only in this case, the epidemiological dynamics in the intermediate host allows a decreasing of the number of outbreaks and the size of the largest outbreak. The use of zooprophylaxis might be an interesting strategy of control. Otherwise, if the reservoir infects the interest population in addition to the intermediate host even if weakly, then an amplified epidemiological dynamics is observed. Understanding the contact processes at the wildlife-human interface is mandatory before applying such an approach.

The outbreaks present in cattle or other animal populations in proximity with humans are empirically linked with an increasing number of infected individuals in humans. For instance outbreaks in pigs or in horses caused respectively by the Nipah or Hendra viruses are associated with the appearance of infected human cases [Bunning et al., 2001]. Indeed, the Nipah and Hendra viruses propagate quickly and easily within non human animal conspecifics. Transmission between pigs in the same farm is attributed to direct contact with excretions and secretions such as urine, saliva, pharyngeal and lung secretions [Chua, 2010]. Once the pathogens are in pigs or horses, then the pathogen can emerge to humans especially to farmer workers. In our results we see that the within-populations transmission increases slightly the peak of infected individuals in the interest population but decreases the number of outbreaks. Indeed, a large number of individuals becomes infected in the intermediate hosts when the transmission within individuals is high leading to the rapid extinction of the outbreak. During the intermediate hosts outbreak, an outbreak also emerges in the interest population and this outbreak slightly increases with the increasing peak in the intermediate host but once the outbreak in the intermediate host goes extinct, the outbreak in the interest population stops. This phenomenon leads to a decreased number of outbreaks and a slightly increase of the size of the largest outbreak. The more important parameter that highly affects the epidemiologi-

cal dynamics of the interest population is the between-populations transmission. Indeed, the contact rate between the interest population and the intermediate host can increase both the peak of infected individuals and the number of outbreaks depending of the parameter values. The density of infected individuals is less important than the contact rate between-populations in the epidemiological dynamics. That can have an impact on strategy of control used. It seems more important to avoid contacts with the infected animal than to decrease the disease in the intermediate hosts.

To conclude, in this paper, we have seen that the addition of an intermediate host can have two opposite consequences. A dilution effect can be observed in the case where the intermediate host is the only source of infection and prevents the direct contact between the reservoir and the interest population and an amplifying effect where the intermediate host acts as a second source of infection even when the pathogen emerges rarely from the reservoir to the interest population.

3.5 Appendices

3.5.1 Algorithm of the full model

Transition		Effect	Transition rate
1	$(S_x, I_x, R_x) \rightarrow (S_x - 1, I_x + 1, R_x)$	Direct transmission	$\beta_x S_x I_x$
2	$(S_x, I_x, R_x) \rightarrow (S_x - 1, I_x + 1, R_x)$	Spillover	$\tau_x S_x$
3	$(S_x, I_x, R_x) \rightarrow (S_x, I_x - 1, R_x + 1)$	Recovery	$\gamma_x I_x$
4	$(S_p, I_p, R_p) \rightarrow (S_p - 1, I_p + 1, R_p)$	Inter incidental transmission	$\pi S_p I_h$

TABLE 3.3 – Transition rates of the stochastic model. The first three transitions correspond to the transitions of the classic SIR stochastic model for the intermediate host and the interest population. The subscript x corresponds to both subscripts h and p that identify respectively the intermediate host and the interest population. Each epidemiological state is defined by S_x : number of suceptible individuals; I_x : number of infected individuals and R_x : number of recovered individuals. β_x indicates the direct transmission rate. τ_x indicates the rate of spillover from the reservoir to both incidental populations and π corresponds to the inter-incidental transmission rate. Individuals recover at rate γ_x.

The epidemiological dynamics of the interest population using the full model (see Figure 3.2) can be simulated with the following algorithm (simulations were run in C++). The population state is assumed to be known at time t. A total event rate (Ω), only depending of the state of the population at time t, is calculated for each iteration.

1. The total event rate Ω of the continuous time stochastic model is given by :

$$\Omega = \beta_x S_x I_x + \tau_x S_x + \gamma_x I_x + \pi S_p I_h.$$

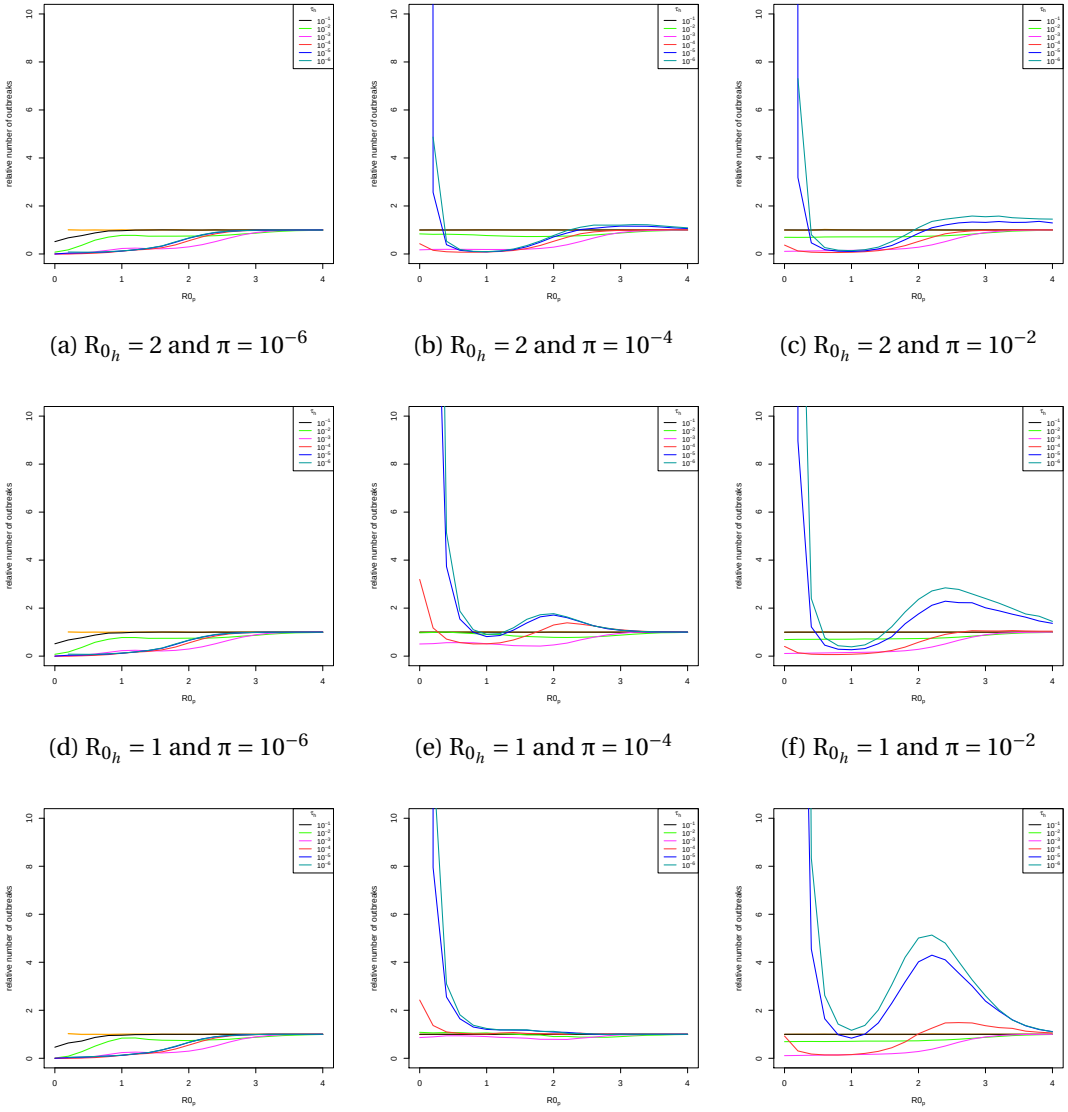
2. The next event time is $t' = t + \delta$ where δ is exponentially distributed with parameter Ω.
3. The next event to occur is randomly chosen : direct transmission, spillover transmission, recover or inter incidental transmission with respective probabilities $\beta_x S_x I_x/\Omega$, $\tau_x S_x/\Omega$, $\gamma_x I_x/\Omega$ and $\pi S_p I_h/\Omega$.

We performed stochastic individual-based simulations of the epidemics with spillover transmission, using rates as presented in Table 3.3. The incidental host is initially ($t = 0$) composed of 1000 susceptible individuals ($N_x = S_x = 1000$). The infection is considered as endemic in the reservoir. Simulations are stopped when there are no susceptible individuals anymore. An outbreak begins when the number of infected individuals reaches the epidemiological threshold c ($c = 5$ infected individuals in the simulations) and ends when

in the interest population there is no infected individuals anymore ($I_p = 0$). Stochastic simulations were run for values of the basic reproductive ratio (R_0) ranging from 0 to 4 and of the spillover transmission (τ_x) and the inter-incidental transmission (π) ranging from 10^{-6} to 10^{-1}, 1000 simulations are performed for each parameter set. All other parameter values are detailed in Table 3.1.

3.5.2 The intermediate host model compared to the reservoir model

The relative number of outbreaks



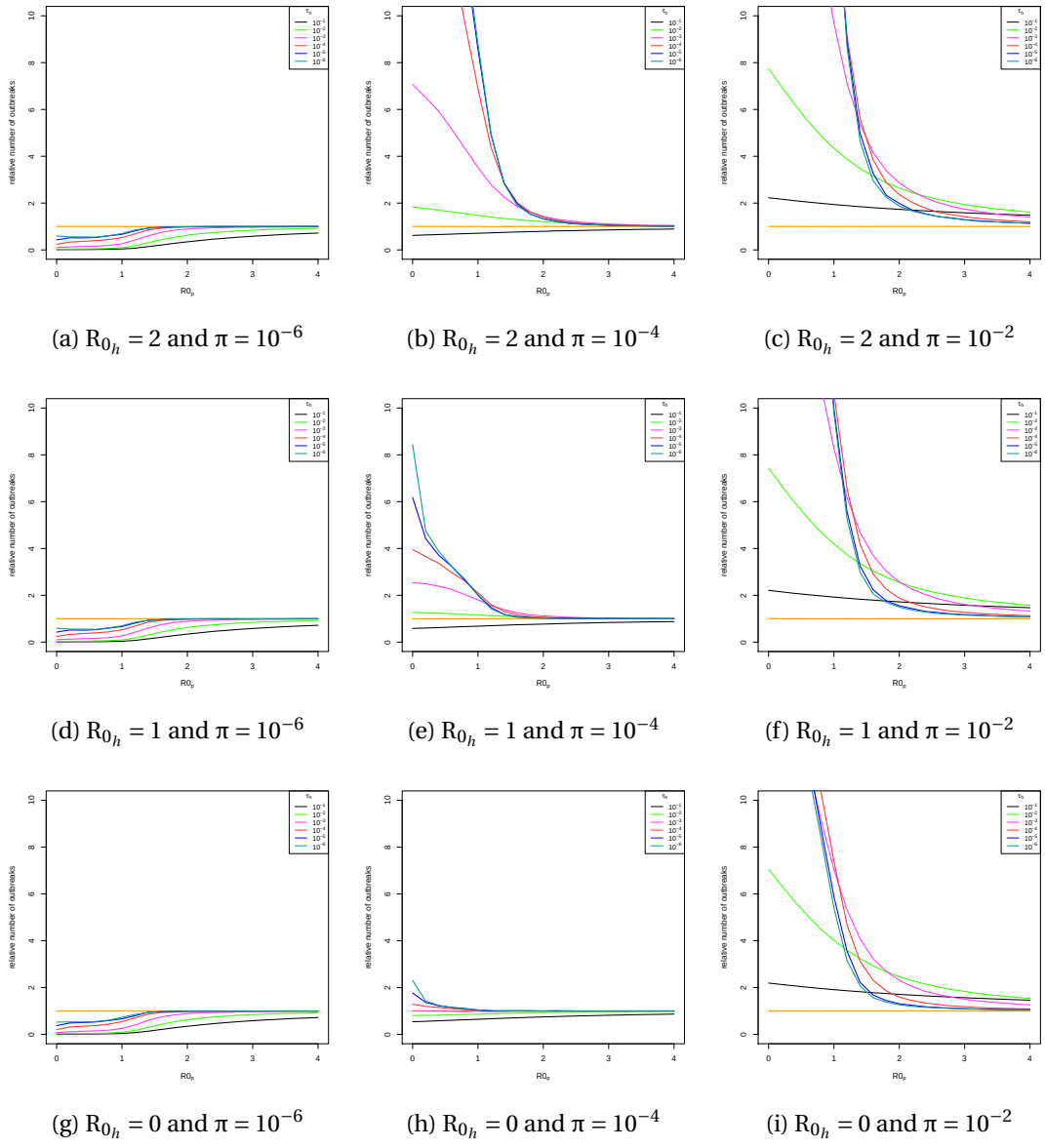
(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

FIGURE 3.10 – Relative number of outbreaks in the interest population in the intermediate host model compared to the reservoir model. A low, intermediate and high value of the within-host transmission in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) is considered. The relative number of outbreaks is depicted as a function of the direct transmission between individuals (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.

The relative size of the largest outbreak



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

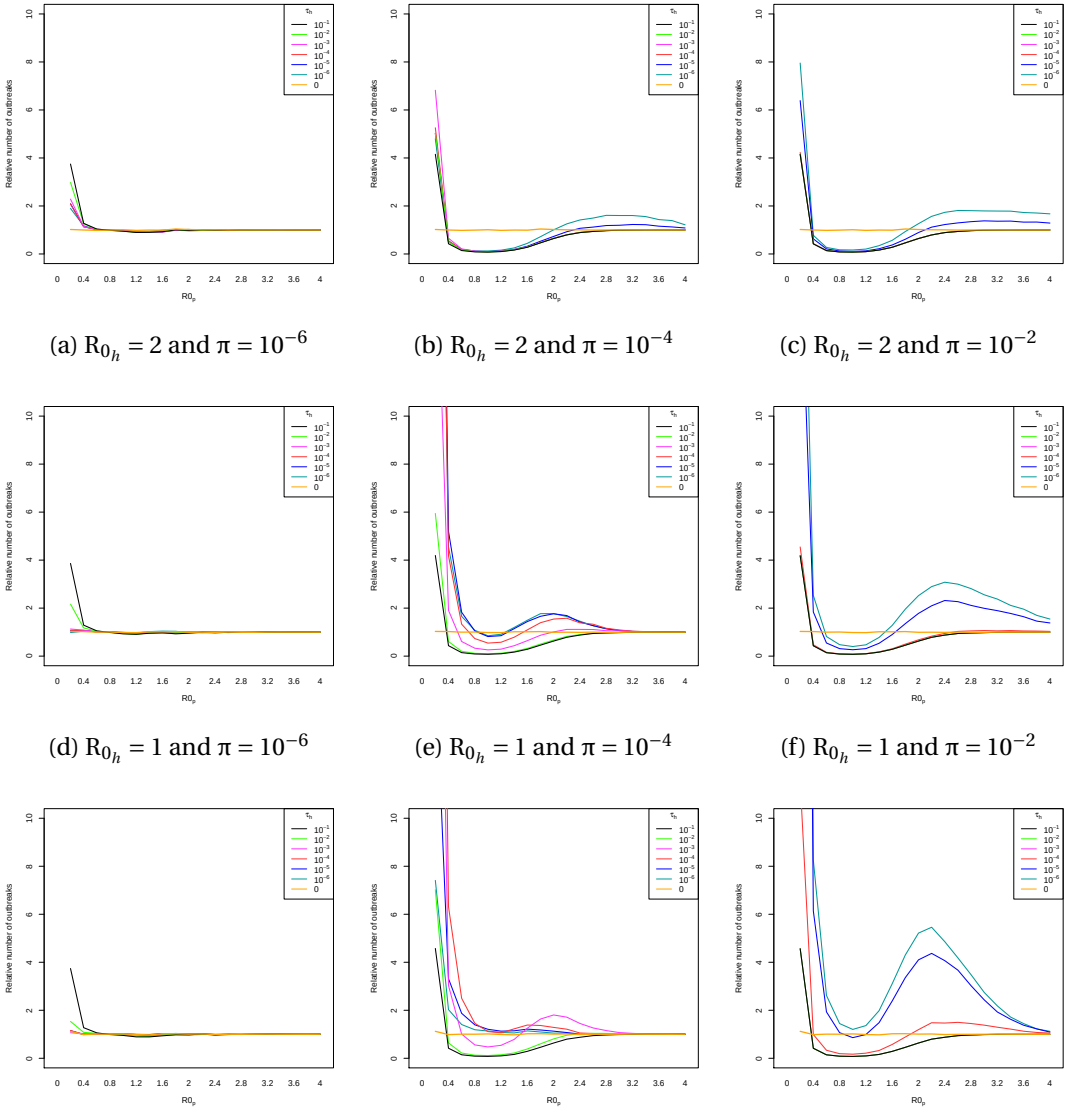
(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

FIGURE 3.11 – Relative size of the largest outbreak in the interest population in the intermediate host model compared to the reservoir model. A low, intermediate and high value of the within-host transmission in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) is considered. The relative size of the largest outbreak is depicted as a function of the direct transmission between individuals (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}.

3.5.3 The full model compared to the reservoir model

The relative number of outbreaks

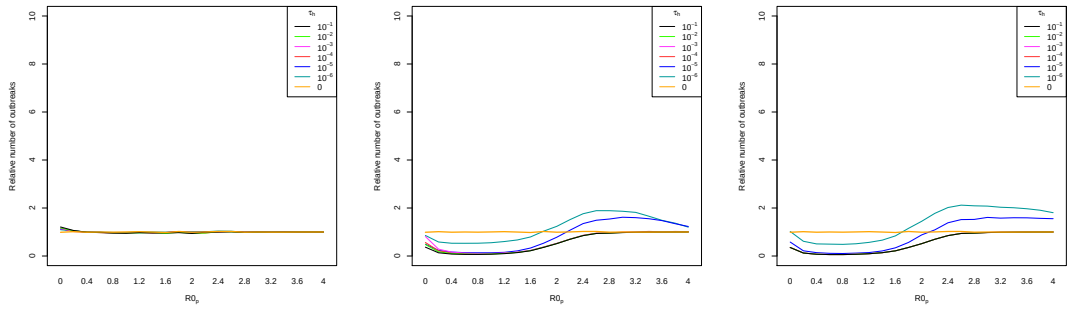


(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

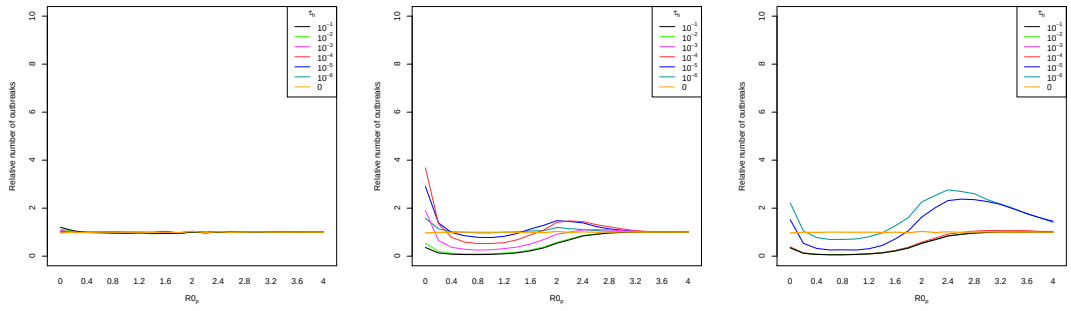
(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

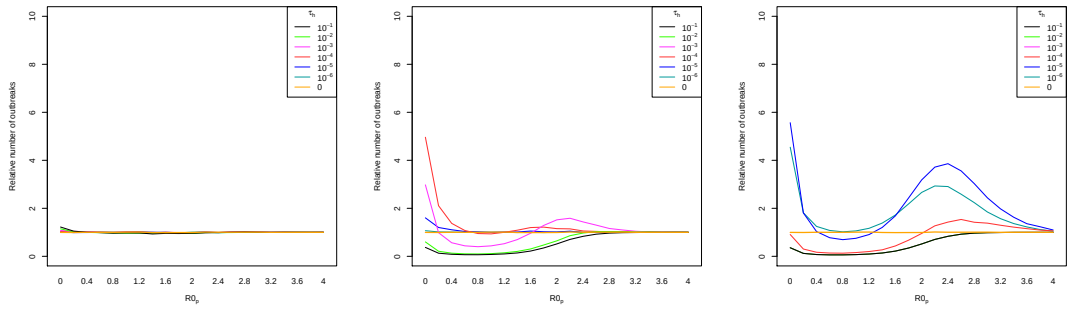
FIGURE 3.12 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. A low effect of the reservoir is considered ($\tau_p = 10^{-6}$).



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

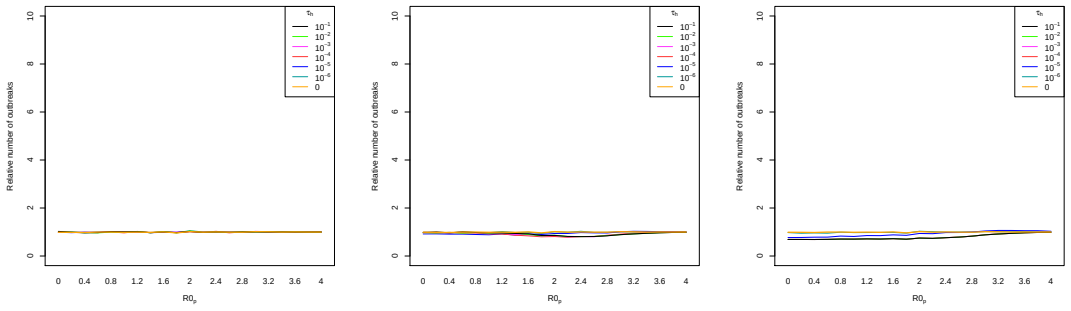


(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

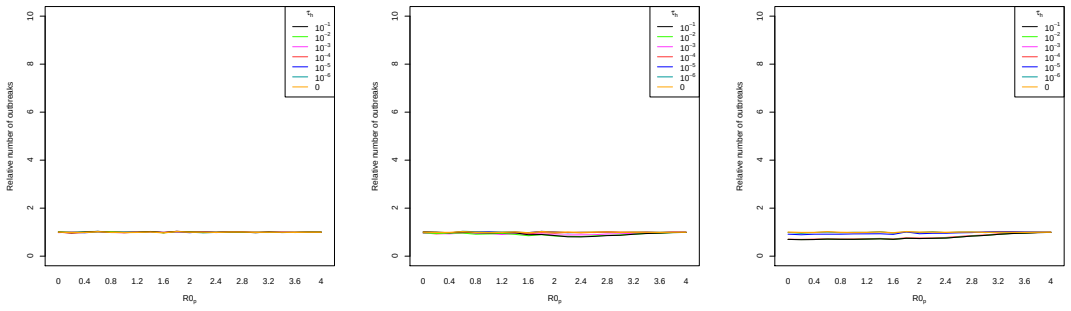


(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

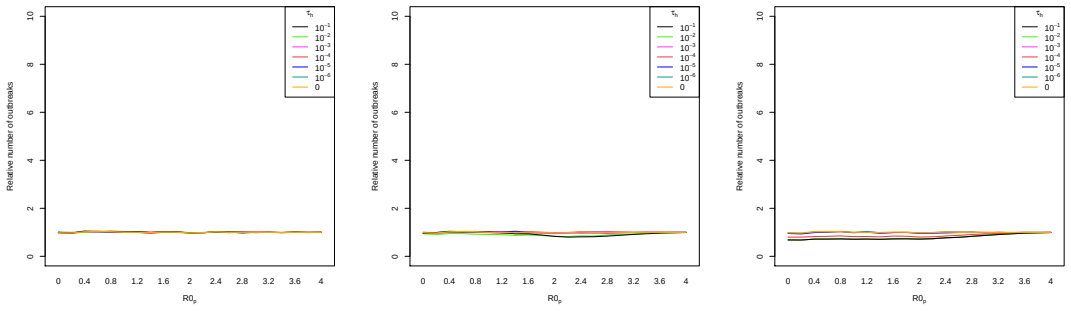
FIGURE 3.13 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. An intermediate effect of the reservoir is considered ($\tau_p = 10^{-4}$).



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$



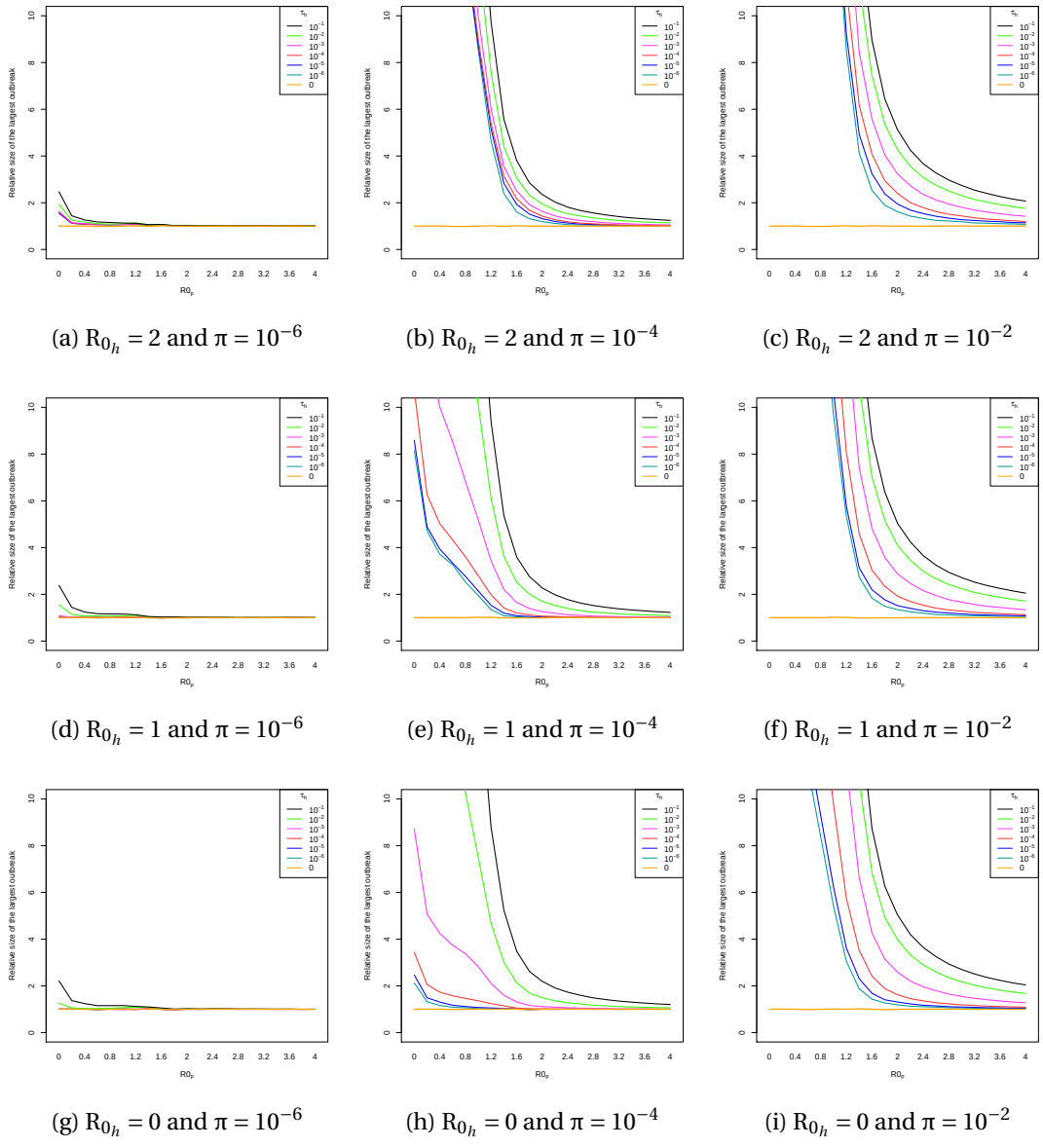
(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$



(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

FIGURE 3.14 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. A high effect of the reservoir is considered ($\tau_p = 10^{-2}$).

The relative size of the largest outbreak

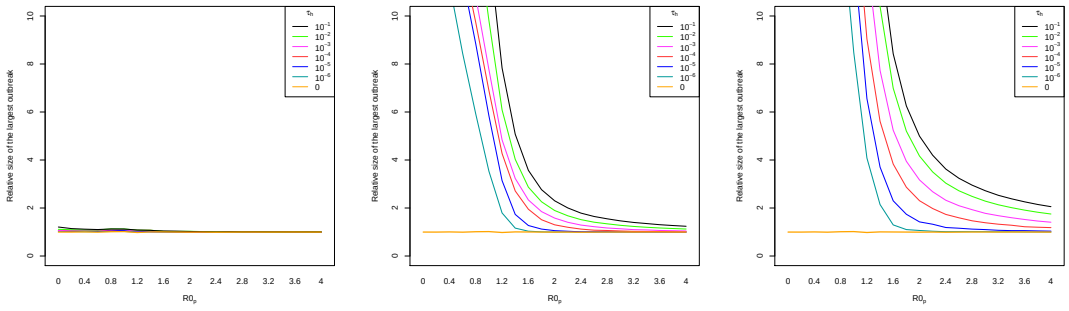


(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

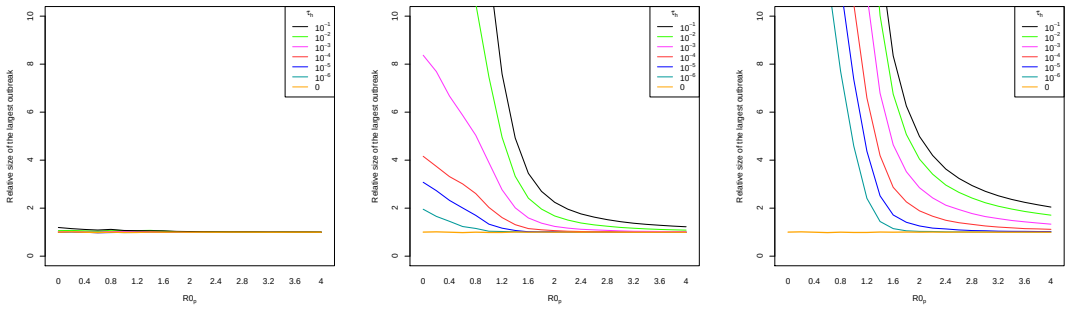
(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

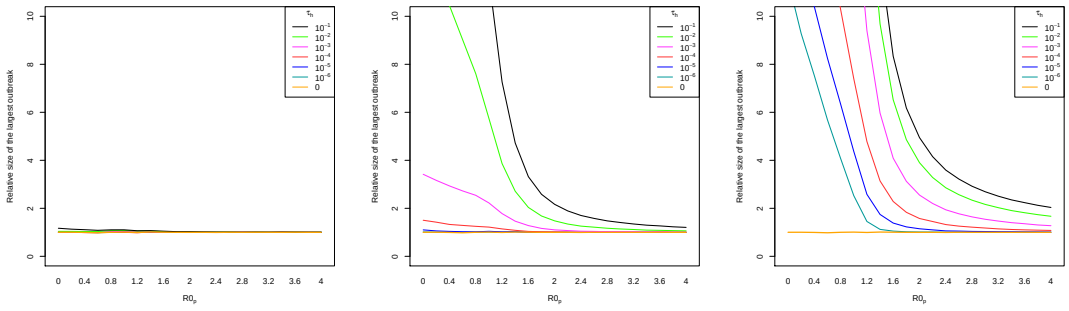
FIGURE 3.15 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. A low effect of the reservoir is considered ($\tau_p = 10^{-6}$).



(a) $R0_h = 2$ and $\pi = 10^{-6}$ (b) $R0_h = 2$ and $\pi = 10^{-4}$ (c) $R0_h = 2$ and $\pi = 10^{-2}$

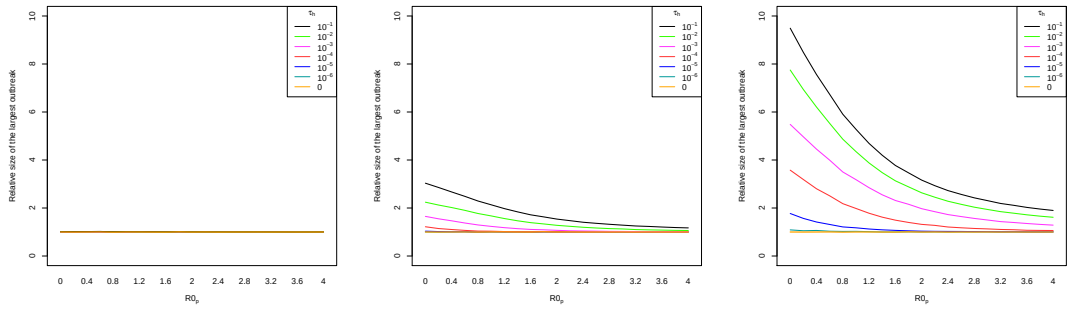


(d) $R0_h = 1$ and $\pi = 10^{-6}$ (e) $R0_h = 1$ and $\pi = 10^{-4}$ (f) $R0_h = 1$ and $\pi = 10^{-2}$

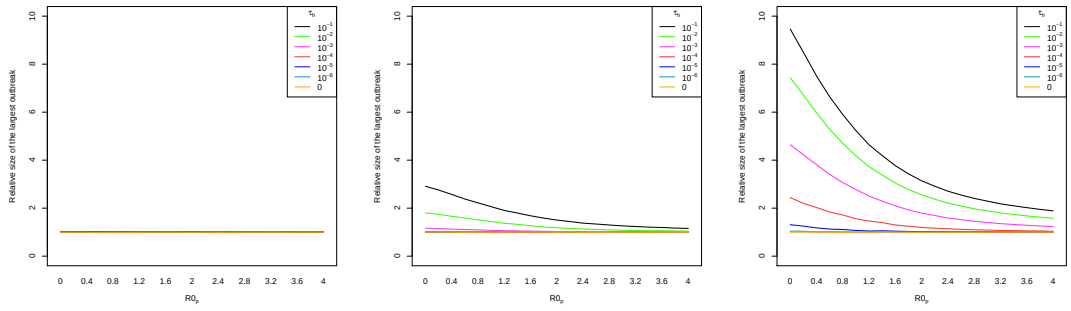


(g) $R0_h = 0$ and $\pi = 10^{-6}$ (h) $R0_h = 0$ and $\pi = 10^{-4}$ (i) $R0_h = 0$ and $\pi = 10^{-2}$

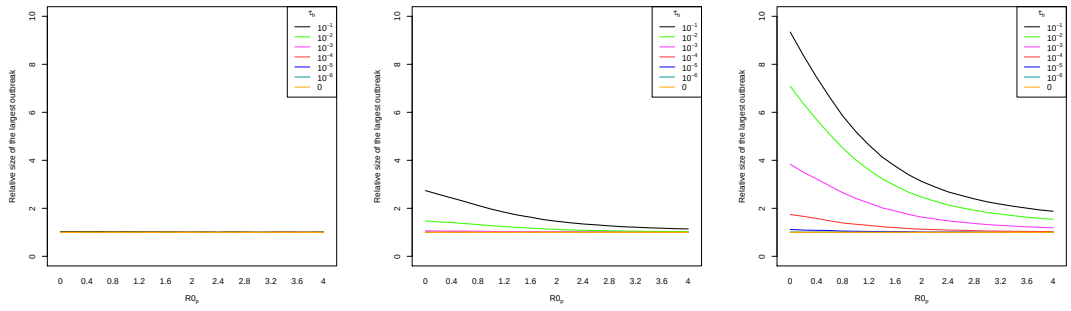
FIGURE 3.16 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R0_h = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population ($R0_p$). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. An intermediate effect of the reservoir is considered ($\tau_p = 10^{-4}$).



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$



(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

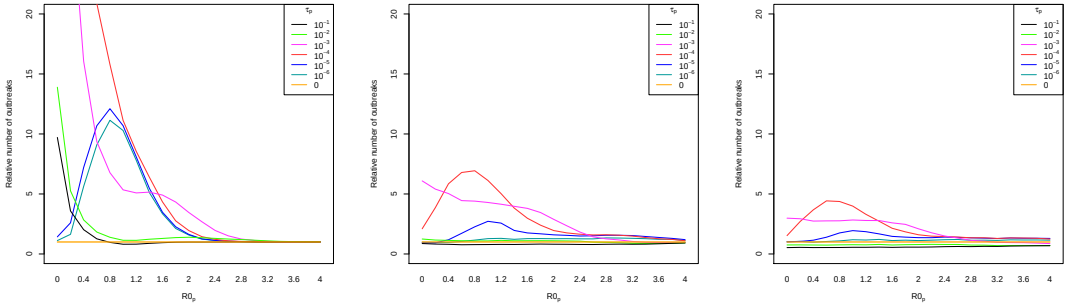


(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

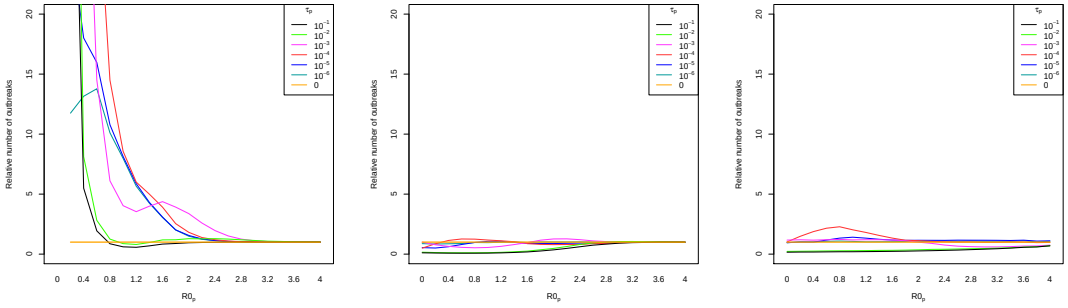
FIGURE 3.17 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the intermediate host (τ_h) ranging from 10^{-6} to 10^{-1}. A high effect of the reservoir is considered ($\tau_p = 10^{-2}$).

3.5.4 The full model compared to the intermediate host model

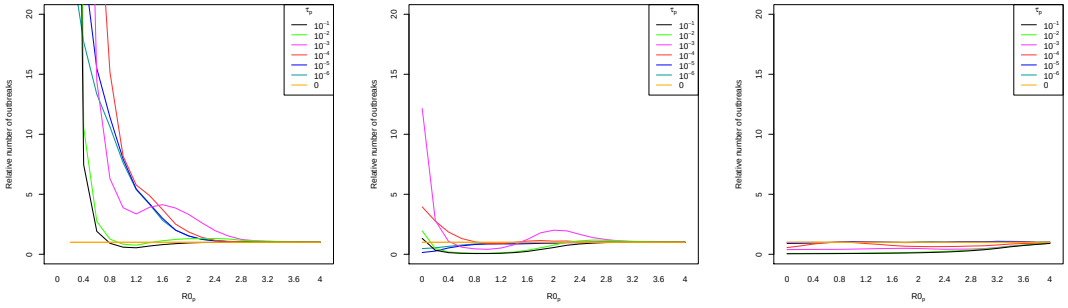
The relative number of outbreaks



(a) $R0_h = 2$ and $\pi = 10^{-6}$ (b) $R0_h = 2$ and $\pi = 10^{-4}$ (c) $R0_h = 2$ and $\pi = 10^{-2}$

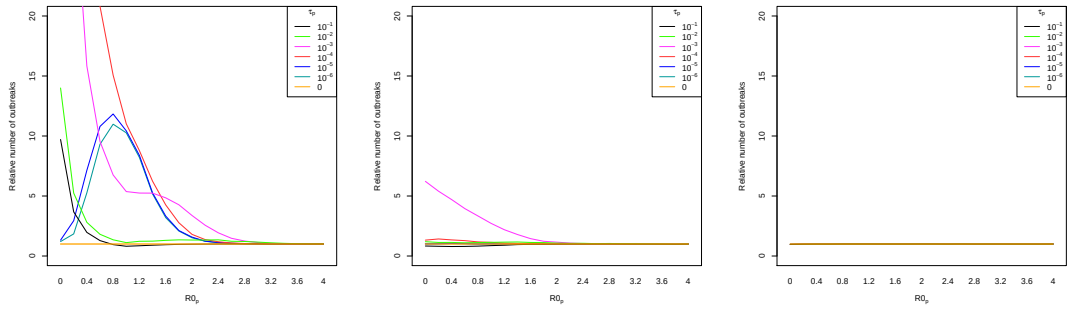


(d) $R0_h = 1$ and $\pi = 10^{-6}$ (e) $R0_h = 1$ and $\pi = 10^{-4}$ (f) $R0_h = 1$ and $\pi = 10^{-2}$

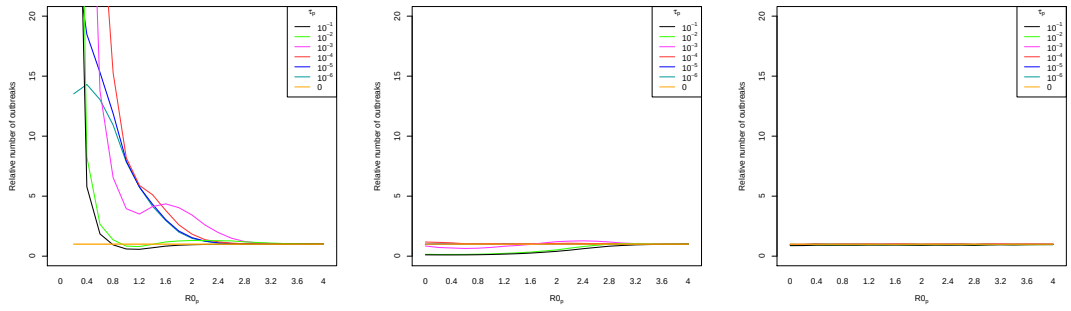


(g) $R0_h = 0$ and $\pi = 10^{-6}$ (h) $R0_h = 0$ and $\pi = 10^{-4}$ (i) $R0_h = 0$ and $\pi = 10^{-2}$

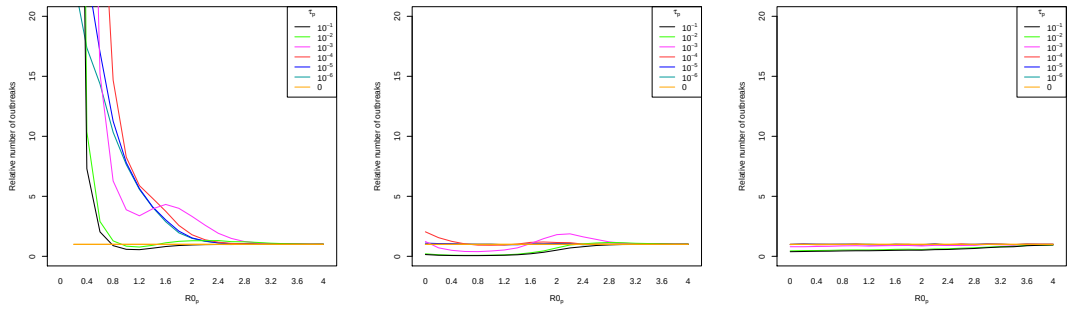
FIGURE 3.18 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R0_h = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population ($R0_p$). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. A low spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-6}$.



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

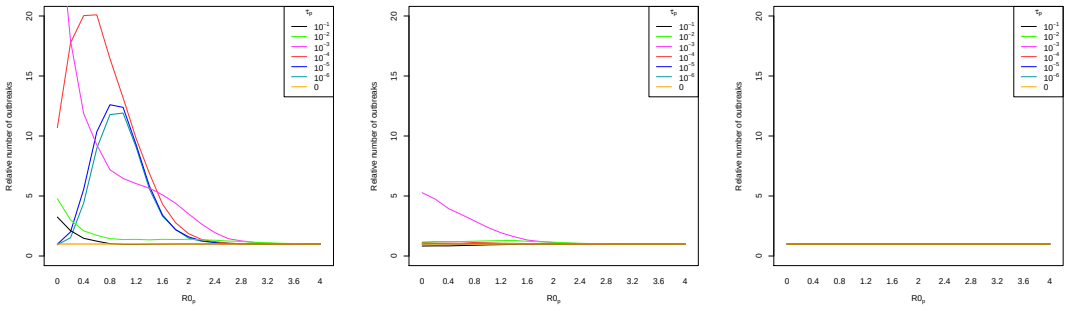


(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

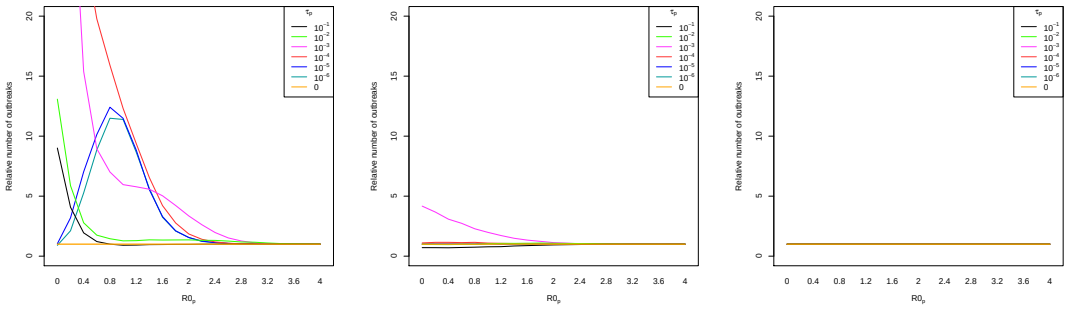


(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

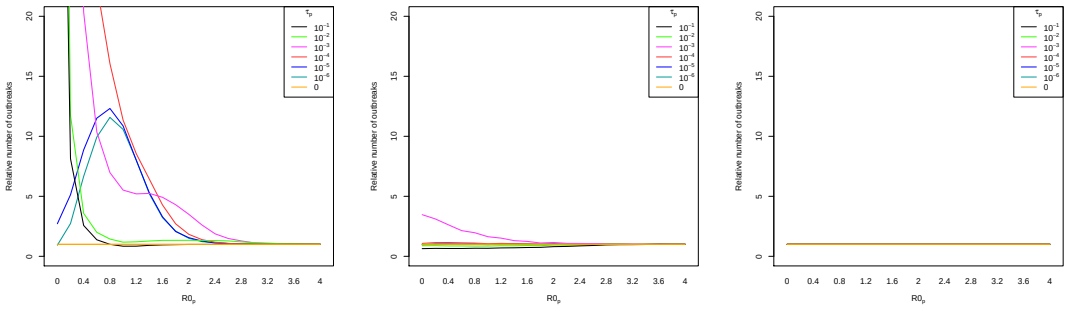
FIGURE 3.19 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. An intermediate spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-4}$.



(a) $R0_h = 2$ and $\pi = 10^{-6}$ (b) $R0_h = 2$ and $\pi = 10^{-4}$ (c) $R0_h = 2$ and $\pi = 10^{-2}$



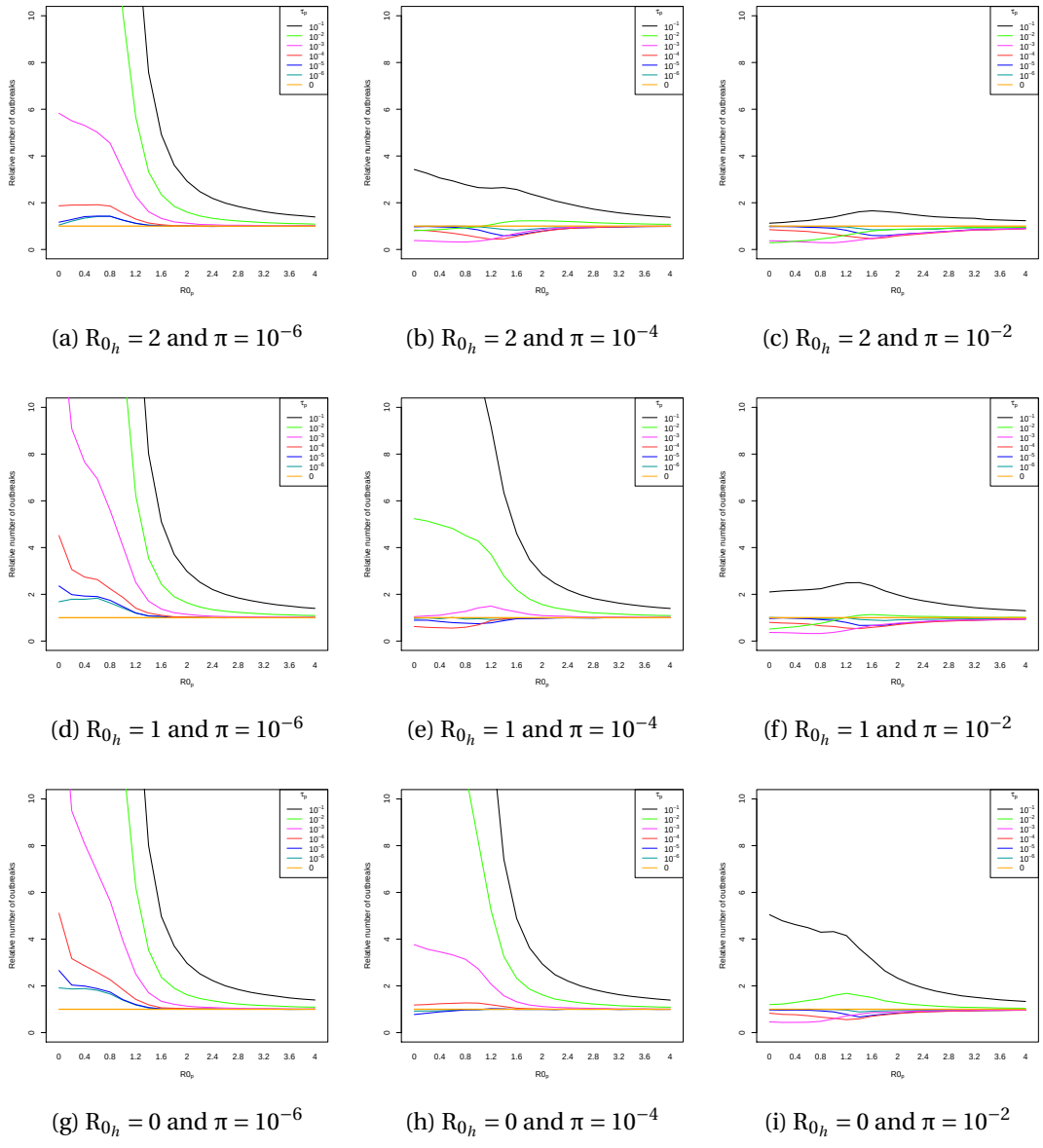
(d) $R0_h = 1$ and $\pi = 10^{-6}$ (e) $R0_h = 1$ and $\pi = 10^{-4}$ (f) $R0_h = 1$ and $\pi = 10^{-2}$



(g) $R0_h = 0$ and $\pi = 10^{-6}$ (h) $R0_h = 0$ and $\pi = 10^{-4}$ (i) $R0_h = 0$ and $\pi = 10^{-2}$

FIGURE 3.20 – Relative number of outbreaks between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R0_h = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative number of outbreaks is depicted as a function of the transmission between individuals in the interest population ($R0_p$). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. A high spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-2}$.

The relative size of the largest outbreak

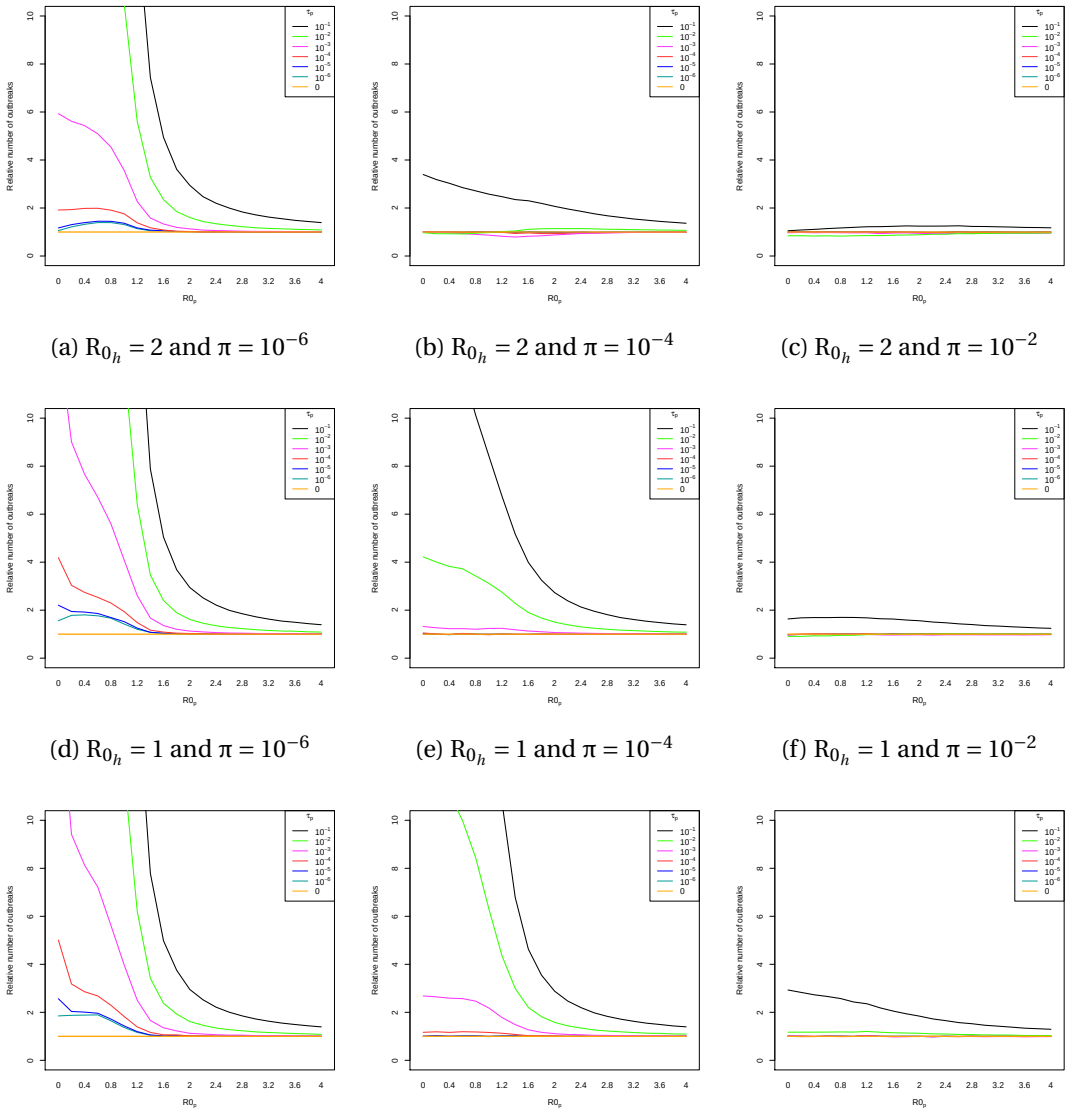


(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$

(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$

(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

FIGURE 3.21 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. A low spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-6}$.

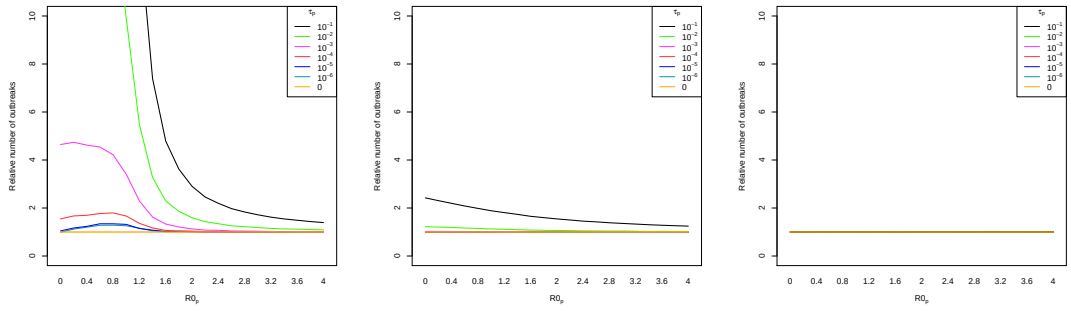


(a) $R0_h = 2$ and $\pi = 10^{-6}$ (b) $R0_h = 2$ and $\pi = 10^{-4}$ (c) $R0_h = 2$ and $\pi = 10^{-2}$

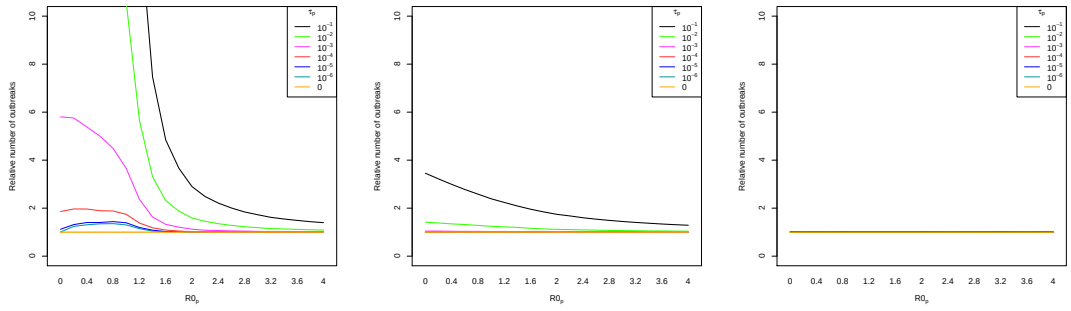
(d) $R0_h = 1$ and $\pi = 10^{-6}$ (e) $R0_h = 1$ and $\pi = 10^{-4}$ (f) $R0_h = 1$ and $\pi = 10^{-2}$

(g) $R0_h = 0$ and $\pi = 10^{-6}$ (h) $R0_h = 0$ and $\pi = 10^{-4}$ (i) $R0_h = 0$ and $\pi = 10^{-2}$

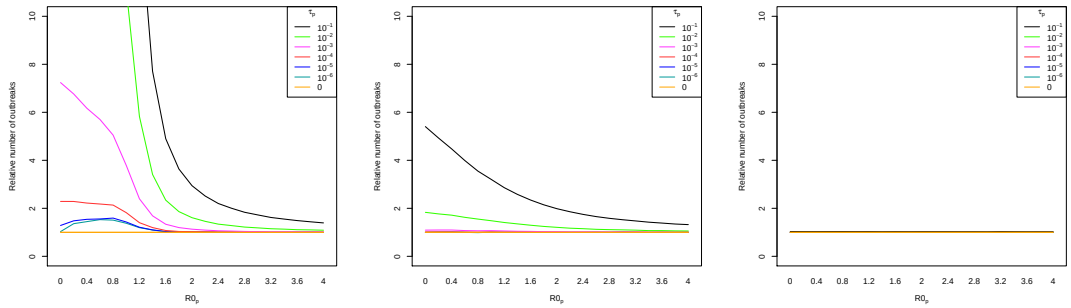
FIGURE 3.22 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R0_h = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population ($R0_p$). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. An intermediate spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-4}$.



(a) $R_{0_h} = 2$ and $\pi = 10^{-6}$ (b) $R_{0_h} = 2$ and $\pi = 10^{-4}$ (c) $R_{0_h} = 2$ and $\pi = 10^{-2}$



(d) $R_{0_h} = 1$ and $\pi = 10^{-6}$ (e) $R_{0_h} = 1$ and $\pi = 10^{-4}$ (f) $R_{0_h} = 1$ and $\pi = 10^{-2}$



(g) $R_{0_h} = 0$ and $\pi = 10^{-6}$ (h) $R_{0_h} = 0$ and $\pi = 10^{-4}$ (i) $R_{0_h} = 0$ and $\pi = 10^{-2}$

FIGURE 3.23 – Relative size of the largest outbreak between the full model and the reservoir model. A low, intermediate and high value of the transmission between individuals in the intermediate host (respectively $R_{0_h} = 0$, 1 and 2) and inter-incidental transmission (respectively $\pi = 10^{-6}$, 10^{-4} and 10^{-2}) are considered. The relative size of the largest outbreak is depicted as a function of the transmission between individuals in the interest population (R_{0_p}). Each curve represents a spillover transmission from the reservoir to the interest population (τ_p) ranging from 10^{-6} to 10^{-1}. A high spillover rate from the reservoir to the intermediate host is considered $\tau_h = 10^{-2}$.

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Chapitre 4

Beyond rational decision-making : modelling the influence of cognitive biases on the dynamics of vaccination coverage

MARINA VOINSON, SYLVAIN BILLIARD, ALEXANDRA ALVERGNE

Sommaire

Nous venons d'analyser, dans les chapitres précédents, la dynamique épidémique des maladies infectieuses émergentes. Cependant, peu de traitements sont disponibles ou alors en cours de développement, c'est notamment le cas de la vaccination contre le virus Ebola. Pour les maladies établies, la vaccination est un moyen reconnu comme efficace pour lutter contre la propagation des maladies infectieuses comme la rougeole, la rubéole, la coqueluche, la grippe saisonnière, la poliomyélite, etc. Cependant, à part la variole dont l'éradication a été déclarée par l'Organisation Mondiale de la Santé en 1980, aucune autre maladie infectieuse n'a pu être éradiquée à ce jour. Les stratégies de vaccination volontaire en seraient la cause. Une protection des populations est possible lorsqu'une fraction importante de la population est vaccinée contre l'infection. La fraction de la population vaccinée est ce qu'on appelle la couverture vaccinale. Cette couverture vaccinale permet de protéger les individus qui ne peuvent pas se faire vacciner, principalement pour des raisons médicales, en atteignant une immunité au niveau de la population. Cependant, lorsque la couverture vaccinale n'atteint pas un certain seuil, les résurgences de maladies infectieuses surviennent.

Pourquoi les programmes de vaccination volontaire réussissent-ils ou échouent-ils ? Au cours des 10 dernières années, un certain nombre de modèles théoriques ont avancé l'argument selon lequel de tels programmes ne parviennent pas à atteindre l'immunité au niveau de la population en raison d'individus "tricheurs" [Bauch and Earn, 2004; Bauch et al., 2003; Chen, 2006]. En effet, ces individus vont profiter de l'immunité de la population sans payer le coût de la vaccination. Ces modèles utilisent l'analyse de la théorie des jeux et supposent que les individus sont des agents économiques qui maximisent leur santé. Cependant, une telle approche est en contradiction avec la littérature psychologique et anthropologique sur la prise de décision humaine [Wheelock et al., 2013]. Nous proposons ici une alternative aux études classiques d'épidémiologie comportementale en considérant un cadre exempt d'optimisation et de calculs d'utilité, et considérant plutôt la prise de décision comme l'expression de dispositions cognitives évoluées.

L'objectif de ce chapitre est d'étudier comment l'interaction entre le comportement humain de prise de décision dune part et l'environnement épidémique et social d'autre part, vont façonner la dynamique de la couverture vaccinale. Pour cela, nous avons développé un modèle d'incidence comportementale dans lequel les individus peuvent être pro-vaccins ou sceptiques. Leur opinion va influer sur la manière dont les coûts réels de l'infection et de la vaccination seront perçus. En modélisant la façon dont les individus

interprètent les informations épidémiologiques, nous nous sommes concentrés sur deux biais cognitifs associés au comportement de vaccination : le biais de confirmation, c'est-à-dire la propension à rechercher des preuves qui confirment les croyances préexistantes ; et le conformisme, c'est-à-dire la propension à suivre l'opinion majoritaire du groupe social.

Globalement, le modèle prédit la dynamique généralement observée de la couverture vaccinale, à savoir l'impossibilité d'atteindre l'immunité collective ainsi que les oscillations de la couverture vaccinale. Cela suggère que les hypothèses de rationalité économique et de maximisation des gains ne sont pas obligatoires pour prédire les dynamiques généralement observées de la couverture vaccinale. Les résultats démontrent que les biais d'apprentissage (c.-à-d. les biais de confirmation et de conformisme), plutôt que la maximisation de la santé, peuvent conduire à la propagation des refus de vaccination. Les résultats ont des conséquences sur la manière dont l'interaction entre l'épidémiologie et la cognition peut entraîner des difficultés pour atteindre et/ou maintenir l'immunité au niveau de la population.

Ce chapitre a fait l'objet d'un article publié dans *PloS One* : Voinson M., Billiard S. and Alvergne A. (2015) Beyond Rational Decision-Making : Modelling the Influence of Cognitive Biases on the Dynamics of Vaccination Coverage. PLoS ONE 10(11) : e0142990. https ://doi.org/10.1371/journal.pone.0142990

Abstract

Background : Theoretical studies predict that it is not possible to eradicate a disease under voluntary vaccination because of the emergence of non-vaccinating "free-riders" when vaccination coverage increases. A central tenet of this approach is that human behaviour follows an economic model of rational choice. Yet, empirical studies reveal that vaccination decisions do not necessarily maximize individual self-interest. Here we investigate the dynamics of vaccination coverage using an approach that dispenses with payoff maximization and assumes that risk perception results from the interaction between epidemiology and cognitive biases.

Methods : We consider a behaviour-incidence model in which individuals perceive actual epidemiological risks as a function of their opinion of vaccination. As a result of confirmation bias, sceptical individuals (negative opinion) overestimate vaccination cost while pro-vaccines individuals (positive opinion) overestimate infection cost. We considered a feedback between individuals and their environment as individuals could change their opinion, and thus the way they perceive risks, as a function of both the epidemiology and the most common opinion in the population. Results : For all parameter values investigated, the infection is never eradicated under voluntary vaccination. For moderately contagious diseases, oscillations in vaccination coverage emerge because individuals process epidemiological information differently depending on their opinion. Conformism does not generate oscillations but slows down the cultural response to epidemiological change.

Conclusion : Failure to eradicate vaccine preventable disease emerges from the model because of cognitive biases that maintain heterogeneity in how people perceive risks. Thus, assumptions of economic rationality and payoff maximization are not mandatory for predicting commonly observed dynamics of vaccination coverage. This model shows that alternative notions of rationality, such that of ecological rationality whereby individuals use simple cognitive heuristics, offer promising new avenues for modelling vaccination behaviour.

Key words : behavioural epidemiology, health psychology, cultural cognition.

4.1 Introduction

Vaccination has greatly reduced the burden of infectious diseases worldwide. However, by 2015, only smallpox has been eradicated by programs of voluntary vaccination and global outbreaks of measles, mumps, whooping cough, polio and rubella are repeatedly being reported in both developed and developing regions. Why voluntary vaccination programs succeed or fail is contingent on the acceptance or rejection of vaccines by individuals; considering the vaccination decision-making process is thus pivotal for making inferences about the dynamics of vaccination coverage and disease transmission. Over the last decade, a number of theoretical studies explicitly modelled human behaviour as a key parameter for determining how vaccines scares unfold (reviewed in [Bauch et al., 2013; Funk et al., 2010]). This led to the new field of behavioural epidemiology [Manfredi and D'Onofrio, 2013] and the development of "prevalence-based" models [Funk et al., 2010] positing that individuals adjust their decisions based on an information relating to the number of infected individuals. Assuming that individuals are rational, that is, agents that optimize their utility i.e. individuals make a logical and coherent choice depending on choices of others, it was concluded that it is not possible to eradicate a disease under voluntary vaccination because of the emergence of non-vaccinating free riders when vaccination coverage is sufficiently high [Bauch and Earn, 2004; Bauch et al., 2003; Chen, 2006]. This approach is at odds with psychological and anthropological literature on human decision-making and insufficient if we are to explain why some vaccine preventable diseases can be either globally eradicated (e.g. small pox) or locally eliminated (e.g. polio in India), or why individuals refuse vaccination despite scientific evidence that it is safe (reviewed in [Streefland et al., 1999]). Here we propose an alternative to classic behavioural epidemiology studies by considering a revised version of rationality, that of an ecological rationality [Hutchinson and Gigerenzer, 2005; Todd and Gigerenzer, 2012], enabled by the mind's "adaptive toolbox" [Gigerenzer and Selten, 2001]. This framework dispenses with optimization and with complex calculations of utilities altogether and views decision-making as the expression of evolved cognitive dispositions (e.g. heuristics or rules of thumb including social learning abilities). This enables us to develop a behaviour-incidence model explicitly considering cognitive mechanisms with the aim to investigate how the feedback between cognition and epidemiology may influence the dynamic of disease transmission.

How do people decide whether or not to vaccinate? A key factor is the perception of risks associated with infection and vaccination [Wheelock et al., 2013]. Risk perception is central to most health behaviour theories and in this line, a recent meta-analysis [Brewer et al., 2007] based on > 15,000 individuals revealed a significant association (measured by a summary effect size r, which was obtained from pooling effect sizes across studies) between vaccine uptake and (i) the perceived likelihood of infection (12 studies, r (summary effect size [range]) = 0.26 [-0.12 ; 0.45]), (ii) the susceptibility to illness (5 studies, r = 0.24 [0.15 ; 0.36]) and to a lesser extent, (iii) the severity of the disease (31 studies, r = 0.16 [-0.18 ; 0.39]) (meta-analysis [Brewer et al., 2007]). In classic behavioural epidemiology, risk perception relates to the prevalence of infected individuals at a given time, either in the general population (non-structured population and homogeneously mixed population) or in a social network [Perisic and Bauch, 2009a,c]. This underlying game theory framework considers that individuals make decisions based on an objective evaluation of the epidemiology, computing statistics using a large data size (but see [Bauch, 2005; Fu et al., 2010; Wells and Bauch, 2012]). However, this assumption is problematic for at least two reasons. First, human cognition has been demonstrated to be inefficient at dealing with uncertainty and computing probability [Gigerenzer and Selten, 2001] ; rather, individuals may use empirical knowledge based on a small number of cases. Second, risk assessment is likely to be partly independent from infection [Funk et al., 2010] as it is shaped by a number of psychological and social factors that may lead to an under- or an overestimation of epidemiological risks, including media coverage [Young et al., 2013], salient previous experience [Wheelock et al., 2013], belief about contagion [Caprara, 1998], family and peers [Scherer and Cho, 2003; Wheelock et al., 2013] and trust in providers, medical professionals and the state [Durbach, 2004; Streefland et al., 1999]. To evaluate temporal and spatial variation in vaccine uptake, one must thus refine assumptions of rationality to consider, not only change in epidemiology, but also how the evolved cognition responds to features of the social and epidemiological environments.

An alternative to current modelling of vaccination decision-making may come from the consideration of evolutionary-ecological models, focusing on the concept of ecological rationality [Oraby and Bauch, 2015; Todd and Gigerenzer, 2012]. In this framework, cognitive dispositions are evolved, i.e. decision rules have been selected for, but the resulting behaviour may or may not be adaptive, i.e. maximizing current individual survival and reproductive success. It follows that to understand the processes underlying vacci-

nation decision-making, one focuses on the environment and the cognitive mechanisms underlying decisions rather than health outcomes of decisions. Proponents of ecological rationality argue that humans have evolved heuristics, i.e. simple cognitive rules processing a few pieces of information available from the environment [Todd and Gigerenzer, 2012]. For the purpose of this paper, which aims to investigate the role of cognitive biases for predicting commonly observed dynamics of vaccination coverage such as the failure to reach herd immunity and oscillations between high and low levels of coverage, we focus on those heuristics or cognitive shortcuts that are likely to allow for heterogeneity and change in opinion about vaccination. In modelling how individuals interpret epidemiological information, we first decided to consider "confirmation bias", i.e. the propensity to look for evidence supporting pre-existing beliefs while considering disconfirmatory evidence with great scrutiny [Bruner and Postman, 1949; Nickerson, 1998]. Confirmation bias has been observed in the context of pertussis vaccination for children : when presented with the same risk-benefit information about vaccination, non-vaccinators became less committed with vaccination, while vaccinators became more committed [Meszaros et al., 1996]. The second heuristic we considered is "imitate the majority" or conformism, as the role of peer influence has repeatedly been invoked for understanding vaccination behaviour [Oraby et al., 2014; Streefland et al., 1999; Sturm et al., 2005].

In this paper, we consider a behaviour-incidence model in which opinion formation mediates a feedback between vaccination behaviour and the disease. As compared to previous behaviour-incidence models, our approach does not make use of game theory analysis (see also [Coelho and Codeço, 2009; Xia and Liu, 2014]). We first consider that disease incidence and vaccination coverage determine how many people suffer from negative effects, an information that represents epidemiological costs. We then assume that an individual interprets those costs as a function of their opinion of vaccination. Specifically, a sceptical individual will be more likely to overestimate a vaccination cost while a pro-vaccine advocate will more likely to overestimate the cost of infection. It follows that given the same epidemiological information, individuals will vaccinate at different rates depending on their a priori opinion. Finally, we consider that individuals respond to their environment over time as they can change their opinion as a function of both epidemiological costs and the most common opinion in the population (conformism). The model assumes that the population mixes homogenously so that anyone can infect any other individual in the population and the information on epidemiological costs is

globally available to everyone through the media. The goal of this study is to investigate how the interaction between human cognition and both the epidemiological and social environments shape the dynamics of vaccination coverage.

4.2 Methods

4.2.1 Rationale

The model corresponds to a SIR (susceptible-infected-recovered/immune) compartmental model capturing the disease transmission process [Kermack and McKendrick, 1927] augmented with a belief model (fig. 4.1). It enables individuals to be characterized by both their epidemiological status and their opinion. Specifically, individuals can belong to one of 4 epidemiological compartments : susceptible, infected, immune through vaccination and immune naturally. In each compartment, individuals can be characterized either as “pro-vaccines” (positive opinion) or “sceptical” (negative opinion). Across time, individuals can change compartments : for instance, susceptible individuals may become infected, or they may choose to vaccinate. The system of compartments and flows between them is defined by a system of ordinary differential equations (see section 4.2.2) to examine numerical simulations at different values of the parameters.

The rate at which individuals become vaccinated is a function of both the epidemiological costs associated with infection and vaccination and the distribution of opinions of vaccination in the population. First, costs are defined by the epidemiology with the number of infected individuals and vaccination coverage determining the number of people suffering negative side effects from infection and vaccination, respectively. Individuals are assumed to vaccinate more quickly when the infection cost is high and more slowly when the vaccination cost is high. Then, given the same epidemiological information on costs, individuals with different opinions vaccinate at different rates. We considered that pro-vaccines individuals give more weight to the role of infection cost in their decision process, while sceptics give more weight to the vaccination cost (due to confirmation bias). Thus, while pro-vaccines individuals always take up vaccines more quickly than sceptics, the difference between them in how rapidly they take up vaccination is considered to be the highest for levels of vaccination coverage that are either low (high infection cost) or high (high vaccination cost). Finally, individuals can change their opinion as a function of

both the epidemiology and the most common opinion in the population.

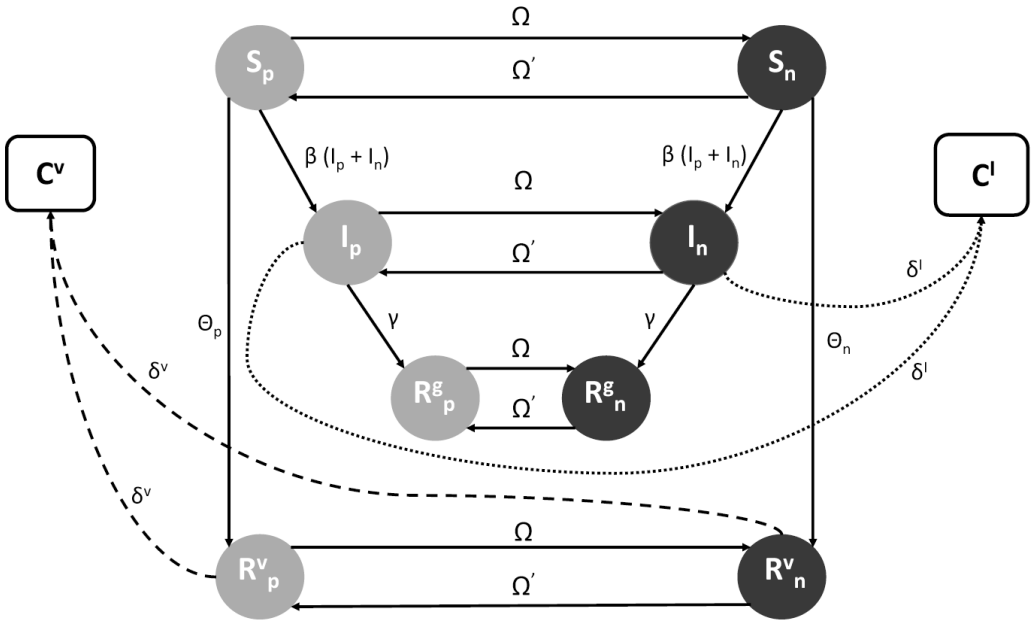

FIGURE 4.1 – Structure of the behaviour-incidence model. The model is an augmentation of a classic SIR compartmental model [Kermack and McKendrick, 1927]. Individuals are characterized by both their epidemiological status (S : susceptible; I : infected; R^{υ} : recovered through vaccination; R^g : recovered naturally) and for each compartment, their opinion of vaccination (positive : subscript p; non-shaded colours; negative : subscript n; shaded colours). C^V and C^I are compartments that indicate the total recalled number of individuals having suffered negative side effects from vaccination and infection, respectively. β indicates the rate of infection transmission; Ω indicates the rate at which individuals change their opinion (from positive to negative Ω or from negative to positive Ω′); δ indicates the number of individuals suffering side effects from either vaccination δ^V and infection δ^I; indicates the rate at which individuals vaccinate. Each individual dies at the same rate d.

4.2.2 The full model

The structure

We considered the case of a single contagious disease, which does not increase the death rate, but which causes negative side effects for infected individuals. Our goal here is not to study a disease in particular but to provide general insights with regard to the effect of opinion on the dynamics of infection and vaccination coverage. We used a compartmental epidemiological model with births and deaths [Kermack and McKendrick, 1927] in which the population is divided into 4 compartments : the number of susceptible (S), the number of infected (I), the number of immune through vaccination (R^{υ}) and the number of immune through natural immunization (R^g). A susceptible individual becomes infected at the rate β (the transmission rate) and vaccinates (transits from compartment S to

R^{ν}) at the rate Θ. Individuals give births to susceptible individuals at the rate b and each individual can die at the rate $d = b$, so that the population remains of constant size. Then, for each compartment, the population is divided into 2 subgroups, with individuals having either a positive opinion of vaccination (pro-vaccines individuals, subscript p) or a negative opinion (sceptical individuals, subscript n). The formation of the opinion and the decision to vaccinate are two separated processes that both depend on the environment. Individuals can change their opinion during their lifetime, and given their opinion at a given time, they decide to get vaccinated or not. At any given time, the total recalled number of individuals having suffered negative side effects from becoming infected or vaccinated constitute a globally available information, which will be used to calculate the epidemiological costs C^I and C^V.

The parameters

The rate of infection transmission : β is expressed in terms of the basic reproductive ratio of the pathogen [Anderson and May, 1991]. R_0 corresponds to the average number of secondary infections produced by an infected individual in an otherwise susceptible population and can be understood as the fitness of the pathogen : for a pathogen to invade the population, R_0 must be >1. In our model R_0 has been calculated as :

$$R_0 = \frac{S_n^* + S_p^*}{d + \gamma} \tag{4.1}$$

where S_n^* and S_p^* are determined numerically using the system of ordinary differential equations (see section 2.iii) assuming no infection. Indeed, S^* is the number of susceptible individuals, i.e. the number of individuals that are not vaccinated before the emergence of the infection. In our model, people can have two different opinions regarding vaccination which implies two different probabilities to accept the vaccine. Thus the number of susceptible individuals S^* depends on the number of individuals who either have a positive or a negative opinion before the emergence of the infectious disease, i.e. $S^* = S_n^* + S_p^*$ where S_n^* and S_p^* represent the population equilibrium of the number of susceptible individuals in the absence of disease.

The information relating to the costs of infection and vaccination : This information, available to everyone, is assumed to be summarized by a function of the number of the

past and present individuals who have suffered negative side effects from infection and vaccination. This information is used by all individuals in order to measure the relating costs of infection and vaccination, respectively denoted C^I and C^V. We supposed that this information is generated and memorized by all individuals at a rate δ^I and δ^V. We also assumed that the information is forgotten at a rate f. At any given point in time, the number of infected individuals is determined by the history of vaccine uptake in the population. Thus, the costs of infection and vaccination depend on both the history of vaccine uptake and the number of infected individuals.

The rate of vaccination : Only susceptible individuals can take up vaccination and the decision to vaccinate depends on both an individual opinion and the costs of infection and vaccination. Individuals with a positive opinion vaccinate at the rate Θ_p ; individuals with a negative opinion vaccinate at the rate Θ_n.

$$\Theta_p = \nu_p\left(\frac{\exp x_p}{1+\exp x_p}\right) \text{ with } x_p = \mu_p C^I - \mu'_p C^V. \tag{4.2}$$

$$\Theta_n = \nu_n\left(\frac{\exp x_n}{1+\exp x_n}\right) \text{ with } x_n = \mu_n C^I - \mu'_n C^V. \tag{4.3}$$

ν_p and ν_n represent the maximum rate at which individuals can be vaccinated. While individuals have access to the same epidemiological information C^I and C^V, the perception of those costs and the subsequent vaccination behaviour is modified by an individual opinion because of a confirmation bias. Confirmation bias is introduced with μ, the weight given to the cost of infection and μ', the weight given to the cost of vaccination. During the vaccination decision-making process, individuals with a positive opinion of vaccines give more weight to the infection cost ($\mu_p > \mu'_p$) while individuals with a negative opinion give more weight to the vaccination cost ($\mu'_n > \mu_n$).

The rate of opinion change : A pro-vaccine individual will become a sceptic at the rate and a sceptic will become a pro-vaccine individual at the rate.

$$\Omega = \omega_{p\to n}\Upsilon_{p\to n}c_n \text{ with } \Upsilon_{p\to n} = \left(\frac{\exp y}{1+\exp y}\right) \text{ and } y = -C^I + C^V \tag{4.4}$$

$$\Omega' = \omega_{n\to p}\Upsilon_{n\to p}c_p \text{ with } \Upsilon_{n\to p} = (\frac{\exp y'}{1+\exp y'}) \text{ and } y' = \mathrm{C^I} - \mathrm{C^V} \tag{4.5}$$

$\omega_{p\to n}$ and $\omega_{n\to p}$ indicate the maximum rates at which an individual changes opinion ; $\Upsilon_{p\to n}$ and $\Upsilon_{n\to p}$ indicate resistance to opinion change, which is a function of the costs of infection and vaccination ($\mathrm{C^I}$ and $\mathrm{C^V}$) ; c_p and c_n indicate the conformity functions, which are non linear frequency-dependent functions, as modelled by [Walters and Kendal, 2013].

$$c_p = a_p[1 + \mathrm{D}(2a_p - 1)(1 - a_p)] \text{ where } a_p = \frac{\mathrm{F}}{\mathrm{N}} \text{ with } \mathrm{F} = \mathrm{S}_p + \mathrm{I}_p + \mathrm{R}_p^{\nu} + \mathrm{R}_p^{g}. \tag{4.6}$$

$$c_n = a_n[1 + \mathrm{D}(2a_n - 1)(1 - a_n)] \text{ where } a_n = \frac{\mathrm{N}_g}{\mathrm{N}} \text{ with } \mathrm{N}_g = \mathrm{S}_n + \mathrm{I}_n + \mathrm{R}_n^{\nu} + \mathrm{R}_n^{g}. \tag{4.7}$$

F and N_g indicate the number of pro-vaccines and sceptical individuals in the entire population denoted N ; D is the conformity coefficient. The more common is a given opinion, the more often it is adopted.

The parameter time unit : It is calibrated in relation to the birth and death rates. We generally set the birth and death rates at the value 1 which, in the case of human populations, could correspond to a time unit of the order of a year or ten years.

The dynamics

The dynamics of the system can be described by the following set of ordinary differential equations :

$$\frac{d\mathrm{S}_p}{dt} = b\mathrm{F} + \Omega'\mathrm{S}_n - \Omega\mathrm{S}_p - \Theta\mathrm{S}_p - \beta\mathrm{S}_p(\mathrm{I}_p + \mathrm{I}_n) - d\mathrm{S}_p, \tag{4.8a}$$

$$\frac{d\mathrm{S}_n}{dt} = b\mathrm{N}_g - \Omega'\mathrm{S}_n + \Omega\mathrm{S}_p - \Theta'\mathrm{S}_n - \beta\mathrm{S}_n(\mathrm{I}_p + \mathrm{I}_n) - d\mathrm{S}_n, \tag{4.8b}$$

$$\frac{d\mathrm{R}_p^{\nu}}{dt} = \Theta\mathrm{S}_p + \Omega'\mathrm{R}_n^{\nu} - \Omega\mathrm{R}_p^{\nu} - d\mathrm{R}_p^{\nu}, \tag{4.8c}$$

$$\frac{d\mathrm{R}_n^{\nu}}{dt} = \Theta'\mathrm{S}_n + \Omega\mathrm{R}_p^{\nu} - \Omega'\mathrm{R}_n^{\nu} - d\mathrm{R}_n^{\nu}, \tag{4.8d}$$

Symbols	Meaning	Default values
b	Reproductive rate	1 UT^{-1}
d	Mortality rate	1 UT^{-1}
R_0	Basic reproductive ratio	variable
γ	Recovery rate	0.1 UT^{-1}
δ_v	Rate - negative side-effects from vaccine	variable
δ_i	Rate - negative side-effects from infection	1 UT^{-1}
f	Forgetting rate	5 UT^{-1}
D	Conformity coefficient	0.7
$\omega_{p\to n}$	Maximum rate of opinion change (from positive to negative opinion)	2 UT^{-1}
$\omega_{n\to p}$	Maximum rate of opinion change (from negative to positive opinion)	2 UT^{-1}
ν_n	Maximum rate to get vaccinated (negative opinion)	2 UT^{-1}
ν_p	Maximum rate to get vaccinated (positive opinion)	2 UT^{-1}
μ_n	Weight given to the infection cost (negative opinion)	0.5 UT^{-1}
μ_p	Weight given to the infection cost (positive opinion)	1 UT^{-1}
μ'_n	Weight given to the vaccination cost (negative opinion)	1 UT^{-1}
μ'_p	Weight given to the vaccination cost (positive opinion)	0.5 UT^{-1}

TABLE 4.1 – Parameters used and their default values. . Parameters used and their default values.

$$\frac{dI_p}{dt} = \beta S_p(I_p + I_n) + \Omega' I_n - \Omega I_p - \lambda I_p - d I_p, \tag{4.8e}$$

$$\frac{dI_n}{dt} = \beta S_n(I_p + I_n) + \Omega I_p - \Omega' I_n - \lambda I_n - d I_n, \tag{4.8f}$$

$$\frac{dR_p^g}{dt} = \lambda I_p + \Omega' R_n^g - \Omega R_p^g - d R_p^g, \tag{4.8g}$$

$$\frac{dR_n^g}{dt} = \lambda I_n + \Omega R_p^g - \Omega' R_n^g - d R_n^g, \tag{4.8h}$$

$$\frac{dC^V}{dt} = \delta(R_n^V + R_p^V) - f C^V, \tag{4.8i}$$

$$\frac{dC^I}{dt} = \delta(I_n + I_p) - f C^I. \tag{4.8j}$$

4.2.3 The nested models

The full model described above combines five elements : (1) the characterization of individuals by their epidemiological status (SIR model) ; (2) the characterization of indivi-

duals by their opinion; (3) a globally available information on the infection and vaccination costs; (4) the interpretation of epidemiological costs as a function of opinion through confirmation bias and (5) the transmission of opinion through conformism. To evaluate the significance of each element in shaping the dynamics of infection and vaccination coverage, we broke down the full model into several nested models differing by 1 element at a time. Specifically, we investigate the same range of parameter values (Table 4.1) for the five nested models in order to be able to detect the effect of each element (Table 2) :

Model 1 : a classic SIR model without the belief component.

Model 2 : a model that characterizes individuals by both their epidemiological status and their opinion. Vaccination rate is fixed ($\Theta_p = \nu_p$ and $\Theta_n = \nu_n$) and individuals with a positive opinion vaccinate more quickly than those with a negative opinion ($\nu_p > \nu_n$). By doing so, vaccination behaviour is a function of opinion but not confirmation bias ($\mu_p = \mu_n = 1$), i.e. the difference in vaccination rates between individuals with opposed opinions is not a function of the number of infected individuals and vaccination coverage. The rate of opinion change is also fixed ($\Omega = \omega_{p\to n} = \Omega' = \omega_{n\to p}$).

Model 3 : This model includes the globally available information on the number of individuals suffering negative side effects from the infection C^I and vaccination C^V. This enables to calculate the epidemiological costs.

Model 4 : This model includes confirmation bias, i.e. the biased perception of costs by individual opinion. In Models 1-3 confirmation bias is not considered so $\mu = \mu'$ regardless of the opinion of individuals.

Model 5 : This model includes conformism and corresponds to the full model. In Models 1-4, conformism is not considered so $c_p = c_n = 1$.

4.2.4 Numerical simulation

We performed all simulations using Mathematica 9.0. First, 500 susceptible positive individuals and 500 susceptible negative individuals are introduced. We ran 100 000 iterations with a time step of 10^{-4}, the number of iterations needed to reach a stable equilibrium, to determine the number of susceptible individuals (S_p^* and S_n^*) and calculate

the rate of infection transmission β with R_0 in the absence of disease. Second, after β was obtained, we introduced two infected individuals, one of each opinion (N = 1002 individuals). We ran 1,000 000 iterations with a time step of 10^{-4} which corresponds to 100 time units (e.g. 100 years), to ensure that we capture the complete dynamics. To evaluate the role of each component of the full model in shaping the dynamics of infection and vaccination coverage, we analysed and compared the results of the nested models. We run all models for values of R_0 ranging from 0 to 10 in steps of 0.5. All other parameter values are detailed in Table 4.1.

4.3 Results

Our results are threefold : (i) for all parameter values investigated, the infection is never eradicated under voluntary vaccination, i.e. vaccination coverage never reaches herd immunity, that is, the threshold of vaccination coverage needed for stopping the spread of the infection; (ii) the dynamics of infection and vaccination coverage depend on the presence/absence of a polymorphism for the opinion of individuals, which is a function of the transmissibility potential of the pathogen (R_0) (fig. 4.2). If the infection is not contagious ($R_0 < 1$), all individuals become sceptical and vaccination coverage remains low; if infection is highly contagious ($R_0 >> 1$), all individuals become pro-vaccines but herd immunity is never reached because the infection spreads too quickly. Yet, vaccination coverage remains high. For intermediate values of R_0, both sceptical and pro-vaccine individuals coexist and oscillations in vaccination coverage are observed (fig. 4.3); (iii) the rule "imitate the majority" is not necessary for oscillations to appear. Rather, the transmission of opinions through conformism increases the delay between changes in epidemiological parameters and the behavioural responses to those changes (4.4).

4.3.1 What is the role of R_0 for the dynamics of vaccination coverage?

Various dynamics are observed depending on the reproductive rate of the infection because the value of R_0 influences the distribution of opinions in the population. For infections that spread very quickly in the population ($R_0 >> 1$), only "pro-vaccines" individuals persist. For intermediate values of R_0, a stable coexistence of "sceptics" and "pro-vaccine" individuals is observed with three possible cases : (1) at equilibrium, a negative opinion of vaccination is more frequent; (2) at equilibrium, a positive opinion of

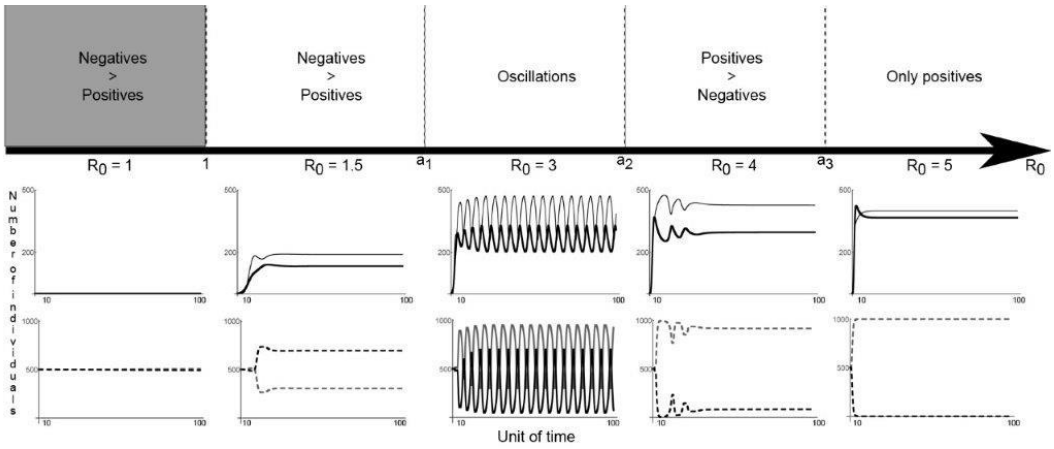

FIGURE 4.2 – Distribution of opinions about vaccination and the dynamics of vaccination coverage as a function of the reproductive rate of the infection (model 5). For each value of R_0 (number of secondary infections which can be understood as the fitness of the pathogen ; it must be > 1 for the pathogen to invade the population), the time-series of the dynamic of epidemiology (top panel ; the thin line corresponds to the number of infected individuals and the thick line corresponds to the number of vaccinated individuals) and (bottom panel ; the dashed grey line indicates the number of individuals who have a positive opinion and the dashed black line indicates individuals who have a negative opinion) are depicted for a rate of negative side effects from vaccination $\delta^{\nu} = 0.7$. Alternative changes of opinions of vaccination and oscillations in vaccination coverage emerge for intermediate values of R_0. When the reproductive rate of the disease is large ($R_0 > 4$), the negative opinion of vaccination disappears and vaccination coverage, while reaching high levels, does not reach herd immunity. This is because the infection spreads too quickly. More generally, four dynamics can be observed and a_1 to a_3 represent their limits which can be moved depending of the values of considered.

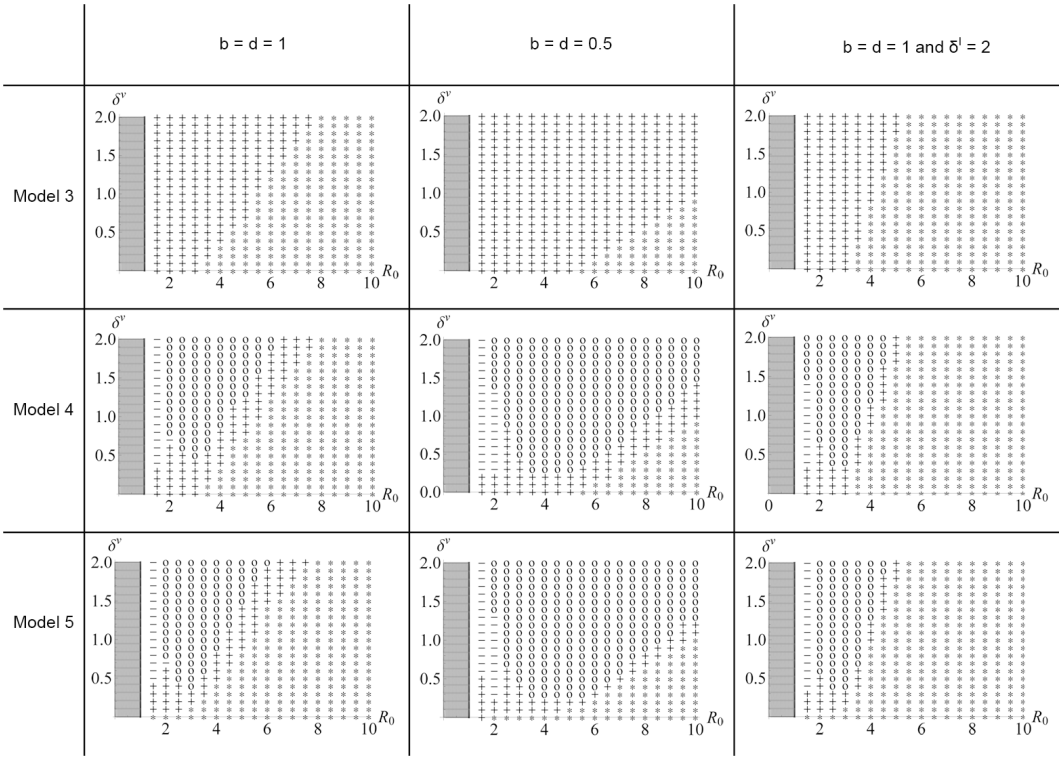

FIGURE 4.3 – Confirmation bias, conformism and the emergence of oscillations in vaccination coverage. The emergence of oscillations (o) is depicted as a function of an infection's reproductive rate (R_0) and the rate of negative side effects from vaccination (δ^v). The emergence of oscillations is contingent on the inclusion of confirmation bias but not conformism and is observed for intermediate values of R_0. Three models are considered : Model 3 (without either confirmation bias or conformism) ; Model 4 (including confirmation bias) and Model 5 (including both confirmation bias and conformism). If no oscillations emerge, three dynamics can be noted for the distribution of opinions of vaccination : (i) coexistence of 2 opinions with a greater number of individuals with a positive opinion (+), (ii) coexistence of 2 opinions with a greater number of individuals with a negative opinion (-), (iii) all individuals have a positive opinion (*). The models are analysed for 2 different generation times (birth (b) = death (d) = 1 and 0.5) and for different values of the rate of negative side effects from infection (δ^I). 1 million iterations were run with a time step of 10^{-4} which correspond to 100 unit of time.

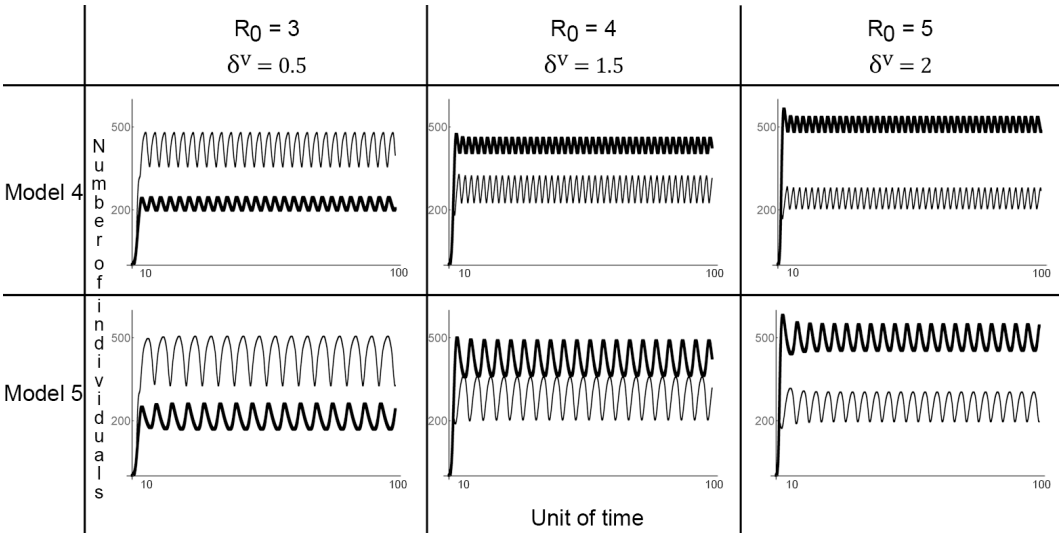

FIGURE 4.4 – Conformism and oscillations in vaccination coverage. The evolution of the number of infected (thin line) and vaccinated individuals (thick line) is depicted. Conformism (illustrated by Model 5) increases the amplitude of oscillations and slows down the rate at which alternative opinions of vaccination alternate. The situation is indicated for infections that are moderately infectious (with a reproductive ratio (R_0) varying from 3 to 5) and with the rate of negative side effects from the vaccination (δ^v) varying from 0.5 to 2.

vaccination is more frequent; (3) which opinion is the most frequent oscillates over time (fig. 4.2). Oscillations are only observed when the cost of vaccination (C^V) is high enough, i.e. when a sufficient number of individuals are vaccinated and suffer from side effects. The influence of other parameters on the emergence of oscillations is depicted fig. 4.3.

4.3.2 The emergence of oscillations in vaccination coverage

The role of cognition (confirmation bias and conformism)

We compared nested models to disentangle the role of confirmation bias and conformism on the distribution of opinions towards vaccination and subsequently, the emergence of oscillations in vaccination coverage. We found that oscillations can only emerge when both negative and positive opinions of vaccination coexist in the population and when a confirmation bias is included (Models 4 and 5, see also fig. 4.5 for various values of μ_p, μ_n and μ_p/μ_n). To confirm the significance of confirmation bias, we reran the full model while excluding confirmation bias ($\mu_p = \mu_n$) : oscillations do not appear (fig. 4.6). Then we found that conformism does not affect the emergence of oscillations in the dynamics of infection and vaccination coverage (fig. 4.3). Rather, oscillations become less frequent and more ample because conformism increases the time necessary for the least frequent opinion to invade the population (4.4). To confirm that conformism does not

produce oscillations, we compared the results obtained for the full model with and without biased social transmission (D = 0.7 and D = 0, respectively) : when confirmation bias is considered oscillations do appear in both situations (fig. 4.6).

The role of epidemiology (vaccination and infection costs)

Once opinion heterogeneity and confirmation bias are considered, the emergence of oscillations in vaccination coverage depends on the ratio between the costs of vaccination and infection. For instance, in the case of an infection with a low epidemic potential (R_0 is low) and few individuals infected, both the infection cost and the vaccination cost are low because only a few individuals suffer negative side effects. Consequently, vaccination coverage remains low and stable over time. For infections with a high reproductive rate (R_0 is high), the infection invades the population more rapidly than vaccination behaviour. Thus, the cost of infection is always higher than the cost of vaccination. Similarly, when the cost of vaccination is low, oscillations do not emerge because the cost of vaccination is always lower than that of infection.

4.4 Discussion

Despite evidence that vaccines are safe, vaccine scares are repeatedly observed in various populations and cause the resurgence of diseases otherwise near eradication (e.g. measles). A key factor in driving vaccination decisions is how epidemiological parameters, in particular the costs associated with infection and vaccination, are perceived. Although perception may be based on epidemiological information, the success of anti-vaccination movements also suggests that individuals vary in the way they interpret scientific evidence. People differ in their opinion of vaccination because of their past experience with immunization, their trust in the state or in the medical profession, the opinion of their parents or the most common opinion in their cultural environment, irrespective of a cost-benefit analysis based on the epidemiology [Streefland et al., 1999]. In this paper, we deviate from previous theoretical studies positing that individuals are economic agents maximizing their health [Bauch, 2005; Bauch and Bhattacharyya, 2012; Bauch and Earn, 2004; Bauch et al., 2003; Bhattacharyya and Bauch, 2010; Schimit and Monteiro, 2011] to consider that individuals make decisions as result of cognitive biases. Specifically, we developed a behaviour-incidence model in which individuals can be pro-vaccines or scep-

tical, their opinion influencing how the costs of infection and vaccination are perceived. Overall, the model predicts the commonly observed dynamics of vaccination coverage, i.e. the failure to reach herd immunity as well as oscillations in vaccination coverage (periods of increase in vaccination coverage followed by disease outbreaks). The results have implications for considering how the interaction between human cognition and the epidemiology may lead to difficulties in reaching and/or maintaining population level immunity.

The emergence of oscillations. D'Onofrio et al. [2013] showed that assuming a memory of the information related to the costs of infection and vaccination can generate oscillations in a SIR model without cognitive bias. Comparing the behaviour of our model with or without cognitive bias we have shown that the confirmation bias is necessary for the emergence of oscillations in the dynamics of infection and vaccination coverage, at least in the parameter range we explore. Our model and that of D'Onofrio et al. [2013] differ by several hypotheses, which could explain why the conditions necessary for the emergence of oscillations differ between the two models. D'Onofrio et al. [2013] assumed that memory is fading following an exponential rate and that the infection rate is frequency dependent while we supposed a memory fading at a linear rate and a density dependent infection rate. In all cases, our model is the first to show that confirmation bias can strongly facilitate cyclical dynamics. The propensity to seek out information that confirms one's pre-existing belief, and the possibility for individuals to change their opinion as a function of the number of vaccinated individuals (i.e. confirmation bias) can thus explain variation into vaccination coverage. When vaccination coverage increases, the cost of vaccination increases too as more individuals suffer vaccination side effects. It leads to a rise in the number of individuals who become sceptical about vaccines. Those "sceptics" are more likely to overestimate the cost of vaccination as compared to that of infection, and thus when most of the population is vaccinated; sceptics perceive the infection as harmless. Eventually, this phenomenon leads to a decrease in vaccination coverage and subsequently, to the resurgence of diseases. In turn, as the number of infected individuals increase, a "pro-vaccine" opinion spreads leading to an increase in vaccination coverage. Those results are not different from those obtained in other models where vaccine cost appears large in comparison to that of infection as the population approaches herd immunity [Bauch and Bhattacharyya, 2012]. However, in some previous theoretical studies, the cost of vaccination does not change as a function of the number of people

vaccinated. Rather, the increase in vaccination cost is imposed using an exogenous description of the evolution of vaccine risk [Bauch and Bhattacharyya, 2012], the inclusion of a cyclical period to simulate a vaccine scare [Bauch, 2005; Oraby et al., 2014] or through a decrease in the accessibility of vaccines [Liu et al., 2008; Schimit and Monteiro, 2011; Vardavas and Marcum, 2013]. While previous studies showed that a vaccine scare could lead to a decrease in vaccination coverage, the present model explicitly articulates a mechanism creating a vaccine scare (i.e. when the cost of vaccination is perceived to be greater than that of the infection cost). The results reported here are contingent on the assumption that the vaccination decision-making process is sensitive to a confirmation bias. This cognitive phenomenon is only one among several, however, as other heuristics have been documented in previous research on vaccine acceptance [Asch et al., 1994; Meszaros et al., 1996], for instance omission bias (when people prefer act of omission over act of commission, even if the outcome of omission is worse) or ambiguity aversion (aversion of ambiguous outcomes). Further work explicitly comparing the significance of various cognitive biases may yield additional insight into the role of cognition in generating vaccine scares.

Social learning and vaccinating decision-making. A number of previous studies have investigated the role of social interactions in shaping the emergence of oscillations in vaccination coverage [Bauch, 2005; Bauch and Bhattacharyya, 2012; Mbah et al., 2012; Oraby et al., 2014; Perisic and Bauch, 2009a; Xia and Liu, 2013, 2014]. This is because vaccination coverage can be relatively stable in the absence of a vaccine scare and the feedback between the number of infected individuals and vaccination behaviour appears insufficient in accounting for the delay between reaching high vaccination coverage and the emergence of a scare. To account for the role of social interactions, behavioural epidemiology models usually consider that individuals imitate the most successful strategy among their neighbouring contacts [Bauch, 2005; Mbah et al., 2012] and such models are better than models considering a homogenous population for fitting data on vaccine scares [Bauch and Bhattacharyya, 2012]. The way social learning is modelled explicitly considers that individuals are rational agents maximizing their payoff. Individuals can be influenced by social interactions in different ways, however, and the role of social influence need not be connected to epidemiological risks [Campbell and Salathé, 2013]. For instance, it has been argued that mothers taking their children for vaccination has become part of their "habitus" (sensu Bourdieu, in [Streefland et al., 1999]). Mothers elicit to vaccinate their children because "everyone else does" and ethnographic studies on the acceptance of vaccines in

various populations revealed that peer opinion matters [Streefland et al., 1999]. In the model developed here, individuals adopt the most common opinion in the population through the phenomenon of conformism. Conformism does not generate oscillations in vaccination coverage but increases the amount of time needed for a change in epidemiology to generate a cultural response. The role of conformism in increasing the time for cultural change has been observed in previous studies [Bauch, 2005].

Limitations. First, the model presented here assumes that both infection and health behaviour are transmitted within a homogeneously mixing population, and those are simplifying assumptions. Humans are connected with a limited number of contact [Watts and Strogatz, 1998] and a number of studies has considered that social heterogeneity influences disease transmission [Miller and Hyman, 2007; Perisic and Bauch, 2009b,c], risk perception [Fu et al., 2010; Perisic and Bauch, 2009c; Scherer and Cho, 2003] and vaccination behaviour [Campbell and Salathé, 2013; Fu et al., 2010; Salathé and Khandelwal, 2011]. Clustered occurrence of beliefs can lead to the clustered occurrence of disease [Salathé and Bonhoeffer, 2008]. Nevertheless, in the context of information transmission, the assumption according to which the population is homogeneously mixed is valid if we focus on the role of the media, i.e. information that is globally available to everyone. The media has had a central role in disseminating vaccine scares and shaping the perception of disease severity [Young et al., 2013]. The media also enables anti-vaccination movements to have a strong impact on vaccination decision-making [Gangarosa et al., 1998; Streefland et al., 1999]. Yet, if the proposed model may be appropriate for exploring the role of conformism, it is insufficient to explore other social transmission processes such as those resulting from the role of opinion leaders (e.g. cultural transmission through prestige-bias [Henrich and Gil-White, 2001]). Religious leaders have been shown to be highly influential in promoting vaccine refusal in their communities (reviewed in [Streefland et al., 1999]) and the role of prestige-biased cultural transmission for either accelerating the pace of change or stopping it altogether remains to be investigated. Second, one may argue that since the costs depend on the number rather than the frequency of individuals suffering side effects, the model is more likely to inform on information that is gathered during social interactions than knowledge acquired via the media. The media report both percentages and anecdotic evidence of side effects associated with vaccination and both are likely to be determinant in driving the formation of opinion. Yet, the relative role of each type of information deserves further investigation. Finally, we assumed

that the rate of opinion change, while a function of epidemiological costs, is independent of the SIR class of the individual. However, an individual suffering infection may be less likely to switch from a positive to a negative opinion and thus we may have overestimated the occurrence of oscillations. Note however that for diseases with a strong epidemic potential, the cost of infection is always higher than that of vaccination and therefore oscillations do not emerge.

This study, along a few others [Campbell and Salathé, 2013; Coelho and Codeço, 2009; Oraby and Bauch, 2015; Xia and Liu, 2014], offers an alternative to payoff maximization for understanding the emergence of oscillations in vaccination coverage. It shows that a decrease in vaccine uptake when a disease is near eradication may not only emerge because of individual free riding but because of cognitive biases that maintain heterogeneity in how people perceive risks. While this study presents limitations that need to be explored in future work, i.e. considering heterogeneity in contact patterns as well as additional cognitive biases, we show that alternative notions of rationality, in particular that of an ecological rationality whereby individuals use simple cognitive heuristics, offer interesting new avenues for modelling vaccination behaviour.

4.5 Supporting Information

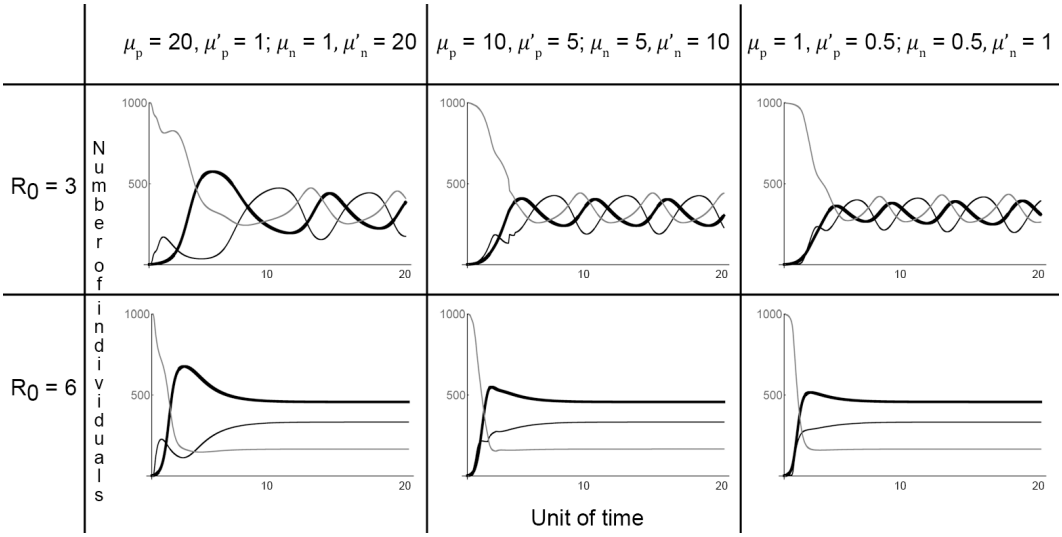

FIGURE 4.5 – The effect of confirmation bias on oscillations. The effect of confirmation bias (i.e. with μ the weight given to the cost of infection and μ' the weight given to the cost of vaccination) on the dynamics of susceptible (solid grey line), infected (thin line) and vaccinated individuals (thick line) is depicted. The amplitude and the frequency of oscillations are modified when the difference between μ and μ' is high. Indeed, the bigger the difference between μ and μ', the more the amplitude of oscillations increases and the more the frequency decreases. The situation is indicated for infections that are moderately infectious, with 2 reproductive ratio R_0, 3 and 6 and with a rate of negative side effects from the vaccination $\delta^{\nu} = 1$.

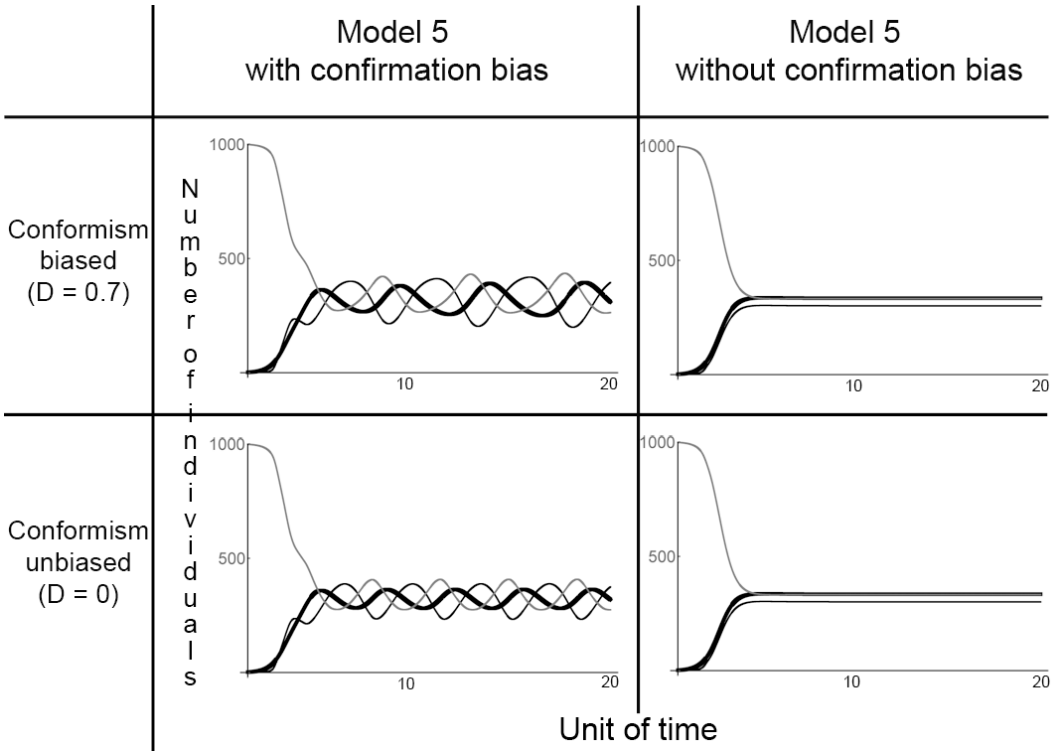

FIGURE 4.6 – The effect of conformism and confirmation bias on the appearance of oscillations. The effect of conformism biased (D = 0.7) and unbiased (D = 0) is depicted with and without confirmation bias. The number of susceptible individuals is represented by the solid grey line, the infected individuals by the thin line and the number of vaccinated individuals by the thick line. Without confirmation bias ($\mu = \mu' = 1$), oscillations do not appear for both types of conformism (biased and unbiased). When the confirmation bias is added, oscillations do appear with no significant differences between the biased and unbiased conformism. The situation is indicated with the reproductive ratio $R_0 = 3$ and with a rate of negative side effects from the vaccination $\delta^{\nu} = 1$.

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Chapitre 5

Cultural adaptations to infectious diseases transmission

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Sommaire

Malgré les progrès médicaux significatifs réalisés au cours des deux derniers siècles tels que l'utilisation de la vaccination, des antibiotiques ou encore l'amélioration des conditions d'hygiène [CDC, 1999] ; les maladies infectieuses demeurent l'une des principales causes de décès dans le monde [Fauci, 2001; WHO, 2000]. La menace de maladies contagieuses est omniprésente avec la résurgence d'anciennes maladies ou de maladies infectieuses émergentes [Jones et al., 2008]. Les êtres humains vivent depuis très longtemps, sinon depuis toujours, avec ces menaces, et des adaptations culturelles peuvent avoir émergé de cette longue coexistence. Le comportement humain est l'un des facteurs le plus important à prendre en compte lors de l'étude de la dynamique d'une maladie épidémique. En modifiant leur niche écologique (p.ex. pour se loger, se nourrir ou développer certaines ressources économiques) ou en ayant des pratiques culturelles, les populations humaines influencent l'émergence et la propagation des maladies infectieuses. Les pratiques culturelles qui amplifient les maladies épidémiques sont très étudiées dans le but de cibler le comportement/la pratique culturelle responsable de l'infection et de mettre en œuvre de meilleures stratégies de contrôle. Lors de la propagation d'une maladie infectieuse, les populations locales utilisent des modèles culturels associés à leurs croyances sur la cause de la maladie. Et parce que la théorie la plus répandue est considérée comme inappropriée, les pratiques culturelles mises en œuvre sont considérées comme inadaptées. En utilisant des données ethnographiques, nous proposons d'examiner les pratiques culturelles qui pourraient empêcher la propagation des agents infectieux au sein d'un groupe ou d'une population locale.

Nous avons recherché dans une base de données regroupant un très grand nombre de données ethnographiques (Human Relations Area Files), les pratiques culturelles qui sont vues par certaines populations locales comme limitant la propagation de l'infection. Nous avons classé ces pratiques en 5 catégories : (1) l'isolement, isolation physique des individus infectés soit dans leurs maisons soit à l'extérieur du village, (2) l'isolation partielle, évitement des contacts avec les individus infectés, (3) l'émigration, les habitants du village quittent le village en laissant les individus infectés, (4) les modifications des pratiques funéraires, pratiques funéraires plus courtes et différentes de ce qui est pratiqué habituellement et enfin (5) les cérémonies, souvent pour chasser le "mauvais sort".

Bien qu'une majorité de ces populations utilisent un modèle de croyance basé sur des faits surnaturels (p.ex. la magie, la sorcellerie, les esprits, les démons, etc.), les pratiques culturelles pourraient être adaptatives et protéger les populations contre la propagation

de certaines maladies infectieuses.

Pour le moment, deux continents ont été analysés, l'Afrique et l'Asie. Cependant, nous visons à poursuivre la même démarche sur les continents européens, américains et océaniques, notre but est également d'établir si les pratiques culturelles sont adaptatives d'un point de vue évolutif. Pour cela, nous devons savoir si nos données sont indépendantes afin de voir si les pratiques culturelles sont adoptées par les populations parce qu'elles procurent un avantage sélectif dans leur environnement donné ou parce qu'elles partagent une histoire commune. Pour ce faire, un arbre phylogénétique des populations devra être construit sur la base de variants culturels neutres tel que le langage [Mace and Holden, 2005]. Si les pratiques culturelles sont des convergences évolutives, c'est-à-dire si elles apparaissent de manière indépendante sur l'arbre phylogénétique, alors il pourra être conclu qu'elles sont adaptatives. Cependant, dans le cas des adaptations dues aux pathogènes, étant donné qu'ils sont omniprésents, on peut également s'attendre à ce que les pratiques culturelles soient partagées par les populations ayant une histoire commune, c'est-à-dire réparties de manière homologue sur l'arbre phylogénétique. Dans ce cas, il sera difficile de conclure sur la non-adaptation des pratiques culturelles puisque la pression de sélection exercée par les pathogène fait partie de l'histoire commune des populations humaines.

5.1 Introduction

Despite the significant medical advances of the last two centuries – e.g. the implementation of vaccination, the discovery of antibiotics and the improvement of hygiene conditions [CDC, 1999] – infectious diseases remain one of the major causes of death worldwide [Fauci, 2001; WHO, 2000]. Given the increasing incidence of both old diseases and newly emerging infectious diseases [Jones et al., 2008], the WHO is now calling for increasing attention to 'global public health threats of the 21st century'. In response to this global challenge, international bodies and the scientific community have (over)studied the cultural practices that amplify epidemic diseases [Inhorn and Brown, 1997; Logan and Hunt, 1978]. The focus of interventions has generally been on changing the local theory of causation through health education to both target the behaviour causing the infection and implement better control strategies. The underlying assumption of this approach is that local practices are maladaptive because the theory of disease causation that underpin such practices differs from germ theory. However, humans have always been living with infectious diseases and broad cultural adaptations may have emerged from this long-life coexistence. In this paper we compile the first review ethnographies across 39 African and 43 Asian cultures to investigate all cultural practices that prevent the spread of infectious agents in the group or local population.

The importance of human behaviours

Patterns of occurrence of infectious diseases at particular times and places are not only a function of the presence of pathogenic microorganisms but also depend on human sociocultural interactions. A well-known example of the importance of cultural practices in shaping patterns of infectious disease transmission is the case of kuru among Fore – a prion that contaminates a segment of the Fore population due to their behavioural practices associated with cannibalism [Logan and Hunt, 1978]. Nations (1986) has summarized some behavioural factors that affect infectious disease transmission and demonstrated how specific cultural beliefs and practices expose people to (or protect them from) the foci of disease transmission, and directly contribute to (or inhibit) infection [Nations, 1986]. Those investigations have led to important studies and reflect that human behaviour is inseparable from the infectious dynamics.

Despite the undeniable importance of culture and social behaviour on the spread of infectious diseases there has been surprisingly few anthropological in-depth investiga-

tion of the cultural responses to infectious disease (but see [Hewlett and Hewlett, 2008]). Benjamin Paul in 1955 was the first anthropologist to focus on how the local populations perceived the control strategies implemented by the World Health Organization (WHO) [Paul, 1955]. However, for decades, the role of epidemiologists has been more prominent than that of anthropologists for implementing global control strategies, perhaps due to major successes like smallpox eradication [Inhorn and Brown, 1997]. Nowadays medical anthropologists are more often part of inter-disciplinary teams with the aim to engage with crucial socio-cultural and political dimensions of outbreaks and build locally-appropriate interventions.

Human ecology, i.e. human interactions with environment, is a major determinant of the emergence and the spread of infectious diseases [Keesing et al., 2010; Murray and Daszak, 2013; Olival et al., 2017]. Human behaviour causing the encroachment of wildlife (e.g. the expansion of human populations, the cutting-down of forests, agricultural practices) increases contact rates between human and animal populations, i.e. the principal source of infection. Approximately sixty percent of human pathogens originate from the vertebrate animals [Jones et al., 2008; Taylor et al., 2001]. Moreover, changes in lifestyle such as migration, moving to big cities or traveling throughout the world, increase the contact rate within humans and may amplify the epidemic [Alland, 1970; Inhorn and Brown, 1990]. Human behaviour by applying drastic changes to the ecological environment modify the spreading of infectious diseases among humans whether by modifying the between-hosts transmission or the within-humans transmission [Keesing et al., 2010; Murray and Daszak, 2013; Shrag and Wiener, 1995].

In view of the long-standing risk of spreading infectious agents, human populations have been forced to adapt culturally [Karlsson et al., 2014]. As agents of natural selection, infectious pathogens may have played a major role in the evolution of human culture. While cultural practices might either foster the contagion or limit it, the focus from international and national bodies (WHO, Center for Diseases and Control) that device control strategies is generally on cultural practices that induce infectious diseases in order to target and to control it [Inhorn and Brown, 1990]. This suggests that local cultural practices in response to disease outbreak are generally viewed as maladaptive.

Life in social groups, although advantageous because of protection from the group, can become disadvantageous in the case of propagation of infectious agents . Due to the social organisation of human populations, in order to protect the group during the propa-

gation of an epidemic disease, adaptive cultural practices can have emerged. The cultural practices are defined as behaviour change face to an infected individual and put in place by the whole group. A recent example of such behaviour is described by Hewlett and Hewlett (2008) during the 2002 outbreak of Ebola in Congo and Uganda [Hewlett and Hewlett, 2008]. They describe the cultural model used by local population to respond to the Ebola outbreak. A cultural model in a broad sense refers to the knowledge and feelings of a person in a particular area. They show that some behaviours allow the local tribes to control the spreading of Ebola, for instance by isolating infected individuals. Knowing the cultural practices implemented by local populations can help targeting effective control strategies and to encourage their use.

Theories of causation

Understanding the theories of contagious diseases held by local populations is key to understanding and predicting the practices used to respond to the epidemic disease [Green, 1999]. In 1980, Murdock defines for the first time the two major theories of causation of illness [Murdock, 1980]. The most widespread and known is the theory of supernatural causation, which refers to all theories that rest on supernatural assumption. It goes without saying that modern medicine does not recognize this model as valid. The second is the theory of natural causation, which refers to the biomedical model. The theory of supernatural causation is probably overestimated due to the strong interest it arises [Green, 1999].

Several cultural models concerning health exist. In particular, a cultural model for a disease is the explanation and predictions that a person makes about this disease [Hewlett and Hewlett, 2008]. In this sense, the biomedical model corresponds to the health model thought and used in Euro-American countries. It takes up the theory of germs widely established and recognized and the practices of care are turned on the individual that is to say that there is little interest for its environment [Sobo and Loustaunau, 2010]. Yet other models exist and are associated with local beliefs [Green, 1999; Murdock, 1980]. All societies have developed a local knowledge of infections and care practices that may differ from the Euro-American cultural model (i.e. the biomedical model). Because the supernatural theories are considered as inappropriate, practices associated with this belief are not considered as adaptive. But does the causation model actually have an impact on the adaptive effect of cultural practices implemented by local population?

In this paper, we use the Human Relations Area Files data base to review how local po-

pulations perceive the infection and how they respond to it. The cultural practices used during an outbreak by human populations are rarely studied [Hewlett and Hewlett, 2008]. Nevertheless, from the point of view of control strategies, this could help to target the strategy to implement in local populations in order to prevent the spread of the infection. Indeed, local's people beliefs and practices may be useful in effort to contain an epidemic. We suggest that human behaviour is generally adaptive during an epidemic disease. We review all behaviours that local populations believe as reducing effectively the transmission of infection in the population and then discuss each behaviour as the appropriate social response.

5.2 Materials and methods

5.2.1 The Human Relation Aera Files data base

The Human Relations Area Files (HRAF) has been examined in order to identify the specific behaviours that constitute the cultural practices during an epidemic disease. This database includes a wide range of ethnographic data. HRAF is a significant tool to conduct cross-cultural research with books, articles and other documents that are subject-indexed at the paragraph level. We used the advanced search by using key-words, the occurence is classified as follow : first as culture-by-region and then within the document and the paragraphs. The aim is to target social strategies implemented by local population without the intervention of public health organizations such as WHO or local public health organizations, to highlight socially acquired behaviours.

5.2.2 Search criteria and compilation method

Cultures from Asia and Africa were searched under these key-words : "infectious disease, contagious disease, contagious illness, infection and contagion". For Africa, thirty nine cultures with the occurrence of two hundreds twenty paragraphs and for Asia, forty three cultures with the occurence of one hundred ninety five paragraphs, have been studied. For each paragraph the whole page has been read as well as the previous and next pages if necessary. In addition to the HRAF database, we also include cultural practices during an epidemic disease found in the anthropological literature.

5.3 Results and Discussion

All cultural practices recorded during an epidemic disease have been classified in five categories : (1) isolation, (2) partial-isolation, (3) emigration, (4) funeral practices and (5) ceremonies. These cultural pratices recorded in Table 5.1 are implemented by people when they believe that a disease is spreading. An epidemic is considered as spreading when the population links the observed symptoms to a known contagious disease or when several individuals suffer or die from the same illness.

Isolation.

Isolation was defined as the voluntary action of putting the infected individuals in an isolated place, preventing or limiting contact with healthy individuals. In the Tuareg population, when a man travelling between villages is sick, the next village is reported long before his arrival and the sick man is systematically isolated [Lhote and Sipfle, 1944]. More generally, the sufferer can be isolated in his/her house or can be excluded from the village. Both methods, i.e. isolation and exclusion, have the same consequences–preventing or limiting the infection to spread within villagers–but the sufferer has not the same chance of surviving. Indeed, when the sufferer is kept inside the village, some care can be practiced and especially food and water are brought although this is not necessarily the case. An abandonment of the contaminated person can also be observed [Ohnuki-Tierney, 1981]. Nevertheless when the infected individuals are driven out from the village, they are left almost entirely to their fate [Korn, 1960].

Isolation is one of the best ways of preventing a communicable disease to spread among persons. It is also used as a common public health practice. And it seems to be an adaptive social response in order to prevent or limit the spreading of the infectious disease among local population. The effectiveness of such a response depends on other factors such as the contagiosity, specifically during the latent period, but generally the maintenance of such a practice is understandable from an adaptive point of view.

Continent	Culture	Disease	Practices	Etiology	Refs
Africa	Acholi	Ebola	Isolation, Partial isolation, Ceremonies	Bad spirit	[Hewlett and Hewlett, 2008]
Africa	Azande	Infection	Partial-isolation and emigration	Evils	[Anderson, 1911]
Africa	Azande	Syphillis	No specific behaviour	Evils	[De Graer and Coughlin, 1929]
Africa	Bagisu	Suicide	destruction and burning the place	–	[Roscoe, 1924]
Africa	Banyoro	Infection	Isolation	Natural	[Shane, 2000]
Africa	Bena	Infection	Isolation	Magic	[Culwick et al., 1935]
Africa	Fon	Leprosy	Funeral practices	Sorcery	[Herskovits, 1967]
Africa	Ganda	Infection	Partial isolation	Natural witchcraft	[Orley, 1970]
Africa	Khoi	Infection	Isolation and Partial isolation	–	[Hoernle, 1918; Schultze et al., 1907]
Africa	Mossi	Infection	No specific behaviour	–	[Mangin et al., 1921]

Continued on next page

Continent	Culture	Disease	Practices	Etiology	Refs
Africa	Nyakyusa	Infection	Ceremonies	Sorcery	[Wilson, 1957]
Africa	Rwandans	Infection	Ceremonies	Evils	[Pages and Scholl, 1933]
Africa	Shona	Infection	Ceremonies	Evils	[Gelfand et al., 1956]
Africa	Tsonga	Leprosy	Partial isolation	–	[Junod, 1927]
Africa	Tuareg	Infection	Isolation	–	[Lhote and Sipfle, 1944]
Africa	Zulu	Infection	Ceremonies	Witchcraft	[Krauss, 1969]
Asia	Ainu	Infection	Emigration and Ceremonies	Demons	[Batchelor, 1927; Ohnuki-Tierney, 1981]
Asia	Balinese	Infection	Isolation	–	[Korn, 1960]
Asia	Burmans	Infection	Ceremonies	Evil spirit	[Scott, 1910]
Asia	Chukchee	Infection	Isolation and Ceremonies	Evil spirit	[Bogoraz-Tan and Germanovitch, 1909]
Asia	Eastern Toraja	Infection	Ceremonies	Spirit	[Adriani and Kruijt, 1951]
Asia	Iban	Smallpox	Isolation	–	[Gomes, 1911]
Asia	Ifugao	Dysenteries	Ceremonies	Spirit	[Lambrecht, 1955]
Asia	Inner Mongolia	Infection	Funeral practices	–	[Chang et al., 1956]

Continued on next page

Continent	Culture	Disease	Practices	Etiology	Refs
Asia	Khasi	Infection	Funeral practices	–	[Gurdon and Thornhagh, 1907]
Asia	Korea	Smallpox	No specific behaviour	Smallpox spirit	[Moose, 1911]
Asia	Miao	Infection	Funeral practices	–	[Wu et al., 1942]
Asia	Nivkh	Infection	Isolation and Funeral practices	–	[Shternberg et al., 1933]
Asia	Okayama	Infection	Funeral practices	–	[Norbeck, 1954]
Asia	Santal	Infection	Funeral practices	–	[Culshaw, 1949]
Asia	Tibetan	Infection	Funeral practices	–	[Bell, 1928]
Asia	Vietnamese	Infection	Ceremonies	Spirit	[Huard and Durand, 1990]

TABLE 5.1 – Cultural practices implemented during an epidemic disease and arranged by continent and culture. The practices have been classified in five categories. The etiology associated with the disease have been noted when reported by the authors of the ethnographic data.

Partial-isolation.

Partial-isolation is used when the sufferer is isolated by non-physical means, that is to say a specific treatment is granted. The most common partial isolation is the separation of utensils and food between infected and healthy people. In these cases, the infected persons live and often participate normally to the social life but they have separate food and dishes. For instance among the Tsonga in South Africa, during beer-parties, healthy persons receive drinking utensils from the master of the village while the lepers bring their own [Junod, 1927]. The social isolation of infected individuals can also be observed.

For instance in Ganda population, because of the fear of contagion from leprosy, epilepsy or tuberculosis, sufferers will typically have their own plates, cups and wash basin, and their clothes are washed separately. They eat their food and sleep in a room on their own and when old enough, they will live in a hut, isolated from the others in the household. Children with epilepsy will not be allowed to play with others [Orley, 1970].

Partial-isolation allows to limit contact with an infected person and can prevent the spreading of a communicable disease. Nonetheless some practices of partial-isolation are discriminatory and can last the life of the infected person without being epidemiologically useful especially if the individual carries stigmas of infection such as scars.

Emigration.

Emigration is the act to move away from the village leaving the infected persons behind. Because of the fear of contagious diseases, the migration of an entire village can be observed. This social response is of a last resort and is implemented when a contagious disease causes a large number of deaths in order to avoid further inflictions of unseen revenge due to evil spirit [Anderson, 1911].

McGrath (1989), reviewed the social disruption resulting from an epidemic disease [McGrath, 1991]. She concludes that flight from the scene of an epidemic disease is common in a case of environmental stress. The emigration is commonly seen as a negative social response, a social disturbance [McGrath, 1991; Strong, 1990].

Funeral practices.

This category groups all behaviour that reports a change in funeral practices or ceremonies. Most of the time, when a sufferer dies from a communicable disease, no ceremony is made on the dead body because of the contagion fear and practices are changed. If usually the dead bodies are burned then in the case of contagious disease, the body will be buried without ceremonies [Herskovits, 1967] and the opposite is true. Sometimes it is buried but when the epidemic and the fear of contagion are passed, it is dug up and burned with all the ceremonies usually carried out [Gurdon and Thornhagh, 1907].

The change of funeral practices and ceremonies can largely improve the health of the local population by limiting the contact between healthy and infected persons. In the case of contagious disease spreading even when the infected individual is dead such as in the case of Ebola [Osterholm et al., 2015], this social response can be adaptive. Although, in

the case of Ebola, the Gulu populations do not show any social response in this sense and their burial practices increase the disease epidemic [Chowell and Nishiura, 2014].

Ceremonies.

The category "ceremonies" contains all social behaviours that are thought by local people as preventing the contagion or driving the epidemic out of the village. The ceremonies performed to stop the spreading of the infection have often a strong connection with the theory of causation. The purpose of such ceremonies is to remove the evil spirit by satisfying the evil spirit with offerings in order to leave [Adriani and Kruijt, 1951; Huard and Durand, 1990; Scott, 1910] or to find the culprit who bewitched the suffering person [Krauss, 1969]. Some other ceremonies are performed to protect the local population from the contagion by painting their faces as safeguard against contagious disease [Bogoraz-Tan and Germanovitch, 1909] or by acting directly on the site where the infected individual lived by purifying it and finally burning the hut [Pages and Scholl, 1933; Roscoe, 1924].

The ceremonies are believed by local population to avoid the risk of contagious disease. Most of them do not have any consequences on the epidemiology of the disease like the ceremonies to remove the evil spirit, for instance. But other ones can have certain consequences. Indeed, if the persons painting their faces believe to be protected against any risks of infection, they may behave with confidence and not have any fear of being infected from the sufferers.

Etiology.

In the ethnographic data analysed, the most widespread theory of contagious disease is the supernatural theory. Because of the high mortality and the unpredictable apparition of infectious agents, the belief of a supernatural cause is not surprising. However, Green (1999) argued that the supernatural theory is a stereotype of indigenous theories of contagious disease [Green, 1999]. This theory is of great interest for anthropologists causing probably an overestimation of it. However, both theories, i.e natural and supernatural, can coexist in the same population and sometimes the cause is supernatural but the causality is natural, or vice versa. An example of coexistence of the two theories was found during the epidemic of the bubonic Plague in Europe. The theory of supernatural and natural causation was common among people. The plague was considered as a divine

scourge, a retribution for the sins [Slack, 1988]. However, the contagiousness of the pathogen was caused by the natural theory, the miasma theory. The miasma corresponded to bad air that surrounded the sufferers causing infection on other people.

Need for further research.

Hewlett and Hewlett (2008) have described a major part of social behaviours listed above by studying how the local populations perceive Ebola and behave during the 2002 Ebola outbreak in Congo and Uganda [Hewlett and Hewlett, 2008]. This study is the first to show that practices do not necessarily amplify the epidemic disease as previously thought. They show that local populations can have an adaptive response even when they believe that a supernatural cause is at the origin of the illness.

The need for anthropological studies is obvious to understand the behaviour during an epidemic in order to adapt the control strategies. Indeed, it has been showed that if local populations do not understand the control strategies implemented by public health organisations then they will not act together in order to prevent the disease, and even can be opposed. There are many examples where recommended behaviours are not followed anymore, such as the stop of boiling water in order to avoid parasitic transmission in Peru [Wellin, 1955], or the flight from the hospital during the Ebola outbreaks.

Cultural practices really adaptive?

Culture is defined as behavioural traditions that are transmitted by social learning. Since cultural practices are transmitted, they can be modified, because of innovations for example, and affect reproduction, survival and fitness then cultural practices can evolve. Because sampled populations are not independant, we do not know if two populations have the same practices because they share the same ecology or the same history. In general, the adaptation can be concluded if cultural practices arise independently rather than by sharing the same common ancestor.

In order to investigate if cultural practices described above are really adaptive, phylogenetic approaches could be implemented by using the phylogenetic comparative tests [Mace and Holden, 2005]. To construct a phylogenetic tree, supposedly neutral cultural variants can be used, such as pottery decorations or languages, in order to reflect population history [Kirby et al., 2016]. Once the phylogenetic tree, regrouping all populations, is built, it is possible to determine whether the cultural practices are adopted because of the

common history or because of the common ecology. For example, if we observe an evolutionary convergence of the cultural practice "isolation", it can be concluded that this cultural practice is a cultural adaptation.

Conclusion.

Health care workers are not accustomed to thinking that local beliefs and practices can assist control efforts. They are trained to identify local beliefs and practices that present barriers to reaching particular biomedical health goals [Hewlett and Hewlett, 2008]. People in Africa and Asia have been living with epidemics a long time and have accumulated knowledge and cultural practices that prevent the disease epidemic. However, human practices during an epidemic are often associated with panic, social disruption and then considered as maladaptive [McGrath, 1991; Strong, 1990] and amplifying the epidemic disease. We show that cultural practices can be adaptive and prevent the spreading of the epidemic disease while specific studies are still needed.

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Chapitre 6

Discussion générale

Sommaire

Les maladies infectieuses sont toujours une cause importante de décès au sein des populations humaines. Et puisque l'humain interagit beaucoup avec son environnement en le modifiant, l'interaction entre les populations animales et les populations humaines est très importante. Elle est même considérée comme la première cause d'émergence de nouveaux pathogènes humains. Ces nouveaux pathogènes sont importants à considérer pour deux raisons majeures : (i) ils sont la cause de milliers de décès chaque année dans les populations humaines mais aussi dans les populations intermédiaires (p. ex. les primates non humains, le bétail, etc.) et (ii) ils peuvent évoluer et s'adapter à la transmission inter humaine comme les virus de l'immunodéficience humaine (VIH). Comprendre leur dynamique afin d'adapter les stratégies de contrôle est primordial pour éviter les futures pandémies. Nous discuterons ici de certaines stratégies de contrôle et de leur efficacité. Nous conclurons dans un premier temps sur les objectifs de thèse et en résumerons brièvement les résultats principaux (section 6.1). L'ensemble de ces résultats sera discuté face à la littérature existante afin d'apporter une réflexion nouvelle ainsi que des perspectives sur les différentes questions abordées et les éléments de réponses apportées. Nous avons vu que la vaccination, pourtant largement acceptée dans les populations euro-américaines, ne permet pas toujours de protéger efficacement les populations, et des maladies que l'on croyait sous contrôle réapparaissent. Nous discuterons de l'efficacité que pourrait avoir la vaccination sur les maladies infectieuses émergentes en documentant plus particulièrement le cas du virus Ebola (section 6.2). Nous avons également vu que certaines pratiques culturelles mises en place par les populations locales d'Afrique et d'Asie, là où le nombre d'émergences de nouveaux pathogènes est le plus important, peuvent être adaptatives et permettent de limiter la propagation du pathogène dans les populations. Nous discuterons ensuite de l'importance d'analyser ces pratiques culturelles en tant que stratégies de contrôle (section 6.3). Lorsqu'une épidémie est déclarée, les organisations de santé publique internationales et nationales se mettent en alerte et les individus infectés sont souvent emmenés dans les hôpitaux les plus proches afin d'être isolés. Nous discuterons donc de l'effet de ces déplacement dans les hôpitaux sur la prévalence des épidémies (section 6.4). Enfin, nous discuterons des causes possibles de l'émergence d'une épidémie ou d'un nouveau pathogène dans les populations humaines (section 6.5).

6.1 Résultats principaux

Au cours de cette thèse, nous avons cherché à répondre à deux objectifs principaux : (1) quelle est la dynamique épidémique des maladies infectieuses émergentes dans les populations humaines ? Et (2) quel est l'impact du comportement humain sur le contrôle des infections ? Afin de répondre à ces questions, nous avons principalement utilisé la modélisation qui nous permet de prédire la dynamique épidémique et de tester l'effet de certains paramètres.

Quelle est la dynamique épidémique des maladies infectieuses émergentes ?

Les maladies infectieuses émergentes sont causées par des agents pathogènes qui ont la particularité d'infecter une large gamme d'espèces hôtes [Jones et al., 2008]. De plus, ces pathogènes sont indéfiniment maintenus dans un réservoir, population animale dans laquelle le pathogène est endémique [Ashford, 1997]. Ces deux caractéristiques font qu'empiriquement, il est difficile de prédire et de prévenir les épidémies causées par les maladies infectieuses émergentes. À notre connaissance, aucune étude théorique n'a montré l'importance de l'émergence du pathogène *via* les populations animales dans la dynamique épidémique observée au sein des populations humaines. Souvent, les épidémies humaines de maladies émergentes sont modélisées au sein de la population humaine sans prendre en compte les émergences récurrentes du pathogène [Lloyd-Smith et al., 2009]. Dans ce cas, seule la transmission inter humaine est responsable de la dynamique épidémique observée. Nous avons donc proposé de modéliser l'effet de la transmission du pathogène *via* le réservoir (voir chapitre 2) et/ou *via* une population intermédiaire (voir chapitre 3).

Dans le chapitre 2, un réservoir, où l'agent infectieux est endémique, est pris en compte. Le pathogène émerge régulièrement dans la population humaine. Il est souvent considéré qu'une épidémie ne dépend que de la transmission inter humaine, nous observons ici que la transmission *via* le réservoir est aussi importante que la transmission inter humaine. Trois différentes dynamiques qui dépendent de l'émergence *via* le réservoir et la transmission inter humaine sont observées : (i) émergences isolées lorsque les deux types de transmission sont faibles, (ii) émergences de nombreuses épidémies, lorsque la transmission *via* le réservoir ou la transmission inter humaine est intermédiaire et (iii) une seule grande épidémie, lorsque la transmission *via* le réservoir ou la transmission inter humaine est forte.

Dans le chapitre 3, en plus du réservoir nous ajoutons une espèce hôte intermédiaire. Empiriquement, il est observé qu'en plus du réservoir, le pathogène peut émerger *via* une population intermédiaire [Haydon et al., 2002]. La population d'hôte intermédiaire subit l'infection autant que la population humaine, elles sont appelées populations incidentes. Deux types de transmission du pathogène sont possibles pour les populations incidentes, (i) émergence du pathogène *via* le réservoir et (ii) transmission inter individuelle. La population humaine en plus de ces deux types de transmission peut recevoir l'infection *via* la population intermédiaire. Nous montrons que lorsque la population humaine a deux sources d'infection (c.-à-d. le réservoir et l'hôte intermédiaire) alors une amplification de la prévalence est observée. Alors que lorsque seul l'hôte intermédiaire est source d'infection, un effet de dilution de la dynamique épidémique est observé. Cet effet de dilution est dû à la dynamique épidémique au sein de la population intermédiaire.

Nous pouvons donc conclure que dans le cas des maladies infectieuses émergentes l'émergence du pathogène *via* le réservoir et les populations intermédiaires est très importante à considérer si on veut comprendre les nombreuses et imprévisibles épidémies que l'on peut observer empiriquement.

Quel est l'impact du comportement humain sur les mesures de contrôle ?

Afin de protéger les populations contre la propagation d'une infection, des mesures de contrôle peuvent être mises en place comme la vaccination, la destruction du lieu de reproduction d'une espèce vecteur d'un pathogène, l'isolement, le port d'un masque, etc. Ces mesures nécessitent toutefois une participation de l'individu. Il a souvent été montré que lorsque les individus ne comprennent pas la nécessité d'un moyen de prévention, l'application en reste limitée et difficile [Paul, 1955]. Hormis ce facteur de compréhension de l'individu, la prise de décision peut également être influencé par ses traits d'histoire de vie (p. ex. croyances religieuses, manque de confiance aux autorités, aspects économiques, etc.)

Dans le chapitre 4, nous avons analysé l'effet de la prise de décision de vaccination sur le maintien de la couverture vaccinale ainsi que l'impact sur la dynamique épidémique. La vaccination est vue comme le moyen le plus efficace pour lutter contre la propagation des épidémies, pourtant de nombreuses résurgences sont observées. En utilisant l'analyse de la théorie des jeux c'est-à-dire en supposant que les individus sont des agents économiques maximisant leur santé, un certain nombre de modèles théoriques

montrent que les programmes de vaccination volontaire ne parviennent pas à atteindre un niveau de couverture vaccinale élevé en raison de "tricheurs" qui profitent de l'immunité de groupe sans payer le coût de la vaccination [Bauch, 2005; Bauch and Bhattacharyya, 2012; Bauch and Earn, 2004; Bauch et al., 2003]. Cependant, cette approche ne prend pas en compte la manière dont les individus prennent une décision. Nous proposons ici une alternative aux études classiques en considérant plutôt la prise de décision comme l'expression de dispositions cognitives.

Nous avons développé un modèle d'incidence comportementale dans lequel les individus peuvent être pro-vaccins ou sceptiques, leur opinion influant sur la manière dont les coûts réels de l'infection et de la vaccination sont perçus. Nous modélisons la façon dont les individus interprètent les informations épidémiologiques en fonction de leur opinion de vaccination en considérant deux biais cognitifs associés au comportement de vaccination : le biais de confirmation, c'est-à-dire la propension à rechercher des preuves à l'appui des croyances préexistantes, et le conformisme [Oraby et al., 2014].

Globalement, le modèle prédit la dynamique généralement observée de la couverture vaccinale, à savoir l'impossibilité d'atteindre l'immunité de groupe, nécessaire à la protection de la population contre la propagation de l'infection, ainsi que les oscillations de la couverture vaccinale. Les résultats démontrent que les biais liés à la prise de décision (biais de confirmation et de conformisme) peuvent conduire à la propagation d'une opinion négative concernant la vaccination et que l'hypothèse concernant la rationalité de la prise de décision individuelle n'est pas nécessaire pour prédire les dynamiques de la couverture vaccinale communément observées.

Dans le chapitre 5, nous avons fait la synthèse des pratiques culturelles qui sont vues par les populations locales comme limitant la propagation de l'infection. Les pratiques culturelles qui amplifient les maladies épidémiques sont très étudiées afin de cibler le comportement responsable de l'infection et de mettre en œuvre de meilleures stratégies de contrôle [Inhorn and Brown, 1997]. Lors de la propagation d'une maladie infectieuse, les populations locales utilisent des modèles culturels associés à leurs croyances sur la cause de la maladie. Et parce que la théorie la plus répandue est considérée comme inappropriée par les populations euro-américaines (c.-à-d. la cause surnaturelle), les pratiques culturelles mises en œuvre sont considérées comme inadaptées. En utilisant des données ethnographiques, nous avons examiné les pratiques culturelles qui empêchent la propagation d'agents infectieux au sein du groupe ou de la population locale.

Nous avons décidé de grouper les pratiques culturelles mises en évidence en cinq catégories principales : (1) l'isolement, isolation physique des individus infectés soit dans leur maison soit à l'extérieur du village, (2) l'isolation partielle, évitement des contacts avec les individus infectés, (3) émigration, les habitants du village quittent le village en laissant les individus infectés, (4) modifications des pratiques funéraires, pratiques funéraires plus courtes et différentes de ce qui est pratiqué habituellement et enfin (5) cérémonies, souvent pour chasser le "mauvais sort".

Pour conclure, l'utilisation du modèle biomédical en Europe et Amérique du Nord (c.-à-d. le modèle de médecine occidentale), considéré comme seul modèle de croyance efficace pour prévenir la propagation des infections [Green, 1999], ne permet pas toujours de réussir à contrôler les infections. La vaccination en est un exemple frappant, bien que considéré comme efficace, la prise de décision individuelle peut amener la stratégie à l'échec. D'autres modèles de croyance sont utilisés par les populations d'Asie et d'Afrique impliquant une cause surnaturelle ou naturelle à l'infection [Green, 1999; Inhorn and Brown, 1997; Murdock, 1980]. Nous montrons que certaines pratiques culturelles pourraient permettre dans certains cas de protéger les populations contre la propagation d'un agent pathogène infectieux.

6.2 Une vaccination efficace contre les maladies infectieuses émergentes

La vaccination est un moyen reconnu comme efficace pour protéger les populations contre la propagation des maladies infectieuses [CDC, 1999]. Pour les maladies infectieuses émergentes, peu de traitements sont possibles et souvent la personne malade est isolée. Dans le cas du virus Ebola responsable d'une fièvre hémorragique, un vaccin expérimental est utilisé sur les populations humaines lorsqu'une épidémie est détectée. Ce vaccin est testé depuis mars 2015 sur les populations humaines et cible la souche virale du Zaïre. Cette souche virale est la plus mortelle avec un taux de létalité associé d'environ 60 à 90 % et est responsable de la majorité des épidémies observées, notamment de la plus grande d'entre elles l'épidémie de 2013-2015. Henao-Restrepo et al. [2015] analysent les premiers résultats de l'essai du vaccin contre le virus Ebola et montrent une efficacité de 100% (voir aussi [Henao-Restrepo et al., 2017]). La stratégie de vaccination est une stratégie dite en *anneau* : une fois qu'un individu infecté est confirmé en laboratoire comme

porteur du virus Ebola, un anneau est défini. Le personnel médical suit l'épidémie en vaccinant les personnes à haut risque de contamination c'est-à-dire les personnes ayant eu des contacts plus ou moins rapprochés avec un individu infecté. Les individus à haut risque de contamination sont les individus qui, au cours des 21 derniers jours (période d'incubation de la maladie), ont vécu dans le même foyer que la personne malade, l'ont reçu chez eux ou ont été chez elle pour une visite. Les contacts des contacts sont également recrutés pour la vaccination [Camacho et al., 2015]. La vaccination en anneau ne correspond pas seulement au réseau social de l'individu malade mais aussi à son environnement géographique, elle a pour but de stopper la flambée épidémique en cours. Puisqu'il s'agit d'une vaccination expérimentale, la stratégie en anneau permet un meilleur suivi des individus vaccinés afin d'évaluer l'efficacité du vaccin ainsi que les effets indésirables potentiels.

Les épidémiologistes se sont intéressés à l'effet des deux stratégies de contrôle majeures dans le cas du virus Ebola, l'isolement des individus infectés et la vaccination. Une grande majorité des modèles converge vers le même résultat, c'est-à-dire que la vaccination est une stratégie de contrôle efficace pour limiter la propagation et réduire la prévalence de l'infection. Les stratégies de vaccination sont souvent des stratégies de vaccination dite *de masse* c'est à dire que la vaccination est proposée à tous les individus [Area et al., 2017; Rachah and Torres, 2015; Tulu et al., 2017]. Kucharski et al. [2016] analysent non pas la stratégie de vaccination de masse mais celle en anneau. Ils en concluent qu'elle n'empêche pas l'infection de se propager dans le cas où l'épidémie est déjà grande car il devient difficile de suivre toutes les chaînes de transmission. Par contre elle est efficace en fin d'épidémie ou quand les épidémies sont petites.

La vaccination en anneau semble facilement applicable lorsque la vaccination est expérimentale et efficace lorsque les épidémies sont petites. Une vaccination de masse sera sans doute plus appropriée pour contenir les grosses épidémies qui sont capables d'émerger. Mais nous avons pu voir dans le chapitre 4, que la vaccination de masse, lorsqu'elle est volontaire, pose un problème. En effet dans ce cas, la prise de décision est importante à considérer pour tester l'efficacité de la vaccination dans les populations. La prise de décision se fait en analysant les coûts perçus liés à la vaccination et à l'infection. Dans le cas du virus Ebola, sa transmission est relativement faible par rapport aux maladies établies que nous connaissons et qui peuvent avoir un R_0 compris entre 4 et 18 alors que le virus Ebola a un R_0 compris entre 1 et 2. On s'attend donc à ce qu'une couverture vaccinale

plus faible protège les populations humaines. De plus, étant donné que le virus Ebola a un taux de létalité entre 50 et 90 %, le coût perçu lié à l'infection devrait faire pencher la balance de la prise de décision vers l'acceptation du vaccin. Cependant, le virus Ebola est un pathogène émergent c'est-à-dire qu'il est présent naturellement dans un réservoir. On a vu que l'effet de l'émergence récurrente du pathogène affecte la dynamique épidémiologique dans les populations humaines. Notamment, de grosses épidémies peuvent être observées alors que la transmission inter humaine est faible (voir chapitre 2). Cette dynamique aura sans aucun doute un effet sur le taux de couverture vaccinale à atteindre pour permettre la protection des populations car si l'émergence du pathogène *via* le réservoir ou une population animale intermédiaire est fréquente alors la moindre personne non infectée risque la contamination.

6.3 Prise en compte des pratiques culturelles en modélisation

Dans le dernier chapitre, nous avons vu que certaines populations d'Afrique et d'Asie pensent que la cause d'une infection provient d'un événement surnaturel c'est-à-dire d'un sortilège, d'un·e sorcier·ère, d'une source magique, d'un démon, etc. Bien que certaines populations aient cette croyance, ils ont pu adopter, du fait de leur longue cohabitation avec les pathogènes infectieux, des pratiques culturelles afin de limiter la propagation du pathogène dans les populations. Même si nous avons regroupé ces pratiques culturelles en cinq catégories générales, les pratiques peuvent différer d'une population à une autre. En effet, si on prend l'exemple de l'isolation partielle, qui semble être une pratique adaptative afin de limiter le contact entre les individus infectés et sains, sa mise en place est différente selon les populations considérées. Souvent les individus infectés ne partagent pas les mêmes objets que les individus sains, ou un évitement social est effectué (voir chapitre 5).

Il est difficile de prédire l'effet des mesures préventives sans utiliser des modèles pour nous guider. La dynamique épidémique est non linéaire et dépend aussi bien du pathogène que du comportement des individus, c'est d'ailleurs ce que nous avons pu voir dans le chapitre 4. Par conséquent, les mesures préventives peuvent avoir des effets contre-intuitifs. Les modèles en épidémiologie standard supposent que le comportement humain n'est pas influencé par l'épidémie et reste constant dans le temps. Bien qu'il soit

souvent reconnu que les humains prennent des mesures préventives au cours d'une épidémie, les modèles intégrant une dynamique comportementale sont généralement beaucoup plus difficiles à analyser. De tels modèles ont commencé à faire l'objet d'une attention accrue et d'importants progrès ont été réalisés pour mieux comprendre l'effet de différents changements de comportement sur la dynamique des épidémies [Funk et al., 2010, 2014]. Leung et al. [2018] montrent par exemple que le comportement individuel de distance sociale peut avoir des effets négatifs sur la prévalence de l'infection. Le comportement individuel de distance sociale est défini comme un comportement qui évite les contacts avec un individu infecté. Cependant, en évitant les contacts avec un individu infecté, les individus sains vont créer de nouveaux contacts, cela va modifier la structure du réseau et donc pourrait potentiellement faciliter la propagation de l'infection à travers ce réseau [Leung et al., 2018].

La modélisation permet de tester les effets des mesures de contrôle et un tel travail devrait être effectué afin de tester les effets des pratiques culturelles sur la propagation d'une épidémie. Cela permettrait de savoir si de telles pratiques peuvent et doivent être encouragées lorsqu'aucun autre traitement n'est possible comme lors des épidémies de certaines maladies infectieuses émergentes ou lorsque les infrastructures sanitaires ne permettent pas de rendre accessibles rapidement les traitements possibles.

6.4 Effets des hôpitaux sur la transmission des pathogènes

Les épidémies sont nombreuses à avoir démarré au sein de centres hospitaliers ou de soins comme les épidémies dues au virus Ebola, au virus Lassa ou encore les épidémies du Syndrome Respiratoire du Moyen Orient (MERS) [Fisher-Hoch et al., 1995; Peters et al., 1994]. Plusieurs facteurs facilitent le démarrage des épidémies, comme une proximité importante les individus infectés et sains (p. ex. les infirmier·ère·s, les médecins ou encore les autres patients), une densité de population plus importante dans un lieu restreint, l'utilisation de pratiques médicales non adaptées, etc. Fisher-Hoch et al. [1995] montrent que les pratiques médicales occidentales sont parfois appliquées sans prendre soin de former correctement les équipes médicales qui les utilisent ou du fait de leur prix élevé, sont limitées dans leur utilisation. Cela a pour effet d'augmenter la prévalence de l'infection dans une localité donnée. Durant une épidémie d'Ebola en République démocratique du Congo en 1995, 20% du nombre d'individus infectés étaient des personnes qui

travaillaient dans le domaine de la santé [Guimard et al., 1999].

De plus, du point de vue des individus infectés, se rendre dans un centre de soin est parfois difficile car géographiquement éloigné du lieu où ils habitent ou car la perception des centres de soins est négative. Hewlett and Hewlett [2008] montrent que lors des épidémies causées par le virus Ebola, certains individus refusent d'être conduits dans les centres de soins ou hôpitaux car ils ont peur d'y mourir. La famille refuse également de peur de ne pas pouvoir récupérer les corps des proches morts de l'infection. Cette perception négative peut avoir des conséquences néfastes comme la fuite des individus infectés, qui vont alors se rendre dans des villages voisins et potentiellement propager l'infection.

Finalement, bien que l'isolement et la mise en quarantaine dans les centres de soins permettent de contrôler et de limiter la propagation d'une infection, des effets contraires peuvent être mis en évidence lorsque les centres de soins ne sont pas adaptés ou que les infirmier·ère·s ou médecins ne sont pas suffisamment formés. De plus, la perception des populations locales concernant l'infection ou les pratiques de soins devraient être davantage prises en compte par les organisations de santé publique nationales ou internationales afin de mieux intégrer les pratiques culturelles des populations locales [Hewlett et al., 2005].

6.5 Émergence dans les populations : un effet stochastique ?

On recherche souvent ce qui a causé l'émergence de nouveaux pathogènes. Des modifications au niveau génétique et/ou écologique peuvent être analysées afin d'expliquer l'émergence nouvelle de pathogènes dans les populations humaines ou des modifications dans le patron de transmission du pathogène (p. ex. l'apparition d'une plus grande épidémie). Le cas du virus Ebola est intéressant car beaucoup d'études ont été publiées afin de comprendre l'émergence du virus mais aussi l'apparition de la grande épidémie de 2013-2015.

D'un point de vue génétique, une hypothèse est qu'une évolution génétique rapide de sa transmissibilité aurait permis son émergence dans les populations humaines et l'apparition de plus grandes épidémies [Hayden, 2014]. Gire et al. [2014] analysent 99 génomes du virus Ebola pendant l'épidémie de 2014 en Sierra Leone et montrent que les modifications génomiques observées sont légères et ne sont pas corrélées avec la gravité de l'épidémie. Ces modifications ne semblent donc pas avoir rendu le pathogène plus trans-

missible entre humains. De même, Hoenen et al. [2015] ne montrent pas d'évolution rapide du pathogène au cours de l'épidémie. L'hypothèse d'une adaptation génétique du virus Ebola n'est donc pour le moment pas démontrée.

D'un point de vue écologique, le comportement humain est souvent vu comme un amplificateur des épidémies. En effet, son interaction avec la faune sauvage, les déplacements des individus même malades, la proximité importante entre individus sont des causes importantes de transmission du pathogène. L'émergence récente des épidémies causées par le virus Ebola peut être expliquée par les changements des populations Africaines. Becquart et al. [2010] montrent en analysant la séropositivité au virus Ebola, que les individus vivant en milieu rural ont une séropositivité plus importante. Les possibilités de contacts avec le virus sont effectivement plus importantes en milieu rural. Une hypothèse à l'émergence d'épidémies de plus en plus importantes est l'augmentation des déplacements effectués par les populations Africaines. Notamment les individus en zone rurale peuvent se déplacer en zone urbaine facilitant ainsi la transmission inter humaine.

Pourtant, l'émergence des épidémies du virus Ebola et leur ampleur semblent souvent imprévisibles avec parfois de longues périodes sans aucun cas répertorié comme entre 1976 et 1995 ou entre 1997 et 2001 avec souvent des épidémies isolées sauf l'épidémie de 2013-2015. En tout, une vingtaine d'épidémies ont été répertoriées depuis sa première émergence reconnue en 1976. Nous savons également qu'en plus de ces épidémies, des émergences isolées n'impliquant pas d'épidémies ont pu être observées [Jezek et al., 1999].

Dans notre modèle développé au chapitre 2, nous montrons que la stochasticité, permet parfois l'émergence de petites épidémies ou de grandes épidémies. Par hasard, le pathogène se propage dans la population humaine ou s'éteint aussi vite qu'il est arrivé. L'effet stochastique n'est pas à négliger même si bien évidemment trouver les facteurs favorisant l'émergence des épidémies permet d'établir des mesures de contrôle plus rapidement et de rendre les épidémies prévisibles.

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Résumé

Les maladies infectieuses émergentes ont façonné l'histoire de l'espèce humaine. Encore aujourd'hui, l'émergence de nouveaux pathogènes menace la santé publique. Comprendre l'interaction entre l'écologie des pathogènes et le comportement humain peut aider à comprendre la dynamique observée dans les populations humaines. Au cours de cette thèse, deux axes principaux ont été abordés : la dynamique épidémique des maladies infectieuses émergentes (MIEs) dans les populations humaines et l'impact du comportement humain sur le contrôle des infections. La dynamique épidémique des pathogènes émergents est peu connue car elle reste souvent étudiée sans prendre en compte l'effet de leurs caractéristiques, à savoir leur maintien dans un réservoir et leur capacité à émerger chez plusieurs espèces animales. Pour la première fois, nous avons modélisé la dynamique des MIEs et mis en évidence que la transmission *via* réservoir et les populations intermédiaires est aussi importante que la transmission inter humaine pour comprendre les nombreuses et imprévisibles épidémies que l'on peut observer. Par la suite, l'impact du comportement humain sur le contrôle des infections a été étudié en considérant deux aspects, la prise de décision de vaccination et les pratiques culturelles. Nous montrons que la considération de biais cognitifs liés à la prise de décision de vaccination et l'interaction entre le comportement et l'épidémiologie peut aboutir aux fluctuations de la couverture vaccinale observées empiriquement. Enfin, l'étude des pratiques culturelles a montré que, bien que souvent considérées comme à l'origine de la propagation de pathogènes dans la population, certaines pratiques peuvent en limiter la transmission. L'ensemble de ces résultats suggère que la prise en compte de l'écologie permet de faire de meilleures prédictions sur l'influence de l'environnement sur l'émergence et la ré-émergence des maladies infectieuses et d'adapter les stratégies de contrôle.

Abstract

Infectious diseases have shaped the history of the human species. Nowadays, the emergence of new pathogens threatens public health. Understanding the interaction between pathogen ecology and human behaviour can help understanding the dynamics observed in human populations. In this thesis, two main axes were studied : the epidemic dynamics of emerging infectious diseases (EID's) in human populations and the impact of human behaviour on the control of infectious diseases. The epidemic dynamics of emerging pathogens is poorly understood because it is often studied without taking into account the effect of their characteristics, namely their persistence in a reservoir population and their ability to emerge in a broad range of species. For the first time, we modeled the dynamics of EID's and highlighted that transmission from both the reservoir and intermediate populations are critically important to consider in order to understand the many and unpredictable outbreaks that can be observed. Thereafter, the impact of human behaviour on infectious diseases control was studied by considering two aspects, vaccination decision-making and cultural practices. We show that consideration of cognitive biases related to vaccination decision-making and the interaction between behaviour and epidemiology can lead to the fluctuations observed in vaccination coverage. Finally, the study of cultural practices has shown that, although often assumed to favour the spread of pathogens in a population, certain practices can limit disease transmission. The results taken together suggest that an ecological approach is key for predicting the dynamics underpinning the emergence and re-emergence of infectious diseases and adapt control strategies.