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► **To cite this version:**

Thibaut Koutangni. Modelling bacterial meningitis in the African meningitis belt for the evaluation of preventive vaccination. Human health and pathology. Sorbonne Université, 2019. English. NNT : 2019SORUS159 . tel-02950924

HAL Id: tel-02950924

<https://theses.hal.science/tel-02950924>

Submitted on 28 Sep 2020

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Sorbonne Université

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Modélisation des méningites bactériennes dans la ceinture africaine des méningites pour l'évaluation de la vaccination préventive.

Par Thibaut KOUTANGNI

Thèse de doctorat d'Épidémiologie

Dirigée par Dr. Judith Mueller et Dr. Pascal Crépey

Présentée et soutenue publiquement le 16/07/ 2019

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Dédicace

À ma famille,

Merci infiniment pour votre soutien le long de cette aventure doctorale. Cette thèse vous est dédiée.

Remerciements

Je voudrais avant tout remercier mes directeurs de thèse Dr. Judith Mueller et Dr. Pascal Crépey pour m'avoir offert l'opportunité de réaliser ce projet de thèse. Merci infiniment à tous les deux pour l'accompagnement et le soutien dont vous avez fait preuve durant toute cette thèse. Merci à Judith d'avoir été au commencement de tout ; de mon premier stage en épidémiologie à ma première expérience professionnelle en tant qu'épidémiologiste à l'École des Hautes Études en Santé Publique (EHESP) - des expériences qui m'ont évidemment conforté dans l'envie de poursuivre une thèse dans cette discipline.

Je me souviens encore de cette réunion à l'Hôtel Dieu, avec Pascal Crépey, dans son magnifique bureau avec vue imprenable sur la cathédrale Notre Dame de Paris, cette réunion qui a déterminé cette aventure de thèse à trois. Merci Pascal de m'avoir fait confiance et d'avoir aussi cru en ma motivation dès le début malgré les challenges techniques posés par ce projet de thèse.

Au Professeur Martine Bellanger, j'aimerais adresser également mes sincères remerciements pour son soutien depuis mon parcours de master. Merci au Dr. Ludovic Trinquart du centre Cochrane Français pour ses conseils méthodologiques statistiques en méta-analyse. Mes remerciements vont également à l'endroit de l'Université Pierre et Marie Curie (UPMC), et l'école doctorale de santé publique (ED393) pour m'avoir octroyé sur concours un financement doctoral sans lequel la concrétisation de mon projet de thèse n'aurait probablement pas été possible.

Merci au Dr. Arnaud Fontanet, responsable de l'unité de recherche en épidémiologie des maladies émergentes à l'Institut Pasteur et au Dr. Olivier Grimaud, chef du département des méthodes quantitatives en santé publique de l'EHESP ; merci beaucoup à tous les deux de m'avoir accueilli dans vos structures respectives dans le cadre de cette thèse. Je n'oublie évidemment pas mes collègues de l'institut Pasteur et de l'EHESP. Merci à toutes et à tous pour avoir rendu mon passage parmi vous très agréable. Ce fut un réel plaisir de travailler avec vous.

Je remercie également le Ministère de la Santé du Burkina Faso et l'Agence de Médecine Préventive (AMP) à Ouagadougou pour la mise à disposition des données de surveillance utilisées dans le cadre de cette thèse, mais aussi toutes les personnes impliquées directement ou indirectement dans la collecte, et la constitution de cette base de données. Merci à tous les collègues du groupe de travail sur les méningites en Afrique MAMEMA (Multidisciplinary Approach for Meningitis Epidemiology and Modelling in Africa).

Je tiens à remercier aussi le réseau doctoral en santé publique animé par l'EHESP, qui m'a offert l'opportunité de me familiariser à d'autres disciplines de santé publique à travers la formation pluridisciplinaire complémentaire dont j'ai bénéficié pendant cette thèse. Les rencontres scientifiques annuelles du réseau doctoral en santé publique m'ont également offert l'occasion de communiquer sur mes travaux de thèse, et d'en apprendre sur d'autres thématiques de recherche en santé publique. L'organisation des séminaires interdisciplinaires en santé publique a été une belle opportunité de collaborer avec les pairs sur des questions scientifiques d'intérêt public.

Merci au Dr. Nathanaël Lapidus (chargé des enseignements dirigés de biostatistiques PACES à l'UPMC au moment de cette thèse) et au Pr. Fabrice Carrat, de m'avoir offert l'ultime opportunité de réaliser des missions d'enseignements dirigés de biostatistiques auprès des étudiants de PACES de la faculté de médecine de l'Université Pierre et Marie Curie. Cette expérience a vraiment contribué à ma formation doctorale et conforté mon intérêt pour l'enseignement universitaire. Enfin merci aux membres du jury qui m'ont fait l'honneur de participer au jury de cette thèse.

Résumé

La méningite bactérienne encore appelée méningite cérébro-spinale est une inflammation grave et potentiellement mortelle des méninges : les membranes enveloppantes protégeant le cerveau et la moelle épinière. Il s'agit d'une maladie infectieuse, strictement humaine principalement causée par trois espèces bactériennes pathogènes courantes : *Neisseria meningitidis* (N.m), *Streptococcus pneumoniae* (S.p) et *Haemophilus influenzae type b* (Hib).

Ces bactéries sont généralement portées de manière asymptomatique au niveau de la muqueuse du nasopharynx et transmises d'une personne à l'autre par des contacts étroits répétés avec les sécrétions respiratoires des porteurs asymptomatiques (porteurs sains). L'infection peut porter des atteintes graves au cerveau et est mortelle dans 5% à 10% des cas même en cas d'initiation d'un traitement (Kaplan 1999). Les décès surviennent généralement dans les 24 à 48 heures suivant l'apparition des symptômes (Roberts, 2008) et un survivant de la méningite bactérienne sur cinq restes avec une séquelle permanente telle qu'une perte de capacité auditive, d'autonomie, et des complications neurologiques (Rosenstein et al., 2001). Les manifestations cliniques courantes associent syndromes infectieux (fièvre > 38,5° C, maux de tête violents, vomissements) et syndromes méningés (raideur de la nuque, léthargie, troubles de la conscience, voire coma). Le diagnostic précoce et la mise en place d'un traitement adéquat sont essentiels pour la survie du patient.

La prévalence des méningites bactériennes varie considérablement à travers le monde, selon l'âge, et même le séro groupe, les prévalences les plus élevées étant observées en Afrique sub-saharienne et plus particulièrement dans une zone géographique connue sous le nom de « Ceinture Africaine des méningites ». Un nom qui, en effet, fait référence à la fréquence plus élevée des cas et à l'épidémiologie distincte des méningites bactériennes dans cette zone géographique.

Le terme de « Ceinture Africaine des méningites » serait utilisé pour la première fois par le médecin militaire et épidémiologiste français Léon

Lapeyssonnie dans un rapport intitulé « la méningite cérébro-spinale en Afrique » publié par l’OMS en 1963 (Lapeyssonnie, 1963). Dans ce rapport, rédigé à la suite de voyages sur le continent Africain, fait de visites personnelles auprès de ministères de la santé, d’hôpitaux et centres de soins (la plupart dans des anciennes colonies françaises), Lapeyssonnie décrit de manière exhaustive, l’incidence des cas de méningite et les caractéristiques épidémiologiques de la maladie. Il souligne le régime « endémo-épidémique » sous lequel sévit la méningite dans une région du continent Africain décrite initialement comme allant du Mali à l’Ouest au Soudan à l’Est. Cette région, située au sud du Sahara, était décrite comme présentant un profil climatique particulier par rapport au reste du continent africain, puisqu’elle coïncide avec une zone de pluviométrie limitée au nord par l’isohyète 300 mm et au sud par l’isohyète 1100 mm de pluie cumulée annuelle (Lapeyssonnie, 1963). Lapeyssonnie y décrit une recrudescence importante des cas de méningites et des épidémies fréquentes uniquement pendant la saison sèche (Janvier à Mai), et un retour à la normale avec des cas sporadiques dès l’arrivée des premières pluies de la saison humide.

La ceinture africaine des méningites est aujourd’hui élargie à d’autres pays limitrophes de la région initialement décrite par Lapeyssonnie, qui présentent le même profil climatique et épidémiologique des méningites. Cette nouvelle définition de la ceinture africaine des méningites inclue 26 pays et s’étant du Sénégal à l’Ouest jusqu’à l’Éthiopie à l’Est avec une population à risque estimée à environ 350 millions de personnes (Greenwood, 1999) (Figure 1).

L’épidémiologie des méningites dans la ceinture des méningites est caractérisée par trois principales situations épidémiologiques : la situation endémique, les hyperendémies saisonnières et les épidémies. La situation endémique correspond à des incidences hebdomadaires de cas notifiés très faibles (de l’ordre de 0 à 0.5 pour 100 000 habitants au niveau du district) et coïncide avec la saison des pluies (juin à novembre) (Mueller & Gessner, 2010). Cette incidence endémique est comparable à celle observée en Europe (Rabab et al., 2013). La situation hyperendémique correspond à une augmentation de l’incidence de l’ordre de 1 à 2 cas pour 100 000 habitants voir plus au niveau du district et coïncide exclusivement avec la saison sèche. Cette situation est

désignée de « saison des méningites ». Comparer à la situation endémique, les incidences des méningites à méningocoques en situation hyperendémique seraient de l'ordre de 10 à 100 fois plus élevés (Mueller & Gessner, 2010).

En plus des hyperendémies observés régulièrement pendant la saison sèche, des épidémies sont observées localement à l'échelle de petites aires géographiques (communautaires) et peuvent affecter les communautés indépendamment de leur proximité géographique. Au niveau du district, les incidences hebdomadaires de l'ordre de 10 cas pour 100000 habitants ou plus sont définies comme épidémiques et servent de seuil d'alerte pour la riposte épidémique. Cependant, la situation épidémique peut être bien plus hétérogène au niveau local communautaire avec des incidences épidémiques de l'ordre de 20 à 100 cas pour 100000 habitants dans quelques communautés seulement (Mueller & Gessner, 2010). Des événements périodique tel que l'introduction d'une nouvelle souche pathogène du méningocoque, ou autres cofacteurs épidémiques peuvent présenter un terrain favorable à l'extension et l'intensification des épidémies localisées donnant lieu à une vague épidémique observée tous les 7 à 10 ans à l'échelle régionale dans la ceinture des méningites.

Les épidémies de méningites bactériennes sévissent depuis des décennies dans la ceinture africaine des méningites malgré la vaccination. Le caractère irrégulier de ces épidémies et les mécanismes de leur survenue ne sont que partiellement compris. Divers sérogroupes du méningocoque sont impliqués dans les épidémies de méningites dans la ceinture africaine des méningites. Historiquement, le méningocoque du groupe A a été le séroroupe le plus impliqué dans les grandes épidémies de méningites dans la ceinture africaine des méningites (Laforce et al., 2009 ; Lingani et al., 2015 ; Moore, 1992). D'autres sérogroupes tels que le W (NmW), le X (NmX) et le C (NmC) sont de plus en plus responsables d'épidémies localisés et occasionnellement impliqués dans des vagues épidémiques (Lingani et al., 2015 ; Mueller et al., 2006 ; Delrieu et al., 2011 ; Boisier et al., 2007). Les méningites à S.p et Hib contribuent à la forte saisonnalité des méningites bactériennes avec une incidence des méningites à S.p due au stéréotype 1 plus élevée chez les adultes (Mueller et al., 2012).

Les efforts de recherche en épidémiologie quantitative descriptive et moléculaire des méningites dans la ceinture des méningites ont permis de générer des hypothèses sur les mécanismes de ces épidémies et parfois apporté de nouveaux éléments à leur compréhension. Ces épidémies, leur périodicité et saisonnalité seraient le résultat d'une interaction complexe de plusieurs facteurs impliquant l'hôte, la bactérie, l'environnement, et des facteurs épidémiologiques (Greenwood, 1987 ; Moore, 1992).

Les facteurs associés à l'hôte pouvant être déterminant dans la survenue des épidémies de méningites incluent la susceptibilité, l'immunité humorale, les co-infections des voies respiratoires supérieures, et l'immunité de groupe (Moore, 1992 ; Griffiss et al, 1987).

L'immunité humorale serait l'un des facteurs déterminant dans la prévention de la méningite à méningocoque (Griffiss et al, 1987 ; Moore, 1992), mais les connaissances sur le rôle de l'immunité de groupe restent limiter dans la ceinture des méningites (Moore, 1992). Des études réalisées dans des populations restreintes (militaires) et même en population générale avaient démontré que le risque de développer une méningite à méningocoque était inversement corrélé au titre des anticorps préexistants dirigés contre le sérotype responsable de la maladie chez ces sujets (Moore, 1992 ; Goldschneider et al., 1969a, Goldschneider et al., 1969b ; Gotschlich et al., 1969c). Ces études ont également apporté des éléments de clarification au sujet du paradoxe de la protection naturelle apparente contre l'invasion bactérienne chez la plupart des porteurs de la bactérie. Malgré un portage élevé de la bactérie dans la ceinture africaine des méningites, le nombre de personnes développant la méningite invasive reste relativement faible. Le développement d'une immunité naturelle dès le jeune âge potentiellement due au portage d'espèces bactériennes non pathogènes du méningocoque tel que *N. lactamica* permettrait de stimuler la production d'anticorps, offrant une protection croisée durant la période nécessaire à l'organisme pour produire une réponse immunitaire spécifique contre la souche pathogène du méningocoque (Gold et al., 1978 ; Griffiss et al, 1987 ; Goldschneider et al., 1969b).

La susceptibilité d'une population aux épidémies de méningites peut augmenter suite à la diminution des anticorps protecteurs acquis par le portage, la maladie ou la perte de l'immunité de groupe acquise par la vaccination (Moore, 1992). Cette perte d'immunité de groupe pourrait contribuer notamment aux cycles épidémiques observés dans la ceinture des méningites. Cependant, des études longitudinales sur l'immunité naturelle et acquise par la vaccination en population générale sur plusieurs vagues épidémiques successives seront nécessaires pour bien clarifier le rôle de l'immunité de groupes dans la survenue des vagues épidémies de méningite dans la ceinture.

D'autres facteurs relatifs à l'hôte pourraient intervenir dans la survenue des épidémies de méningites. Par exemple les co-infections respiratoires. Celles-ci pourraient engendrer une réduction circonstancielle des capacités immunitaires au sein de la population et augmenter ainsi le risque de transmission et ou d'invasion des bactéries capables de causer la méningite (Mueller & Gessner, 2010 ; Mueller et al., 2017).

Les facteurs relatifs à la bactérie pourraient inclure la virulence des souches impliquées dans les épidémies. Par exemple des épidémies de méningites à méningocoques du groupe B sont survenues en Europe de l'Ouest (Poolman et al., 1986) mais leur taux d'attaque est 2 fois moindre que celui du méningocoque du groupe A observé dans la ceinture des méningites (Moore, 1992). Différentes souches du groupe A du méningocoque peuvent également avoir une capacité différente à causer une épidémie (Olyhoek et al., 1987). La virulence des clones du groupe A du méningocoque serait donc un élément déterminant dans leur capacité à causer des épidémies dans la ceinture des méningites.

Par ailleurs, d'autres études ont suggéré que des modifications antigéniques « antigenic shifts » au sein de clones du méningocoque du groupe A auraient pu déclencher des épidémies en réduisant considérablement l'immunité de groupe à la souche pathogène existante (Achtman, 1990 ; Moore, 1992). Les mouvements importants de populations (engendrés par les pèlerinages et marchés traditionnels locaux et régionaux) connus pour être des facteurs de risque épidémiques (OMS, 2018) pourraient également favoriser la survenue des épidémies de méningites

d'une part en introduisant de nouveaux clones et d'autre part en réduisant l'immunité de groupe au sein de la population résidente (Moore, 1992).

Les facteurs environnementaux tel que le climat sec, les vents chargés de poussières en saison sèche, ont été évoqué comme facteurs susceptibles d'augmenter l'invasion bactérienne en affectant directement la muqueuse du nasopharynx de l'hôte ou en inhibant le développement de l'immunité mucoale (Moore, 1992). Ainsi, ces facteurs environnementaux contribueraient aux épidémies de méningite en augmentant la probabilité d'une invasion bactérienne chez les individus ayant acquis le portage.

Des travaux plus récents se sont particulièrement intéressés aux épidémies à une échelle locale (épidémies localisées de méningites bactériennes) et ont exploré le rôle de facteurs aussi bien climatiques, qu'épidémiologiques, et socio-démographiques dans leur survenue. (Paireau et al., 2014 ; Mueller et al., 2017)

Par exemple, Paireau et collaborateurs (Paireau et al. 2014) ont démontré l'influence de facteurs climatiques tels que l'humidité relative moyenne, et la précocité de la saison des pluies sur les variations interannuelles des incidences épidémiques observées aussi bien à une échelle spatiale réduite (communautaire) qu'au niveau national.

L'identification de facteurs épidémiologiques et socio-démographiques apportent de nouveaux éléments à la compréhension de ces épidémies. La proportion de communautés voisines ayant des cas de méningites et la préciosité de la survenue de cas dès le début de la saison sèche (avant le 31 décembre) seraient corrélées à une augmentation du risque d'épidémie dans une communauté donnée (Paireau et al., 2014). Par ailleurs, la taille finale de l'épidémie à l'échelle du pays était significativement corrélée au nombre d'épidémies localisées pendant la « saison des méningites », et dans une moindre mesure, à l'intensité de ces épidémies localisées (Paireau, 2014). L'existence d'infrastructures routières importantes reliant les communautés et la proximité de ces dernières seraient associées à un risque élevé de survenue d'épidémies. Ces facteurs favoriseraient les mouvements de populations et les contacts humains ; deux éléments importants contribuant aux épidémies (Paireau et al., 2014 ; Bharti et al., 2012). En outre, la survenue des

épidémies localisées serait fortement associée à une incidence élevée de coinfections des voies respiratoires supérieures (Mueller et al., 2017) dans la ceinture des méningites.

Au-delà des épidémies localisées de méningites présentant un caractère irrégulier et imprévisible, la saisonnalité annuelle régulière des cas de méningites (hyperendemicité) observées dans tous les pays de la ceinture des méningites reste un élément important de l'épidémiologie des méningites bactériennes non encore bien compris.

Depuis des décennies, des études menées dans la ceinture africaine des méningites ont exploré la relation entre les variables climatiques et l'incidence des méningites bactériennes. Ces études ont souvent modélisé des données épidémiques au niveau du district sanitaire (2^{ème} niveau de la pyramide sanitaire après les formations sanitaires) en fonction de variables climatiques telles que l'humidité relative, la température, la pluviométrie, la quantité de particules fines dans l'air, et les poussières atmosphériques, etc. Ces études démontrent des associations plus ou moins fortes entre l'incidence des méningites et ces variables climatiques et suggèrent que l'incidence de la méningite et sa saisonnalité régulière observée seraient fortement influencées par la dynamique temporelle du climat de la saison sèche dans la ceinture des méningites. (Sultan et al., 2005; Agieret al., 2013; Martiny & Chiapello, 2013; Yaka et al., 2008)

Si l'existence d'un lien entre le climat de la saison sèche et la dynamique temporelle des méningites est démontré et largement accepté par la communauté scientifique, les mécanismes par lesquels ce climat sec contribuerait à la recrudescence et à la saisonnalité régulière des cas incidents de méningites restent largement débattus et hypothétiques. La compréhension de ces mécanismes sous-jacents et des facteurs déterminants la dynamique endémo-épidémique et saisonnière de la maladie est cruciale pour optimiser les programmes de santé publique dédiés à la prévention et la lutte contre les méningites bactériennes dans la ceinture africaine des méningites.

Le développement et l'introduction relativement récent (fin 2010) d'un vaccin conjugué monovalent contre les méningites bactériennes notamment celles

dues au sérotype A du méningocoque (MenAfriVac), promet une riposte efficace aux épidémies de méningites par une réduction de la transmission et de l'acquisition du portage asymptomatique, contrairement aux vaccins polysérotypiques utilisés jusqu'ici dans la ceinture des méningites (Frasch et al., 2012). MenAfriVac a été initialement introduit sous la forme de campagnes ponctuelles de vaccination de masse ciblant les 1 à 29 ans. En 2015, des stratégies à long terme incluant ce vaccin dans le calendrier de routine du programme élargi de vaccination ont été recommandées par l'OMS (OMS, 2015). Au même moment, le vaccin conjugué contre le pneumocoque était introduit dans le programme de vaccination de routine. Cependant, les adultes représentant la population la plus susceptible à l'infection à pneumocoque pourraient ne pas être suffisamment protégés pour permettre une réduction de l'incidence de la maladie.

L'introduction du MenAfriVac a réduit considérablement le portage et la fréquence des épidémies dues au sérotype A du méningocoque dans les années suivantes dans les pays de la ceinture des méningites (MenAfriCar consortium, 2015; Kristiansen et al., 2014; Mustapha & Harrison, 2018), mais des épidémies dues à d'autres sérotypes du méningocoque (X et W) sont de plus en plus rapportées dans la ceinture des méningites (Greenwood, 2007; Delrieu et al., 2011). L'émergence d'épidémies causées par le sérotype C aussi bien à l'intérieur (Nigeria, Niger) qu'à l'extérieur de la ceinture des méningites (Liberia) (Mustapha & Harrison, 2018; Sidikou et al., 2016; Bozio et al., 2018) suggère la nécessité d'introduire des vaccins multivalents conjugués dirigés contre les sérotypes majeurs à potentiel épidémique dans la ceinture des méningites. Par ailleurs, la réduction importante du portage asymptomatique et des cas de méningite dus au groupe A du méningocoque n'exclut pas de continuer à optimiser les stratégies de contrôle de la méningite à méningocoque A.

D'un point de vue de santé publique, les responsables de programme de vaccination ont maintenant à trouver la stratégie vaccinale la plus efficace, voire plus efficiente, pour maintenir un niveau de protection et une immunité durable avec le vaccin conjugué MenAfriVac au sein des populations cibles.

Les modèles mathématiques ont été largement utilisés pour répondre à ce type de question pour diverses maladies évitables par la vaccination. À titre

d'exemple, ils ont été utilisés pour évaluer l'impact à moyen et long terme de diverses stratégies vaccinales pour le vaccin conjugué développé contre le sérotype C du méningocoque en Angleterre (Trotter et al., 2005). Néanmoins, l'utilité des modèles mathématiques dans l'identification de stratégies vaccinales optimales est limitée par le niveau de connaissance et de compréhension de la biologie de l'infection, des mécanismes sous-jacents de la transmission, du développement et de la persistance de la maladie au sein de la population cible. Dans le contexte particulier de la ceinture africaine des méningites, et contrairement aux pays de l'hémisphère nord où les cas de méningites restent sporadiques et souvent sans liens apparents, la question se pose de savoir comment bien reproduire l'incidence des méningites bactériennes y compris sa saisonnalité annuelle régulière en lien avec la saison sèche, dans des modèles mathématiques de transmission. Pour la ceinture africaine des méningites, de tels modèles requièrent des hypothèses sur la transmission de la bactérie, le portage asymptomatique et le risque de méningite en relation avec les saisons locales, qui ne sont pas encore clairement tranchées et qu'il est nécessaire d'évaluer.

Objectifs

Cette thèse a pour objectif d'appliquer des modèles statistiques et mathématiques à des données épidémiologiques et de surveillance des méningites bactériennes, en vue d'évaluer des hypothèses à propos de mécanismes physiopathologiques potentiellement impliqués dans la saisonnalité annuelle régulière des cas incidents de méningites bactériennes dans la ceinture africaine des méningites.

Ses objectifs se déclinent en 3 axes.

- Analyser les données d'incidence des méningites, de prévalence de portage asymptomatique et de ratios cas-porteurs des méningocoques issus de la ceinture africaine des méningites et voir dans quelle mesure leurs variations pourraient aider à la compréhension du phénomène saisonnier de la ceinture des méningites.
- Modéliser la méningite bactérienne saisonnière en formulant des modèles mathématiques incluant des hypothèses concurrentes sur les mécanismes

potentiellement impliqués dans la saisonnalité des cas de méningites dans la ceinture africaine des méningites.

- Évaluer la capacité des modèles mathématiques développés à reproduire l'incidence et la saisonnalité annuelle des cas de méningites bactériennes observée, en prenant les données du Burkina Faso comme exemple.

Hypothèses de recherche

Deux des hypothèses principalement discutées dans la littérature scientifique et en rapport direct avec les mécanismes potentiellement impliqués dans la dynamique saisonnière des méningites bactériennes dans la ceinture des méningites, ont particulièrement retenues notre attention. Si elles sont vérifiées, elles pourraient être utilisées pour mieux capter la dynamique des méningites bactériennes dans la ceinture africaine des méningites et améliorer les prédictions de futurs modèles mathématiques pour l'évaluation de stratégies vaccinales dans cette population.

- L'hypothèse 1 suggère que le climat de la saison sèche, caractérisé par une humidité relative faible pouvant aller en dessous de 10%, et un taux élevé de poussières ou aérosols de particules fines d'origine minérale dans l'air, fragiliserait la surface de l'épithélium du nasopharynx, augmentant ainsi le risque d'invasion de la muqueuse du nasopharynx par la bactérie chez les porteurs sains, et donc de nouveaux cas de méningite.
- L'hypothèse 2, suggère que la saisonnalité régulière et la recrudescence des cas de méningites pendant la saison sèche seraient principalement dues à une variation saisonnière importante de la transmission des bactéries facilitée par le climat sec et relativement frais (exemple : influence sur les mouvements, les habitudes et comportements des populations, etc.). Cependant, selon les études de portages asymptomatiques au sein de populations de la ceinture des méningites (à l'exception d'une (Christensen et al. 2010)), la prévalence du portage ne varierait pas systématiquement entre les saisons (Trotter & Greenwood, 2007a).

Pour évaluer ces hypothèses nous avons procédé de la manière suivante :

Dans un premier temps, nous réalisons une revue systématique de la littérature scientifique sur les méningites bactériennes dans la ceinture des méningites et procédons à une méta-analyse des données d'incidence, de portage asymptomatique et de ratio cas-porteurs des méningocoques issues de cette littérature. Nous ciblons particulièrement les études en population générale publiant des données de surveillance active des cas de méningites et de prévalence du portage asymptomatique au sein de la même population sur une même période.

Les études devraient rapporter les données par sérotype du méningocoque et donner des indications sur le contexte épidémiologique de l'étude (situation endémique, hyperendémique, ou épidémique) et la saison locale au moment de l'étude (saison des pluies, ou saison sèche). Nous avons développé et utilisé un algorithme basé sur l'incidence, la pluviométrie et l'humidité relative pour définir le contexte épidémiologique et la saison locale dans le cas où les indications fournies sur ces deux éléments dans les études ciblées ne sont pas suffisamment claires. Nous procédons ensuite à une extraction des données d'incidence, et de portage par sérotype selon la saison locale et le contexte épidémiologique de l'étude. Nous estimons pour chacune des populations des études incluses, le ratio cas-porteurs (considéré ici comme un proxy écologique du risque d'invasion méningée chez les porteurs asymptomatiques du méningocoque). Enfin, nous procédons à une méta-analyse des taux d'incidences, de prévalences de portage asymptomatiques rapportés, et des ratios cas-porteurs par saison et par contexte épidémiologique, puis décrivons les variations de ces quantités entre les saisons, et d'une situation épidémiologique à l'autre. Cette première étape de la thèse a permis l'identification de variations potentiellement saisonnières (ou non-saisonnières) de la prévalence du portage asymptomatique et du ratio cas-porteurs selon le contexte épidémiologique, nous permettant ainsi de répondre au premier axe des objectifs de cette thèse.

La deuxième partie de cette thèse, s'est articulée autour du développement de modèles mathématiques de transmission des méningites bactériennes dans la ceinture africaine des méningites. Ces modèles catégorisent les individus de la population en compartiments selon leur statut au regard de l'infection et de la maladie (la méningite). Ainsi, nous distinguons :

- Les individus susceptibles à l'infection (noté S),
- Les individus infectés porteurs asymptomatiques de la bactérie (noté C, pour 'Carriers' en anglais),
- Les individus ayant développé la méningite à l'issue d'une période de portage asymptomatique (noté I, pour 'Ill' en anglais),
- Les individus ayant guéri de l'infection ou de la maladie (notés R, pour 'Recovered' en anglais). Ces individus du compartiment R peuvent développer une immunité naturelle temporaire suite au portage asymptomatique ou suite à la maladie, et redeviennent susceptibles à l'infection.

Ainsi les modèles développés sont des modèles SCIRS en références aux compartiments Susceptibles – Carriers – Ill – Recovered – Susceptibles.

Les travaux présentés se limitent à l'analyse des variations entre situation endémique (saison humide) et hyperendémique (saison sèche habituelle sans épidémie). L'analyse de la survenue des épidémies est ainsi exclue.

Trois variantes du modèle SCIRS ont été développées et simulées. La première inclut l'hypothèse de variation saisonnière du risque d'invasion méningée de la bactérie chez les porteurs asymptomatiques. La deuxième inclut l'hypothèse d'une variation saisonnière de la transmission de la bactérie, et enfin la troisième inclut l'hypothèse de variations saisonnières à la fois de la transmission de la bactérie et du risque d'invasion méningée de la bactérie chez les porteurs asymptomatiques. Ces variations ont été modélisées à l'aide de fonctions sinusoïdales dont la période est de 1 an.

Les paramètres des modèles et leurs valeurs sont décrits au chapitre 4. Les valeurs de certains de ces paramètres étaient non connues et non documentés dans la littérature scientifique. C'est le cas par exemple du taux de transmission moyen des méningocoques ou des pneumocoques dans la ceinture des méningites, ou de la durée moyenne du portage asymptomatique et de l'immunité naturelle, mais aussi le taux d'invasion méningée de la bactérie chez les porteurs asymptomatiques.

Les paramètres dont les valeurs étaient inconnues ont été estimés à partir des données de surveillance des cas suspects de méningites bactériennes issues des formations sanitaires au Burkina Faso; l'un des pays de la ceinture des méningites bénéficiant d'un système renforcé de surveillance des méningites bactériennes. Les modèles sont simulés sur la base de l'ensemble des valeurs de paramètres y compris celles estimées. Les estimations d'incidences hebdomadaires des trois modèles sont ensuite comparées aux données observées. Le meilleur modèle étant celui qui présente des estimations concordantes ou très proches des données observées.

Cette deuxième analyse nous a ainsi permis de répondre au deuxième et troisième objectif de cette thèse.

L'ensemble des résultats des analyses détaillés aux chapitres 3 et 4 apportent des éléments en faveur des deux hypothèses décrites précédemment. S'il est trop tôt pour conclure définitivement sur les mécanismes déterminants la saisonnalité régulière des cas de méningites bactérienne pendant la saison sèche dans la ceinture africaine des méningites, les résultats de cette thèse suggèrent que les modèles mathématiques ayant pour objectif de prédire les incidences des méningites bactériennes et l'impact de stratégies vaccinales, tout en reproduisant au mieux la saisonnalité des cas dans la ceinture des méningites, devraient au moins prendre en compte les variations saisonnières du risque d'invasion méningée chez les porteurs asymptomatiques ainsi que celles de la transmission des bactéries. L'importance relative des variations de ces deux paramètres reste un champ à explorer.

Ces résultats ouvrent des perspectives sur l'utilisation de modèles mathématiques de structure similaires à ceux proposés dans cette thèse pour évaluer la contribution relative des variations saisonnières de la transmission bactérienne et du risque d'invasion méningée (chez les porteurs sains) aux épidémies localisées dans la ceinture des méningites. Les résultats présentés au chapitre 3 de cette thèse, suggèrent que les épidémies localisées seraient vraisemblablement associées à une augmentation importante du portage asymptomatique pendant la saison sèche et dans une moindre mesure à un changement du risque d'invasion méningée chez les porteurs sains. L'utilisation

des modèles proposées dans cette thèse sur des données épidémiques seront d'intérêt pour tenter d'expliquer au moins en partie la distinction entre les hyperendémies saisonnières et les épidémies localisées. Une approche stochastique pourra être privilégiée pour prendre en compte le caractère sporadique irrégulier des épidémies localisées. Pour aller plus loin, les modèles proposés dans cette thèse pourront également servir de base au développement de modèles de métapopulations, permettant de modéliser explicitement les interactions entre populations au niveau communautaire et de prédire l'incidence au niveau communautaire, mais aussi du district ou de la région. L'approche méta-populationnelle pourrait permettre de reproduire et de prédire la distribution dans le temps et dans l'espace des épidémies localisées et apporter de nouveaux éléments à la compréhension de ces épidémies dans la ceinture des méningites. L'évaluation de moyens de contrôles y compris la vaccination et les traitements contre la méningite pourraient être intégrés à ce type de modèle pour identifier la stratégie la plus efficace pour contrôler la maladie et les épidémies dans la ceinture des méningites.

Par ailleurs, certains des paramètres issus de la littérature, utilisés pour paramétrer les modèles développés dans cette thèse étaient issues des données du méningocoque. L'incidence des méningites à pneumocoques présentent une dynamique saisonnière similaire à celle des méningocoques et participe de fait à la saisonnalité régulière des cas de méningites bactériennes dans la ceinture des méningites. Cependant, la dynamique et la distribution selon l'âge du portage asymptomatique ne semblent pas être les mêmes que celles observées pour le méningocoque dans la ceinture des méningites. Une adaptation de ces paramètres pourrait être donc nécessaire selon que les modèles proposés dans cette thèse soient utilisés pour l'estimation de l'incidence ou du portage des méningites à pneumocoques spécifiquement.

List of publications

The publications and communications related to this thesis are as follows:

Published articles

- **Koutangni T**, Boubacar Maïnassara H, Mueller JE. 2015. Incidence, Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt : A Systematic Review and Meta-Analysis. *PLoS ONE*. 10(2):e0116725. doi: 10.1371/journal.pone.0116725
- **Koutangni T**, Crépey P, Woringer M, Porgo S, Bicaba WB, Tall H, Mueller JE. 2018. Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt. *Epidemiology and Infection*, 1-11. doi:10.1017/S0950268818002625

Scientific oral and posters presentations:

Compartmental models for seasonal hyperendemic bacterial meningitis in the African meningitis belt.

- 20th International Pathogenic Neisseria Conference, Manchester, England, September 2016. (Poster)
- Annual Scientific Meeting of the EHESP French School of Public Health Doctoral Network, Paris, France, March 2016. (Oral presentation)
- Annual Congress of Pierre Louis Doctoral School of Public Health, Saint Malo, France, October 2015 (Poster)

Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt: A Systematic Review and Meta-Analysis.

- Annual Scientific Meeting of the EHESP French School of Public Health Doctoral Network, Paris, France, April 2015. (Poster)
- Annual Congress of Pierre Louis Doctoral School of Public Health, Saint Malo, France, October 2014 (Poster)

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Chapter 1. Introduction

This chapter states the research context, objectives, hypotheses and the structure of this thesis manuscript. The literature supporting the research hypotheses is further presented in the *Chapter 2. State of the art*.

Research statement

Bacterial meningitis is a serious and life-threatening inflammation of the meninges: the thin membranes surrounding and protecting the brain and spinal cord. It is a human infectious disease mainly caused by three common pathogens: *Neisseria meningitidis* (*N.m*), *Streptococcus pneumoniae* (*S.p*), and *Haemophilus influenzae type b* (*Hib*) (Doran et al., 2016). These bacteria are commonly carried asymptotically in the nasopharynx and transmitted from person to person through repeated close contacts with respiratory secretions of carriers. The infection can lead to severe brain damages, and is fatal despite treatment in 5% to 10% of cases (Kaplan 1999). Common clinical manifestations include acute onset of fever (typically > 38.5 °C rectal or 38.0 °C axillary), headache, neck stiffness, altered consciousness or other meningeal signs. Early diagnostic and treatment are critical to survive the disease. Even with early diagnosis and the start of adequate treatment, 5 to 10% of meningitis patients die within 24-48 hours of symptoms onset (Roberts 2008) and one in five of survivors of bacterial meningitis are left with permanent sequel such as hearing or limb loss and neurological disability (Rosenstein et al., 2001).

Invasive meningococcal disease in the meningitis belt include a preponderance for meningitis syndrome than septicaemia (although surveillance may underestimate the latter due to limited access to healthcare) as opposed to Europe where meningitis case are normally sporadic and invasive meningococcal disease is considered rare (Whittaker et al., 2017; Harrison et al., 2009; Greenwood et al., 1979).

The incidence of bacterial meningitis varies greatly worldwide, but the highest are reported in sub-Saharan Africa, primarily in a geographical area

known as “the African meningitis belt”. Here, meningitis has a pronounced annual seasonality, with incidence of cases peaking every dry season but very low in the rainy season. Although predictable, the dynamic of this recurrent seasonality is not fully understood.

Several studies explored the relation between climatic variables and bacterial meningitis incidence in the meningitis belt. They usually model district-level epidemic data as a function of variables such as dust load, rainfall, air humidity etc. These studies suggest that meningitis incidence and its recurrent seasonality are mostly influenced by the temporal dynamics of the sub-Saharan Africa dry climate; e.g. low relative air humidity, dusty air, temperature etc. (Sultan et al., 2005; Agier, A. Deroubaix, et al., 2013; Martiny & Chiapello 2013; Yaka et al., 2008). However, the mechanisms through which the climate of the dry season would contribute to the recurrent seasonality of meningitis incidence remain poorly understood and hypothetical. Understanding of the key factors driving this seasonal dynamic and the underlying mechanisms is crucial to optimize public health programs devoted to meningitis prevention and control in the meningitis belt, for example, vaccination.

The recent development and introduction of a group A meningococcal conjugate vaccine in Africa (MenAfriVac A) specifically for preventive use, promises substantial decrease in meningococcal group A epidemics for the coming decade. From a public health perspective, policy maker would want to know the most effective vaccination schedules or strategies to sustain protection and immunity at population level. Mathematical models are useful to evaluate different vaccination strategies and their long-term impact. For example they have been used in the UK to investigate group C conjugate vaccine impact (Trotter et al., 2005).

The usefulness of mathematical models in identifying the effective vaccination strategies and schedules, however, is limited to the extent our understanding of the important mechanisms underlying the disease transmission and persistence in the target population is correct. In the particular context of the African meningitis belt, it is still unclear how best to capture meningitis incidence recurrent seasonality and to accurately predict the disease incidence with

mathematical models. These dynamical models of meningitis require assumptions about the transmission and disease risk patterns in relation to the local season, which has not yet been clarified.

Objectives

The objectives of this thesis are to apply statistical and mathematical modelling methods to analyse bacterial meningitis data collected in the meningitis belt, with a view to evaluate hypotheses about potential mechanisms involved in the recurrent seasonality of meningitis.

Specific aims are:

- To describe season-specific bacterial meningitis incidence, carriage and case-carrier ratios in the African meningitis belt and how their variations relate to the observed epidemiology.
- To model seasonal bacterial meningitis in the African meningitis by translating competing hypotheses of the potential mechanism involved, into mathematical models.
- To compare these mathematical models of bacterial meningitis in terms of their ability to accurately capture the seasonal patterns seen in meningitis incidence data both quantitatively and qualitatively.

Hypotheses

Two of the most discussed hypotheses in the scientific literature for the potential mechanisms underlying the striking seasonality of bacterial meningitis in the African meningitis belt, retained our attention as they pertain to how bacterial meningitis recurrent seasonality can be captured in mathematical models in an attempt to make good prediction of meningitis incidence in the meningitis belt.

- Hypothesis 1 implies that bacterial meningitis recurrent seasonality is most likely driven by seasonal changes in the risk of invasive meningitis among colonized individuals.

- Hypothesis 2, on the other hand, implies that the recurrent seasonality of bacterial meningitis in the African meningitis belt is most likely driven by seasonal change in transmissibility of the bacteria.

These two hypotheses are further described in chapter 2 of this thesis.

Thesis structure

This thesis consists of 5 chapters including this introduction chapter. In chapter 2 we describe the African meningitis belt (our study setting) and provide a state of the art on bacterial meningitis epidemiology, surveillance and vaccination in this setting. We review risk factors of meningitis and hypothetical models of the observed epidemiology in the African meningitis belt and further clarify the hypotheses addressed in this thesis. Chapter 2 also provides a brief overview of the methods used to evaluate our research hypotheses, including systematic reviews and meta-analysis of primary research, and the mathematical modelling of recurrent infectious diseases.

Chapter 3 and 4 presents application of these methods to data from the African meningitis belt to reach the three specific aims of this thesis described previously. In chapter 3 we present a systematic review and meta-analysis of meningococcal serogroup specific incidence, carriage and case-carrier ratios across the meningitis belt. We then quantify their variations according to local season and epidemiological context and describe how these variations may relate to the recurrent seasonality of bacterial meningitis and epidemic meningitis in the African meningitis belt.

In chapter 4 we developed compartmental models of seasonal bacterial meningitis including one or a combination of the competing hypotheses described previously. Each of the model's predictions were compared to bacterial meningitis surveillance data observed at community level in Burkina Faso, a country in the African meningitis belt. In order to fairly compare the competing models, we first tried to find out what is the best each model can do. Practically speaking, we found the values of the models' parameters that give the closest correspondence between model predictions and the observed incidence.

In Chapter 5 we summarise our findings and discuss strengths and limitations of our methodological approach and the contribution of this thesis to existing knowledge of the meningitis belt phenomenon and the implications of our findings for future work on meningitis modelling in the African meningitis.

Chapter 2. State of the art

Background: Bacterial meningitis in sub-Saharan Africa

The epidemiology of bacterial meningitis in sub-Saharan Africa is different than that observed in the northern hemisphere's continents such as Europe and the United States (US), where meningitis cases are sporadic with no apparent link. This section will review the distinctive epidemiology of bacterial meningitis in the meningitis belt, including its link with the local climate, meningitis surveillance, past and present vaccination strategies, and the risk factors and hypothetical models proposed for the observed epidemiology.

The African meningitis belt

Meningitis sometimes called cerebrospinal fever or cerebrospinal meningitis (CMS) probably emerges as a new infection in Africa more than 100 years ago (Greenwood 1999). Isolated outbreaks were reported in Africa starting from the middle of the eighteenth century (Greenwood 1999). The first report was that of an outbreak in soldiers in Algiers (North-East Africa) between 1840-47 (Chalmers & O'Farrell 1916). It was only in 1905 that the first major epidemic of meningitis was recorded. This epidemic started in northern Nigeria (West Africa) in 1905 with many thousands of deaths, before another epidemic, likely due to the same strain, occurred a year later in Ghana, killing at least 8000 people (Greenwood 1999). It was suggested that the outbreak strain would have been introduced into West Africa from the Sudan, where an epidemic is known to have occurred a few years previously, by pilgrims returning from the Haj around the turn of the century (Greenwood 1999).

The 1906 epidemic in Ghana spread rapidly into the French colonies territories and outbreaks of meningitis have become frequent in West Africa since then. In the following decades, meningitis epidemics were reported repeatedly over the Sahelian region; in Niger alone, annual incidence was over 100 per 100 000 in 1921-1924, 1938-9, 1944-6, 1949-51 and 1961-62 (Lapeyssonnie 1963). It is in the wake of the last of these waves that Lapeyssonnie produced a

comprehensive report on cerebrospinal meningitis in West Africa. This report entitled “La méningite cérébrospinale en Afrique” was based on extensive review of published and unpublished records, obtained by personal visits to ministries of health and hospitals in West Africa. In his report, Lapeyssonnie documented nearly all the characteristic epidemiological features of cerebrospinal meningitis in Africa and drew attention to the fact that it is only in a restricted area of the continent that the infection behaves in a peculiar way; including: massive size of epidemics, periodicity, geographical restriction, and marked seasonality. This led him to define the ‘African meningitis belt’, bounded to the north by the Sahara and to the south by areas of tropical rain forest. The ‘African meningitis belt’ was initially described by Lapeyssonnie as extending from Mali in the West to Sudan in the East, a geographical area in between latitudes 4° and 16° north which coincided with the 300-1100 mm mean annual rainfall isohyets from the south of Sahara, in which the semi-arid sub-Saharan Africa and Sahel is enclosed within. In his original report, Lapeyssonnie did not describe meningitis epidemiological features at the eastern and western border of the meningitis belt.

The meningitis belt spans almost the entire width of the African continent from the Gambia and Senegal in the west all the way to Sudan and Ethiopia in the East (Molesworth et al., 2002) (Figure 1). However, in the last decade outbreaks with epidemiological features similar to those observed in the meningitis belt, such as seasonality, have also been reported in central and southern African countries such as Kenya, Zambia, Angola, Burundi, and Rwanda (LaForce et al., 2007; Cuevas et al., 2007). This suggest a possible expansion of the meningitis belt out of its traditional bounds in the future, perhaps due to climate changes effects such as a reduction in rainfall and humidity in sub-humid areas adjacent to belt (Molesworth et al., 2003; Molesworth et al., 2002). The African meningitis belt has a population at risk of approximately 350-430 million and includes 26 countries (Meningitis Vaccine Project (MVP), website).

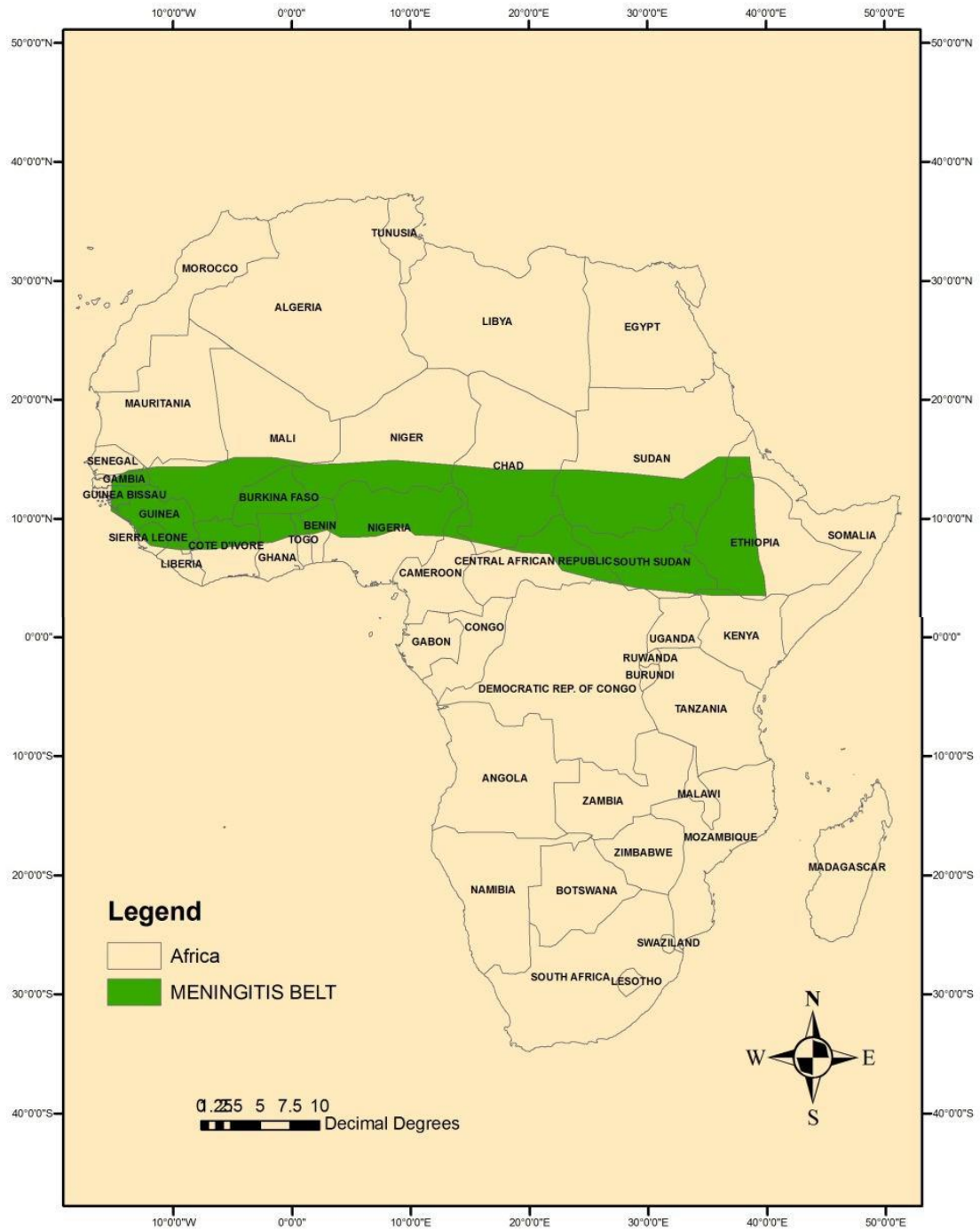


Figure 1: The African Meningitis Belt.

Image source (Umaru E.T, et al., 2013)

Epidemiology

Bacterial meningitis accounts for an estimated annual 170 000 deaths worldwide (Anon 2012). The African meningitis belt contributes the highest to the global burden of bacterial meningitis. Since the introduction of H. influenza type b (Hib) conjugate vaccines, *S. pneumoniae* and *N. meningitidis* tend to be the commonest causes of bacterial meningitis worldwide (Kinoshita & Tsuji 2000; Doran et al., 2016).

Neisseria meningitidis have nearly always been involved in meningitis epidemics (small and large size) (Anon, 2016). The highest reported meningococcal meningitis epidemic in the history of the world was in 1996 and most of the cases were found in Africa (Greenwood, 2006; Broutin et al., 2007). In that year, over 250,000 cases with 25,000 deaths were reported to the World Health Organization (WHO) (Broutin et al., 2007). Between 1998 and 2002, countries within the meningitis belt reported more than 224,000 new cases of meningococcal meningitis (Anon, n.d.). 3000 to 10,000 deaths mainly among children under 15 years old are recorded annually according to intensity of the epidemics (Teyssou & Muros-Le Rouzic 2007). In the 2009 epidemic season, 88199 suspected cases of meningitis including 5352 deaths were reported to WHO from 14 African countries (Anon n.d.).

Grouped cases and secular trends of invasive pneumococcal disease (such as pneumonia and bacteraemia) have been observed in several countries worldwide, but most cases of pneumococcal meningitis appear to be confined in Africa including countries such as Burkina Faso, Ghana, Chad etc. (Ihekweazu et al., 2010; Leimkugel et al., 2005). Pneumococcal meningitis incidence is up to ten times higher in the dry season than in the wet season (Mueller et al., 2012), with most cases occurring in older children and young adults (Gessner et al. 2010; Leimkugel et al., 2005). A study including both urban and rural population in Burkina Faso showed that from 2007 to 2009, annual pneumococcal meningitis incidence rates were highest among infants <6 months old (58 per 100,000 population) and teenager and young adults 15 to 19 years –olds (15 per 100,000 population) in the dry season. Pneumococcal carriage prevalence in

nasopharyngeal swabs was 63% among <5-year-old children and 22% among \geq 5-year-old persons (Mueller et al., 2012). Reported case fatality are high in the meningitis belt (36%–66%) (Gessner et al., 2010). Between 2004 and 2013, more than 4000 cases of bacterial meningitis reported in the meningitis belt were caused by *S. pneumoniae*, representing about 27% of confirmed cases (World Health Organization & WHO 2014). The true number of cases is likely much higher given that the proportion of suspected cases with laboratory confirmation is relatively low across the meningitis belt (6 -7 %) (World Health Organization & WHO 2014).

Seasonality and epidemics

The characteristic features of bacterial meningitis in the African meningitis belt include strong seasonality (figure 2) with endemic incidence in the rainy season, hyper-endemic incidence, or localized epidemics in the dry season, and large epidemic waves in the dry season which are observed every 5 to 12 years (figure 3) with attack rates up to 1,000 cases per 100,000 population (Mueller & Gessner 2010b). Other regions of the world have lower rates of disease and experience occasional outbreaks, with annualized attack rates of around 0.3 to 3 per 100,000 population (Anon n.d.).

Seasonality

Incidences are typically endemic during the rainy wet season, with weekly incidences around 0-0.5 per 100,000 populations at the district level (Mueller & Gessner 2010a). In the dry season, however, the number of cases increases predictably and progressively and usually reaches 10-100 times the endemic incidences: a situation commonly described as seasonal hyperendemicity (Mueller & Gessner 2010a). The incidence of cases then declines with the onset of the first rains of the year. In addition to this regular seasonal hyperendemicity observed every year, irregular localized epidemics are observed at community level only during the dry season with attack rates up to 1% of the population. These epidemics often disrupt routine health care services. Depending on their numbers, scales, spatial and temporal distribution, localized epidemics can translate into large epidemics at district or national

level.

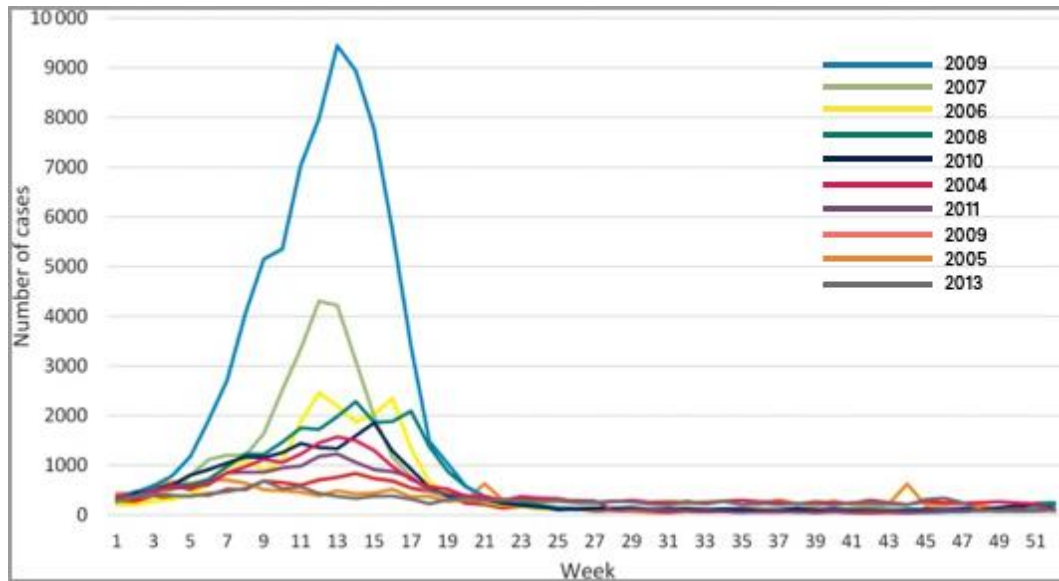


Figure 2 : Weekly number of suspected and confirmed meningitis cases in the meningitis Belt.

Source: (Lingani et al., 2015)

Epidemics

Large-scale epidemics waves are observed periodically at the country level, but the periodicity vary across countries and time (figure 3). Different authors suggested periodicity of these epidemic waves ranging from 5-14 years (Greenwood, 1999; Moore, 1992; Gagneux et al., 2002) . Broutin et al., showed that a period of 8-12 years is typical and the epidemic waves cycle is not generally synchronized across countries (Broutin et al., 2007). Large epidemics waves may span two to three dry seasons with very low incidence in the intervening rainy season(Greenwood). The distinction between epidemic year and non-epidemic years is not always neat looking at district or national level surveillance data only; for example about 13750 suspected cases of bacterial meningitis were reported in 2009 in Burkina Faso compared to just 1050 cases during 2007(Anon, n.d.).

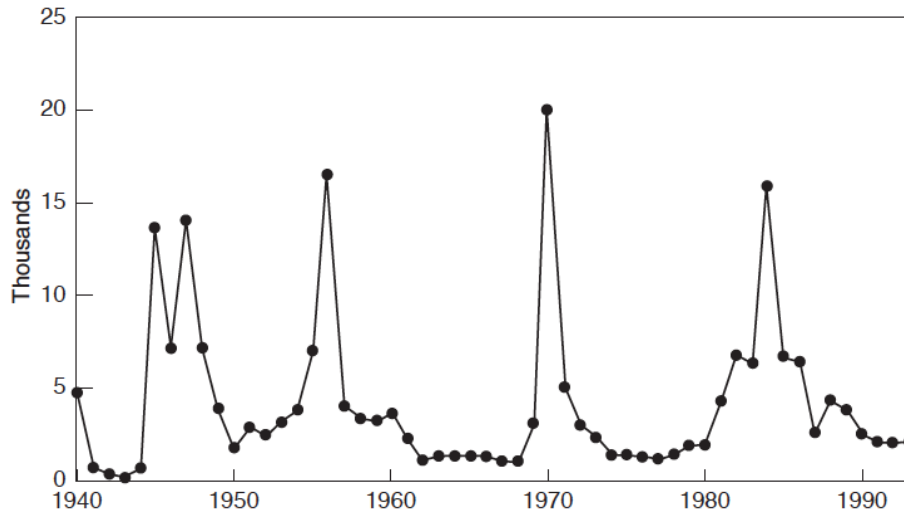


Figure 3: Annual number of reported meningitis cases in Burkina Faso Data (1940 – 1990). courtesy: WHO

Beyond the pattern of disease observed at the district or country level, the picture is more complex at community level. In district that has declared epidemics, the outbreak is typically limited to the catchment area of a handful of health care centres, with other experiencing no more than the expected number of cases (Mueller et al., 2011; Sié et al., 2008; Tall et al., 2012; Paireau et al., 2012). Localized epidemics often affect communities in a matter of weeks (Greenwood, 1999; Mueller et al., 2011). Furthermore within a given health centre’s catchment area, a village may be very affected, whilst its neighbours are practically untouched.(Greenwood, 1999; Mueller et al., 2011). Spatial heterogeneity is not limited to dry season with large epidemics and are also observed during seasons with minor epidemics.

Health-related and economic impact of meningitis

At the national level, median annual incidence rates per 100 000 inhabitants are in the range 5-20 in most areas of the meningitis belt, but are 50-60 in Niger and Burkina Faso(Molesworth et al., 2002; Novak et al., 2012). During epidemic years attack rates can easily reach 200 per 100 000 inhabitants(Molesworth et al., 2002). At the district level, typical epidemic year attack rates are between 100 and 500 per 100000 inhabitants (de Chabalier et

al., 2000; Tall et al., 2012). This rate is even more extreme at the health centre or community level; where between 1% and 10% of the population may experience meningitis during an epidemic (Greenwood, 1999; Tall et al., 2012).

The age distribution of cases can vary between epidemics, with peak attack rates ranging from 0-4 year olds to 10-14 year olds (Trotter & Greenwood 2007a), although children aged 1-14 consistently account for the majority of cases (Novak et al. 2012; Decosas & Koama, 2002; Mueller et al., 2011). Meningitis is rather rare amongst those 30 or over (Mueller et al. 2011; Novak, Kambou, F. V. K. Diomandé, et al. 2012), however, this age groups is still frequently found to be carriers (Trotter & Greenwood 2007a). This is in contrast to Europe, where attack rates are highest in the under ones, with a secondary peak in the late teenage years (LaForce et al. 2007; Trotter et al. 2006). In a detailed study of the age distribution of cases that is conducted in a large population, in Niamey, Niger (Campagne et al., 1999), it was found that the age-distribution of cases in epidemic and non-epidemic years were similar, although there was a small but significant increase in the proportion of cases that occurred in the under-fives in epidemic years.

Reported meningitis mortality rates in sub-Saharan Africa are around 8-12% (Decosas & Koama, 2002; Besancenot et al., 1997; Hodgson et al., 2001; Boisier et al., 2007). Similar rates are observed in developed countries (Stephens et al., 2007), but meningitis mortality is probably underreported in Africa and captures only death occurring at the health centres (Greenwood 1999). Meningitis can result in permanent sequelae, including hearing loss, and brain damages in about quarter of its survivors (Roberts, 2008; LaForce & Okwo-Bele, 2011; Boisier et al., 2007).

In addition to its high fatality and morbidity and its potential for leaving patients with life-long disability, meningitis has a high financial cost. In Burkina-Faso (one of the countries in the meningitis belt) for example, meningitis disease would cost a patient's household approximately US \$90, which represents about 34% of the country annual GDP per capita (Colombini et al., 2009). The cost can rise up to US \$154 for patients with sequelae. This

poses a high economic burden on households especially in a poverty context where most african households have no or little income (Colombini et al., 2009; Roberts, 2008). Aside the disease economic burden to patients' household, the cost incurred for meningitis management is also high for governments. In 2007 when Burkina-Faso experienced meningitis epidemic with 25,852 cases, about 2% of the country total health budget (about US \$7.1 million) was spent in cases management and the epidemic control (Colombini et al., 2009).

Since epidemic meningitis are mostly unpredictable and feared in the region (Roberts, 2008), outbreaks have a profound impact on other healthcare provisions, with routine services and vaccination campaigns ceasing as frightened people, sick or otherwise, seek consultation (LaForce & Okwo-Bele, 2011).

The bacterium *Neisseria meningitidis*

Neisseria meningitidis (the meningococcus) is a Gram negative and an oxidase-positive diplococcus (Pollard & Frasch, 2001) whose only natural reservoir is humans (Rosenstein, Perkins, Stephens, Tanja. Popovic, et al. 2001). The bacterium is a commensal of the human nasopharynx mucosa and can be encapsulated or unencapsulated (Stephens et al., 2007). The capsule plays an important role in virulence and protection of the meningococcus against opsonisation, phagocytic and complement mediated bactericidal killing. This allows the bacteria to survive longer after invading the bloodstream (Rosenstein et al., 2001; Tzeng & Stephens, 2000), as well as increases its chances of transmission (Stephens et al., 2007). Some authors argue that being unencapsulated can allow the meningococcus to escape the host's immune defence (Yazdankhah, 2004; Frosch & Maiden, 2006), while others suggested that the capsule could be advantageous for colonization of the nasopharynx mucosa (Stephens et al., 2007).

Based on the immunochemistry of the coating capsular polysaccharide, the meningococcus, is classified into 13 serogroups, named A, B, C, D, 29E, H, I, K, L, W, X, Y and Z (Vedros, 1987; Branham, 1953). Other important antigens or proteins commonly expressed on the outer-membrane of the bacterium allow to

further classifying it into serotypes and serosubtypes (Tsai et al., 1981; Frasch et al., 1985; Rouphael & Stephens, 2012). These commonly expressed outer-membrane proteins are the porins PorB and PorA respectively. Hence, a meningococcus strain is commonly designated by: the serogroup: the serotype: the serosubtype. For example, B: 15: P1.7, 16 (P1 being the class 1 protein (Abdillahi & Poolman, 1988) or PorA). Increasingly, meningococci are being characterised by their genotype using molecular methods, with a proposed molecular classification being serogroup: PorA type: FetA type: sequence type (clonal complex)(Jolley et al., 2007; Rouphael & Stephens, 2012).

Of the 13 serogroups of *N. meningitidis*, six (A, B, C, W, X, and Y) are recognized to be responsible for almost all cases of meningococcal meningitis worldwide (Stephens et al., 2007). The pathogenicity, immunogenicity, and epidemic capabilities of the main disease-causing serogroups differ, and so does their geographical distribution worldwide (Figure 4). In Europe, South America and Australia, serogroup B and C predominate; whereas in Asia serogroup A and C are most common. In North America most meningococcal disease is caused by serogroups B, C, and Y (Molesworth et al., 2002). In sub-Saharan Africa, and particularly in the meningitis belt, serogroup A has been responsible for major epidemics, but outbreaks due to W135 and X serogroups are often reported as well (Stephens et al., 2007; Molesworth et al., 2002; Nicolas et al., 2005; Delrieu et al., 2011; Caugant et al., 2012).

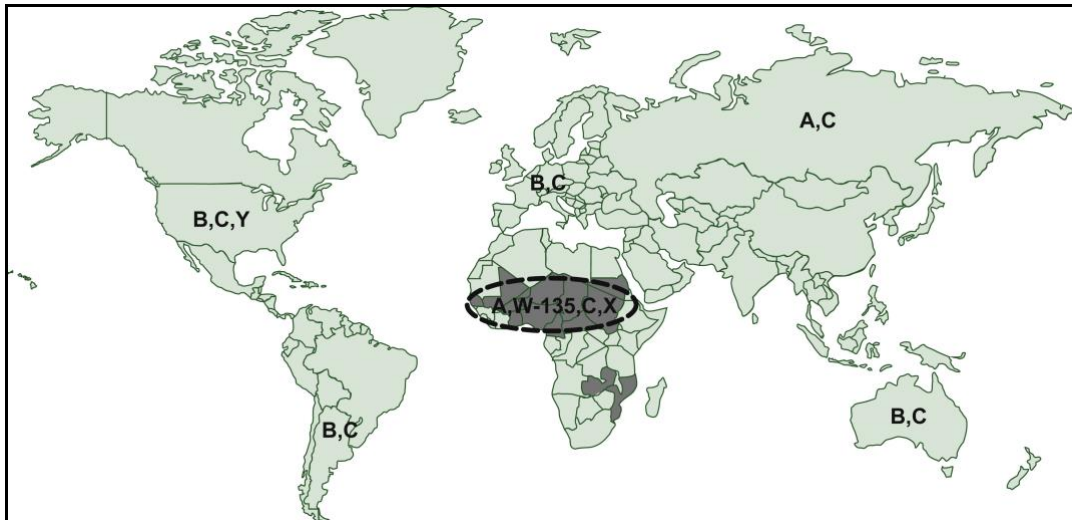


Figure 4: Predominant serogroups associated with invasive meningitis worldwide.

Source: (Pelton, 2016)

Asymptomatic carriage

Both pneumococci and meningococci can harmlessly colonize the human nasopharynx after being transmitted to a susceptible host via aerosols of respiratory secretions (Rosenstein et al., 2001). After escaping the host immune defences, the bacteria can attach itself to mucosal cells of the human nasopharynx epithelium through its outer membrane proteins known as pili. In the nasopharynx, it can multiply to form colonies (Rosenstein et al., 2001). At this stage of the infection and following colonization, the host can carry the bacteria without developing invasive meningitis symptoms. This state of the infection is described as asymptomatic carriage. Most infection with the bacteria results in asymptomatic carriage, which plays an important role in spread of the bacteria. Therefore, carriage studies are critical for understanding the underlying transmission dynamics.

Meningococci asymptomatic carriage varies greatly according to serogroups, the epidemiological context as well as age, and settings, but is generally between 3% to 30% (Christensen et al., 2010; Trotter & Greenwood 2007a). In high-income countries, meningococcal carriage occurs most frequently in older children and young adults and is linked to smoking, nightclub attendance, and intimate kissing (Christensen et al., 2010; Trotter & Greenwood, 2007a). In the meningitis belt age distribution of meningococcal carriage does not seem

consistent across studies but is generally common in young children (Trotter & Greenwood, 2007a). Few meningococcal carriage studies have been conducted in the meningitis belt in recent years (Leimkugel et al., 2007; Mueller et al., 2007; Kristiansen et al., 2011), and earliest studies reported different estimations of the carriage prevalence likely because they were conducted at different times of the year and/or used different methods (Trotter & Greenwood, 2007a). One of the most recent multi-country carriage study (MenAfriCar) conducted across 7 countries of the meningitis belt used standardized methods. (The MenAfriCar consortium, 2015). Carriage surveys were conducted prior and post the introduction of the new meningococcal serogroup A conjugate vaccine. Serogroup A meningococcal carriage prevalence of about 1% was estimated outside epidemics in the surveys prior the vaccination and the rates are overall lower in the post-conjugate vaccine era. The prevalence of carriage by age was 1.8% among <1 year, 2.6% among those 1–4 years, 4.9% among 5–14 years, 3.6% for 15–29 years, and 2.6% for ≥ 30 years olds (The MenAfriCar consortium 2015), suggesting that carriage was generally common in young children as in the systematic review of carriage studies conducted in the meningitis belt prior to 200 (Trotter & Greenwood, 2007a). Carriage prevalence seemed higher in males than in females with marked difference seen in 15-19 years old. Difference in overall meningococcal carriage prevalence between the rainy and the dry season does not appear consistent across surveys (Trotter & Greenwood, 2007a; The MenAfriCar consortium, 2015; Kristiansen et al., 2011).

Risk factors for meningococcal carriage in high income countries include smoking, respiratory tract infections and attendance at pubs and clubs (MacLennan et al., 2006; Yazdankhah, 2004). In the meningitis belt, age, sex, season, rural site, crowding (≥ 2 people per room), indoor kitchen facilities, exposure to kitchen fire smoke and respiratory tract infections are among reported risk factors for carriage of meningococci (The MenAfriCar consortium, 2015; Mueller et al., 2008). An inverse relationship between carriage of *Neisseria meningitidis* and non-pathogenic *Neisseria* have been reported in the meningitis

Carriage of the bacteria can be transient or may last up to several weeks or months for meningococci (Cartwright, 1995), before being cleared naturally by the host. Little is known about the duration of carriage episodes of these bacteria in sub-Saharan Africa. A longitudinal survey conducted in northern Nigeria in

1982 was the only study reporting a meningococcal carriage half-life of three months. However, the survey included only 58 carriers of the bacteria (Blakebrough et al., 1982).

There are few studies on pneumococcal carriage in the Meningitis belt and the carriage prevalence is generally high in the African continent, particularly in young children. Asymptomatic carriage is estimated to be 63% among <5-year-old children and 22% among ≥ 5 -year-old persons in a study including both rural and urban areas in Burkina-Faso (2007-09) (Mueller et al. 2012), and 72% in rural areas in rural Gambia (Hill et al., 2006). In a recent (2013) systematic review of pneumococcal carriage in sub-Saharan Africa, pneumococcal carriage was neither associated with season nor with gender but higher rates were reported among children from rural areas compared to those in urban areas (Usuf et al., 2014). High prevalence ($>0.85\%$) was recorded in children in countries of the meningitis belt such as Ethiopia and the Gambia. The systematic review included 57 studies: 23 from southern Africa, 20 from West Africa with more than half of these from The Gambia, and 2 from East and Central Africa. The prevalence of pneumococcal carriage varied considerably between studies (Heterogeneity index of 99%)(Usuf et al., 2014).

Immunity

Following colonization or invasive disease, individuals can develop natural immunity. A study of immunity to the meningococcus among new military recruit in the USA (1969) measuring the level of bactericidal activity in participants' serum showed that participants who had a serum bactericidal activity, or SBA titer with human complement ≥ 4 were less likely to develop meningitis than those who did not (Goldschneider et al., 1969; Goldschneider et al., 1969). This is held a surrogate for protection against serogroup C meningococcal Infection (Borrow & Miller, 2006; Frasch et al., 2009). Contrastingly, a correlate of protection against the serogroup A is not established yet (Borrow & Miller, 2006). Given the lack of correlate of protection and the high baseline serum bactericidal antibody (SBA) titers, serogroup A meningococcal vaccines were licensed based on the demonstration of a 4-fold increase in rabbit complement (rSBA) after immunization (Sow et al., 2011), Licensure of serogroup C conjugate vaccines

were based on the demonstration of a rSBA titers ≥ 8 (Andrews et al., 2003).

Meningococcal carriage can promote bactericidal activity, and repeated carriage episodes can confer some protection against future carriage and disease (Stephens et al., 2007; Pollard & Frasch, 2001), including some cross-strain immunity (Goldschneider et al., 1969; Borrow & Miller, 2006). This could in part explain the increasing antibody seroprevalence as one gets older. Carriage of unencapsulated and non-pathogenic bacterial species such as *Neisseria lactamica* may provide natural protection to some extent against asymptomatic carriage and invasive disease. This natural protection can result from the production of cross-reacting antibodies against *N. meningitidis* (Pollard & Frasch, 2001; Gold et al., 1978; Evans et al., 2011). However, there is limited evidence from studies conducted in the meningitis belt supporting the hypothesis of cross-protection from *N. lactamica* carriage against other pathogenic species (Trotter & Greenwood, 2007a; Blakebrough et al., 1982; Kristiansen et al., 2012). The spatial and temporal variation observed in carriage of *N. meningitidis* did not appear to depend on that of *N. lactamica* which showed no consistent spatial and temporal variation in the large carriage study by Kristiansen et al (Kristiansen et al., 2012). Immunity can also be acquired through vaccination. Vaccine induced immunity is reviewed in the “treatments and vaccinations” section of this chapter.

Clinical course of the infection

In most cases, successful transmission of the bacteria to a susceptible host is limited to colonization and asymptomatic carriage. Occasionally the bacteria can pass through the mucosal tissue, allowing it to invade the bloodstream (Stollenwerk et al., 2004). This usually, but not always, takes place within two weeks of acquisition of carriage (Yazdankhah, 2004; Tzeng & Stephens, 2000; Stephens, 1999; Neal et al., 1999). Whilst invasion of the bacteria into the bloodstream can be transient (Tzeng & Stephens, 2000), it can lead to septicaemia if the bacteria multiply, and shed concentrated amounts of endotoxin. Septicaemia is rare and if the bacteria spread to the cerebrospinal fluid (CSF), the result is acute meningitis, the inflammation of the meninges, the membranes that surround the brain and the spinal cord. There is some evidence that the bacteria could also

directly invade the meninges without passing through the bloodstream (Sjölinder & Jonsson, 2010). Using an intranasal challenged mouse disease model, a study showed that twenty percent of the mice developed lethal meningitis even though no bacteria could be detected in blood, suggesting that *N. meningitidis* is able to pass directly from nasopharynx to meninges through the olfactory nerve system (Sjölinder & Jonsson, 2010). Patients may present with both acute meningitis and septicaemia (Stollenwerk et al., 2004) . Acute meningitis seems to be common than septicaemia in the sub-Saharan Africa compared to industrialized countries.

Clinical symptoms of acute bacterial meningitis can appear quickly or over several days. Typically they develop within 3 to 7 days after exposure (Center for Disease Control and Prevention (CDC) n.d.). In new-borns and babies, the classic meningitis symptoms of fever, headache, and neck stiffness may not be present or obvious. The baby may appear to be irritable, vomiting, feeding poorly, or inactive. In the absence of quick diagnostic and adequate treatment, acute meningitis can lead to serious symptoms (e.g. seizures, coma). Individuals who develop meningitis are often bound to bed and may recover from disease or die within a few hours of the first symptoms appearing (Maiden & Caugant, 2006). This likely reduces the contribution of severe cases of acute meningitis to dissemination of the bacteria.

Diagnostic and surveillance of bacterial meningitis

Diagnosis

The first step in the diagnosis of bacterial meningitis is the recognition of its clinical signs or symptoms, including acute onset of fever (Usually > 38.5 °C rectal or 38.0 °C axillary) headache and one of the following signs: stiff neck, altered consciousness and other meningeal signs (Vaccine Assessment and Monitoring Team 2003). If meningitis is suspected, samples of blood or cerebrospinal fluid (CSF) are collected and sent to the laboratory for testing. The diagnosis is then confirmed by the presence in the CSF or blood samples, of one of the common known causes of bacterial meningitis: *Haemophilus influenzae* b (Hib), *N. meningitidis*, or *S. pneumoniae*.

The WHO defines and classified bacterial meningitis cases as follows:

- **Suspected:** Any person with sudden onset of fever (> 38.5 °C rectal or 38.0 °C axillary), headache and one of the following signs: stiff neck, altered consciousness and other meningeal signs.
- **Probable:** A suspected case with CSF examination showing at least one of the following: turbid appearance; leukocytosis (>100 cells/mm³); leukocytosis ($10 - 100$ cells/mm³) with either an elevated protein (>100 mg/dl) or decreased glucose (<40 mg/dl).
- **Confirmed:** A case that is laboratory-confirmed by growing and identifying a bacterial pathogen (meningococcus, pneumococcus or *H. influenzae*) in the CSF or from the blood in a child with clinical syndrome consistent with bacterial meningitis. Identification of the bacteria is made through Gram stain, antigen detection methods (latex agglutination, co-agglutination, enzyme-linked immunosorbent assay (ELISA), or Polymerase Chain Reaction (PCR).

Surveillance

Surveillance of bacterial meningitis and the laboratory confirmation of suspected cases, is important for detecting the early signals of epidemics and formulating an appropriate response, as well as for evaluating vaccination impact. In countries of the meningitis belt, suspected cases of bacterial meningitis are systematically notified from the peripheral level (local health centres) to the intermediate (district) and central (national) levels since the establishment of an enhanced meningitis surveillance network in 2003 across the meningitis belt with the support of the WHO. Suspected and probable cases are notified from the local health centres on a weekly basis and must be reported even when there is zero case at all levels. In epidemic context, the positive and negative predictive values of clinical signs and the visual appearance of CSF increases, thus, facilitating the diagnosis of bacterial meningitis in the absence of microscopic examination of CSF (especially at the peripheral level where adequate laboratory facilities for case confirmation often lack).

With WHO's enhanced surveillance network in place, alert and epidemic thresholds are defined at the district or subdistrict level to monitor the disease

incidence. Alert threshold was defined as an attack rate of 5 suspected cases per 100 000 inhabitants per week in a district or subdistrict (in populations $\geq 30\ 000$); or as 2 cases in 1 week, or a higher incidence than in a non-epidemic year (in populations $< 30\ 000$)(Anon n.d.). Crossing this threshold triggers the reinforcement of surveillance. Epidemic threshold was defined as an attack rate of 15 suspected cases per 100 000 inhabitants in 1 week in a district or subdistrict, or 10 per 100 000 if considered at high risk of an epidemic (in populations $\geq 30\ 000$); or as 5 cases in 1 week or a doubling of incidence in a 3-week period (in populations $< 30\ 000$)(World Health Organisation 2000). Crossing this threshold triggers the launch of vaccination campaigns when the predominance of *N. meningitidis* is confirmed and the use of a specific antibiotic treatment protocol.

Given the severity of meningitis, one can assume that most meningitis patients will likely seek care, but some patients might not do so for various reasons (including accessibility to health care). Thus, meningitis routine surveillance potentially underestimates true disease incidence. In epidemic context, however, the influx of patients is often higher.

Risk factors for meningitis and its epidemiology

Several decades after the first description of meningitis epidemics in sub-Saharan Africa and the meningitis belt(Greenwood 2006; Lapeyssonnie 1963), the complex epidemiology of the disease remains in part unexplained. In particular risk factors for the disease and cycles of hyperendemicity and epidemics. This section will review some of the factors that have been suggested to influence disease and outbreaks occurrence in the meningitis belt and the main hypotheses for its seasonality. The epidemiology of bacterial meningitis in the meningitis belt results from a complex interplay between Individual and population risk factors, factors related to the bacteria, and environmental – climatic factors.

Individual and population risk factors

Age is likely a risk factor for invasive meningitis with an increasing risk among young children < 15 years old and a decreasing risk from adulthood. Disease becomes rare after 30 years (Campagne et al., 1999; Maïnassara et al., 2014). In epidemic context, age-groups most affected by invasive meningitis include older

children, adolescents and young adults in addition to younger children(Moore, 1992a; Peltola et al., 1982). During inter-epidemic years, most cases are in the <5 years old age group.

Host immunity also plays a critical and obvious role in the development of invasive meningitis. Natural and vaccine acquired immunity would both play an important role in the course of meningitis infection. The role of humoral immunity in preventing invasive meningitis was well described by Goldschneider et al. in their seminal work entitled “Human immunity to the meningococcus“(Goldschneider et al., 1969; Goldschneider et al., 1969) and published in 1969. An inverse relation between serum bactericidal antibody titer and the risk of invasive meningitis was demonstrated, however there is no known correlate of protection for meningococcal serogroups causing epidemics (e.g. N.mA) in the meningitis belt (Trotter et al., 2013). Mucosal immunity which can be defined as the presence of bactericidal antibody in nasopharyngeal secretions may limit or prevent colonization and invasion of the bacteria(Pollard & Frasch, 2001).

Individuals with underlying immune defects such as asplenia or hyposplenic function are at increased risk of acquiring invasive meningitis because once meningococci enter the bloodstream, the spleen is important for clearance of the bacteria(Condon et al., 1994). Also because complement proteins play a central role in host immune defences against invasive disease, individuals with underlying deficiencies of some of the complement proteins or components such as properdin C3 or C5 through C9 respectively are at increased risk of invasive meningitis(Linton & Morgan, 1999). Host genetic factors likely influence susceptibility to disease through immunity and the lack of expression of some genes modulating the host immune response against the bacteria.

At a population level, lack of herd immunity, accumulation of unexposed individuals (e.g. through migrations) or unvaccinated birth cohort would determine susceptibility for epidemics. Waning immunity after a relatively short period in exposed groups (e.g. following epidemics or vaccination) further contribute to recurrent epidemics susceptibility (Moore, 1992)(Greenwood ,1999).

Respiratory viral co-infections such as flu-like diseases may facilitate both the bacteria transmission and invasion(Moore, 1992; Moore et al., 1990; Mutonga et al., 2009). Facilitation of transmission of the meningococcus or the pneumococcus can be through coughing and sneezing (Mueller et al., 2008;

Raghunathan et al., 2006). Viral co-infection can cause alterations in the mucosal surface that enhance bacterial binding or decrease the ability of the host to clear the organism from the nasopharynx, thus, facilitating invasion (Moore, 1992; Mueller & Gessner, 2010; Alonso & Taha, 2003). Studies have shown a temporal relationship between epidemics of acute respiratory viral-infections such as flu and bacterial meningitis outbreaks (Cartwright et al., 1991; Harrison et al., 1991; Hubert et al., 1992)

Some social behaviour such as cigarette smoking, prolonged exposure to indoor firewood stoves, and social gathering have also been associated with increased rates of meningococcal carriage and disease (Tanko et al., 2013).

Socioeconomic and demographic factors

Bacterial meningitis and its epidemiology are somewhat influenced by the socio-economic and demographic factors. Several studies conducted in developed countries suggested that meningococcal disease has a direct relationship with poor housing condition, smoking, and household overcrowding (Baker et al., 2000; Fone et al., 2003; Olowokure et al., 2006). However, socio-economic factors, overcrowding, smoking and passive exposure to tobacco smoke were not found to be risk factors for meningitis in a study in Ghana (Hodgson et al., 2001).

Travel and migration could facilitate the circulation of virulent strains inside a country or from country to country. The gathering of susceptible individuals is a relevant risk factor for epidemics. Many outbreaks have occurred, among new military recruits. Large movements and mixing of population, such as brought by pilgrimage, play an important role in the spread of infectious disease. The outbreaks which occurred following the end of pilgrimage in Mecca in 1987, and 2000 respectively, caused more cases among pilgrims than among the general population of Saudi Arabia (Wilder-Smith et al., 2003).

Returning pilgrims have also been suspected to have introduced virulent strain of meningococcus serogroup A in their communities triggering the epidemics observed in Chad in 1988, or Sudan in 1988. Other population displacements such as those of refugees, also pose epidemic risks (Santaniello-Newton & Hunter, 2000).

Meningitis cases are more recurrent in urban districts probably due to high contact rates but proximity to main roads are also thought as a risk factor for the disease (Bharti et al., 2012). Studies conducted in the sub-Saharan Africa showed that school attendance, sharing a meal with many people at a time (which is often the case among siblings of the same household) or having a recent case of meningitis in the household increase the risk of carriage acquisition (Raghunathan et al., 2006; Mueller et al., 2008). In many rural areas of sub-Saharan Africa, kitchens with firewood stoves are used for cooking. Exposure to smokes from firewood stoves was found as a risk factor of invasive meningitis in two studies from Ghana and Kenya (Mutonga et al., 2009; Hodgson et al., 2001), and so does sharing a bedroom with a meningitis case.

Climatic and geographical factors.

The climate in the meningitis belt is characterised by a distinct rainy and dry season during the year. The typical dry season is from December to May. During the dry season, absolute humidity is often very low, and a cold, dry and dusty north-easterly wind locally termed 'Harmattan', blows particles and dust from the Sahara desert over the West African subcontinent into the meningitis belt between December and the middle of March (Anon, n.d.). The air is particularly dry and desiccating. It contains fine dust and sand particles. Temperatures are as low as 9 °C but can reach as high as 30°C, and relative humidity less than 10%. These weather conditions cause irritation to the nasopharyngeal mucosa, and chapped lips (Besancenot et al., 1997).

A characteristic feature of bacterial meningitis seen in the meningitis belt is the way in which the disease incidence always increase in the middle of the dry season, rapidly built up to a peak at the end of the dry season and then subsided abruptly with the coming of the rains, only to start again in the dry season of the following year (Lapeyssonnie, 1963; Greenwood, 1999). This pattern has persisted with almost no exceptions but there is still no clear explanation for this remarkable seasonality. Due to the coincidence of the dry season with increased incidence, several studies have attempted to analyse the link between the climate and meningitis. Rainfall is suggested as one of the many risk factors of meningitis outbreaks. Lapeyssonnie observed in 1963 that epidemics largely occurred in a

semi-arid zone south from the Sahara, with 300–1,100 mm mean annual rainfall(Lapeyssonnie, 1963). Jackoub-Boulama et al. showed an inverse relation between rainfall and meningitis incidence in Niger (Jackou-Boulama et al., 2005). Another study conducted in Mali showed that maximum wind speed in the dry season was correlated with the time of the onset of epidemics, but not with the sizes of epidemics (Sultan et al., 2005). Other studies have shown annual meningitis incidence being associated with early season rainfall and dust levels (Thomson et al., 2006), and with low humidity and wind speed (Besancenot et al., 1997), but associations were weak. A study by Yaka et al. manage to explain 25% of the variability in each year's incidence of meningitis in Niger using a multivariate linear model that incorporate a set of climatic variables such as relative humidity, surface temperature, wind speed etc. However the same model failed to predict data from Burkina Faso (Yaka et al., 2008). Martiny et al. showed in a study of the impact of mineral dust on meningitis in Niger and Mali, that each meningitis annual peak is preceded by a dust peak, with a 0 to 2 week lead-time during the most dusty period of the season (February to April)(Martiny & Chiapello, 2013). A similar lead-time (1.56 weeks) was highlighted by Agier et al., between aerosols load and meningitis incidence at the district level in Niger(Agieret al., 2013). Moreover, the 0-2-week lead-time appears to coincide with the incubation period of meningitis which usually varies between 1 and 14 days (Stephens et al., 2007). Humidity, rainfall, wind speed, temperature, and atmospheric dust were all associated to some degrees to bacterial meningitis incidence in various studies. The sometimes weak association between some of these climatic variables and disease incidence emphasis the potential implication of other risk factors (Yaka et al., 2008) such as population immunity as previously described.

It is well accepted that meningitis dynamic is related to the temporal dynamic of the meningitis belt climate, but the mechanisms through which fluctuation in climatic variables would impact the disease at both individual and population level remain unexplained and hypothetical.

Hypotheses and hypothetical model

Various hypotheses have been formulated to explain the potential mechanisms underlying the meningitis belt phenomenon. Some authors postulated that the peculiar weather conditions of the dry season including the very low humidity, dry and dusty air cause irritation and weaken the nasopharyngeal mucosa membrane (Besancenot et al., 1997), thus increasing the risk of invasion of the bacteria among colonized individuals (Moore, 1992; Greenwood et al., 1985). This hypothesis seems biologically plausible but has not been proved yet. If the hypothesis is true, the seasonality observed in the incidence of cases of bacterial meningitis reflects a change in the ratio of cases of disease to nasopharyngeal carriers, normally in the range of 1–100, rather than a change in the overall incidence of infection (Greenwood et al., 1985).

Alternatively, the climate of the dry season could affect transmission or carriage acquisition directly or indirectly through biological mechanisms or change in population behaviour. First, effective transmission of bacteria from respiratory droplets released in the air could possibly be facilitated by the low humidity (Ghipponi et al., 1971). Second, transmission of the bacteria could be facilitated by high contact rate between individuals during the dry season; for example, through frequent social gatherings, seasonal migrations due to the climate reducing farming activities in the dry season, or cold temperature in the night favouring overcrowding in poorly ventilated housings (Greenwood, 1999; Waddy, 1952). However, there is little or no evidence for a seasonal change in carriage prevalence (Trotter & Greenwood, 2007b), suggesting that the climate of the dry season may facilitate invasion of the bacteria more than its transmission (Blakebrough et al., 1982; Greenwood, 1999).

Mueller and Gessner presented a "hypothetical explanatory model", for the observed epidemiology of meningococcal meningitis in the meningitis belt, incorporating spatial factors. They described four incidence states: a low endemic incidence during the rainy season, an ubiquitous hyper-endemicity during the dry season, on top of which occasional and geographically restricted epidemics are observed (localised epidemics) and epidemic waves spanning several years at the country level depending on the frequency and sizes of localised epidemics (Mueller & Gessner, 2010).

The authors suggested that the transition from endemic to the hyper-endemic incidence (seasonality) reflects changes in the ratio of clinical to subclinical cases of infection due to an increased risk of invasion facilitated by climatic conditions irritating the pharyngeal mucosa as postulated by other authors (Moore, 1992; Greenwood et al., 1985). They further proposed that this transition would involve a 10 to 100-folds increased risk of invasion among colonized individuals between the wet and dry season. At the community level, the transition from hyper-endemic to epidemic incidence would involve a 10 to 100-folds increased transmission or colonisation of the bacteria possibly facilitated by co-occurrence of viral respiratory infection epidemics in the dry season such as influenza (which are themselves likely related to climate). Other authors hypothesise that seasonal physiological changes in host susceptibility, possibly driven by changes in photoperiod, could explain the seasonality of the disease (Dowell et al., 2003). Finally, epidemic waves are observed at the regional or country level, if more and more communities experience long lasting epidemics in time and space, or if a new virulent strain of the bacteria emerges, thus escaping pre-existing immunity.

In summary, these hypotheses and hypothetical explanatory model need formal evaluation and validation using sound methods and appropriate epidemiological data from the meningitis belt. Their confirmation would improve our understanding of some of the mechanisms underlying the effect of the climate on meningitis seasonality and epidemic occurrence in the meningitis belt.

Meta-analysis and systematic review of existing incidence and carriage data as well as transmission models of bacterial meningitis parameterized using appropriate data from the meningitis belt can be useful in assessing these hypotheses.

Systematic Reviews and Meta-analysis: An overview

Background

This chapter provides an overview of systematic reviews and meta-analyses as an objective research methodology that provides a transparent assessment and overview of “all” evidence surrounding a particular question. We review the key steps involved in a typical systematic review and meta-analysis and discuss the strengths and limitations of this approach.

Systematic reviews and meta-analysis are actively conducted in various fields, with the aim to summarize the body of knowledge on a particular question, and to provide a bigger picture on existing evidence rather than just one piece of isolated research. Meta-analysis is often performed as part of a systematic reviews and provides a quantitative synthesis of primary data or estimates from primary research studies whenever possible based on well-defined statistical methodology for combining or pooling results of these studies.

Because the summary estimates obtained from a meta-analysis are computed from the results of different studies which attempted to answer the same question, it's considered more reliable than the results of isolated studies. This holds true provided that the individual studies whose results are pooled together have good internal validity (a sound methodology) and are relevant to the research question being explored.

Systematic reviews and meta-analyses have been traditionally used in the clinical field to summarize evidence on effects of interventions or treatments of specific health conditions and help clinicians and policy makers make informed decisions or recommendations based on the evidence available from the larger body of existing literature assessing a particular intervention, sometimes with conflicting results. There is a general consensus that there is a hierarchy of evidence such that some research evidences are stronger than other in addressing various types of questions. One of the well-known hierarchies of evidence is that proposed by Sackett et al (Sackett et al. 1996), which ranks the strength of

evidence in relation to the effectiveness of an intervention or a treatment. Systematic reviews and meta-analyses are placed higher up in this hierarchy of evidence followed by randomized controlled studies, and observational studies including cohort studies, case-control studies, and cross-sectional surveys. Cases reports, qualitative studies and experts' opinions respectively are at the bottom of this hierarchy of evidence.

Traditionally, the Cochrane collaboration has put a great emphasis on the importance of randomized controlled studies (RCTs) and their inclusion in systematic reviews and meta-analyses. This emphasis on RCTs is primarily due to the nature of research questions the Cochrane collaboration primarily sought to address: i.e. questions about effectiveness of interventions and treatments. However, depending on the research question being addressed, randomization of intervention is sometimes not possible for different reasons, and study designs other than RCTs, such as cohorts, case-control, cross-sectional and others studies are adopted. For this reason, observational studies results are also increasingly included into systematic reviews and meta-analyses of primary research. It is widely recognized that systematic reviews should seek to include the type of research that are most likely to address the research question of interest.

To ensure objective, systematic, and transparent assessment of the existing literature and provide a high level of evidence and minimize potential for bias in the review process, systematic reviews and meta-analyses must be documented in a protocol prior to knowledge of the available studies. The protocol documents the research question and objective and the methodology for retrieving and selecting relevant studies and primary data, for abstracting, synthesizing and combining results from the selected studies, as well as assessing the internal and external validity of included studies. As such, systematic reviews are considered original empirical research.

Guidelines have been developed to help assess and document reviews and meta-analysis of primary research. Well-known guidelines include the "Cochrane Handbook for Systematic Reviews of Interventions"(Higgins and Green 2011) and the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" statements (Liberati et al. 2009; Stewart et al. 2015). These guidelines focused on the review of randomized controlled studies but can also apply to reviews of other study design. Specific guidelines for assessment and

reporting of systematic review and meta-analyses of observational studies have also been proposed including the “MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies” (Stroup et al. 2000), and the Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses”(Wells et al. 2019) though these guidelines may not be as widely adopted as the Cochrane guidelines and PRISMA statements. There is no official consensus on how systematic review and meta-analysis of observational studies should be done, many recommendations from the aforementioned guidelines for the review and meta-analysis of observational studies were adapted from reviews of randomized controlled controls studies (Mueller et al. 2018). Here we summarize approach and methodology involved in a typical systematic review and meta-analysis of primary research and data.

Defining the research question and objective

Beginning with a well-defined research question and objective is the first step in conducting a systematic review and meta-analysis and is as important as in any other research project. This sets the scope of the review and guides subsequent decisions about which studies to target and methods to be used to answer the particular research question. A clear statement of the question and objective ensure that only studies addressing that particular question are targeted. A well-defined systematic review objective often states: 1) what is being assessed (this could be a treatment, a particular intervention, or epidemiological parameter), 2) the outcome of interest (this could a disease or any other outcome measure), 3) the population of interest (i.e. the population in which the intervention, treatment or epidemiological parameter is assessed). For systematic reviews of interventions or treatments, it is also recommended to clearly state the comparator of the intervention or treatment being assessed (if any). Hence, the Population, Intervention, Comparison, Outcomes (PICO) represents a general and widely used framework on which systematic reviews research questions are formulated to facilitated literature review (Ahn and Kang 2018; Higgins and Green 2011). Other models for framing a review question have also been proposed, including: the Sample, Phenomenon of interest, Design, Evaluation, Research type

(SPIDER) model for review of qualitative and mixed methods research studies (Cooke, Smith, and Booth 2012), and the Setting, Perspective, Intervention, Comparison, Evaluation (SPICER) model adapted for the field of laboratory medicine (Oosterhuis et al. 2004).

Studies identification

After defining the systematic review question and objective, the next step in the systematic review process is to define the sets of criteria for inclusion and exclusion of studies from the review and meta-analysis. The main rationale for defining inclusion and exclusion criteria is to limit the scope of the search and focus the literature search to studies that fit the needs of the review. These criteria must articulate the type of study (study designs), the population involved in the research (key participants characteristics), the interventions (if any) and outcome measures. Additional criteria may include, publications language of the studies, time period of the research or publication period, geographical scope of the studies and any other criterion as long as they are justified and motivated.

With the inclusion and exclusion criteria defined, a search strategy must be defined and document the systematic approach to searching and retrieving relevant studies for the systematic review. The search strategy generally combines electronic publications databases search, hand-searching key journals and reference lists of relevant publications as well as searching the “grey literature” (e.g., conference abstracts, preprints or theses) and contacting experts or known research groups in the field and publication authors to identify any published or unpublished study or data which may be relevant. For electronic databases searches, a comprehensive list of keywords and search terms related to each component of the pre-defined inclusion criteria is defined. At this stage it is important to not only define text words, but also determine synonyms of the text words, control for different spelling or using appropriate truncations, and to identify controlled vocabulary or terms used for indexing publications in the electronic databases. These keywords are used to design search equations for retrieving studies in the publication databases. The search equations generally combine the defined keywords with logical operators “AND”, “OR” and “NOT” and the reviewers must decide whether to perform a “focused” or “exploded”

search. Test searches may be conducted to adjust the strategy. The key is to come up with an optimal search equations and strategy which balance sensitivity (i.e. retrieving a high volume of potentially relevant studies in the first place) with specificity (i.e. retrieving a relatively low and manageable proportion of potentially relevant studies). Finding a good balance between sensitivity and specificity is critical for retrieving most relevant studies, but although preferred, sensitivity may be limited the resources available to conduct the systematic review (e.g. time, and/or human resources). The search strategy should be customized to the different publication databases targeted as these databases may have different approaches to usage of wildcards, search terms truncations, the fields to search and their controlled vocabulary for indexing publications. All relevant publication databases, including regional medicus index must be identified and searched if possible to ensure a systematic retrieval of relevant studies. Depending on the research question being investigated, typical databases to search may include: general databases such as PUBMED, MEDLINE, EMBASE, and specialized databases such as CINAHL, the Cochrane controlled register of trials (CENTRAL), clinicaltrials.gov, and other databases indexing regional or national studies.

Studies selection

All studies retrieved though the systematic search strategy typically go through a first screening based on their titles and abstract to decide whether or not each retrieved study is within the scope of the review and should be considered for a full text screening. Duplicates publications are also identified at this screening stage. Studies that pass the initial title and abstract screening are further scrutinized with regard to the pre-defined inclusion and exclusion criteria which may lead to either their definite inclusion or exclusion from the systematic review and/or meta-analysis. The Cochrane standards for systematic reviews, recommends that studies screening be conducted independently by two reviewers and any conflict resulting from the exclusion or inclusion of studies retrieved from the initial search be resolved and the final decision of inclusion or exclusion be motivated and agreed by the two reviewers. When information on a key inclusion or exclusion criteria is unclear or missing, it is good practice to attempt to obtain

the missing information from the study authors whenever possible. Reviewers should record and report reasons for exclusion to enhance transparency of the study selection process. This is often summarized in a flow chart of study selection.

Data extraction

For studies considered eligible for the systematic review, data is extracted using standardized data extraction forms developed for the purpose of the specific review. The data extraction form is pilot tested on a few studies and adjusted before being used on all studies to ensure their capture all information required to answer the review question. Information extracted may include but are not limited to:

- **Study characteristics** such as first author, year(s) of conduct, publication year, location (country involved), funding source (public, private, no funding, or unreported), monocentric or multicenter study and number of centres involved, total number of participants enrolled/randomized, number of participants per study groups if applicable, recruitments period, start and end-date, duration of follow-up, study design etc...
- **Participants characteristics** such as number included/randomized per groups if applicable, demographic characteristics (average or median age, gender etc..), relevant clinical characteristics (e.g. underlying comorbidities), diagnostic criteria, etc...
- **Intervention(s)** including the main intervention (s) evaluated, relevant concurrent- or co-interventions or comparison group intervention if applicable, timing and schedule of interventions (for repeated intervention) and other information which might be relevant to describe and account for about the intervention(s) evaluated.
- **Outcomes measures** including primary and secondary outcomes of interest, their definitions, time points collected or reported and unit of measurement if relevant. Summary data for each studied group are also extracted and the type of summary data extracted depends on whether the outcome is continuous or dichotomous (e.g. Mean and standard deviation

for continuous outcomes, and number of events of interest observed in each studied group for dichotomous outcomes).

- **Information for assessing the risk of bias from each study**

- *For randomized controlled trials*, these include information on how intervention allocation sequence was generated, allocation concealment, blinding of patients, blinding of care providers and outcome assessors, complete outcome data reporting (including both intention to treat and missing data), selective reporting of outcomes. These are standard items are part of the Cochrane tool for assessing risk of bias in randomized clinical trials (Higgins and Green 2011)
- *For observational studies*, extracted information may include any indication for selection bias, attrition bias (i.e. overall or differential nonresponse, dropout, loss to follow-up, or appropriate handling of participants exclusion), performance bias (i.e. impact from a concurrent intervention or an unintended exposure on results ruled out by authors), detection bias, and reporting bias.

This extracted information from each study further support judgement for the level of risk of bias of each study included in the systematic review.

Data extraction for observational studies may appear more challenging than for controlled trials as multiple analyses is often performed and different observational design will have different type of data to extract.

Data extraction is usually conducted by two reviewers independently for consistency and to reduce data extraction errors. The data extraction form with extracted data represents a documented record from which study results can be synthesized and can serve as a basis for future update of the review and meta-analysis when more studies become available.

Synthesis of individual study results

This step often consists of preparing the extracted data for meta-analysis or simple descriptive analysis. The outcomes data may have been reported in various format across the included studies and it is often useful to convert them into a format suitable for the meta-analysis. This conversion often involves recalculation of the outcome measures whenever possible across all included studies. For studies

reporting continuous outcomes, data sought during extraction often include number of participants, mean and standard deviation of outcome for each study groups of interest, but these statistics might not be directly reported in the desired form in the studies. However, they can be calculated from alternative statistics (e.g. the standard deviation may be estimated from the standard error, confidence interval, or test statistics reported). Similarly, for dichotomous outcomes, outcome measures can be recalculated from the number of participants who experienced the outcome of interest and the number of participant in each study groups. When this information is not readily available, but effect estimates such as the relative risk (RR), odd ratio (OR) or risk ratio (RiR) are reported, these estimates may be included in the meta-analysis as long as their measure of uncertainty is also reported (i.e. standard error, or 95% confidence interval, or p-value)(Higgins and Green 2011). Approaches to extracting and preparing different types of outcomes including: counts, time-to-event, ordinal, continuous, or dichotomous outcomes are well documented in the Cochrane handbook for systematic reviews of interventions (Higgins and Green 2011).

Assessment of risk of bias

The quality and strength of recommendations from a meta-analysis results depends on the quality of evidence generated by the studies included in the analysis. Therefore, evaluation of the quality of evidence of each study included in a systematic review and meta-analysis is critical. The quality of evidence is assessed based on the study methodology and aims to identify limitations, and risk of bias that may affect the internal and external validity of studies selected for inclusion in the meta-analysis. For randomized studies, the Cochrane tool for assessing risk of bias is the standard (Higgins and Green 2011). For non-randomized studies of interventions, the ROBINS-I tool is developed (Sterne et al. 2016).

Several tools for accessing the quality of observational studies have been proposed including the Newcastle-Ottawa Scale (NOS) (Wells et al. 2019), the Downs and Black scale (Downs and Black 1998) or the ROBINS-E (Morgan et al. 2017). However, studies have questioned the reliability of these scales (O'Connor et al. 2015; Bero et al. 2018; Stang 2010). At the time of writing there is no

known official tool for assessing the risk of bias in observational studies that do not compare interventions. Most of the tools used to assess risk of bias in observational studies to date are developed from items of the Cochrane tools for assessing risk of bias in randomized and non-randomized studies of interventions.

Standard risk of bias assessment tools aims at consistent evaluation of the potential bias in all the included studies (i.e. the risk of over- or underestimating the true value of the estimate or effect size of interest). Entries of the risk of bias assessment tools aims to assess selection bias, performance bias, attrition bias, detection bias, information bias, reporting bias and other bias that do not fit into these categories (Higgins and Green 2011).

Specific features of the studies are assessed and a judgment is made for each entry of the assessment tool about the risk of bias on study results. The risk of bias is categories into one of low risk, high risk, or unclear risk based on information reported in the study publication or obtained from the study authors about the entry. Unclear risk of bias is reported when there is uncertainty over the potential for bias or lack of information to make a judgment on the risk of bias for an entry of the assessment tool.

The higher proportion of studies are at high risk of bias in a systematic review and meta-analysis the cautious the analysis and interpretation of their results should be and the lower the level of evidence provided by the meta-analysis (Higgins and Green 2011).

The result of risk of bias assessment can be incorporated into meta-analyses, for example by restricting analysis to studies with low risk of bias (primary analysis), or stratifying the meta-analysis by low, high and unclear risk of bias if possible. All studies results may be pooled with or without studies with high-risk of bias. This provides a sensitivity analysis on how conclusion of the meta-analysis might be affected by when studies of high-risk of bias are considered. Risk of bias assessment results can be incorporated in meta-regression to quantify the magnitude of the impact of bias on the results of meta-analysis.

Exploring sources of heterogeneity

Heterogeneity refers to differences between studies results, and it is important to identify the source of these heterogeneities in study results when the difference in

study results is greater than would be expected by chance alone. Important heterogeneities between studies results may result from differences in characteristics of participants of the included studies, interventions, or methodological differences between studies included in the review etc... Hence exploring the sources of heterogeneities between studies is to attempt to identify study-level characteristics that are associated with observed variations in the included studies results. Subgroups analysis and meta-regression are two common methods for exploring source of heterogeneity between studies included in a systematic review and meta-analysis (Ahn and Kang 2018; Higgins and Green 2011).

Meta-analysis of study results

Meta-analysis involves using statistical methods to combine or pool the data or results from several studies investigating the same research question into a single estimate or summary effect size (Uman 2011; Higgins and Green 2011). This analysis often involves estimation of a weighted average of all studies eligible for inclusion in the meta-analysis. Commonly pooled study estimates include, RR, OR, RiR (risk ratios), rate ratios, standardized/or weighed mean difference (SMD) (Uman 2011; Higgins and Green 2011). Studies included in a meta-analysis should ideally be similar in terms of patient characteristics, interventions, and study characteristics to produce a reliable overall estimate. However, studies included in a systematic review will generally vary to some degree with respect to populations, design, and risk of bias. If studies eligible for inclusion in the systematic review reveals important heterogeneity in their characteristics and/ or results and significant risk of bias, a meta-analysis may become irrelevant and the results of the individual studies are rather presented and discussed together with their limitations without considering their pooled analysis.

When a meta-analysis is performed, it's results are presented using a forest plot displaying the effect size estimated for individual studies together with their confidence intervals, and the pooled estimate of all the studies and its uncertainty (confidence interval). Additional information such as the Cochrane Q test, or the Higgins I-squared (I^2) statistics are also computed and displayed on the forest plot, to test for statistical heterogeneity of studies results.

Statistical heterogeneity between studies results are revealed by the forest plot, the Cochran's Q chi-squared (χ^2) test for heterogeneity, and the I^2 statistics. The Q test assess whether observed difference between included studies results are likely to chance alone, while the I^2 quantify the amount of variations between included studies that are not attributable to chance (Dekkers et al. 2019). A visual inspection of the forest plot showing important overlap between the confidence intervals of the point estimate of each study included in a meta-analysis indicates low statistical heterogeneity and may advocate for considering pooled estimate. Similarly, when the p-value of the Cochran Q test is greater than 0.1, or the I^2 statistic (estimated as $I^2 = 100\% \times (Q - df)/Q$, where Q is the chi-square statistic and df, the degree of freedom of the Q statistic) is less than 25%, statistical heterogeneity is considered low (Ahn and Kang 2018; Higgins and Green 2011)

However, considerations for or against pooling the study results should also account for risk of bias, methodological and clinical heterogeneity and should not be solely based on statistical measures of heterogeneity (Dekkers et al. 2019). Contrastingly, it is possible to combine results from studies that are considered at low-risk of bias but show some moderate statistical heterogeneity of results using meta-analysis methods accounting for such statistical heterogeneity. The meta-analysis may be performed using a fixed effect or random effects model or both, and subgroup analysis and or meta-regression is performed to explore and explain the source of the statistical heterogeneity.

Fixed effects models

Fixed effect models are simple weighted averages of individual study estimates. They assume that all studies estimate the same underlying quantity or effect size and that any observed difference between the studies estimates is due sampling variations (i.e. random errors). Common methods for combining study results using a fixed effect model include: the inverse variance weighted estimation (used when the meta-analysis include a small number of studies with large sample), the Peto method useful when event rate is low or one of the compared study groups have zero incidence, or the Mantel-Haenszel method used when the number of studies is large but with small sample sizes (Ahn and Kang 2018). In the fixed effect model, results from larger studies are weighted more than results from

smaller studies. This makes fixed-effects meta-analysis more sensitive to the results and potential biases of larger studies.

Random effects models

Random-effects models assume that the underlying true value of the quantity or effect size of interest differ among studies. Hence, they assume heterogeneity between studies being combined (between-study variability in results) that goes beyond random error and can be considered even when statistical heterogeneity is low, but important differences are identified in studies characteristics, methods etc. Common methods for pooling studies results when using a random-effect model include, the DerSimonian and Laird method (mostly used for combining dichotomous outcomes) or the inverse-variance weighted method (used for combining continuous outcomes) (Ahn and Kang 2018). The the Hartung-Knapp-Sidik-Jonkman method is preferred to the DerSimonian and Laird method when the number of studies included in the meta-analysis is small (<10) (Ahn and Kang 2018). When there is important statistical heterogeneity, the pooled estimate from the random- and fixed-effects model often differ because of the different weighting of smaller studies. Furthermore, the uncertainty around the pooled estimate from a random-effects model integrated the between-study variability in addition to the random error, leading to a wider confidence interval than with the fixed effect model (Dekkers et al. 2019). When statistical heterogeneity is very low or absent, the pooled estimate of the fixed-effect and random-effect model are very close, if not identical.

Both fixed-effects and random-effects meta-analysis can be conducted and the results compared and reported as long as this was planned in the systematic review and meta-analysis protocol. In the case of observational studies, the fixed-effect model' assumption that all included studies estimate the same true value of the quantity or effect size of interest is rarely justified and random-effect model might be preferred for combining the results of observational studies in the first place. However, if random-effects models account for between-study heterogeneity they do not provide any explanation of the source of the heterogeneity. As previously stated, the source of heterogeneity is commonly investigated using subgroup analysis and/or meta-regression.

Subgroup-analysis and Meta-regression

The rationale for subgroup analysis is to group data or studies into subgroups that are similar enough for their results to be pooled together. Hence, subgroup analysis is performed based on study categorical characteristics which are suspected to introduce heterogeneity into studies results. Subgroup analysis is therefore an exploratory approach which attempts to identify sources of heterogeneity in studies results and needs to be planned in the systematic review and meta-analysis protocol. Depending on the number of studies available for the meta-analysis, subgroup analysis might not be possible. Alternatively, meta-regression uses standard regression methods to model the studies point estimate or effect size of interest as a function of study characteristics that might influence the estimate of interest (Higgins and Green 2011). Meta-regression is not considered when there are less than 10 studies (Higgins and Green 2011). Both univariate or multivariate regression analysis can be considered.

Publication bias

Publication bias refers to the bias introduced into a meta-analysis results due to the different likelihood of smaller vs larger studies as well as non-significant vs significant study results to be published. Hence smaller studies or those with non-significant results have higher probability of not being published and thus of not being included in the meta-analysis. The presence, absence or degree of publication bias is commonly assessed using a funnel plot. The funnel plot is a graphical tool to assess whether estimates from larger studies differ significantly from estimates of smaller studies (Dekkers et al. 2019; Higgins and Green 2011). It is represented as a scatter plot with study size on the x-axis and sample size or precision on the y-axis. The study estimates are scattered symmetrically around a central value if the observed difference in studies results are only due to random sampling errors. Asymmetry of the funnel plot indicates that there is an association between study size and study estimate, which is commonly referred to as “small-study effect” (Dekkers et al. 2019). Publication bias may be suspected in such case. Other statistical methods to assess publication bias have been reported including the Begg and Mazumdar’s rank correlation test which uses

correlation between the ranks of study estimates or effect sizes and the rank of their variance (Begg and Mazumdar 1994) or Egger's test which test for the degree of asymmetry of the funnel plot as measured by the intercept from the regression line between the precision of the studies and the standardized estimates or effect size (Egger, Schneider, and Davey Smith 1998). When the regression line originates at zero of the y-axis there is no evidence of publication bias and the further away from zero the more evidence of publication bias there is. When there is evidence of publication bias, this can be corrected using the trim and fill method (Duval and Tweedie 2000).

Conclusion

Overall, systematic and meta-analysis is a rigorous and original empirical research methodology to summarize both qualitatively and quantitatively available and sometimes conflicting evidence from primary research. Hence, a carefully designed and conducted systematic review and meta-analysis can provide more reliable and robust evidence than isolated studies would and also provide a bigger picture on a given research question. However meta-analysis may also result in misleading results if not properly conducted or when attempting to pool results from poorly conducted studies or studies with high degree of heterogeneity with respect to the participants, design, interventions and outcome measures.

Infectious diseases seasonality and modelling.

Background

This chapter of the thesis reviews the seasonality of infections focusing on the possible causes and mechanisms of seasonal change in the incidences of human infectious diseases. Common approaches to modelling infectious diseases seasonality are reviewed and a brief overview of research exploring seasonality and recurrence of infectious diseases is provided.

Many infections affecting humans and/or the wildlife, displays seasonal patterns characterized by periodic and recurrent increase in disease incidence during a particular time period. This time period may coincide with seasons (e.g. winter, or summer) or other calendar periods (Fisman 2007). Example of seasonal human infectious diseases of public health relevance include: childhood diseases such as measles, chickenpox, diphtheria, pertussis; vector-borne diseases such as malaria, dengue fever, chikungunya; faeco-oral diseases including cholera; and other diseases including influenza, gastroenteritis, meningitis, and sexually transmitted infections such as gonorrhoea (Grassly & Fraser 2006a). The seasonal timing and window of occurrence of some infections may vary depending on the locations. It may also differ for different diseases within the same location (Martinezid 2018). Some seasonal infections are observed only in certain region, while others occur across regions. For example, influenza outbreaks occur during winter in temperate countries of the northern and southern hemisphere, but the disease seasonality is less defined in tropical regions (Viboud et al. 2006). Malaria outbreaks occur shortly after the rainy season begins in Africa, and South East Asia but the disease is not observed in temperate countries of the northern hemisphere. Furthermore, some diseases have strong seasonality in some regions and no seasonality in others. A typical example of such disease is bacterial meningitis which appears to be endemic with strong annual seasonal pattern only within a region of Africa known as the meningitis belt (Lapeyssonnie 1963;

Molesworth et al. 2002). Seasonality appears to be a common feature of epidemic-prone diseases (Martinezid 2018).

Understanding of the mechanisms responsible for infectious diseases seasonality and its consequences on the diseases epidemiology have been the focus of several researches since decades (Soper 1929; M Fine & Clarkson 1982; Bartlett 1957). This is motivated by the idea that a better understanding of infectious diseases seasonality will result in a better understanding of their optimal control strategies and improve the design of forecasting systems (Grassly & Fraser 2006a). Furthermore, understanding the timing, and causes of seasonality provides opportunity to gain insights into host-pathogen-environment interaction, and how, when and which control strategies should be applied (Altizer et al. 2006a).

Different approaches have been used to gain insight into the seasonality of infectious diseases including time series analyses of surveillance data such as autoregressive (integrated) moving average (ARMA, ARIMA) models, autocorrelation methods, periodograms, complex demodulation, and mathematical transmission models (Hogan et al. 2017; Fisman 2007).

Causes of infectious disease seasonality

The possible causes and drivers of seasonality, and longer periodicity in some infectious diseases incidence have long been explored by epidemiologists and disease ecologists (Altizer et al. 2006a; Fine & Clarkson 1982; Grassly & Fraser 2006a; Pascual & Dobson 2005; Keeling et al. 2001). Measles is one of such diseases which had particularly attracted much attention in the 20th century (Soper 1929; Fine & Clarkson 1982; Heesterbeek 2005). Its severity, high incidence, worldwide spread, the regularity of its clinical course, and the dramatic pattern of its recurring epidemics probably made measles a historical prototype for the study of acute seasonal infection dynamics (Fine & Clarkson 1982).

Arthur Ransome was one of the firsts who attempted to explore in 1880 possible mechanisms that could explain the regular and periodic behavior of measles epidemics and other childhood diseases such as smallpox. He postulated that a

childhood disease must have affected nearly all susceptibles in a given population that it must wait for some time before the pool of susceptibles is sufficient enough again or attains a critical threshold for the epidemic to occur again (Ransome 1880). Based on this postulate, Ransome suggested change in the density of susceptibles as the most likely explanation for periodicity (Ransome 1880). Soper (1929) further focused on analyzing monthly case reports of measles recorded in Glasgow between 1905 and 1916 and noted that the data showed large sustained oscillations while the dynamic predicted by simple models of measles was damped oscillations. He suggested that the basic model must be missing a key component: seasonal change in transmission of measles infections. He argued that one possible cause of this seasonal change in transmission of measles was aggregation of children during school terms. London and Yorke further studied the recurrent outbreaks of measles, chickenpox and mumps by analyzing monthly number of reported cases for each of the three diseases in New York, and Baltimore (USA) over 30 to 35 years (London & Yorke 1973). Using a mathematical model of ordinary differential delay equations, the authors estimated monthly mean contact rates (which they defined as “the fraction of susceptibles contacted per day by an infective”) and showed that the average contact rate for all three diseases, was 1.7 to twice as higher in winter months (which coincides with school terms) than in summer months (which coincided with school holidays). Based on these findings, they used seasonal varying contact rates to reproduce the annual outbreaks of mumps and chickenpox and the biennial outbreaks of measles which were consistent with observed cases reports (London & Yorke 1973). According to London and Yorke two classes of factors could affect the contact rate: First, the social behavior of children who presumably make more contacts at school, and second, climatic factors such as cold weather would cause the children to spend more time indoors with each other at home. Other factors such as “decreased indoor relative humidity and decreased resistance to infectious diseases during colder months” might enhance transmission. Years later, the overall synchrony between contact rates patterns and school terms detected in measles data by Soper (1929), and London and Yorke (1973), were later confirmed by other authors using measles weekly cases reports data from England and Wales (Fine & Clarkson 1982; Finkenstadt & Grenfell 2000).

Although seasonal change in contact rates and or transmissibility has been suggested as the main driver for the previously described childhood diseases, it is likely that several seasonal drivers will interact in a complex manner to generate the seasonal dynamic observed in many infectious diseases. In a broader sense, the causes of seasonality can be classified into 1) host behavior and dynamic, 2) pathogen survival outside the host, 3) environmental factors, 4) host immune functions and susceptibility, 5) vectors population dynamic, 6) co-infections (Grassly & Fraser 2006a; Martinezid 2018; Altizer et al. 2006a).

Environmental factors

Climatic conditions and variables such as temperature, humidity, rainfall, cold weather, water salinity have been widely associated with the cycle in many infectious diseases' incidence. They influence disease transmission or susceptibility via their effect on the host, vector and or the pathogens (Martinezid 2018). Rainfall and temperature determine vectors abundance and bites rate and parasites development within the vector leading to pick transmission during warm or rainy seasons for diseases such as malaria, the African sleeping sickness (Knight 1971; Hoshen & Morse 2004; Altizer et al. 2006a). Rainfall can favor the development of vectors with aquatic larval stages via multiplication of available breeding sites which are essential for the vector reproduction. The effect of temperature and humidity (ambient and relative) on flu transmission have been demonstrated (Martinezid 2018; Shaman et al. 2010; Lowen et al. 2007). Environmental and climatic factors have also been suggested to partially control the temporal variability and seasonal dynamic of cholera (Emch et al. 2008; Bouma & Pascual 2001). Environmental factors (e.g. temperature) can also have an impact on pathogens cycle of development, especially for parasites with environmental life stages (larval stage, development rate), and modulate the time window during which infections probability is high (Altizer et al. 2006a). In addition, pathogens whose predominant route of transmission is air-borne (aerosol, droplets) are affected by environmental conditions such as humidity.

Host behaviors and population dynamic

Periodicity in human social interactions, and populations movements such as might be brought by regular social gatherings, or events, local markets, school terms (for childhood diseases), rural-urban migrations can modulate directly transmissible infections rates by increasing the pool of susceptibles and contact rates through the year (Martinezid 2018; Grassly & Fraser 2006b). Anderson and colleagues (Anderson & May 1992) noted that “bringing students together at the start of the school year (can) produce annual cycles in disease transmission efficiency.” Dowell noted from US population-based surveillance data of invasive pneumococcal disease that the mid-winter pick observed in the disease incidence occurred at the time when US families used to gather for Christmas and new year holidays (Dowell et al. 2003). Fishman (Fisman 2007) suggested that “Such gathering could provide opportunities for increased transmission of pneumococcus from asymptotically colonized children to older relatives at risk for invasive disease”.

Similarly, seasonal trends in sexually transmitted infections such as syphilis and gonorrhea have been linked to change in risk-taking behaviors and frequent partner changes during the summer (Hethcote & Yorke 1984; Zhang et al. 2016). Furthermore, host demographic processes such as birth cohorts have been suggested to impact the longer periodicity observed in some infectious diseases, through replenishment of the pool of susceptible hosts (increased density of susceptibles) (Altizer et al. 2006a). Seasonality in births can reduce existing herd immunity when new host enter a population, increasing the risk of infection in susceptible adults (Martinezid 2018). In summary, population dynamic and hosts behaviors that can result in periodic increase in local host density and greater proximity of hosts in time and space could be translated to periodic disease transmission and incidence.

Vectors population dynamics

Seasonality in vector population density, including mosquitoes, fleas, ticks, and flies are well-documented causes of seasonality in vector-borne diseases incidences (Hoshen & Morse 2004; Watts et al. 1987; Grassly & Fraser 2006b).

Seasonal variations in temperature have been reported to limit the abundance, survival, or activity of arthropod vectors such as mosquitoes, and ticks. The later can die, become less active below winter-like temperatures ultimately leading to a seasonal pattern in disease transmission and incidence (Altizer et al. 2006). Alternatively, seasonal increase in mosquitoes density during the rainfall as seen in many tropical regions is associated with strong seasonal pattern in malaria incidence (Hay et al. 2003). Similarly seasonal peak in fly numbers have been associated with seasonality in diarrheal disease in children (Das et al. 2018), and intervention reducing fly density have proven effective in reducing childhood diarrhea seasonal epidemics (Das et al. 2018; Chavasse et al. 1999) Furthermore, vectors such as mosquitoes bite more frequently, and reach sexual maturity earlier during warmer season thus potentially increasing the rate of parasite transmission (Altizer et al. 2006a). Change in tsetse fly distribution as might be brought by the rainy season have been associated with seasonal change in human-tsetse fly contact rate and subsequently seasonal variation in incidence of African sleeping sickness in Western, Southern and Central Africa (Franco et al. 2014; Alderton et al. 2018). The fly (vector of the disease parasite) has a variable lifespan depending on the season, which is typically longer in the rainy season (3–5 months) and shorter in the dry season (1–2 months) (Franco et al. 2014).

Host susceptibility and immune function

Host susceptibility to infections can be influenced either by the direct effects of environmental factors on the host defenses, or seasonal change in the host immune function. (Fisman 2007) Dowell (Dowell 2001) suggested that regular annual variations in the incidence of many infectious diseases may be due to changes in susceptibility of the human host to the particular pathogen, and that the changes in susceptibility may be distinct for different pathogens (Dowell 2001). He proposed that changes in host susceptibility may be timed to the physiological reaction of the humans (and other mammalians) organisms, to the length of day or night (i.e. photoperiodism) “typically mediated by changes in the duration of the daily melatonin pulse” one of the key hormone mainly produced at night known to control biorhythms (Dowell 2001). These changes in susceptibility may result

from a broad range of physiologic changes such as “changes in the characteristics of mucosal surfaces, expression of epithelial receptors, leukocyte numbers or responsiveness or other features of specific or nonspecific immunity” (Dowell 2001). Based on this hypothesis, Dowell postulated that pathogens may be circulating year-long in a population, but seasonal epidemic would occur when susceptibility of the population increases enough to sustain them. Greenwood (Greenwood 1999) and Sultan (Sultan et al. 2005) further suggested that a decline in mucosal immunity during the dry season in Africa could be associated with the seasonal increase observed in bacterial meningitis cases every dry season. If this hypothesis holds, this would translate in an increased risk of invasive meningitis among colonized individuals, rather than increased transmission, especially because the bacteria transmission would not stop during rainfall season humid season (Blakebrough et al. 1982).

Seasonal changes in Vitamin D (deficiency) (an hormone which appears to play a key role in phagocyte function regulation and associated with antibacterial and antiviral peptides elaboration by immune cells) have also been hypothesized as an important driver of impaired immune functions and increased susceptibility to infectious diseases during wintertime (Fisman 2007; Cannell et al. 2006). Similarly, physiological stress has also been suggested as a potential mechanism for annual variations in the immune functions(Grassly & Fraser 2006a).

Co-infections

Association of seasonal invasive pneumococcal disease with respiratory seasonal co-infection such as caused by respiratory syncytial virus and influenza virus have been demonstrated in a community-wide surveillance program in Houston (USA) by Kim and colleagues(Kim et al. 1996). The authors argue that viral co-infections spreading through the population during winter time would increase predisposition to pneumococcal pneumonia and bacteremia which peaked often during midwinter and declined strikingly in the midsummer. The dynamic of some seasonal infections can be modulated by other co-infections through immune suppression, cross-immunity and these interaction can lead to seasonal

dynamic which can only be captured by studying concurrent infections dynamics together rather than each infection in isolation (Grassly & Fraser 2006b).

Pathogen survival

Environmental factors such as temperature and humidity, pH may play an important role in the pathogens survival outside their host (Grassly & Fraser 2006b). Annual change in such factors can result in annual or complex seasonal variation in disease incidence (Grassly & Fraser 2006b). Influenza incidence peaks every winter in temperate regions. Studies showed that both relative humidity and absolute humidity influence influenza virus survival and transmissibility (Shaman & Kohn 2009; Koep et al. 2013). In temperate regions, indoor and outdoor absolute humidity displays strong seasonality, with lower humidity in winter (Koep et al. 2013; Shaman & Kohn 2009). This seasonal cycle in humidity has been consistent with increased survival of influenza virus during the winter and hypothesized as a plausible driver of influenza disease seasonality (Koep et al. 2013; Shaman & Kohn 2009). Peaks in gastroenteritis in wintertime have also been associated with enhanced survival of rotavirus and norovirus at low temperature during the winter (Mounts et al. 2000).

Seasonality modelling approaches

Seasonality have been incorporated in population models using different approaches either by dividing time into discrete interval or introducing time delay into continuous-time models or using seasonally forced oscillators (i.e. periodical external force such as might be brought by environmental factors for example) (Altizer et al. 2006a). The forced oscillator is often applied to model parameter (s) to achieve seasonally varying parameters which act as the forcing mechanism (Keeling & Rohani 2008). Seasonally forced parameters may include but are not limited to: birth rate, contact rate, transmission rate, immunity rate, disease progression etc. The explicit inclusion of seasonality into simple mechanistic model of infectious diseases such as SIS, SIR or SEIR models have been useful to produce the observed cycles in disease incidence. Mathematical analyses of these seasonally forced models have shown that they can exhibit a stable periodic

solution with undamped oscillation and complex or chaotic dynamic (Keeling & Rohani 2008). Here we briefly describe how seasonality commonly have been captured or introduced into dynamical models of infections.

Discrete time and continuous-time models with delay

Seasonality in disease incidence can also be introduced by delay due to temporary immunity (Taylor & Carr 2009). Using the case of temporary immunity in an SIR-based model with delayed coupling between the immune (recovered) and susceptible classes, Taylor and Carr (Taylor & Carr 2009) found parameters conditions for which the model is able to produce recurrent periodic outbreaks. The authors showed that for diseases that confer temporary immunity to a fraction of recovered individuals in the diseased population, the system can display periodic solution when temporary immunity has a fixed duration of time and modeled by a delayed term in the susceptible and recovered population equations. In such case, the SIRS model equations then become a system of differential delayed equations. In such model the duration of immunity or delay time plays a critical role in determining whether the model display periodic solution. Taylor and Carr showed that “there is a minimum delay time such that if the temporary immunity duration is less than the required minimum time, then recurrent epidemic will not occur”. Similarly, the fraction of recovered who become susceptible should attain some threshold value (generally higher values) for such system to display oscillatory solution that indicates recurrent epidemics in the studied population. Delay in infectious time may also be modeled similarly to temporary immunity delay (Taylor & Carr 2009).

Alternatively, delay can be introduced explicitly into the model by replacing the infectious or recovered immune class by two or more states such that individuals can be significantly delayed in the intermediate immune or infectious classes (Hethcote et al. 1981). Hethcote et al (Hethcote et al. 1981) incorporated a delay term into the recovered population of an SIR model to delay the return of individuals to the susceptible class. The authors showed that introducing multiple recovered classes (i.e. using a multicompartiment ordinary differential equation-based models) such that the SIR model becomes SIR_1R_2S or more generally

SIR₁... R_nS can cause the model to have periodic solutions for some parameter values if $n \geq 2$. Seasonality can also be introduced into a discrete or continuous time model by treating the transmission parameter as a discrete event that takes on specific constant value at fixed period of time.

Forced oscillators

A number of researchers have captured seasonality in disease incidence cycle in compartmental models by making the transmission rate β periodic in time (Dietz 1976; Aron & Schwartz 1984; London & Yorke 1973). The transmission parameter was described in the models as oscillating around an average/baseline value β_0 with a forcing term β_1 usually coupled with a periodic function. The functional form of the periodic function can have an impact on the model dynamic and may determine the model ability to distinguish the factors associated with seasonal changes in the disease incidence from those causing its long-term dynamic (Altizer et al. 2006a). Furthermore, Boatto et al (Boatto et al. 2018) showed using seasonal forced SIR model that the forcing amplitude and period of the forced oscillator and importantly the initial conditions (model initial states) all have an important influence on the asymptotic stability of the dynamics of the seasonally forced model. Population models with seasonally forced dynamics including births, deaths, host aggregation, disease transmission etc) revealed a variety of possible dynamics, ranging from simple annual cycles, through cycles that repeat with longer periods, to irregular chaotic dynamics (Taylor & Carr 2009). The common periodic functions which have been used to capture or introduce seasonality into infectious disease models include square waves (also referred to as step function or term-time switch forcing) and sinusoidal functions (Augeraud-Véron & Sari 2014; Bolker & Grenfell 1993; Schenzle 1984; Keeling et al. 2001; Moneim 2007; Black & McKane 2010; Fine & Clarkson 1982; Earn et al. 2000; Finkenstädt & Grenfell 2000; Keeling & Rohani 2008).

Square wave forcing and sinusoidal forcing

In the case of measles as a childhood infection, Schenzle (1984) first proposed transmission functions that mimic school days and holidays to model change in

measles transmission. School closing and reopening are considered quasi-instantaneous events resulting in periodic abrupt re-aggregation of children, thus increasing transmission probability due to an increased contact rate. Hence a term-time (square wave) seasonal function would generate switched dynamics between two attractors. This approach has been adopted by several authors to model seasonality in contact rate especially in childhood infections (Bolker & Grenfell 1993; Fine & Clarkson 1982; Schenzle 1984; Keeling et al. 2001; Moneim 2007; Black & McKane 2010; Augeraud-Véron & Sari 2014; Earn et al. 2000; Finkenstädt & Grenfell 2000; Keeling & Rohani 2008; Grassly & Fraser 2006b; Altizer et al. 2006b). Simple SEIR models based on term-time forcing were capable of reproducing many of the observed measles dynamics without resorting to more complex age-structured models (Earn et al. 2000). The transmission rate was modelled as a switch signal $\beta(t) = \beta_0 (1 + \beta_1 \text{Term}(t))$, where the parameter β_1 represents the seasonal forcing amplitude and $\text{Term}(t)$ is +1 during school time and -1 otherwise. Hence β_1 alternates at a steady frequency between minimum and maximum values. The duration of school terms (D_t) and holidays (D_h) during the year are further accounted for, resulting in a seasonal transmission function: $\beta(t) = \frac{\beta_0}{\frac{1}{2\pi}((1+\beta_1)D_t + (1-\beta_1)D_h)} (1 + \beta_1 \text{Term}(t))$ (Keeling & Rohani 2008; Keeling et al. 2001).

Alternatively, seasonal transmission was often assumed to be sinusoidal such that $\beta(t) = \beta_0(1 + \beta_1 \sin(2\pi t/365))$, where t is in unit of days. Sine or cosine function have been used (Miller et al. 2017; Grassly & Fraser 2006b; Bolker & Grenfell 1993). Keeling and Grenfell (Keeling & Grenfell 2002) parameterized both sinusoidal and term-time forced SIR and SEIR deterministic and stochastic models of measles using measles case report data. They showed that although both the sinusoidal and term-time periodic function would achieve good fit to the observed data, the term-time seasonal forcing function predicted measles cases and dynamics which were highly consistent with the observed case reports than the sinusoidal function.

Similarly, using two standard SIR and SEIR epidemic models of measles, chickenpox, mumps, and rubella with time varying periodic contact rate, Moneim (Moneim 2007) investigated when it is acceptable to use the simpler model and which of the square wave or sinusoidal forcing allows achieving model

predictions consistent with observed data. Based on this extensive simulation work, the author showed that “the SIR model with sinusoidal forcing is usually sufficient for chickenpox” to reproduce observed dynamic. Contrastingly, for measles, the author found that SEIR model with a square wave function for the transmission rate would be more appropriate than a simple SIR model with sinusoidal forcing of transmission. As for mumps seasonality, Moneim found that the SIR model with sinusoidal contact rate (i.e. transmission) displayed biennial solution, which was not observed when using the SEIR model instead. However, the dynamic of the SIR and SEIR model was similar when using the periodic square wave function with period of 1 year. Finally, for rubella, both the SIR and SEIR models seems to display chaotic behavior with the sinusoidal function and produces the widest range of possible behaviors (Moneim 2007). Consequently, choosing when sinusoidal forcing can be used instead of square wave or term-time function may appear as important as choosing the appropriate model structure, and more accurately when latent infection period can be ignored.

Age-dependent contact

Age-structured mixing of populations has been incorporated into mathematical models with the primary purpose to accurately describe heterogeneity in transmission. Its importance in transmission models of childhood diseases such as measles, rubella, mumps etc... have been demonstrated to obtain more accurate fit to epidemic data and account for the effect of immunization programs (Anderson & May 1985; Greenhalgh 1988). Using age-structured models of these childhood diseases including vaccination, Greenhalgh (Greenhalgh 1988) illustrated epidemic pattern of regular recurrent disease incidence consistent with observed data. Similarly, Schenzle’s (Schenzle 1984) work on measles has also demonstrated that including age dependent contact into measles model such that most contact occur between the same school year cohorts can accurately predict persistent cycles in measles incidence that is consistent with observed data. However, other authors have shown that models not incorporating age-dependent contact patterns into measles transmission model can also reproduce measles recurrent epidemic (for example through seasonal forcing of contact rate, change in birth and vaccination rates etc.) (Earn et al. 2000), suggesting that heterogenous-mixing may not be the key driver of the observed seasonality.

Though age dependent contacts rates may implicitly introduce delay into the model due to contacts patterns being also driven by school term and holidays in the case of measles.

Stochasticity

Disease dynamics can be also influenced by demographic and environmental stochasticity (Altizer et al. 2006b). It has been well documented that perturbation of the endemic equilibrium of the simple SIR deterministic model without seasonal forcing results in damped oscillations of the disease incidence with a natural period T (Grassly & Fraser 2006b; Keeling & Rohani 2008). However, when some randomness is assumed in the transmission process (stochastic transmission), this continuously perturbs the model from its steady endemic equilibrium which can sustain oscillations in disease incidence at the system natural period T as long as the population size is sufficiently large (Black & McKane 2010). In large populations, stochastic models without external forcing can display large oscillations due to stochasticity exciting the system's natural frequency (Black & McKane 2010). In smaller populations, the cycles will typically fade out due to reduction of susceptibles individuals. As pointed out by Bartlett (Bartlett 1956) and Stirzaker (Stirzaker 1975) the regular periodic oscillations of measles incidence could be explained by the introduction of stochastic effects into the model.

Conclusion:

Infectious diseases seasonality has long been recognized and explored, and although relevant progress has been made in understanding the main drivers of seasonality in some infectious diseases, the mechanism underlying several infectious diseases seasonality remains hypothetical and poorly understood. Improvement of the understanding of the mechanisms involved, will help improve public health interventions as well as the methodological tools and modelling approaches for the study of seasonal infectious diseases. The multiple factors proposed to be involved in the seasonality of infections, also call the opportunity for cross-disciplinary research and collaboration among, ecologists,

microbiologists, epidemiologists, climate scientists, public health policy makers, statisticians and mathematical modelers. The next chapter of this thesis focused on assessing some of the most discussed yet uncovered hypotheses for the mechanisms underlying the ubiquitous seasonality of bacterial meningitis in Africa, using mathematical transmission models integrating one of seasonality modeling approaches described in the current chapter.

Chapter 3. Review and meta-analysis of epidemiological data

In this chapter, we provide the French abstract of the first article published out of this thesis, then the rest of this chapter is made of the full text of the article itself. Only references, tables and figures numbers are edited for fitting the published article' text into the format and referencing of this manuscript. The PDF of the full text as published in PloS ONE is provided as an appendix to this thesis manuscript. The reader might choose to read either of the text of this chapter or the published article itself as they are the same.

This part of the thesis focused on reviewing and summarizing meningococcal carriage, incidence and case-carrier ratios data available from the literature, as a first attempt for exploring how colonisation and susceptibility to meningitis given colonisation change over seasons and epidemiological context (wet/endemic, dry/hyperendemic, dry/epidemic). Dynamics of colonisation can be estimated in carriage studies. The case-carrier ratio (CCR) is an ecological proxy for the risk of meningitis given colonisation and can be estimated by dividing meningitis incidence by concurrent carriage prevalence. We therefore conducted a systematic review with meta-analysis to provide best evidence on how serogroup-specific incidence, carriage and case-carrier ratio vary according to epidemiological context (endemicity, hyperendemicity and epidemic) in the African meningitis belt. This analysis is therefore conducted to respond to the thesis first objective.

Résumé de l'article 1

Contexte : Pour faciliter l'interprétation de l'épidémiologie de la méningite à méningocoque dans la "ceinture Africaine de la méningite", nous nous sommes fixés pour but d'obtenir des estimations d'incidences, de prévalences de portage asymptomatique, et du ratio cas-porteur par sérogroupes spécifiques des méningocoques dans la ceinture Africaine des méningites, et de décrire leurs variations selon les saisons et le contexte épidémiologique.

Méthodes : Nous avons réalisé une revue systématique et méta-analyse des études rapportant l'incidence et la prévalence mensuelle du portage asymptomatique par séro groupe du méningocoque au sein d'une même population sur la même période. Les analyses ont été réalisées par contexte épidémiologique et par saisons. Les contextes épidémiologiques ont été définis comme endémiques (saison des pluies, sans épidémie), hyperendémiques (saison sèche, sans épidémie) et épidémiques (saison sèche, avec épidémie).

Résultats : Huit études rapportant au total quatre-vingts couples d'estimation d'incidences de méningite et de prévalence de portage asymptomatique des méningocoques ont été incluses dans cette revue. Pour le séro groupe A, la transition de la phase endémique à la phase hyperendémique était associée à une multiplication par 15 de l'incidence et de 120 pour la transition de la phase hyperendémique à la phase épidémique. Les prévalences du portage asymptomatique associées aux deux transitions étaient respectivement multipliées par 1 et 30.

Pour les sérogroupes W et X du méningocoque, la transition de l'incidence endémique à l'incidence hyperendémique impliquait une augmentation de 4 fois et de 1,1 fois respectivement. Les augmentations de la prévalence du portage pour cette même transition étaient de 7 fois et 1,7 fois respectivement. Aucune donnée n'était disponible pour estimer les variations de l'incidence durant la transition hyperendémie-épidémie pour ces sérogroupes.

Nos résultats suggèrent que la variation saisonnière régulière de l'incidence de la méningite à méningococcie dû au séro groupe A entre la saison des pluies et la saison sèche pourrait être principalement liée à un changement saisonnier du ratio-cas-porteurs. En revanche, l'observation d'incidences épidémiques est liée à une augmentation importante de la prévalence du portage et, dans une moindre mesure, aux changements du ratio cas-porteur.

Conclusion : Les changements saisonniers du risque de méningite chez les porteurs asymptomatiques ainsi que les variations saisonnières de la transmission du portage devraient être pris en compte dans les modèles visant à reproduire l'épidémiologie de la méningite à méningocoque et principalement à prédire les épidémies de méningite dans la ceinture africaine de méningite.

Article 1: Incidence, Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt: A Systematic Review and Meta-Analysis.

Thibaut Koutangni^{1,3}, Halima Boubacar Maïnassara², Judith E. Mueller^{1,3}. Incidence, Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt: A Systematic Review and Meta-Analysis. *PLoS One*. 2015; 10(2):e0116725. doi: 10.1371/journal.pone.0116725. eCollection 2015.

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Abstract

Background: To facilitate the interpretation of meningococcal meningitis epidemiology in the "African meningitis belt", we aimed at obtaining serogroup-specific pooled estimates of incidence, carriage and case-carrier ratios for meningococcal meningitis in the African meningitis belt and describe their variations across the endemic, hyperendemic and epidemic context.

Methods: We conducted a systematic review and meta-analysis of studies reporting serogroup-specific meningococcal meningitis monthly incidence and carriage in the same population and time period. Epidemiological contexts were defined as endemic (wet season, no epidemic), hyperendemic (dry season, no epidemic), and epidemic (dry season, epidemic).

Findings: Eight studies reporting a total of eighty pairs of serogroup-specific meningococcal meningitis incidence and carriage estimates were included in this review. For serogroup A, changes associated with the transition from endemic to hyperendemic incidence and from hyperendemic to epidemic incidence were 15-fold and 120-fold respectively. Changes in carriage prevalence associated with both transitions were 1-fold and 30-fold respectively. For serogroup W and X, the transition from endemic to hyperendemic incidence involved a 4-fold and 1.1-fold increase respectively. Increases in carriage prevalence for the later transition were 7-fold and 1.7-fold respectively. No data were available for the hyperendemic-epidemic transition

for these serogroups. Our findings suggested that the regular seasonal variation in serogroup A meningococcal meningitis incidence between the rainy and the dry season could be mainly driven by seasonal change in the ratio of clinical cases to subclinical infections. In contrast appearance of epidemic incidences is related to a substantial increase in transmission and colonization and to lesser extent with changes in the case-carrier ratio.

Conclusion: Seasonal change in the rate of progression to disease given carriage together with variations in frequency of carriage transmission should be considered in models attempting to capture the epidemiology of meningococcal meningitis and mainly to predict meningitis epidemics in the African meningitis belt.

Introduction

The epidemiology of bacterial meningitis in the African meningitis belt is characterized by regular hyperendemicity during one single dry season (approximately November-May), which alternates with endemic incidence during the rainy season (June-October) (Lapeyssonnie, 1963; Molesworth et al., 2002). Epidemics of meningococcal meningitis occur on the community level irregularly, but always limited to the second half of the dry season. In cycles of 7– 10 years, epidemics form waves that span larger regions and consecutive dry seasons. Until the introduction of a meningococcal serogroup A conjugate vaccine (MenAfriVac) in the meningitis belt from 2010 on, these epidemics were mostly due to serogroup A *Neisseria meningitidis* (NmA), but since then, no NmA epidemics have occurred. However, since 2000, serogroups W (NmW) and X (NmX) have repeatedly caused epidemics, sometimes with local incidence rates comparable to NmA epidemics (Delrieu et al., 2011).

The factors leading to epidemics remain hypothetical (Mueller & Gessner, 2010), but their identification would help to better predict epidemics and designing control strategies, including vaccination. Several hypotheses exist as to why seasonality and seasonal epidemics occur (Greenwood et al., 1985; Yaka et al., 2008; Palmgren, 2009; Moore, 1992), but apart from modelling studies of meteorological information and some opportunistic studies during outbreaks, no hypothesis-driven research has occurred.

In a conceptual model for meningococcal epidemics in the meningitis belt, Mueller & Gessner (Mueller & Gessner, 2010) suggested that the transitions from endemicity (during the wet season) to seasonal hyperendemicity and sporadic epidemics (during the dry season) are two distinct phenomena caused by different mechanisms. These mechanisms would include increased risk of invasion given pharyngeal colonisation during the dry season, and surges in colonisation leading to epidemics. Building on this model, we aimed at exploring how colonisation and susceptibility to meningitis given colonisation change over seasons and epidemics. Dynamics of colonisation can be estimated in carriage studies. The case-carrier ratio (CCR) is an ecological proxy for the risk of meningitis given colonisation and can be estimated by dividing meningitis incidence by concurrent carriage

prevalence. We therefore conducted a systematic review with meta-analysis to provide best evidence on how serogroup-specific incidence, carriage and case-carrier ratio vary according to epidemiological context (endemicity, hyperendemicity and epidemic) in the African meningitis belt.

Methods

This review was conducted based on a written systematic review and meta-analysis protocol (Text S1). Reporting is done according to the PRISMA 2009 checklist. We aimed at including studies that (1) reported serogroup-specific meningococcal carriage and laboratory-confirmed meningococcal meningitis cases over the same time period in the same population; (2) were conducted in populations within the African meningitis belt; (3) included a representative sample of the general population for carriage evaluation (at least cluster sampling free of coverage bias) and enrolled suspected meningitis cases in exhaustive way; (4) were conducted from 1969 onward. Studies targeting children and/or young adults attending schools were also eligible provided that school attendance was common. We included only studies conducted after 1969, when the distinction between *N. meningitidis* and *N. lactamica* was possible (Hollis et al., 1969). We searched MEDLINE, Academic Search Complete via EBSCOhost and the African Index Medicus for medical subject headings and text words representing the concepts meningococcal meningitis, colonisation and African meningitis belt countries (Text S2). Databases searches were initially performed in February 2012 and the search was updated in December 2013. Our selection criteria included publications written in English and French. We hand searched references lists of included articles, relevant reviews and contacted relevant research groups to identify unpublished data. After a first screening based on titles and abstracts of retrieved records by one reviewer, two reviewers conducted full text screening and data extraction. Study and participants' characteristics, as well as relevant meningococcal serogroup-specific data were extracted from eligible studies by one reviewer (Table1, Table S1). We used Graph Extract v2.5 (QuadTech Associates) for data extraction from graphs in two studies (Leimkugel et al. 2007; Hassan-King, 1988).

Eligible articles were scrutinized to identify additional information required, which then was sought from the articles' authors, using data collection sheets. This included the number, over specific time periods, of confirmed Nm cases by serogroup, suspected case reporting and age-stratified data. A pair of incidence and carriage estimates during a given month in a given community was

Tableau 1 : Summary characteristics of included studies reporting meningococcal serogroup-specific incidence and carriage prevalence of the same population and time period.

First author. Year [Reference]	Settings	Age range (years)	Sampling time point/ Follow-up	Study participants	Vaccination status of study population (date of vaccine campaign) ¶	Epidemiological context of study / Season
Boisier et al. 2006			May 2003			Hyperendemic / post-epidemic (first rains mid-May, humidity <40% until end of May)
	Djinguinis, Azao, Fardak and Dallé villages (Tahoua region, Niger)	2–65		Residents of villages referring to Illela health centre and having registered at least one NmW case during March and April 2003 in the district of Illela.	No	
			February 2004			Hyperendemic / Dry
Hamidou et al. 2006			February 2003			Hyperendemic / Dry
	Primary schools in Niamey (Niger)	7–16	March 2003	Primary schools children in Niamey	Yes (2001/2002)	Hyperendemic / Dry
			May 2003			Hyperendemic / Dry (first rains mid-may humidity <40% until end of May)
Hassan-King et al. 1987[11]	Farafeni (Gambia)	2–20	January to April 1983	Residents living in two villages in the centre of the Farafeni study area.	No	Serogroup A epidemic / Dry
Leimkugel et al. 2007	Kessena Nankana district (Ghana)		April from 1998 to 2005			Endemic / Wet
		< 5–50+		Inhabitants of Kessena Nankana district	Yes (1997/2005 yearly campaigns)	
			November from 1998 to 2005			Hyperendemic / Dry
Mueller et al. 2011			March 2006	Residents of Kofila and Konkourouna	No	Serogroup A epidemic / Dry

	Lena, Kofila, and Konkourouna villages (Burkina Faso)	1–39				
			March 2006	Residents of Lena	Yes (March 12-15, 2006)	Serogroup A epidemic / Dry
Mueller et al. 2006	Urban Bobo-Dioulasso (Burkina Faso)	4–29	February, March, and April 2003	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-June 2003 (urban Bobo-Dioulasso)	Yes (2002)	Hyperendemic / Dry
Sié et al. 2008	Nouna district (Burkina-Faso)	not reported	April 2006	Resident of the Nouna Demographic Surveillance System Area	No	Hyperendemic / Dry
Trotter et al. 2013	Urban Bobo-Dioulasso (Burkina Faso)	0–59	February to March 2008	Residents of the urban area of Bobo-Dioulasso	No	Hyperendemic / Dry

¶ Yes, if the study population have been vaccinated within 2 weeks to 3 years prior to the onset of carriage and surveillance studies, using a vaccine against one or several meningococcal serogroups. All campaigns were conducted using serogroup A/C meningococcal polysaccharide vaccines.

called “Case Carrier Observation Unit” (CCOU)” and was described by size of the surveyed population, carriage study sample size, serogroup-specific number of confirmed cases and carriers, and monthly incidence and carriage prevalence with measures of variance (standard errors or deviation). Each CCOU was categorised according to season (wet/dry) and epidemiological context (endemic, hyperendemic, or epidemic). The categorisation was conducted by two reviewers based on information provided by authors in the article, weekly incidence rates of suspected meningitis cases relating to the follow up period if available, and meteorological data as provided by authors or available on tutiempo.net following an algorithm (Figure 5). Mean daily Relative Humidity (MRH) in the study area in the two weeks preceding study onset was the main criteria for season assignment. When only the month of study was reported, this was considered for MRH. Meteorological situations with $MRH > 40\%$ and $MRH < 40\%$ were defined wet and dry, respectively. If $35\% < MRH < 45\%$, the mean precipitation (mm) during the two weeks preceding the study was considered. During dry seasons with no reported epidemic, weekly incidence rates of suspected cases less than ten per 100,000 populations were classified as hyperendemic (Tall et al., 2012; Anon 2000). Based on authors’ information, we assigned a causal serogroup to epidemics, and classified study populations as “vaccinated” if they have received a meningococcal mass vaccination against the relevant serogroup one week to three years prior to the study onset.

We evaluated the risk of bias in studies using the following criteria: (1) appropriateness of reported inclusion and exclusion criteria, (2) appropriateness of carriage study sampling design, (3) described bacterial identification protocol in accordance to World Health Organization (WHO) standards (Mindy J Perilla et al 2002), (4) diagnostic criteria for meningitis diseased in accordance to WHO standards (World Health Organization: Regional Office for Africa 2009), (5) appropriateness of reported swabbing protocol, and (6) whether swabs were plated on site during population based carriage surveys.

Serogroup-specific case–carrier ratios (CCR) were computed for each CCOU as:

$$CCR = \frac{ncases / npopulation}{ncarriers / nsample}$$

Haldane’s continuity correction (Haldane 1996) was applied on CCOUs if cases,

but no asymptomatic carriers have been identified. Using the Delta method(Hosmer et al. 2008), the variance of the natural logarithm of the CCR was calculated as:

$$Var = \frac{npopulation - ncases}{(npopulation)(ncases)} + \frac{nsample - ncarriers}{(npopulation)(ncases)}$$

Where n denotes numbers. For each epidemiological context, pooled serogroup-specific meningitis incidence, carriage prevalence, and CCR were estimated with 95% confidence intervals (95%-CI) using the inverse-variance random-effects model.

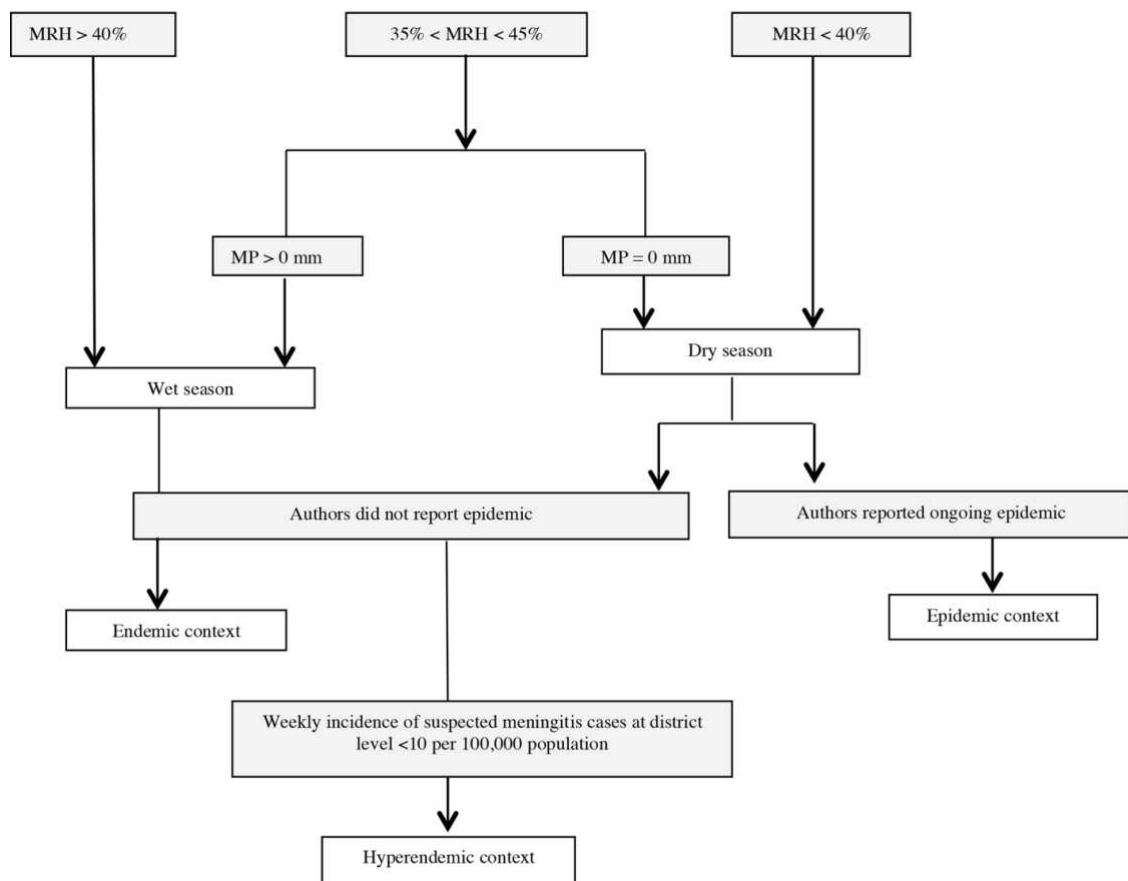


Figure 5: Algorithm for the definition of season and epidemiological context

of case-carrier observation units reported by publications. MRH= Mean daily relative humidity in the two weeks preceding study onset or MRH of the study month (when only month of study was reported) MP: Mean daily precipitation amount (mm) during the two weeks preceding the study.

This approach uses the inverse-variance weighting method to combine study-specific estimates into a weighted average estimate. Prior to combining study results, each study-specific estimate is weighed in inverse proportion to its variance. Inconsistency among CCRs of the same epidemiological context was quantified as the inconsistency index (I^2): $I^2 > 50\%$ was considered substantial heterogeneity and $I^2 < 50\%$ moderate inconsistency. The I^2 statistics computed based on the Q statistics of the Cochran's Q test has the advantage of not inherently depending on the number of studies included. Analyses were performed using STATA 11.2 (StataCorp LP) and The R foundation for statistical computation software v. 3.0.1.

Results

We retrieved 367 records from the initial search of which ten were eligible based on full text screening (Figure 6). Three studies were excluded from the review because we failed to obtain information from authors on study population size (Emele et al. 1999), because the carriage study carried on a convenience sample (Djibo et al., 2004), and because there was a mismatch between the time periods of meningitis surveillance and carriage survey, respectively (Raghunathan et al., 2006). The search update yielded 477 records with one recently published eligible study identified (Trotter et al., 2013). Overall, eight studies (Table 1) reporting 29 eligible CCOUs were available for meta-analysis on NmA, seven (27 CCOUs) on serogroup W and six (24 CCOUs) on serogroup X (Table S1). Four studies were conducted in Burkina Faso (Trotter et al., 2013; Mueller et al., 2006; Mueller et al., 2011; Sié et al., 2008) (eight CCOUs for NmA, eight for NmW), two in Niger (Boisier et al., 2006; Hamidou et al., 2006) (five for NmA, five for W, two for NmX) one in Ghana (Leimkugel, et al. 2007) (14 CCOUs for NmA, 14 for NmW, 14 for NmX) and one in the Gambia (Hassan-King, 1988) (two CCOUs for NmA). One of the two NmA CCOUs in the Gambian study (Hassan-King, 1988) was lately excluded from meta-analysis after contact with the main author,

because neither requested information nor meteorological data was available to allow classification into the appropriate season and epidemiological context. For two studies (Hassan-King, 1988; Sié et al., 2008), confirmed cases in the hyperendemic context could only be obtained for 4- and 7-month periods, and we approximated monthly incidence as the average incidence. For NmA, four eligible CCOUs corresponded to the dry/epidemic context, 18 to the dry/hyperendemic context, and six to the wet/endemic context. For NmW, six CCOUs corresponded to wet/endemic context, and 21 to the dry/hyperendemic

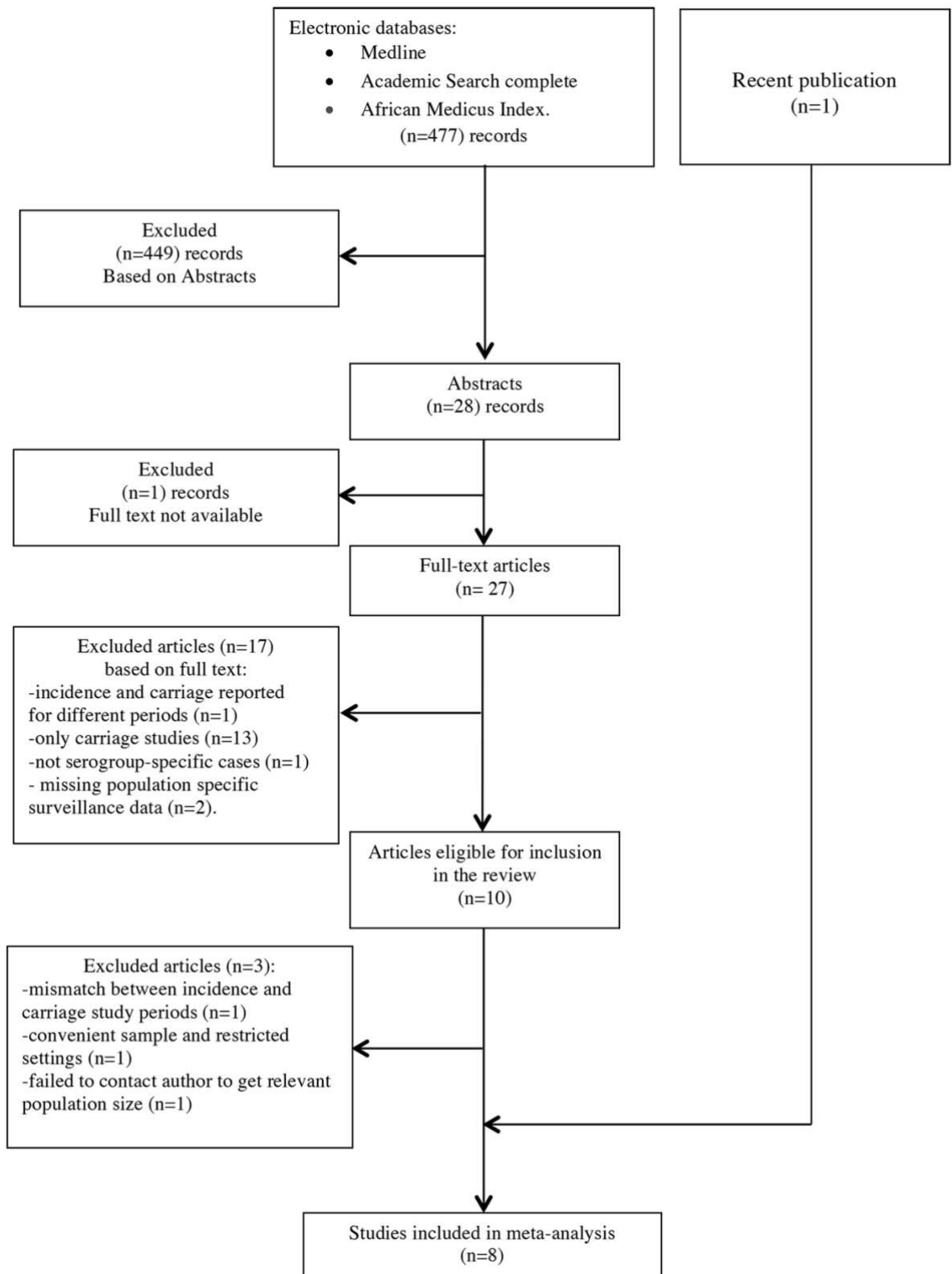


Figure 6 : Flow diagram of study identification and inclusion in the systematic review on meningococcal case-carrier ratios in the African meningitis belt.

context. For NmX, six and 18 CCOUs corresponded to wet/endemic and dry/hyperendemic respectively.

Two studies (Boisier et al., 2006; Hassan-King, 1988) had an unclear risk of bias with regards to their carriage study sampling design. One of these two studies was conducted in 1983 and was missing diagnostic criteria for meningitis cases. Another study (Hamidou et al., 2006) was subject to potential selection bias even though authors considered that the participants were representative of the target population (Figure S1).

Age-specific estimates were accessible only for 7 CCOUs, all from studies conducted in Burkina Faso (three in epidemic context and four in hyperendemic context); in consequence, we did not conduct age-stratified analyses.

The pooled estimate of NmA carriage prevalence was similar in the endemic and hyperendemic context [0.53% (95%-CI, 0.09%–1.31%) and 0.50% (0.17%–0.98%), respectively], but 30-fold higher in the epidemic context [15.28% (8.58%–23.48%)]. Corresponding NmA meningitis monthly incidence rates per 100,000 were 0.17 (0.01–0.58), 2.64 (0.90–5.30) and 319 (150–549), respectively (Figure 7). The resulting CCRs were 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2}) for endemic, 0.5×10^{-2} (0.2×10^{-2} – 1.2×10^{-2}) for hyperendemic, and 2.0×10^{-2} (1.3×10^{-2} – 3.3×10^{-2}) for epidemic situations (Figure 8). Heterogeneity between CCOUs was low for the endemic ($I^2 = 0.0\%$, $P = 0.903$), substantial for the hyperendemic ($I^2 = 69.5\%$, $P = 0.000$) and moderate for the epidemic context ($I^2 = 46.8\%$, $P = 0.131$).

The heterogeneity of the hyperendemic estimate was reduced by stratification by vaccination status (14 CCOUs were observed 1 week to 3 years after serogroup A meningococcal polysaccharide vaccine campaigns) (Figure S2 and Figure S3). For the endemic situation, CCR was now 0.1×10^{-2} (95%-CI, 0.0×10^{-2} – 0.1×10^{-2} ; $I^2 = 0.0\%$, $P = 0.903$; $N = 6$) among vaccinated, while no data were available for unvaccinated populations. For the hyperendemic context, CCR was 0.2×10^{-2} (0.1×10^{-2} – 0.5×10^{-2} ; $I^2 = 37.9\%$, $P = 0.106$; $N = 14$) among vaccinated and 8.8×10^{-2} (1.7×10^{-2} – 46.0×10^{-2} ; $I^2 = 0.0\%$, $P = 0.899$; $N = 4$) for unvaccinated populations. For the epidemic context, CCR was 1.5×10^{-2} (0.8×10^{-2} – 2.7×10^{-2} ; $N = 1$) among vaccinated and 3.3×10^{-2} (1.2×10^{-2} – 4.4×10^{-2} ; $I^2 = 52.7\%$, $P = 0.120$; $N = 3$) among unvaccinated populations. We could not identify any other factor of heterogeneity. For NmW, the pooled carriage prevalences in endemic and hyperendemic

contexts were 0.15% (0.02–0.37%) and 1.08% (0.46–1.95%), respectively. Corresponding monthly incidence rates per 100,000 were 0.18 (0.01–0.58) and 0.73 (0.26–1.43), respectively. No carriage and incidence data were available for the epidemic context with serogroup W. The CCR was 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2} (only one CCOU provided information) and 0.1×10^{-2} (0.1×10^{-2} – 0.2×10^{-2} ; $I_2=37\%$, $P=0.103$) for endemic and hyperendemic contexts, respectively. No carriage and incidence data were available for the epidemic context.

Pooled carriage prevalence of NmX was 1.40% (0.07–4.34%) in the endemic and 0.78% (0.15–1.90%) in the hyperendemic context. Corresponding monthly incidence rates per 100,000 were 0.18 (0.01–0.58) and 0.19 (0.06–0.39), respectively. The resulting CCR was 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2} ; $I_2=7.4\%$, $P=0.373$) for the endemic context, and had an upper 95% confidence limit below 0.0005 for the hyperendemic context (the software did not specify the central estimate at the fourth decimal below 0.000). No carriage and incidence data were available for epidemic context with serogroup X.

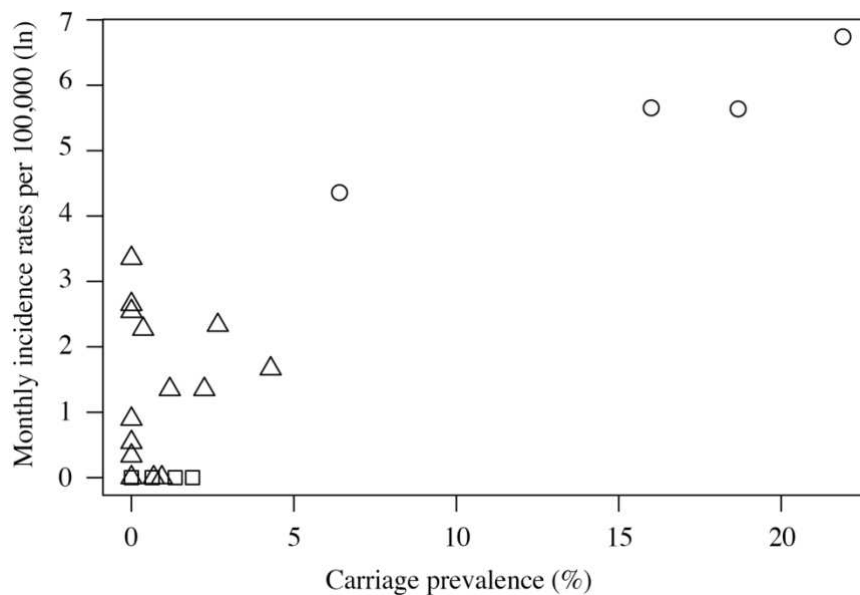


Figure 7 : Scatterplot of meningococcal serogroup A monthly incidence rates and carriage prevalence across CCOUs

Squares show data points in endemic context; triangles show data points in hyperendemic context, and hallow circle show data points in epidemic context.

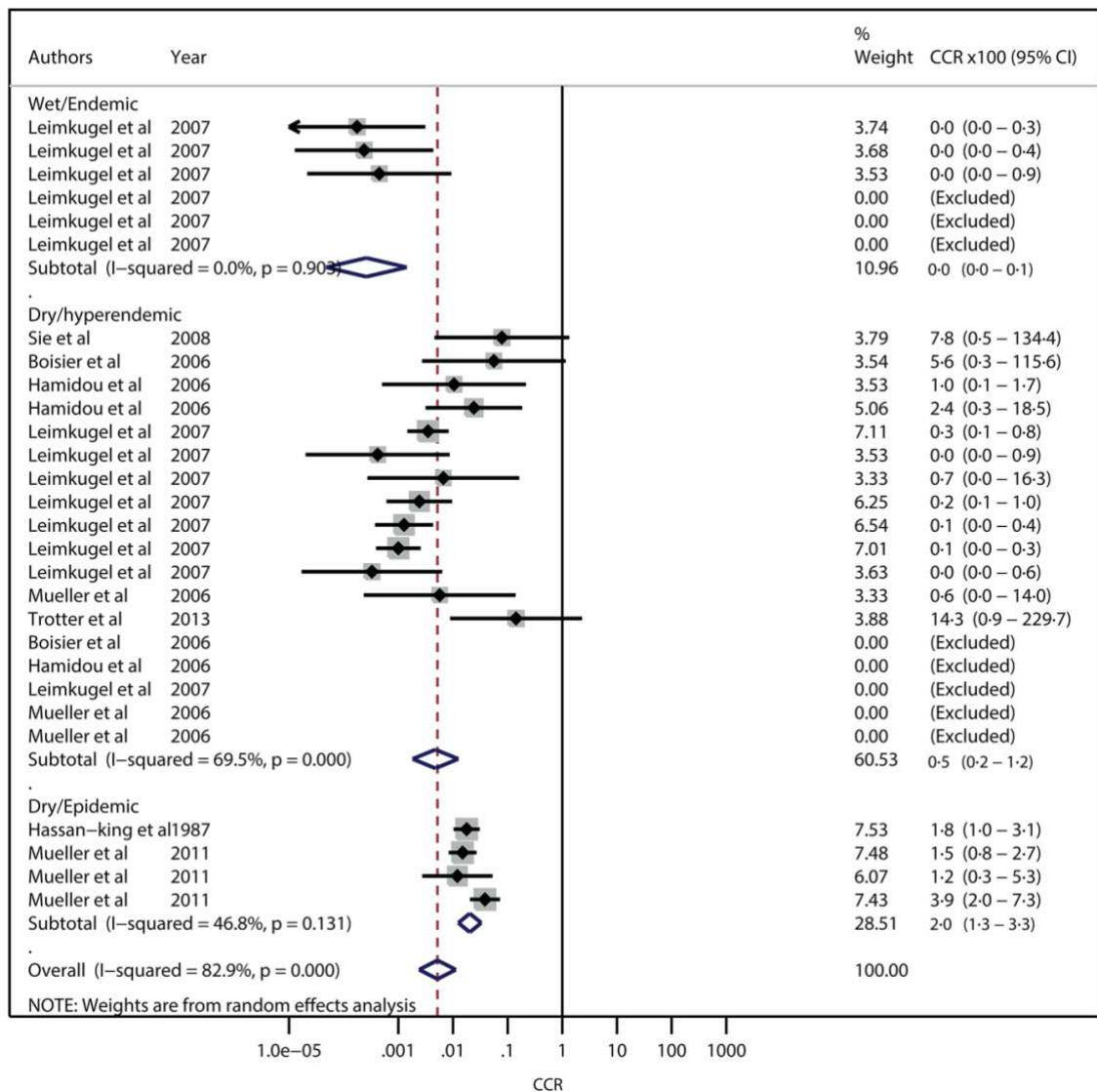


Figure 8 : Forest plots for meta-analysis of serogroup A meningococcal meningitis case-carrier ratio according to epidemiological context in the African meningitis belt.

Discussion

This is the first study that systematically reviews and synthesizes available serogroup-specific incidence and carriage data of meningococcal meningitis in the meningitis belt. The substantially higher CCR during non-epidemic dry seasons, compared to wet season suggests that seasonal hyperendemicity of NmA meningitis appears related to an increased risk of meningitis given asymptomatic colonisation, but not related to an increase in transmission and colonisation. In contrast, the occurrence of NmA epidemics appears related to a substantial

increase in meningococcal transmission and colonisation, and to a lesser extent with increased risk of meningitis given carriage. These results lend force to some hypotheses on the causation of seasonal hyperendemicity and epidemics and infirm others.

In pooled analyses, meningococcal carriage prevalence of NmA, NmW and NmX did not increase substantially from endemic (wet season) to hyperendemic context (dry season). NmW did show a significant difference, however, its magnitude (0.15% vs. 1.08%) probably is not important from a biological standpoint: using a recently published model for meningococcal meningitis epidemics (Irving et al., 2012), for a fixed rate of progression from carriage to disease, seasonal oscillations of disease incidence with magnitudes as observed (10-100-fold) could be produced by seasonal variations of carriage prevalence between <1% and 40%. A review of carriage studies in the meningitis belt concluded that changes in the prevalence of carriage are not linked to season in any consistent way (Trotter & Greenwood, 2007b). Minor variations have been described in series of cross-sectional studies (Kristiansen et al. 2011), but should not be interpreted as systematic seasonal variation. They likely correspond to long-term strain variations rather than a seasonal phenomenon. In consequence, seasonal differences in bacterial transmission e.g. mediated by improved pathogen survival (Ghipponi et al., 1971) or different social mixing patterns, should be dismissed as explanation for seasonality of meningococcal meningitis (Greenwood 1999).

Statistical analyses only allowed an approximation of fold-increase in CCR from wet to dry season between >5 to infinite. This was due to endemic incidences being close to zero, with an endemic CCR of 0.00. Given that carriage prevalence was the same for endemicity and hyperendemicity, but incidence differed 15-fold, we can assume the increase in CCR being around 15-fold. Meteorological modelling studies suggest that relative humidity below 40% in combination with high aerosol load strongly correlates with hyperendemicity of meningococcal meningitis in the meningitis belt (Martiny & Chiapello, 2013). No demonstrated pathophysiological explanation exists on how dry and dusty air can facilitate meningitis, but it could be intuitive that such exposure can weaken the nasopharyngeal mucosa and therefore facilitate meningococcal invasion into

tissues and bloodstream. Meningococcal septicaemia is rarely observed in the meningitis belt, suggesting that facilitated meningococcal invasion may not typically involve invasion into the blood stream. In addition, meningococcal invasion of olfactory nerve structures mounting towards the meninges has been found in mice(Sjölinder & Jonsson, 2010). In this scenario, environmental damage of the mucosa would lead to facilitated direct meningeal invasion by meningococci. In theory, increased meningitis incidence also could be attributed to reduced immune function during the dry season, but no data are available to inform this hypothesis. In any case, this around 15-fold seasonal increase in invasion is one of the strongest impacts that usual meteorological variations have on health. Upcoming climate changes may increase the proportion of the world's population exposed to such prolonged dry seasons and high aerosol load and may increase the resulting global burden of disease. Pneumococcal meningitis, a major cause of morbidity and mortality in the African meningitis belt, also shows a 10-fold increase in incidence during dry seasons,(Mueller et al., 2012) and similar mechanisms may be involved. Measures to prevent this seasonally increased risk of invasive disease given asymptomatic bacterial infection could be developed, in addition to pathogen-specific vaccines.

As opposed to constant NmA carriage between endemicity and hyperendemicity, we found 30-fold increased NmA carriage prevalence during epidemics, which may be causal for, or a consequence of epidemics. Meningitis patients do not transmit meningococci substantially more frequently than healthy persons, as disease-specific spreading behaviour such as vomiting occurs after disease onset, when patients are already bound to bed. It is therefore more likely that increased acquisition and transmission contribute to the occurrence of epidemics. If the dry season environment greatly facilitated invasion of colonising meningococci, an increase in colonisation would simply lead to proportionally increased meningitis incidence. However, the estimated 30-fold increase in NmA carriage prevalence suggests that the carriage increase is not sufficient to explain on its own the 130-fold increase in incidence, as postulated in the hypothetical model by Mueller & Gessner. According to our results, a further slight increased risk of invasion given colonisation occurs during epidemics (4-fold increase in CCR). Respiratory virus infections could play such a double role, as they probably facilitate

meningococcal adhesion to the mucosa or increase transmission via coughing and sneezing, and also temporarily reduce immune defence against bacterial disease by disrupting the immune response against encapsulated bacteria (Rameix-Welti et al., 2009). This is supported by observations during NmA meningococcal epidemics, where carriage was associated with respiratory infection symptoms (Moore et al., 1990; Mueller et al., 2008) and participants reporting recent flu-like symptoms were at increased risk of subsequently presenting with confirmed or purulent meningitis (Mueller et al., 2011).

Although the hypothetical model by Mueller and Gessner concentrated on climatic factors to explain the variation between endemic and hyperendemic situation, in principal, seasonal variations of viral co-infections, or other intermediary factors, could contribute to increase risk of meningococcal invasion (but not transmission, given our results)

Our analyses stratifying by vaccination status suggest that polysaccharide vaccination against serogroup A related to a reduced risk of meningitis given colonisation, possibly more in hyperendemic (where there was a significant difference in CCR between vaccinated and unvaccinated populations) than epidemic situations. However, interpretation by epidemiological situations may be inappropriate due to the small number of relevant observations for unvaccinated populations and potential heterogeneity between studies.

We cannot provide clear evidence on the question whether NmW behaves similar to NmA, as no data for the epidemic context were available. Both incidence and CCR increased from endemic to hyperendemic context, although to lesser extent than NmA. We did not observe a clear seasonality for NmX meningitis. Leimkugel et al. observed periods of substantially increased NmX carriage during hyperendemicity (prevalence 17%), but outside epidemics, NmX meningitis incidence usually remained low at levels comparable to endemic periods of NmA and NmW. The risk of meningitis given colonisation appears to be substantially lower compared to NmA (Leimkugel et al. 2007). It is unclear whether this is due to better natural immunity or a lesser capacity for invasion. Combined carriage and surveillance studies during periods with strong serogroup X or W incidence and epidemics are needed to better understand the epidemic behaviour of these serogroups.

There are some limitations to our analysis. The estimated CCRs are imprecise, as surveillance systems unlikely achieve complete case identification and carriage studies probably underestimate colonisation prevalence (Greenwood, 2013). Furthermore, except for one study performing repeated assessments (Leimkugel et al. 2007), we cannot follow the CCR variation of incidence-carriage pairs across epidemiological contexts, but are limited to group comparison. Methodological differences between studies may have led to over- or underestimating CCR changes between epidemiological contexts; e.g. the series of CCOUs reported by Leimkugel et al. (Leimkugel et al. 2007) showed lower CCR in general. Finally, we did not analyse age-specific CCRs, due to difficulties in re-analysing original data collected up to 20 years ago. Such age stratification would provide insight into the high incidence among teenagers, but its omission unlikely biases our results. In this study, we cannot evaluate the association between specific meteorological features, such as humidity or aerosol load, and changes in meningococcal meningitis epidemiology. To identify the mechanism through which dry season is associated with higher meningitis incidence, correlation studies between meteorological and incidence data are more appropriate.

The most important limitation is that we transfer results from an ecological analysis to the individual level of susceptibility for disease, which will only be a further step in evaluating a hypothesis and does not have the validity of clinical evidence.

Conclusion

In conclusion, this study provides orientation on how risk of bacterial invasion and transmission or colonisation may interact to produce the particular epidemiology of the African meningitis belt. The findings will be useful for developing models to evaluate vaccination strategies, and to develop further relevant research. They leave room to hypothesis that other diseases, such as pneumococcal meningitis and pneumonia, may be concerned by a complex interaction between climatic environment, bacteria, potentially co-infections, and human mucosal and immune defence.

Acknowledgements

We are grateful to Dr. Trinquart Ludovic for advice with meta-analysis and to Dr. Boisier Pascal and Dr. Musa Hassan-King for providing additional information on their publications.

Author Contributions

Conceived and designed the experiments: TK JEM. Performed the experiments: TK. Analyzed the data: TK. Contributed reagents/materials/analysis tools: HBM. Wrote the article: TK JEM.

Article 1' supporting information

Text S1. Protocol of the systematic review and meta-analysis.

Accessible online at:

<http://journals.plos.org/plosone/article/file?type=supplementary&id=info:doi/10.1371/journal.pone.0116725.s006>

Text S2. Search Strategy

Medline via EBSCOhost research platform

#1) SH Meningitis, Meningococcal

#2) TI (Meningitis, Meningococcal, Serogroup Y) or TI (Serogroup Y, Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup Y) or TI (Meningitis, Meningococcal, Serogroup C) or TI (Serogroup C Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup C)

#3) TI (Meningitis, Meningococcal, Serogroup B) or TI (Serogroup B Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup B)

#4) TI (Meningitis, Meningococcal, Serogroup A) or TI (Serogroup A Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup A)

#5) TI (Meningococcal Meningitis, Serogroup W 135) or TI (Serogroup W-135, Meningococcal Meningitis) or TI (Serogroup W 135)

#6) TI (Meningitis, Meningococcal, Serogroup X) or TI (Serogroup X Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup X)

#7) (#2 or #3 or #4 or #5 or #6)

#8) AB (Meningitis, Meningococcal, Serogroup X) or AB (Serogroup X Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup X)

#9) AB (Meningitis, Meningococcal) or AB (Meningococcal Meningitis) or AB (Neisseria meningitis) or AB (Meningitis, Cerebrospinal) or AB (Acute meningitis) or AB (Epidemic meningitis) or AB (Meningitis, Meningococcic)

#10) TI (Meningitis, Meningococcal) or TI (Meningococcal Meningitis) or TI (Neisseria meningitis) or TI (Meningitis, Cerebrospinal) or TI (Acute meningitis) or TI (Epidemic meningitis) or TI (Meningitis, Meningococcic)

- #11) AB (Meningitis, Meningococcal, Serogroup Y) or AB (Serogroup Y, Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup Y) or AB (Meningitis, Meningococcal, Serogroup C) or AB (Serogroup C Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup C)
- #12) AB (Meningococcal Meningitis, Serogroup W 135) or AB (Serogroup W-135, Meningococcal Meningitis) or AB (Serogroup W 135) or
- #13) AB (Meningitis, Meningococcal, Serogroup A) or AB (Serogroup A Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup A)
- #14) AB (Meningitis, Meningococcal, Serogroup B) or AB (Serogroup B Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup B)
- #15) (#8 or #9 or #10 or #11 or #12 or #13 or #14)
- #16) #7 or #15
- #17) #1 and #16
- #18) MH Africa/ or MH African meningitis belt/ or MH meningitis belt/ or MH Africa south of the Sahara/ or MH sub-Saharan Africa / or MH Burkina Faso/ or MH Niger/ or Niamey/ or MH Mali/ or MH Togo/ or MH Ghana/ or MH Côte d'Ivoire/ or MH Ivory Coast/ or MH Senegal/ or MH Chad/ or MH Ethiopia/ or MH Sudan/ or MH Benin/ or MH Nigeria/ or MH Cameroun/ or MH The Gambia/ or MH Gambia/
- #19) #17 and #18

Academic Search complete via EBSCOhost research platform

- #1) DE "Meningitis, Cerebrospinal"
- #2) TI (Meningitis, Meningococcal, Serogroup Y) or TI (Serogroup Y, Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup Y) or TI (Meningitis, Meningococcal, Serogroup C) or TI (Serogroup C Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup C)
- #3) TI (Meningitis, Meningococcal, Serogroup B) or TI (Serogroup B Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup B)
- #4) TI (Meningitis, Meningococcal, Serogroup A) or TI (Serogroup A Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup A)
- #5) TI (Meningococcal Meningitis, Serogroup W 135) or TI (Serogroup W-135, Meningococcal Meningitis) or TI (Serogroup W 135)

- #6) TI (Meningitis, Meningococcal, Serogroup X) or TI (Serogroup X Meningococcal Meningitis) or TI (Meningococcal Meningitis, Serogroup X)
- #7) (#2 or #3 or #4 or #5 or #6)
- #8) AB (Meningitis, Meningococcal, Serogroup X) or AB (Serogroup X Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup X)
- #9) AB (Meningitis, Meningococcal) or AB (Meningococcal Meningitis) or AB (Neisseria meningitis) or AB (Meningitis, Cerebrospinal) or AB (Acute meningitis) or AB (Epidemic meningitis) or AB (Meningitis, Meningococcic)
- #10) TI (Meningitis, Meningococcal) or TI (Meningococcal Meningitis) or TI (Neisseria meningitis) or TI (Meningitis, Cerebrospinal) or TI (Acute meningitis) or TI (Epidemic meningitis) or TI (Meningitis, Meningococcic)
- #11) AB (Meningitis, Meningococcal, Serogroup Y) or AB (Serogroup Y, Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup Y) or AB (Meningitis, Meningococcal, Serogroup C) or AB (Serogroup C Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup C)
- #12) AB (Meningococcal Meningitis, Serogroup W 135) or AB (Serogroup W-135, Meningococcal Meningitis) or AB (Serogroup W 135) or
- #13) AB (Meningitis, Meningococcal, Serogroup A) or AB (Serogroup A Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup A)
- #14) AB (Meningitis, Meningococcal, Serogroup B) or AB (Serogroup B Meningococcal Meningitis) or AB (Meningococcal Meningitis, Serogroup B)
- #15) (#8 or #9 or #10 or #11 or #12 or #13 or #14)
- #16) #7 or #15
- #17) #1 and #16
- #18) ZG “Africa” or ZG “African meningitis belt” or “ZG meningitis belt” or ZG “Africa south of the Sahara” or ZG “sub-Saharan Africa” or ZG “Burkina Faso” or ZG “Niger” or ZG “Niamey” or ZG “Mali” or ZG “Togo” or ZG “Ghana” or ZG “Côte d’Ivoire” or ZG “Ivory Coast” or ZG “Senegal” ZG “Chad” or ZG “Ethiopia” or ZG “Sudan” or ZG “Benin” or ZG “Nigeria” or ZG “Cameroun” or ZG “The Gambia” or ZG “Gambia”
- #19) #17 and #18

African Medicus Index.

Meningitis [Descriptor] or Meningite [Descriptor] or Neisseria meningitidis [Descriptor] or meningitis [Key Word] or meningite [Key Word] or Neisseria meningitidis [Key Word] or meningitis [Title] or meningococcal [Title] or meningococcic [Title] or méningite [Title] or Neisseria [Title] or Neisseria and meningitidis [Title]

Table S1. Summary of serogroup-specific Case Carrier Observation Unit by epidemiologic context.

Authors. Publication Year [Reference]	Study Month-Year	Monthly incidence		Carriage prevalence	
		cases/N	incid/100,000 pop	carriers/n	(%)
Endemic/Wet, Serogroup A					
Leimkugel et al. 2007	Nov-2004	0/140000	0·0	2/313	0·64
Leimkugel et al. 2007	Nov-2002	0/140000	0·0	6/319	1·88
Leimkugel et al. 2007	Nov-2005	0/140000	0·0	0/334	0·00
Leimkugel et al. 2007	Nov-2003	0/140000	0·0	4/297	1·35
Leimkugel et al. 2007	Nov-2000	0/140000	0·0	0/301	0·00
Leimkugel et al. 2007	Nov-2001	0/140000	0·0	0/306	0·00
Hyperendemic/Dry, Serogroup A					
Boisier et al. 2006	May-2003	2/7237	27·6	0/80	0·00
Boisier et al. 2006	Feb-2004	0/7469	0·0	0/70	0·00
Hamidou et al. 2006	Feb-2003	2/138057	1·4	0/287	0·00
Hamidou et al. 2006	Mar-2003	12/138057	8·7	1/277	0·36
Hamidou et al. 2006	May-2003	0/138057	0·0	0/272	0·00
Leimkugel et al. 2007	Apr-2002	4/140000	2·9	4/339	1·18
Leimkugel et al. 2007	Apr-2001	1/140000	0·7	0/310	0·00
Leimkugel et al. 2007	Apr-2004	6/140000	4·3	15/350	4·28
Leimkugel et al. 2007	Apr-1998	13/140000	9·3	8/301	2·65
Leimkugel et al. 2007	Apr-2000	0/140000	0·0	0/298	0·00
Leimkugel et al. 2007	Apr-2005	0/140000	0·0	3/321	0·93
Leimkugel et al. 2007	Apr-2003	4/140000	2·9	7/312	2·24
Leimkugel et al. 2007	Apr-1999	0/140000	0·0	2/292	0·68
Mueller et al. 2006	Apr-2003	0/253605	0·0	0/469	0·00
Mueller et al. 2006	Mar-2003	1/253605	0·4	0/482	0·00
Mueller et al. 2006	Feb-2003	0/253605	0·0	0/448	0·00
Sié et al. 2008 [24]	Apr-2006	9/76847	11·7	0/316	0·00
Trotter et al. 2013	28th Feb –7th Mar - 2008	82/623303	13·1	0/538	0·00
Epidemic/Dry, Serogroup A					
Hassan-King et al. 1987	Jan–Apr-1983	37/13000	284·6	16/100	16·00
Mueller et al. 2011	Mar-2006	13/4640	280·2	59/316	18·67
Mueller et al. 2011	Mar- 2006	2/2600	76·9	13/203	6·40
Mueller et al. 2011	Mar- 2006	14/1660	843·4	23/105	21·90
Endemic/ Wet, Serogroup W					
Leimkugel et al. 2007	Nov-2003	0/140000	0·0	0/297	0·00
Leimkugel et al. 2007	Nov-2002	0/140000	0·0	0/319	0·00

Leimkugel et al. 2007	Nov-2005	0/140000	0-0	0/334	0-00
Leimkugel et al. 2007	Nov-2000	0/140000	0-0	0/301	0-00
Leimkugel et al. 2007	Nov-2001	0/140000	0-0	0/306	0-00
Leimkugel et al. 2007	Nov-2004	0/140000	0-0	2/313	0-64

Hyperendemic/ Dry, Serogroup W

Boisier et al. 2006	May-2003	5/7237	69-1	21/80	24-41
Boisier et al. 2006	Feb-2004	0/7469	0-0	7/70	10-00
Hamidou et al. 2007	Feb-2003	1/138057	0-7	13/287	4-53
Hamidou et al. 2006	Mai-2003	0/138057	0	13/272	4-78
Hamidou et al. 2006	Mar-2003	4/138057	2-9	8/277	2-89
Leimkugel et al. 2007	Apr-2004	0/140000	0-0	3/350	0-85
Leimkugel et al. 2007	Apr-2003	0/140000	0-0	0/312	0-00
Leimkugel et al. 2007	Apr-2000	0/140000	0-0	0/298	0-00
Leimkugel et al. 2007	Apr-2005	0/140000	0-0	0/321	0-00
Leimkugel et al. 2007	Apr-1999	0/140000	0-0	0/292	0-00
Leimkugel et al. 2007	Apr-1998	0/140000	0-0	1/301	0-33
Leimkugel et al. 2007	Apr-2001	0/140000	0-0	0/310	0-00
Leimkugel et al. 2007	Apr-2002	0/140000	0-0	0/339	0-00
Mueller et al. 2006	Mar-2003	7/253605	2-8	4/482	0-83
Mueller et al. 2011	Mar-2006	0/1660	0-0	0/105	0-00
Mueller et al. 2011	Mar-2006	0/4640	0-0	0/316	0-00
Mueller et al. 2006	Apr-2003	5/253605	2-0	6/469	1-28
Mueller et al. 2006	Feb-2003	4/253605	1-6	8/448	1-78
Mueller et al. 2011	Mar-2006	0/2600	0-0	0/203	0-00
Sie et al. 2008	Apr-2006	0/76847	0-0	0/316	0-00
Trotter Trotter et al. 2013	Feb 28-Mar 7 2008	0/623303	0-0	2/538	0-37

Authors. Publication Year	Study Month-Year	Monthly incidence		Carriage prevalence	
		cases/N	incid/100,000 pop	carriers/n	(%)

Endemic/ Wet, Serogroup X

Leimkugel et al. 2007	Nov-03	0/140000	0-0	3/297	1-01
Leimkugel et al. 2007	Nov-02	0/140000	0-0	2/319	0-63
Leimkugel et al. 2007	Nov-05	0/140000	0-0	0/334	0-00
Leimkugel et al. 2007	Nov-00	0/140000	0-0	33/301	10-96
Leimkugel et al. 2007	Nov-01	0/140000	0-0	4/306	1-31
Leimkugel et al. 2007	Nov-04	0/140000	0-0	0/313	0-00

Hyperendemic/ Dry, Serogroup X

Boisier et al. 2006	May-2003	0/7237	0-0	0/80	0-00
Boisier et al. 2006	Feb-04	0/7469	0-0	2/70	2-85
Leimkugel et al. 2007	Apr-2004	0/140000	0-0	0/350	0-00

Leimkugel et al. 2007	Apr-2003	0/140000	0-0	0/312	0-00
Leimkugel et al. 2007	Apr-2000	2/140000	1-4	52/298	17-45
Leimkugel et al. 2007	Apr-2005	0/140000	0-0	0/321	0-00
Leimkugel et al. 2007	Apr-1999	1/140000	0-7	10/292	3-42
Leimkugel et al. 2007	Apr-1998	0/140000	0-0	0/301	0-00
Leimkugel et al. 2007	Apr-2001	0/140000	0-0	49/310	15-80
Leimkugel et al. 2007	Apr-2002	0/140000	0-0	2/339	0-59
Mueller et al. 2006	Mar-2003	0/253605	0-0	1/482	0-21
Mueller et al. 2011	Mar-2006	0/1660	0-0	0/105	0-00
Mueller et al. 2011	Mar-2006	0/4640	0-0	0/316	0-00
Mueller et al. 2006	Apr-2003	0/253605	0-0	2/469	0-43
Mueller et al. 2006	Feb-2003	0/253605	0-0	0/448	0-00
Mueller et al. 2011	Mar-2006	0/2600	0-0	0/203	0-00
Sié et al. 2008	Apr-2006	0/76847	0-0	0/316	0-00
Trotter et al. 2013	Feb 28-Mar 7th 2008	0/623303	0-0	1/538	0-18

	Described bacterial identification protocol in accordance to WHO standards ¹⁴	Diagnostic criteria for diseased, precise, and in accordance with WHO standards ¹⁵	Swabs plated on site	Swabbing protocol reported and appropriate	Carriage study sampling design valid and appropriate	Inclusion criteria described and appropriate
Sie et al. 2008	+	+	+	+	+	+
Hassan-King et al. 1987	+	?	+	+	?	+
Mueller et al. 2006	+	+	+	+	+	+
Mueller et al. 2011	+	+	+	+	+	+
Leimkuguel et al. 2007	+	+	?	+	+	+
Trotter et al. 2013	+	+	+	+	+	+
Boisier et al. 2006	+	+	+	?	?	+
Hamidou et al. 2006	+	+	+	+	-	+

Legend :




 Low risk of bias
  Unclear risk of bias
  High risk of bias

Figure S1. Risk of bias summary for included studies.

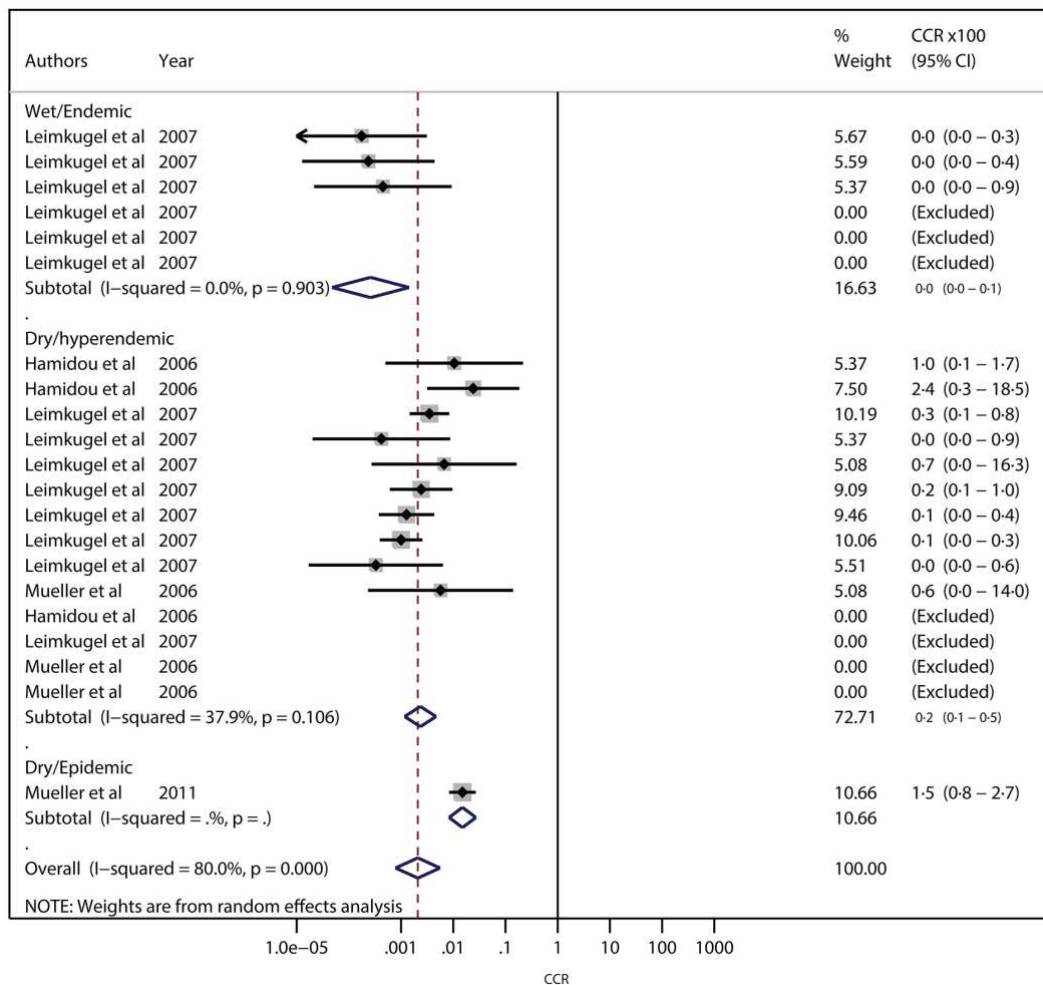


Figure S2. Forest plot for meta-analysis of serogroup A meningococcal meningitis case-carrier ratios in vaccinated populations according to epidemiological context in the African meningitis belt.

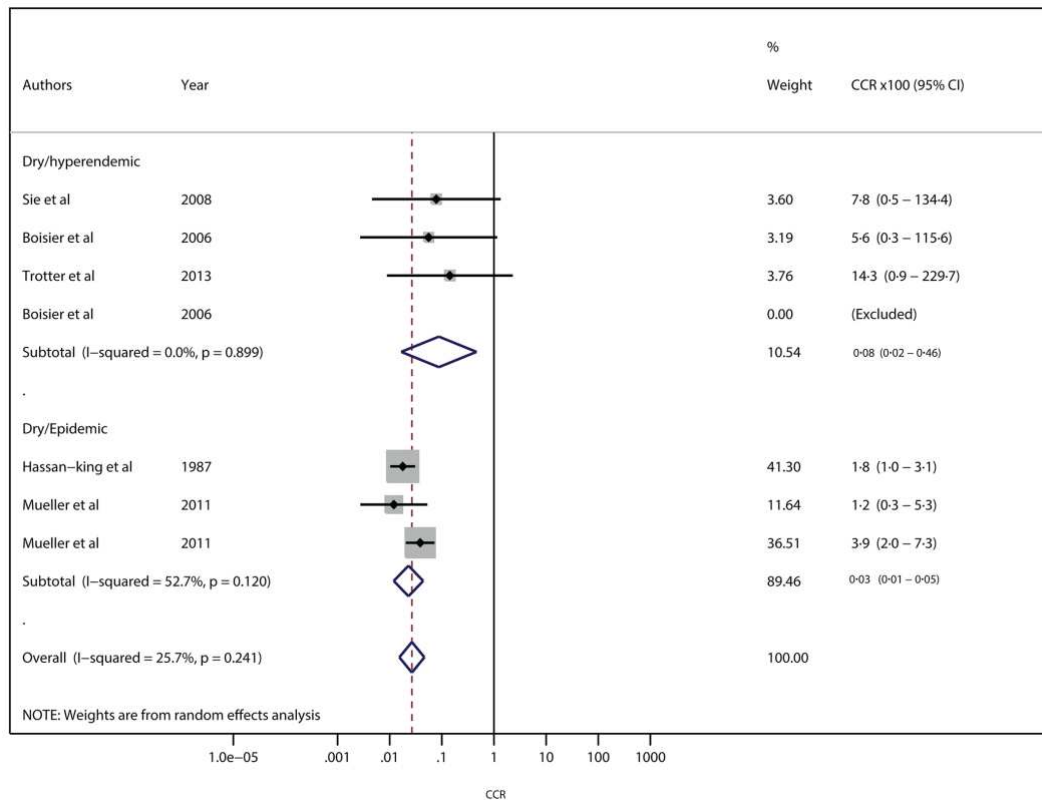


Figure S3. Forest plot for meta-analysis of serogroup A meningococcal meningitis case-carrier ratios in unvaccinated populations according to epidemiological context in the African meningitis belt.

Chapter 4: Modelling bacterial meningitis seasonal hyperendemicity

In this chapter, we provide the French abstract of the second article published out of this thesis, then the rest of this chapter is made of the full text of the article itself. Only references, tables and figures numbers are edited for fitting the published article' text into the format and referencing of this manuscript. The PDF of the full text as published in PloS ONE is provided as an appendix to this thesis manuscript. The reader might choose to read either of the text of this chapter or the published article itself as they are the same.

Résumé de l'article 2

Les mécanismes pathophysiologiques potentiellement impliqués dans la saisonnalité régulière et l'hyperendemicité des méningites bactériennes dans la ceinture des méningites restent encore non expliquer. Comprendre les causes de cette saisonnalité régulière des cas de méningites est essentiel pour une meilleure prévention et pour mieux modéliser la maladie. Ici nous évaluons les deux principales hypothèses formulées au chapitre 1 de cette thèse pour expliquer les hyperendemies saisonnières régulières observées exclusivement pendant la saison sèche dans la ceinture des méningites. La première hypothèse évoquait un risque accru de l'invasion bactérienne (du méningocoque ou du pneumocoque) chez les porteurs asymptomatiques de la bactérie. La deuxième hypothèse évoquait plutôt une transmission accrue des bactéries par les porteurs asymptomatiques pendant la saison sèche. Dans la présente étude, nous avons formulé trois modèles mathématiques déterministes de la méningite bactérienne hyperendémique incluant chacune des hypothèses (modèle 1 – “inv” ou modèle 2 – “transm”) ou les deux à la fois (modèle 3 – “inv-transm”).

Nous avons ensuite paramétré les modèles en utilisant des données épidémiologiques publiées et des données de surveillance des cas suspects de méningite bactérienne aiguë notifiés par les formations sanitaires au Burkina Faso entre 2004 et 2010 à travers le système de national de surveillance renforcée des

méningites bactériennes. Nous évaluons et comparons ensuite la capacité des modèles mathématiques proposés à reproduire les incidences hebdomadaires observées dans les formations sanitaires du Burkina Faso. Les trois modèles reproduisent relativement bien les incidences observées (coefficient de détermination $R^2 = 0,76, 0,86$ et $0,87$ respectivement). Le modèle 2 – “transm” et le modèle 3 – “inv-transm” ont mieux reproduit les pics d'incidences saisonnier. Cependant, le modèle 2 - "transm" requiert un taux d'invasion moyen élevé pour un taux de transmission moyen de la bactérie équivalente à celui du modèle 3 – “inv-transm”. Ces résultats suggèrent que l'hypothèse de variations saisonnières du risque d'invasion méningé de la bactérie et de la transmission est plausible et que ces variations saisonnières sont impliquées dans les hyperendémies saisonnières régulières des méningites bactériennes dans la ceinture africaine des méningites. En conséquence, des interventions visant à réduire le risque d'invasion nasopharyngée et la transmission des bactéries, en particulier pendant la saison sèche, pourraient limiter la recrudescence annuelle des cas de méningites bactériennes régulièrement observés dans la ceinture de la ceinture africaine des méningites.

Article 2: Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt.

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Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt. *Epidemiology and Infection*, 1-11.

doi:10.1017/S0950268818002625

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Abstract

The pathophysiological mechanisms underlying the seasonal dynamic and epidemic occurrence of bacterial meningitis in the African meningitis belt remain unknown. Regular seasonality (seasonal hyperendemicity) is observed for both meningococcal and pneumococcal meningitis and understanding this is critical for better prevention and modelling. The two principal hypotheses for hyperendemicity during the dry season imply (1) an increased risk of invasive disease given asymptomatic carriage of meningococci and pneumococci; or (2) an increased transmission of these bacteria from carriers and ill individuals. In this study, we formulated three compartmental deterministic models of seasonal hyperendemicity, featuring one (model1-‘inv’ or model2-‘transm’), or a combination (model3-‘inv-transm’) of the two hypotheses. We parameterised the models based on current knowledge on meningococcal and pneumococcal biology and pathophysiology. We compared the three models’ performance in reproducing weekly incidences of suspected cases of acute bacterial meningitis reported by health centres in Burkina Faso during 2004–2010, through the meningitis surveillance system. The three models performed well (coefficient of determination R^2 , 0.72, 0.86 and 0.87, respectively). Model2-‘transm’ and model3-‘inv-transm’ better captured the amplitude of the seasonal incidence. However, model2-‘transm’ required a higher constant invasion rate for a similar average baseline transmission rate. The results suggest that a combination of seasonal changes of the risk of invasive disease and carriage transmission is involved in the hyperendemic seasonality of bacterial meningitis in the African meningitis belt. Consequently, both interventions reducing the risk of nasopharyngeal invasion and the bacteria transmission, especially during the dry season are believed to be needed to limit the recurrent seasonality of bacterial meningitis in the meningitis belt.

Introduction

Africa has the highest contribution to the global burden of bacterial meningitis, a severe disease with up to 30% case fatality despite timely antibiotic treatment and 20% of survivors living with psychomotor sequelae (Greenwood, 1999; Rosenstein et al., 1999; Cartwright et al., 2001; Rosenstein et al. 2001). In the African meningitis belt spanning the Sahel from Senegal to Ethiopia (Molesworth et al., 2002), meningococcal and pneumococcal meningitis incidence displays a seasonal pattern during the dry season (December through May) with a 10- to 100-fold increase of weekly incidences, which subsides with the onset of the rainy season (Mueller et al., 2012; Koutangni et al., 2015).

This seasonal increase in the disease incidence in the dry season is observed every year and consistent across countries of the so-called African meningitis belt: a situation commonly described as ‘ubiquitous seasonal hyperendemicity’. In addition, localised epidemics of meningococcal meningitis occur unpredictably limited to one or few villages, with attack proportions beyond 1% (Greenwood, 1999). Despite introduction of effective and affordable conjugate vaccines against meningococcal serogroup A (in December 2010) (Daugla et al., 2014) and 10–13 pneumococcal serotypes in 2013 (World Health Organisation 2016) through mass vaccination campaigns and infant routine immunisation, respectively, this pattern continues, mainly due to the persistence of other epidemic meningococcal serogroups and high adult pneumococcal meningitis incidence. A distinction between the mechanisms underlying meningitis ubiquitous annual seasonality (hyperendemicity) and localised epidemics would have implication on how the disease is mathematically modelled and how control strategies are designed in the meningitis belt (Greenwood, 1999; Mueller et al., 2012; Koutangni et al., 2015). A better understanding of the mechanisms behind this epidemiology is therefore needed, along with appropriate mathematical models allowing the identification of optimised preventative vaccination strategies.

Previous modelling efforts relied on a wide range of unknown parameters values (Irving et al., 2012) given the lack of surveillance data from which parameters could be estimated. Others have used incidence data for model fitting at low spatial resolution, mainly data aggregated at district level (Tartof et al., 2013; Karachaliou et al., 2015). This does not allow differentiating between dry seasons with localised epidemics and dry seasons without localised epidemics, as localised epidemic usually can be seen at the health centre level only (Tall et al., 2012; Paireau et al., 2012). To go further from these previous efforts, we have developed a model in which unknown parameters values are estimated based on meningitis surveillance data at a fine spatial (health centre) and temporal (weekly) scale. This study focuses on modelling the regular seasonal hyperendemicity, observed during all dry seasons across the meningitis belt and used surveillance data from Burkina Faso for parameters estimation and model validation. Burkina Faso lies within the meningitis belt with an enhanced surveillance system for bacterial meningitis.

Two main explanations have been suggested for the hyperendemic incidence increase during the dry season. First, the climatic conditions such as low relative air humidity and high aerosol load experienced across countries of the meningitis belt during the dry season (November through May) could damage the nasopharyngeal mucosa and thus facilitate invasion of meningococci and pneumococci into nasopharyngeal tissues, which results in meningitis (Greenwood et al., 1984). The second hypothesis suggests that these climatic conditions or related behavioural changes could facilitate the bacterial transmission in the population and thus proportionally increase disease incidence (Greenwood et al., 1984). Mueller and Gessner's hypothetical explanatory model builds on the first hypothesis (increased invasion rate) (Mueller & Gessner, 2010). In a systematic review and meta-analysis of published data from the meningitis belt (Koutangni et al., 2015), seasonal hyperendemicity of meningococcal meningitis was associated with a seasonal increase of the case-carrier ratio, while the prevalence of meningococcal carriage assessed in cross-sectional carriage studies did not change with season, thus supporting the first hypothesis. However, in a multisite series of cross-sectional meningococcal carriage studies, Kristiansen et al. (Kristiansen et al., 2011) reported minor but statistically significant changes in serogroup A

meningococcal carriage prevalence between the rainy and dry season (from 0.24% to 0.62%), a finding supporting the second hypothesis (increased transmission rate). The present study aimed at using mathematical models to assess which of these competing hypotheses or their combination best explained observed hyperendemic incidence pattern of suspected bacterial meningitis in Burkina Faso.

Methods

Study setting and surveillance data

In countries of the meningitis belt, suspected cases of bacterial meningitis (as defined by the WHO) are systematically notified from the peripheral level (local health centres) to the intermediate (district) and central (national) levels since the establishment of an enhanced meningitis surveillance network in 2003 across the meningitis belt with the support of the WHO. Suspected meningitis cases are notified from the local health centres on a weekly basis and the number of cases must be reported even when there is zero case at all levels. Burkina Faso is one of the countries entirely located within the meningitis belt for which we had access to weekly counts of suspected bacterial meningitis cases at the health centres level. In the country, prior to 2010, suspected meningitis case notification was often supplemented by laboratory investigation of a subset of the notified cases; especially when epidemic threshold defined at the district level is crossed, to guide epidemic preparedness and choice of polysaccharide vaccine. Acute bacterial meningitis in the meningitis belt is most commonly caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and, since introduction of a conjugate vaccine, to a lower extent *Haemophilus influenzae* Type b (Sidikou et al., 2007; Novak et al. 2012).

Suspected and laboratory-confirmed cases correlate well usually (Mueller et al., 2006) and suggest a relatively good performance of the surveillance system and appropriateness of the data for epidemiologic studies. Until 2010, and before the introduction of serogroup A meningococcal conjugate vaccine in December 2010, meningitis epidemics were predominantly caused by *N. meningitidis* across the belt. Pneumococcal meningitis contributes to meningitis hyperendemicity and

mimics the seasonality of meningococcal meningitis across the meningitis belt (Kambiré et al., 2016). In this study, to estimate the unknown parameter values and to evaluate our models' performances, we used data from routine surveillance of suspected acute bacterial meningitis cases recorded from 2004 through 2010 in health centres in Burkina Faso (a period preceding introduction of the MenAfrivac serogroup A meningococcal vaccine). While data aggregated at the district level are available in routine surveillance reports, this database of original weekly health centre data had been compiled in a collaborative effort between the Direction de la Lutte contre la Maladie (DLM) of the Ministry of Health of Burkina Faso, EHESP French School of Public Health, and the Agence de Médecine Préventive (AMP), Paris, France. We selected four health districts (Houndé, Lena, Karangasso Vigué and Séguénéga) for the completeness of data, providing 126 health centre years. Seasonal hyperendemicity and localised epidemics are two distinct phenomena involving potentially different mechanisms (Mueller & Gessner, 2010). Therefore, we separated health centre years with localised epidemics from those with usual hyperendemic incidences, using the threshold definition of 75 weekly cases per 100 000 maintained during at least two consecutive weeks (Tall et al., 2012). Thus, only hyperendemic health centre year curves are used for models' analysis in this study. Seasonal hyperendemicity of bacterial meningitis is a regular phenomenon observed every year in the belt. Localised meningitis epidemics are irregular in the meningitis belt. Therefore, we considered a deterministic framework as a reasonable first step over a stochastic framework in modelling hyperendemic meningitis in the belt. Overall, 64 hyperendemic health centre years (out of the 126) identified based on the defined threshold were used in the primary analysis (Supplementary Fig. S1–S3).

A second threshold of 50 weekly cases per 100 000 maintained during at least two consecutive weeks was used for sensitivity analyses. This sensitivity analysis was performed to assess the efficiency of the model when using a lower incidence threshold definition of hyperendemic incidence excluding health centre years with outlier peak incidence from the primary analysis. Fifty-seven out of the initial 64 hyperendemic health centre years were then identified and used in the sensitivity analysis. We smoothed incidence time series using a simple moving

average on a 3-week window to reduce random noise in the data and the influence of instable estimates of incidence potentially due to delays in reporting. We used the SMA function in the TTR R package to achieve this.

Model structure

Similar to Irving et al. (Irving et al., 2012), we used a compartmental deterministic Susceptible –Carrier – Ill – Recovered - Susceptible (SIRS) model, which divides the population into four mutually exclusive groups (Figure 9): individuals susceptible to infection (S); asymptomatic carriers (C) who can transmit the bacteria (meningococci or pneumococci) to susceptibles; individuals ill from meningitis (I) following contagion and who are also infectious; and individuals who have recovered (R) from asymptomatic carriage or meningitis. Recovered individuals have developed temporary immunity and become susceptible once immunity has waned (Agier et al. 2017). Transition rates include rates for birth, natural death and death from meningitis (Table 2). The system of ordinary differential equations defining the model dynamic is as follows:

$$\frac{dS}{dt} = \varphi R + b - \beta_t S(C + I) - \mu S \quad 1)$$

$$\frac{dC}{dt} = \beta_t S(C + I) - a_t C - \alpha C - \mu C \quad 2)$$

$$\frac{dI}{dt} = a_t C - \rho I - (\mu + \gamma) I \quad 3)$$

$$\frac{dR}{dt} = \rho I + \alpha C - (\varphi + \mu) R \quad 4)$$

$$a_t = a_0 \left[\left(\frac{\varepsilon_a}{2} \right) \cos \left(2\pi \left(t - \frac{\theta}{365} \right) \right) + \left(1 + \frac{\varepsilon_a}{2} \right) \right] \quad 5)$$

$$\beta_t = \beta_0 \left[1 + \varepsilon_b \cos \left(2\pi \left(t - \frac{\theta}{365} \right) \right) \right] \quad 6)$$

Variables S , C , R , and I are proportions of the total population at time t in the respective compartments of the model. The models' parameters are described in Table 2.

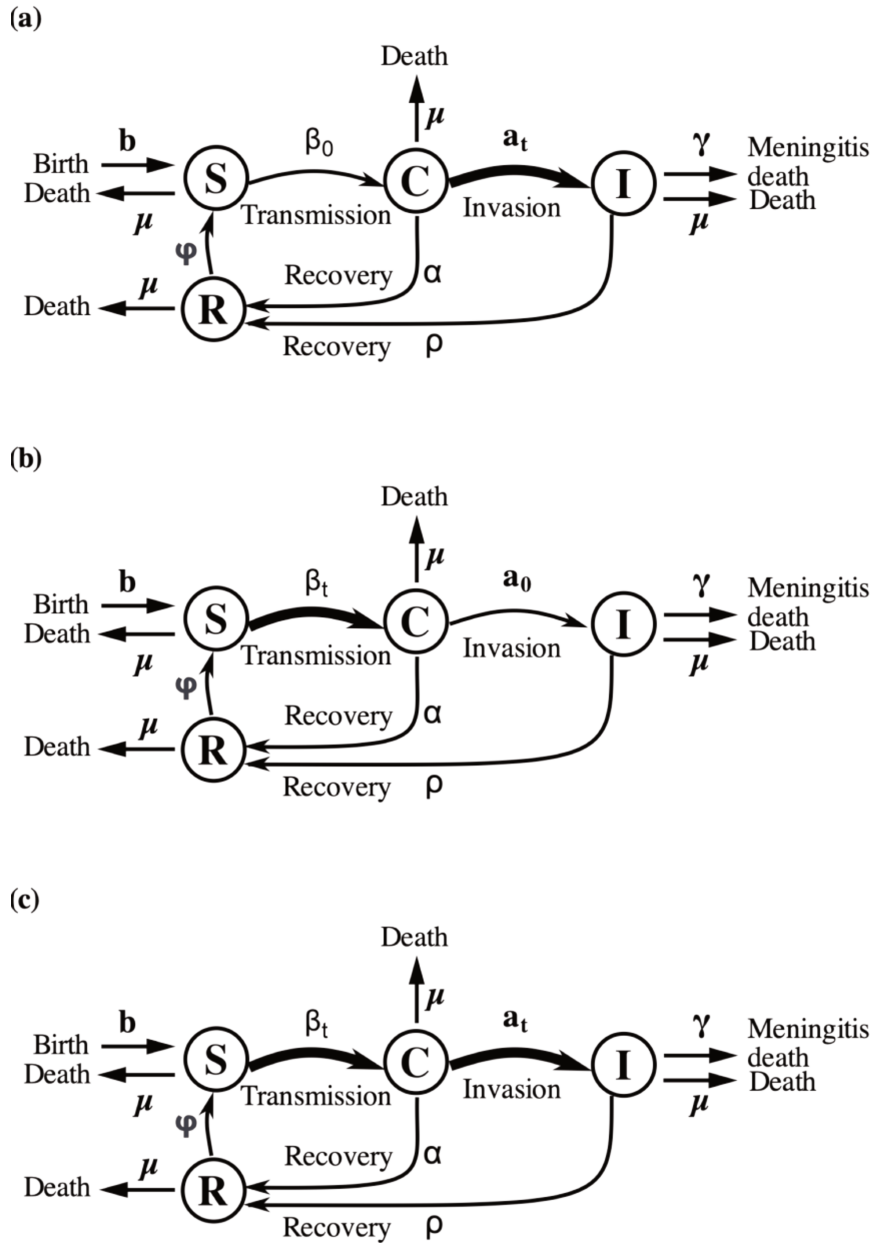


Figure 9: Flow chart of state progression of individuals between the different epidemiological classes of the SCIRS models

Thick black arrows indicate parameters with seasonal forcing. (A) model1-“inv”: seasonal forcing of the invasion rate alone, (B) model2-“transm”: seasonal forcing of the transmission rate alone, (C) model3-“inv-transm”: seasonal forcing of the transmission and invasion rate.

Table 2. Fixed and unknown parameters values and ranges

Parameter	Short Description	Plausible Range	Initial Value ^a	Unit	Comments and Sources
<i>Unknown parameters</i>					
β_0	Meningococcal mean transmission rate	>0	0.5	day ⁻¹	Unknown. Only positive values
a_0	Meningococcal mean invasion rate given carriage	0.002 – 0.012	0.007	month ⁻¹	Inferred from case-carrier ratios estimated in a systematic review, specific for season and epidemiological context (Koutangni et al., 2015).
α	Rate of loss of carriage	1 – 52	12	year ⁻¹	Unknown, carriage duration between 1 week and 1 year, range inferred from (Kambiré et al., 2016; Agier et al., 2017).
ϕ	Rate of loss of natural immunity	0.2 – 12	4	year ⁻¹	Unknown, persistence of natural immunity of between 1 month and 5 years, range inferred from (Kambiré et al., 2016; Blakebrough et al., 1987).
ε_a	Amplitude of seasonal forcing of invasion rate	0 – 100	50		An amplitude of 0 means that the baseline invasion rate remains constant across seasons; of 100 means it increases up to 100- fold.
ε_b	Amplitude of seasonal forcing of meningococcal transmission rate	0 – 1	0.5		An amplitude of 0 means that the baseline transmission rate remains constant across seasons, and values up to 1 means presence of seasonality.
θ	Calendar day of maximal invasion rate	91 – 112	97		Assuming correlation with aerosol load during period of relative humidity <40% (calendar week 13 through 16)(Norheim et al., 2008) .
S_0	Proportion of initial susceptibles in the population	0 – 1	0.5		The proportion of susceptible at the beginning of the calendar year (January 1 st .)
C_0	Proportion of initial carriers in the population	0 – 1	0.01		The proportion of carriers at the beginning of the calendar year (January 1 st)
<i>Fixed parameters values</i>					
γ	Death rate from meningitis	5.2		year ⁻¹	Case fatality = 10% (Greenwood, 1999)
μ	Natural death rate	0.02		year ⁻¹	Life expectancy = 54 years (Boisier et al., 2007)

ρ	Recovery rate	52	year ⁻¹	Acute phase of bacterial meningitis disease lasts a week on average (Martiny et al., 2012)
b	Birth rate	$b = \mu + \gamma I$	year ⁻¹	Scaled to keep total population size constant

^a Values used as initial values for parameters optimization routine.

Seasonality

To represent the two hypotheses of increased invasion or transmission rate during the dry season, we included seasonal forcing of the transition rate to invasive disease given carriage (model1-“inv”), or the bacterial transmission rate (model2-“transm”), or both (model3-“inv-transm”). The invasion and transmission parameters (a_t and β_t) were represented with periodic sinusoidal functions (equations 5 and 6). Based on the explanatory model by Mueller and Gessner (Mueller & Gessner, 2010), and the systematic review of season specific case-carrier ratio in the meningitis belt (Koutangni et al., 2015; Mueller & Gessner 2010), the case-carrier ratio (a proxy for the risk of invasive meningitis given colonization) could increase up to 100 –fold during the dry season. We included this information by parameterizing the periodic function of the invasion rate such that variations of up to 100 –fold are possible in the dry season depending on the seasonal forcing amplitude (ϵ_a) estimate which can take on values from 0 to 100. The seasonal forcing amplitudes ϵ_a and ϵ_b dictate the magnitude of seasonal variation of the invasion and transmission rate respectively (equation 5 and 6).

Model assumptions

The model structure assumed a steady and well-mixed population with frequency-dependent transmission. Age-structure of the population was deliberately not included in this proof of concept. However, the potential effects of heterogeneous mixing were explored in complementary analyses. Immunity from asymptomatic carriage and disease was assumed temporary. We assumed immunity provided by carriage and disease to be of similar duration, and asymptomatic carriers are as likely as ill individuals to transmit the infection to a susceptible. Ill individuals may be at greater risk to transmit only from vomiting but are usually bound to bed.

Parameterization

We obtained parameters values including natural death rate, death rate from meningitis, recovery rate after bacterial meningitis, and birth rate from the

scientific literature (Table 2). Case fatality rates of 10 to 15% were reported during serogroup A epidemics meningitis in the meningitis belt (Greenwood 1999). We inferred natural death rate as the inverse of life expectancy at birth, (average life expectancy was 54 years in Burkina Faso) (The World Fact Book, 2015), and the average recovery rate as the inverse of duration of acute phase of meningitis, (acute phase of bacterial meningitis would last a week on average) (Stephens et al., 2007) (Table 2). Parameters that are not available in the literature were estimated using suspected bacterial meningitis cases report data from Burkina Faso; a country within the meningitis belt. The data consist of weekly counts of new suspected cases of bacterial meningitis recorded at health centers of 4 four districts of the country from 2004 to 2010 together with the population sizes covered by each health center. The estimated parameters were: the average meningococcal transmission and invasion rates, the amplitudes of seasonal forcing of transmission and invasion rates, the rate at which asymptomatic carriers and ill individuals recover, the duration of temporary immunity, and the timing of weekly incidence peak relative to January 1st. Initial susceptibles and carriers population size at the start of calendar years were also estimated for each health centre year hyperendemic's curves, as they could not be inferred directly from the literature. We limited the space of potential parameters values to be tested to plausible values according to published literature if possible (Table 2). For example, we used the 95% confidence interval of the meningococcal case-carrier ratio estimate during the dry hyperendemic season in the meningitis belt (Koutangni et al. 2015) as plausible values range for the average bacterial invasion rate (a_0). We estimated all unknown parameters values using a maximum likelihood approach. For each model, parameters values were selected to maximize the Poisson likelihood of observed bacterial meningitis incident cases. We used the COBYLA algorithm, a derivative-free optimization algorithm, implemented in the R package **nloptr** for parameters optimization routine (Powell, 1994). We chose this algorithm for its relatively fast, it allows good convergence of the coefficients estimated on our data, and it supports optimization constrains such as parameter range. Several initial values were tested, and best-fit parameters estimates were obtained after 40000 iterations. Implementations details of the optimization routine are provided in Supplementary Material S1. In the complementary exploratory analysis

investigating heterogeneous mixing of the population age groups in the models, we inferred the effective contact matrix from age-specific force of infection estimates in dry season with “minor epidemics” as reported by Tartof et al. (Tartof et al., 2013) in Burkina Faso.

Model simulation and evaluation

We implemented and simulated the models using R statistical computing software (R Core Team 2015), and the lsoda function (deSolve package) for numerical integration of the ordinary differential equations with 1-day time step. We computed weekly incidence as:

$$\int_t^{t+(1/52)} a_t C dt \quad (7)$$

With $a_t C$, the proportion of asymptomatic carriers who becomes ill at time t .

We quantitatively assessed the models’ performance accuracy using the coefficient of determination (R^2), the Percent Bias (PB), and the ratio of the Root-Mean-Squared-Error (RMSE) to observation standard deviation (RSR) (Supplementary Material S1). These three statistics quantify errors in models’ predictions. Percent bias compute the average absolute bias in model predictions of observations. It gives an indication on whether the model results are consistently under- or overestimated compared to the observations (Moriasi et al., 2007). The optimal value of PB is 0. RSR standardizes the RMSE using the observations standard deviation. It incorporates the benefits of error index statistics and includes a scaling/normalization factor, so that the resulting statistic can be compared across data with different variance. The lower RSR, the better the model simulation performance. We also compared carriage prevalence predicted by the models with carriage prevalence reported by series of meningococcal carriage studies and a review of carriage during wet endemic and dry hyperendemic seasons in the meningitis belt (Koutangni et al., 2015; Kristiansen et al., 2011; Leimkugel et al., 2007).

We assessed the models' performance qualitatively by visual inspection of trajectories matching plots of model predictions of weekly incidence and observed data, and the ability of the models to fit data across all health centre years with a relatively good accuracy, i.e., capture both the seasonal trend in data, as well as timing and amplitude of observed seasonal peaks. Finally, the three models were compared based on their Akaike Information Criteria (AIC) to account for model complexity associated with the number of input parameters. The lower the model's AIC the better and an absolute difference in AICs between 0-2 was considered weak to distinguish two models.

Uncertainty and parameter sensitivity analysis

The Latin Hypercube Sampling (LHS) uncertainty technique (Blower & Dowlatabadi, 1994) was used to assess the model robustness to varying fixed and estimated parameters values (uncertainty analysis). Primarily, we evaluated the effect of parameters estimates uncertainty on predictions of the annual cumulative meningitis incidence and the annual average asymptomatic carriage prevalence. The estimates of these two model's state variables were obtained from the results of uncertainty analyses, and their distribution described for each model. Probability distribution functions (pdfs) of the estimated parameters were unknown. Therefore, we set the parameters pdfs to the uniform distribution. We also set the minimum and maximum values of the uniform distributions to be the 1st and 3rd quartiles of each of the estimated parameters distribution per model. Models were simulated with each of 1000 sets of parameters values sampled based on the LHS schema. We sampled a large number of values (1000) without replacement, within the boundaries of each parameter space to ensure that a great number of plausible parameters values combinations were explored. We calculated Partial Rank Correlations Coefficients (PRCC) between each of the estimated parameters and the sensitivity outcome variable: the annual cumulative incidence of meningitis cases. Scatterplots (of each input parameter against the sensitivity outcome variable) were generated to check that the assumption of monotonicity was satisfied. The sign of the PRCC identifies the specific qualitative relation between each of the estimated parameters and the sensitivity

outcome variable. We used the PRCC to identify key parameters that contributed the most to the models' predictions imprecision.

Results

Model fit

The three models reproduced the weekly incidence of meningitis cases across the sixty-four health centre years with a good accuracy. Median R^2 over all health centre years was 0.72, 0.86, and 0.87 for model1-“inv”, model2-“transm”, and model3-“inv-transm” respectively (Table 3). On average, Model1-“inv” underestimated observed values, namely the peak incidence values (highest weekly incidence in the year) by two per cent, while model2-“transm” and model3-“inv-transm” overestimated observed incidences by five per cent and one per cent respectively. The error rates of the three models were relatively low but model 1-“inv” had an error rate (RSR = 0.52) that is about 40% higher than for model2-“transm” and model3-“inv-transm” (Table 3). Adding annual seasonality of the transmission parameter to seasonality of the invasion rate (model3-“inv-transm”) improved the weekly incidence predictions of model1-“inv” overall (R^2 and error rate RSR improved). However, the gain in prediction accuracy was marginal when comparing model3-“inv-transm” to model2-“transm” performances (Table 3).

The Akaike information criterion (AIC) of the three models were on average similar, suggesting that the models cannot be distinguished based on their quantitative performance alone (mean AIC = 46, Standard deviation SD = 19 for model1-“inv”; mean AIC = 44, SD = 20 for model2-“transm” and mean AIC = 46, SD = 20. Trajectories matching plots between the models predictions of weekly incidences and data at each health centre year suggested that seasonal trends in data were captured well by the three models, but model2-“transm” and model3-“inv-transm” captured annual peaks of disease incidence better than model1-“inv” in some health centre-years (Figure 10, supplementary Fig S1, Fig S2, and Fig S3).

Model1-“inv” involved an average 2.9 fold-increase, SD = 5.5 of the baseline invasion rate, while model2-“transm” involved an average 2.0 fold-increase, SD = 0.3, of the baseline transmission rate. When both seasonality of the invasion and transmission rate is included (model3-“inv-transm”), an average 2.0 fold increase, SD = 1.2 of the invasion rate is involved versus an average 1.6 fold increase of the transmission, SD = 0.3.

The weekly carriage prevalence predicted by all three models during endemic wet season were <1% and in agreement with meningococcal serogroup A carriage prevalence studies outside epidemic periods in the meningitis belt (Koutangni et al. 2015; Kristiansen et al. 2011). During the dry season, the median value of weekly carriage prevalence peaks (across all 64 health centre years) was 12%, (1st, 3rd quartile = 7%, 18%) for model1-“inv”; 17%, (1st, 3rd quartile = 13%, 26%) for model2-“transm”; and 11%, (1st, 3rd quartile = 15%, 25%) for model3-“inv-transm”. Including age-structure in the models did not improve the models fit to data nor significantly change the results. This complementary analysis and the fits results are presented in Supplementary Material S2.

Table 3. Quantiles of the distributions of parameters estimates across the 64 health center years per model.

Parameters	Model1-inv			Model2-trans			Model3-inv-trans		
	25%	50%	75%	25%	50%	75%	25%	50%	75%
Baseline transmission /day (β_0)	0.312	0.349	0.413	0.229	0.326	0.451	0.274	0.332	0.507
Carriage duration (weeks) (α)	1.002	1.1611	1.4187	1.0027	1.0027	1.190	1.0027	1.0658	1.3336
Immunity duration (years) (φ)	1.640	2.374	5.000	0.701	1.108	5.000	0.866	1.554	5.000
Initial susceptibles (S_0)	6443.310	7128.267	8205.869	4282.658	6289.297	8356.209	4199.00	6002	6712
Initial carriers (C_0)	1.000	1.000	1.251	1.000	1.000	1.558	1.000	1.000	1.201
Peak time (week number) (θ)	13	14	14	14	14	15	13	14	14
Seasonal forcing of invasion (ε_a)	0.002	0.004	0.012	-	-	-	0.002	0.005	0.013
Baseline invasion (a_0)	1e-4	1e-4	1e-4	1e-4	2e-4	2e-4	1e-4	1e-4	2e-4
Seasonal forcing of transmission (ε_b)	-	-	-	0.822	0.970	1.000	0.700	0.847	0.970

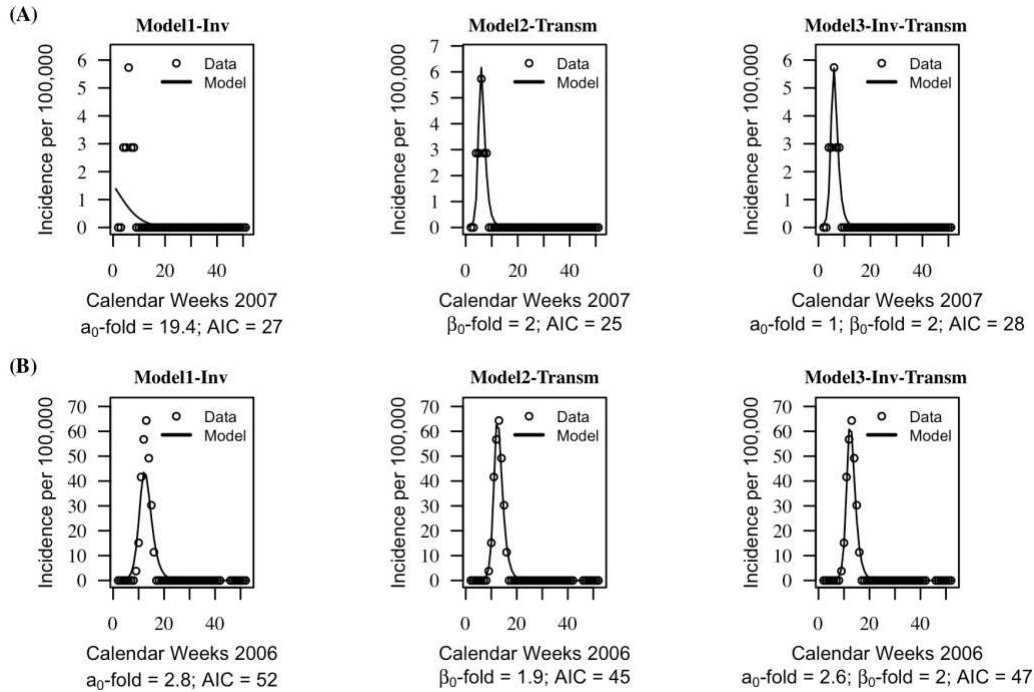


Figure 10. Trajectory matching plots of observed weekly incidence data and models' predictions.

Data (hallow circles), and models' predictions (black solid line). (A) Health centre year with the poorest-fitted data. (B) Health centre year with the best-fitted data. a_0 -fold and β_0 -fold indicate the seasonal -fold increase of the invasion and transmission rate (respectively) relative to their baseline or average value. Model1-“inv”: seasonal forcing of the invasion rate alone, model2-“transm”: seasonal forcing of the transmission rate alone, and model3-“inv-transm”: seasonal forcing of the transmission and invasion rate. Trajectory matching plots for all 64 health centre years are provided in supplementary Fig S1, Fig S2, and Fig S3. Simulations are based on best fit estimates of the parameters.

Parameter estimation

Estimates of the baseline transmission rate were similar in the three models, as were estimates of the average duration of immunity, the timing of weekly incidence peak, and the initial susceptibles population size in model2-“transm” and model3-“inv-transm”. However, with model1-“inv”, duration of immunity tended to be longer, and the initial susceptibles population size larger

(Figure 11, Table 3). The average invasion rate estimated by model2-“transm” was four-fold higher than that of model1-“inv” and model3-“inv-transm”. Overall, parameter estimates with model3-“inv-transm” had smaller between-health centres variances than with model1-“inv” and model2-“transm” (Figure 11, Table 3). Sensitivity analyses with hyperendemic health centre years defined as 50 weekly cases per 100000 maintained during at least two consecutive weeks did not yield substantially different results (data not shown).

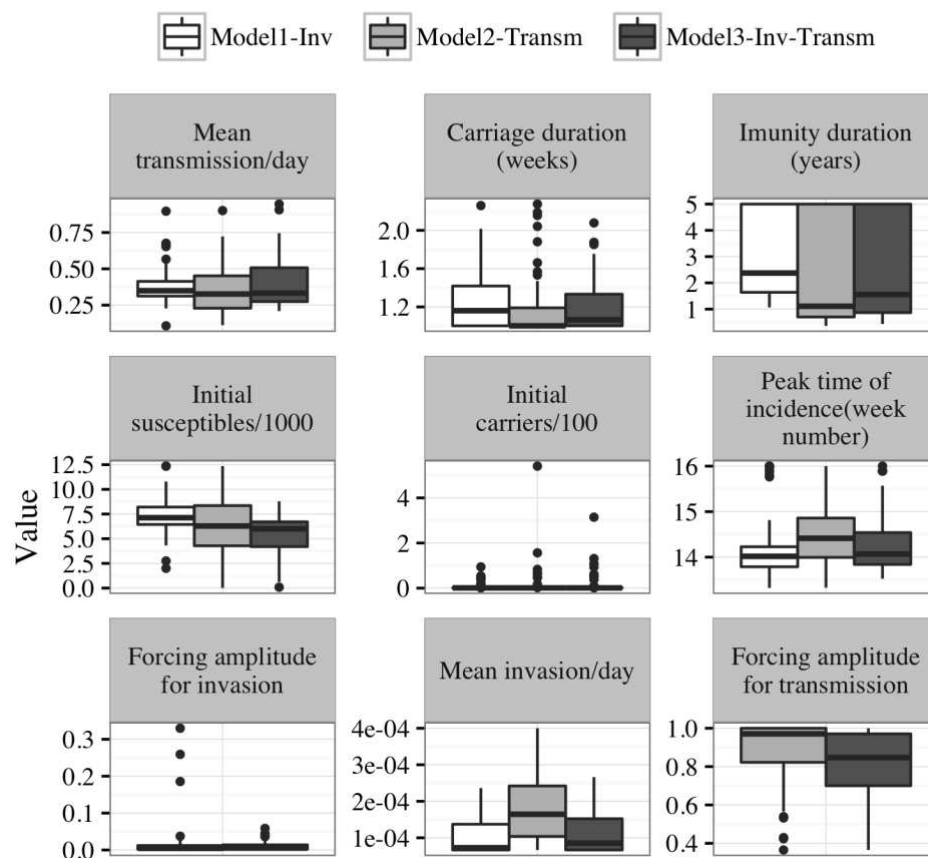


Figure 11. Boxplot showing the distribution of parameters estimates across all health centres years per model.

The boxes include 50% of the distribution, and dots represent outliers’ values. Tick horizontal lines in the boxes represent the median value of the estimates. Values below the boxes are less than the 25th percentile and values above the boxes are greater than the 75th percentile of the distributions. Initial susceptibles and carriers’ populations estimates are reported as proportion of the population as

of 1st January of the calendar years. Model1-“inv”: seasonal forcing of the invasion rate alone, model2-“transm”: seasonal forcing of the transmission rate alone, and model3-“inv-transm”: seasonal forcing of the transmission and invasion rate

Uncertainty and parameters sensitivity

Uncertainty analysis results (Table 4) show that the prediction precision of the three models is low due to high degree of estimation uncertainty for the baseline values of the estimated parameters. Model2-“transm” has the higher prediction imprecision with a larger variance of the predicted annual cumulative incidence : 6346 compared to 439 for model1-“inv”, and 731 for model3-“inv-transm”. Uncertainty in estimating five of the nine estimated parameters was most critical in affecting the prediction precision of the three models. The five most critical parameters were the baseline transmission and invasion rates, average duration of asymptomatic carriage, the duration of immunity to infection and disease and the initial susceptibles population size (Table 5). The effect of uncertainty of carriage duration on prediction imprecision was more important with model1-“inv”, than with model2-“transm” and model3-“inv-transm”. Parameter sensitivity ranking based on the PRCCs indicates that with model1-“inv”, the baseline invasion rate was the most sensitive parameter, followed by the duration of asymptomatic carriage. With model2-“transm”, the most sensitive parameters were duration of immunity to infection and disease, and the baseline invasion and transmission rate. With model3-“inv-transm”, the baseline transmission and population immunity were the first two most critical parameters. However, initial proportion of carriers at the beginnings of the dry season also appears critical for the later (Table 5).

The positive value of the PRCC for the majority of the estimated parameters values implies that when the values of these input parameters increases, the future number of meningitis cases will increase. As immunity wanes quickly, the future number of meningitis cases is likely to increase. One possible way this can occur is by fast replenishment of the pool of susceptible individuals. With higher pool of susceptible individuals and lower population level immunity, comes increased likelihood of effective transmission of infection.

Table 4. Description of Predicted Annual Incidence and Weekly Carriage Prevalence (Averaged over the Year) using 1000 Combinations of Parameters Values from the Latin Hypercube Sample

Values	Annual incidence per 100,000 inhabitants			Average weekly carriage prevalence (%)		
	Model1	Model2	Model3	Model1	Model2	Model3
Minimum	28.70	0.06	0.28	0.90	0.00	0.01
Maximum	125.4	355.0	139.0	3.8	3.7	3.5
Mean	67.0	115.0	59.0	1.9	1.6	1.8
Median	62.3	105.0	54.0	1.8	1.5	1.7
Variance	439.9	6346.0	731.0	0.3	0.7	0.6
5th percentile	37.70	1.50	18.00	1.10	0.02	0.70
95th percentile	108.8	273.0	110.0	2.7	3.1	3.2

Table 5. Partial Rank Correlation Coefficients (PRCC) Between the Latin Hypercube Samples of estimated parameters and the Annual Cumulative Incidence of Meningitis (Sensitivity Analysis).

Parameter	Short description	Model1-“inv”		Model2-“transm”		Model3-“inv-transm”	
		PRCC ^a	95% Confidence Interval	PRCC	95% Confidence Interval	PRCC	95% Confidence Interval
β_0	Meningococcal mean transmission rate	0.76***	0.68, 0.84	0.80***	0.75, 0.86	0.91***	0.88, 0.96
a_0	Meningococcal mean invasion rate	0.90***	0.86, 0.96	0.84***	0.76, 0.94	0.81***	0.75, 0.89
α	Rate of loss of carriage	-0.89***	-0.93, -0.86	-0.49***	-0.65, -0.31	-0.63***	-0.75, -0.54
φ	Rate of loss of natural immunity	0.80***	0.73, 0.88	0.87***	0.82, 0.93	0.90***	0.87, 0.95
θ	Calendar day of maximal invasion rate.	0.18	-0.01, 0.36	0.03	-0.17, 0.27	-0.04	-0.26, 0.19
ε_a	Seasonal forcing amplitude of invasion rate	-0.15	-0.34, 0.05	NA	NA	-0.025	-0.25, 0.22
ε_b	Seasonal forcing amplitude of meningococcal transmission rate	NA ^b	NA	0.18	0.03, 0.37	-0.11	-0.31, 0.11
S_0	Initial Susceptibles' Proportion	0.86***	0.81, 0.93	0.73***	0.66, 0.84	0.81***	0.74, 0.90
C_0	Initial Carriers' Proportion	0.09	-0.08, 0.33	0.11	-0.095, 0.28	0.22*	0.04, 0.40

^a Partial Rank Correlation Coefficients estimates are significantly different than 0 at 0.05 level (*), and $<10^{-10}$ level (***) two-sided p values. They quantify the statistical relationship between each parameter and the model output.

^b NA stands for Not Applicable to the model.

Discussion

This modelling study is a first attempt to fit compartmental models based to surveillance data of suspected bacterial meningitis at a fine spatial (health centre) and temporal (weekly) scale in the African meningitis belt. Two publications, by Karachaliou et al. (Karachaliou et al., 2015) (building on Irving et al. work (Irving et al., 2012)), and Tartof et al. (Tartof et al., 2013) used meningitis compartment models to evaluate long-term vaccination strategies with serogroup A conjugate vaccine. Both studies included seasonal change of the transmission and invasion rate in an age-structured model but did not aim at comparing models with different types of seasonal forcing with regard to the transition from endemic to hyperendemic situation. Our study aimed at investigating the pathophysiology of the seasonal hyperendemicity of bacterial meningitis in this region at a fine scale, which is extraordinarily pronounced with a 10- to 100-fold increase observed every year in all districts (Mueller et al., 2012; Koutangni et al., 2015). We found that compartmental models using seasonal forcing of risk of invasive disease given carriage, transmission, or both, all produced seasonal disease incidence patterns consistent with the observed data, while models containing a seasonal effect on transmission improved the fit of seasonal incidence peaks. The latter finding appears to be somewhat in contrast with the hypothetical model presented by Mueller and Gessner (Mueller & Gessner, 2010).

While the three models required similar estimates of the endemic transmission rate to reproduce the observed disease incidence, the model including seasonality of transmission only (model2-“transm”) involved a 2 to 4 times higher endemic invasion rate. This suggests that it is not sufficient to have higher transmission in the dry season to accurately reproduce the observed hyperendemicity, the level of meningitis disease risk given colonization is important as well. Also, we found that seasonal change occurred in both the transmission and invasion rate in the model including seasonality of these two parameters. Our findings seem to conflict with results from Tartof et al. (Tartof et al., 2013) who published an age-structured model of MenA in the meningitis belt

showing that observed data trends could be explained by a model with varying infection rates, but little seasonal variation in risk of disease given colonization. Adding a similar age-specific contact pattern to our models did not significantly change our results nor improve the fit to the data (Supplementary Material S3). The age-specific contact matrix (Supplementary Material S2) for this complementary analysis was extrapolated from Tartof et al. (Tartof et al., 2013) article and its supplemental materials, which may have its own limitations. However, discrepancies with the Tartof et al. study may be explained by differences in the spatial scale and scope of data analyses. Tartof et al. used data aggregated at the district or national level and aimed at explaining the occurrence of larger epidemic clusters or epidemic waves spanning several consecutive years. In contrast, our exercise aimed at studying the transition from endemic to hyperendemic situations, excluding localized epidemics detected based on high resolution data (health centre level). The two models therefore differ in aim and spatial scale. Their use of larger scale data, i.e. district or national while we use local health centres, may prevent from accurately discriminating epidemic from regular hyperendemic events, thus mixing two distinct disease spreading mechanisms. Until appropriate contact pattern data from the meningitis belt population become available, our complementary analysis of the models including an age-structured of transmission (Supplementary Material S2, and Supplementary Material S3) should be considered exploratory.

The average annual carriage prevalence estimates from our models' uncertainty analysis exceeded one per cent (1.9%). Carriage prevalence studies conducted in the meningitis belt show that, outside of epidemics, MenA carriage prevalence rarely exceeds one per cent. Lack of serogroup specific surveillance data for our model estimation may explain this behavior, and the obtained carriage estimates represent both meningococci and pneumococci, all serogroups and type combined. Carriage studies using classical swabbing and culture inoculation techniques may have also underestimated prevalence of nasopharyngeal carriage (Mueller et al., 2012; Basta et al., 2013; Sim et al., 2000; Manigart et al., 2016). Seasonal variations of the transmission rate in each health centre year appear to mirror the small or absent seasonal variations of carriage prevalence observed in

available epidemiological studies (Kristiansen et al., 2011; Leimkugel et al. 2007).

The model including only seasonal forcing of invasion (model1-“inv”) required a substantially longer persistence of natural immunity following carriage or disease (median = 2.5 years vs 1 and 1.5 years), where the few serological studies available suggest rather shorter immunity persistence (Mueller et al., 2006; Norheim et al., 2008). An additional limitation of model1-“inv” was its lower accuracy in reproducing annual peaks of data in several health centre years, which was improved by an additional forcing of the transmission rate. An explanation for this could be that some health centre-years incidence curves were classified as hyperendemic incidence based on the epidemic threshold definition used but were small-localized outbreaks resulting essentially from an accelerated transmission of the bacteria in the community as explained in the explanatory model suggested by Mueller and Gessner. However, sensitivity analyses with a lower epidemic threshold (50 weekly cases per 100000) did not impact the models’ results.

The fold-increase of the transmission rate was not systematically higher than that of the invasion rate. It appears that both pathophysiological mechanisms are relevant and may reflect the impact that climatic conditions have on bacterial meningitis.

This study builds on the model published by Irving et al. (Irving et al., 2012) who investigated how well simple deterministic models were able to qualitatively reproduce the meningitis epidemiology in the African meningitis belt. Their study was limited to larger epidemic waves that are observed every 7-10 years at the national level and did not use surveillance data for parameterization or evaluation of model performance. The authors found that the model captured the irregular pattern of meningitis epidemics qualitatively and concluded, under the assumption of an increased bacterial transmission during the dry season, that the dynamics of population immunity could explain disease dynamics. Our study focused on hyperendemic incidences during the dry season, and results from the two studies should be considered as complementary, in particular as; as suggested by Mueller and Gessner (Mueller & Gessner, 2010),

hyperendemicity, localized epidemics and epidemic waves may be distinct phenomena with distinct pathophysiological and epidemiological mechanisms. However, it appears essential to use surveillance data for parameterization and quantitative evaluation. The availability of such data at high spatial (health centre) and temporal (weekly) resolution will allow adapting our model to reproduce the occurrence of localized epidemics, epidemic waves and meningitis incidence at the regional level using meta-populations models. Eventually integrating immunization interventions, such models will serve to develop optimized vaccination strategies against meningococcal and pneumococcal meningitis. We identified key parameters for which more data from clinical and epidemiological studies are needed to improve prediction, in particular duration of immune protection and carriage episodes, rates of invasion and transmission of the bacteria, and their variation by season.

Our study has some limitations inherent to the deliberately simple model structure and assumptions. We assumed that mixing among individuals was homogeneous. Meningococcal carriage and disease affect different age groups at different rates (Leimkugel et al. 2007) and it is expected that contacts will be more intense between individuals in the same age group, in particular for older children and young adults. Limitations inherent to our extrapolation of age-specific contact pattern from Tartof et al. article may have prevented our age-structured model from achieving better fit to the data than the simpler model. Similarly, we assumed only one level of protection against carriage and disease, given the sparsity of evidence, while models evaluating vaccination strategies will require more distinct assumptions.

We used sinusoidal functions to force the seasonality of the transmission and invasion parameters, while an improved approach could consist in modelling these two parameters as a function of climatic variables, such as mean aerosol load, that are known to correlate well with seasonal meningitis incidence (Agier, et al. 2013; Martiny & Chiapello, 2013; García-Pando et al., 2014). In some health centres with small population size, we had to limit the effect of random noise in the data by smoothing the time series to focus on the underlying seasonal trend. Chance variations of some unknown parameters, in particular the extent of

climate conditions changing from year to year, was not explicitly included in the model structure. We addressed this in part by fitting the parameters on a yearly basis rather than using a single multiple year time series. However, stochastic models may be more appropriate when these fluctuations are important. Stochastic models shall be explored in the future for they appear to be particularly relevant when modeling localized epidemics. We used a model structure of overall meningococcal carriage and infection. The epidemiology of carriage likely differs between meningococcal and pneumococci meningitis but the limited knowledge about both bacteria dynamics made it challenging to adapt the proposed model to include pneumococci carriage data. Finally, our analysis carried on hyperendemic bacterial meningitis, i.e. both meningococcal and pneumococcal meningitis, assuming similar pathophysiologic mechanisms (Traore et al., 2009). This assumption may not hold with regard to a variety of factors, including age structure of carriage, duration of carriage and immunity. However, given the lack of pathogen-specific meningitis surveillance data over a long period and in a large area, our approach appears justified, while it should be improved as appropriate surveillance data become available.

Despite these limitations, our findings suggest that the ubiquitous hyperendemicity of bacterial meningitis during the dry season in the African meningitis belt occurs due to a combination of increased risk of meningitis given asymptomatic carriage and meningococcal transmission. Despite the description of this phenomenon by Lapeyssonnie (Lapeyssonnie, 1963) more than 50 years ago, the biological mechanisms for this pronounced seasonality remain largely unknown and little is known about the impact of aerosols and low air humidity on the human mucosal structures, immune system, and interaction with the bacteria.

Acknowledgements

We acknowledge staff of health centres in Burkina Faso who participated in the meningitis surveillance, the Ministry of Health of Burkina Faso, The Ecole des Hautes Etudes en Santé Publique, Rennes, France, and the Agence de Médecine Préventive, Ouagadougou, Burkina Faso for their collaborative effort in combining and making the surveillance data available for used in this study.

Funding: This work was supported by the Université Pierre et Marie Curie, Paris 6.

Declaration of interest: None

Article 2' supporting information

Supplementary Material S1. Model Fitting and Parameters Estimation.

We used maximum likelihood approach to numerically estimate the models unknown parameters and reproduce the observed trend in bacterial meningitis.

For each model, we compute the log likelihood of the data given the model predictions and its parameters. Parameters were choosing to maximize the Poisson Log-likelihood (logL) of observed data series.

Given a set of N data points representing weekly number of reported meningitis cases, k_w (with $w = 1, 2 \dots N$) by a given health center and year, the probability or likelihood L of observing those data points with model predictions for each point, λ_w , is:

$$L = \prod_{w=1}^N \frac{\lambda_w^{k_w} e^{-\lambda_w}}{k_w!} \quad (1)$$

The log-likelihood to maximize was therefore defined as

$$\log L = \sum_{w=1}^N (k_w \log \lambda_w - \lambda_w) \quad (2)$$

Again, k_w and λ_w are the observed and simulated cases for week w respectively, and N is the number of weeks of the calendar year (typically 52 or 53).

The process of finding the set of parameters values that maximize the Poisson Log-likelihood of observed data was conducted using the COBYLA algorithm, a derivative-free optimization algorithm (implemented in R package nloptr [1, 2]) which allows setting lower, and upper bounds on the parameters space to search as well as nonlinear constraints. We defined a constraint on the average magnitude of change of carriage prevalence between the wet endemic and dry hyperendemic season, to reflect that observed in a carriage study [3]. We also set lower and upper bounds on the parameter space to search based on the scientific literature if possible. Because the COBYLA algorithm implementation was design to minimize an objective function, we rather minimized the negative log likelihood (-logL), which is equivalent to maximizing the logL.

$$\boxed{-\log L = \sum_{w=1}^N (-k_w \log \lambda_w + \lambda_w)} \quad (3)$$

We run the 3 models separately with each of the health center-year data. An optimal solution was reached before the set maximum number of iterations (40000). We then simulate each model with its best-fit parameters estimates and compare it predictions of weekly cases with the health center-year weekly incident cases reports.

Models performances and comparison.

To evaluate how well each model performs in predicting a given health center year incidence data we used the following criteria.

The coefficient of determination (R^2). This quantity measured the amount of variance in the health center-years data explained by a given model.

$$\boxed{R^2 = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y}_i)^2}} \quad (4)$$

y_i is the observation data point, \hat{y}_i its predicted value, and \bar{y}_i the mean of the n observation data points.

The percent bias (PBIAS) measures the average trend of simulated values to be smaller or larger than their observed ones. The optimal value of PBIAS is 0.0, with low-magnitude values indicating accurate model simulation. Positive values indicate overestimation bias, whereas negative values indicate model underestimation bias [4].

$$\boxed{PBIAS = \left(\frac{\sum_{i=1}^n (\hat{y}_i - y_i)(100)}{\sum_{i=1}^n (y_i)} \right)} \quad (5)$$

Another model evaluation statistic used was the Ratio of the Root Mean Squared Error between simulated and observed values to the standard deviation of the observations (RSR). RSR standardizes the Root Mean Squared Error using the observations standard deviation, and has the benefits of combining both an error index and scaling/normalisation factor (Legates and McCabe, 1999). RSR varies from the optimal value of 0.0, which indicates zero RMSE and therefore perfect model simulation, to a large positive value. The lower RSR, the lower the RMSE, and the better the model simulation performance.

$$RSR = \frac{[\sqrt{\sum_{i=1}^n (y_i - \hat{y}_i)^2}]}{[\sqrt{\sum_{i=1}^n (y_i - \bar{y}_i)^2}]} \quad (6)$$

To compare and determine which model was most realistic regarding its ability to reproduce observed meningitis cases reports while accounting for model complexity, we computed the Akaike Information Criteria (AIC). The AIC was computed as follows: $AIC = 2p - 2\ln(L)$ where p is the number of estimated parameters of the model and L the maximum likelihood. The lower the AIC the better the model. As a rule for decision we considered as model significantly different than another if the absolute difference in their AIC is at minimum of 2 units.

Supplementary materials

All supplementary figures are provided below. They are also available for download at Epidemiology and Infection Journal website using this link:

<https://www.cambridge.org/core/journals/epidemiology-and-infection/article/compartmental-models-for-seasonal-hyperendemic-bacterial-meningitis-in-the-african-meningitis-belt/3A511F9A1E04935A99FB237B37C32104#fndtn-supplementary-materials>

S3 Fig 1. Model1-"inv" trajectories matching plots of simulated (black curve) and observed (black dots) weekly data, for 64 health center-years with complete data, across four health districts of Burkina faso (2004–2010).

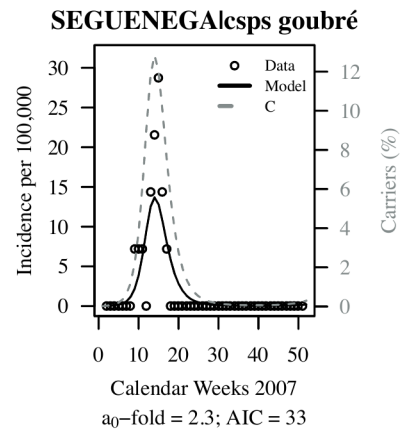
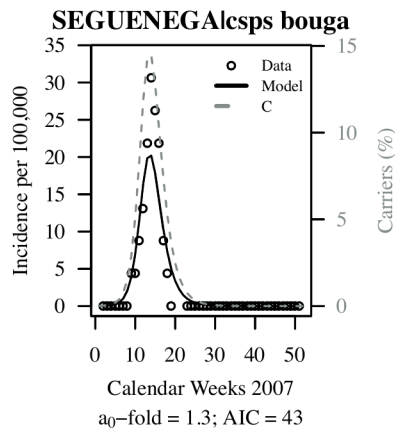
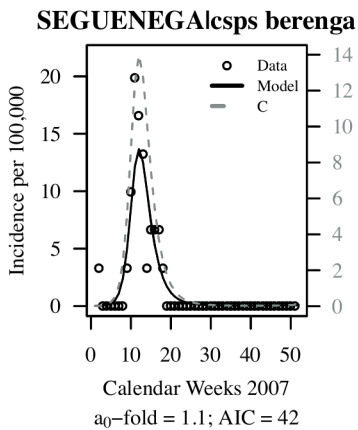
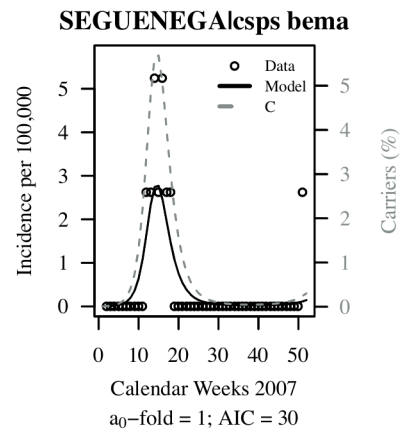
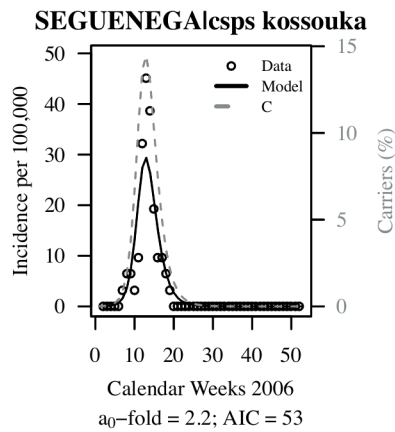
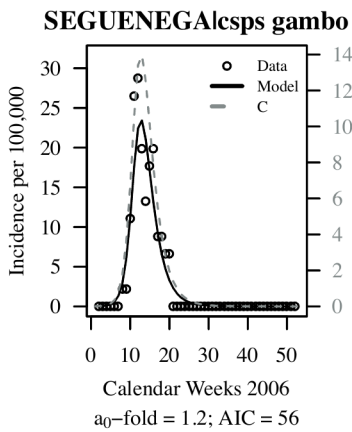
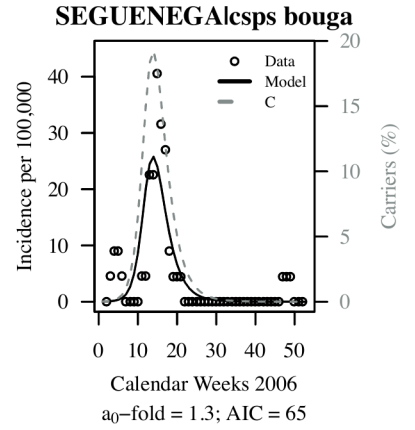
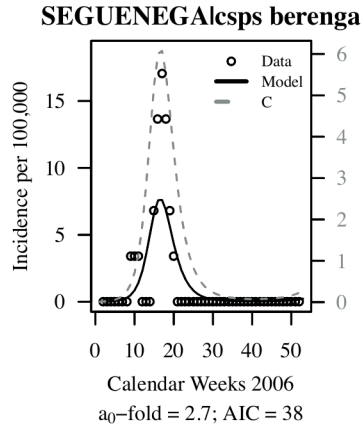
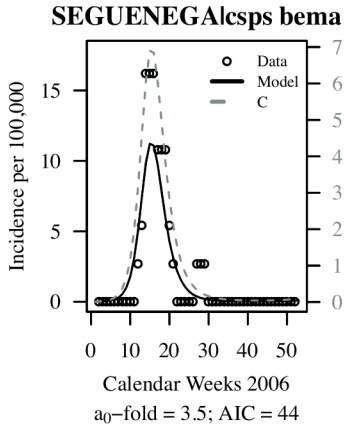
Dashed lines curve represents weekly carriage prevalence predictions. α_0 -fold and β_0 -fold indicate the fold increase of the invasion and transmission rate (respectively) from their baseline value. R^2 : The percentage of total variability in observed data explained by the model. Model1-"inv": seasonal forcing of the invasion rate alone.

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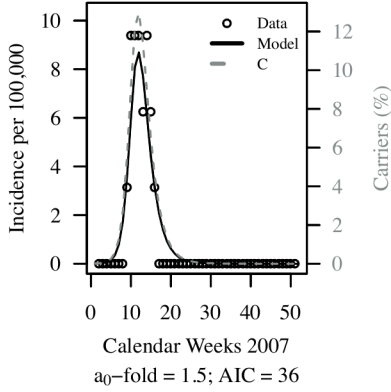
Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt

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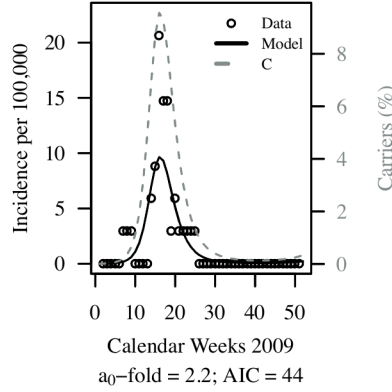
Supplementary Fig S1. Model1–"inv" predictions and observed data in all 64 health centre years with complete data across four health districts of Burkina faso (2004–2010). α_0 -fold and β_0 -fold indicate the fold increase of the invasion and transmission rate (respectively) from their baseline value. AIC is the Akaike information criterion. In figures. "Model" stands for incidence prediction of the model, "C" stands for carriage prediction



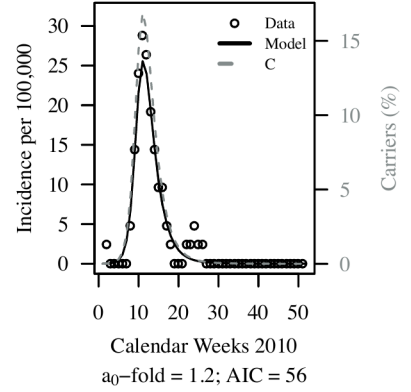
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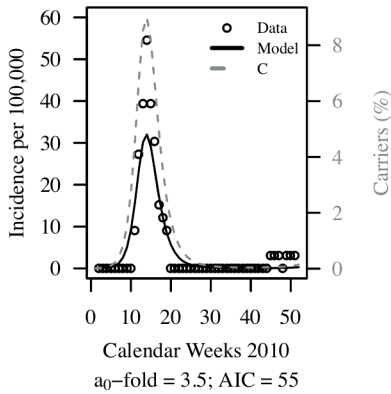
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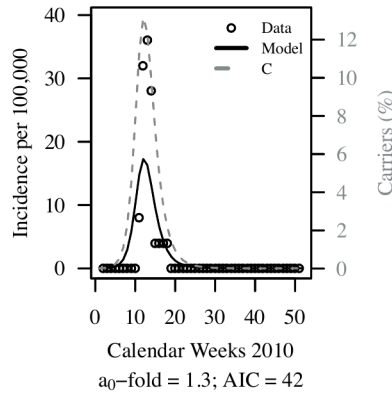
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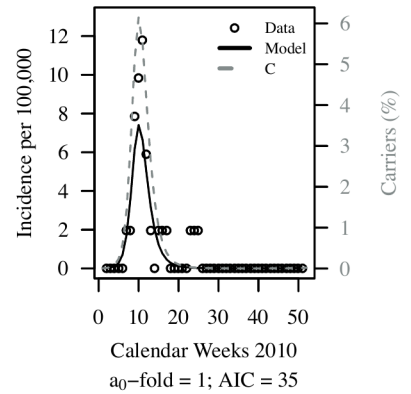
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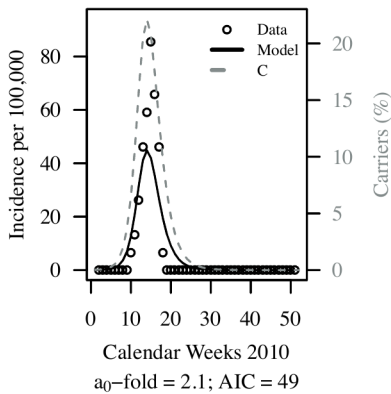
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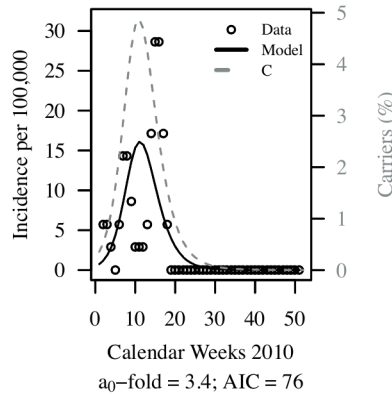
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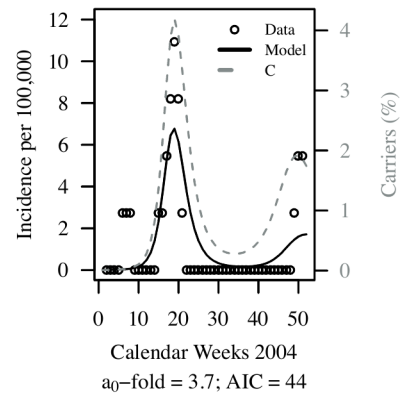
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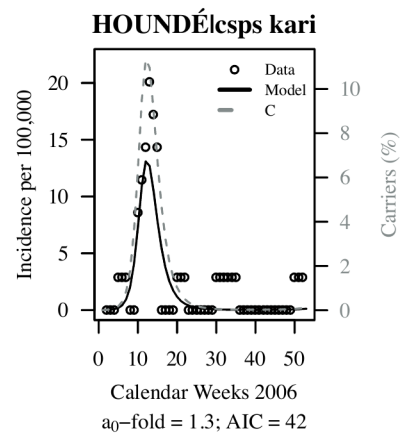
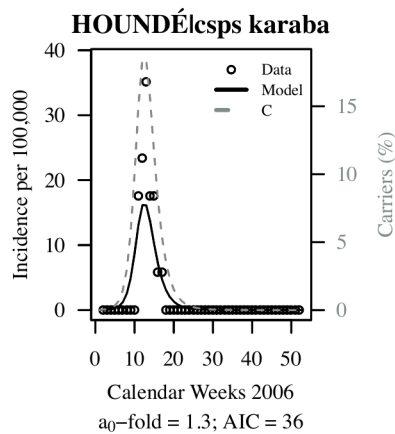
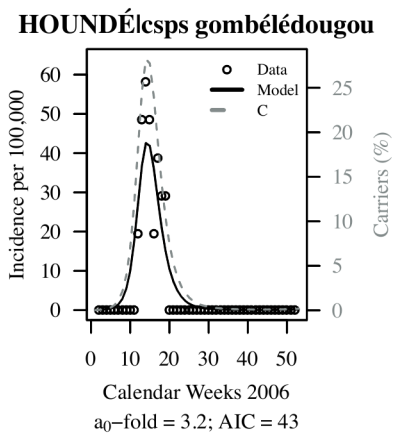
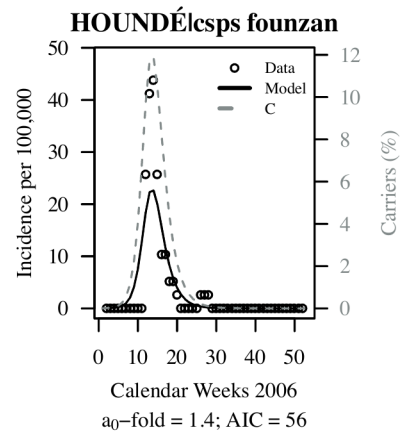
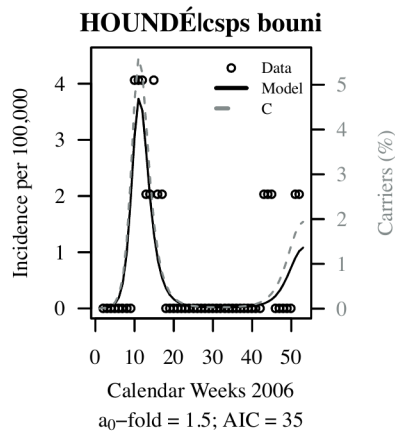
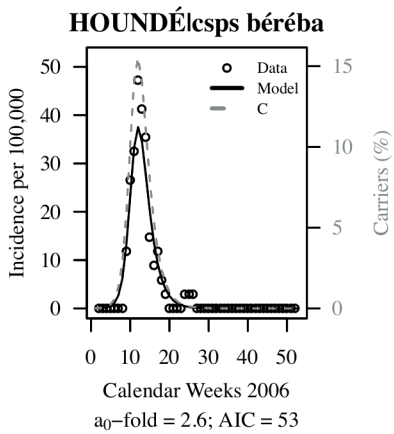
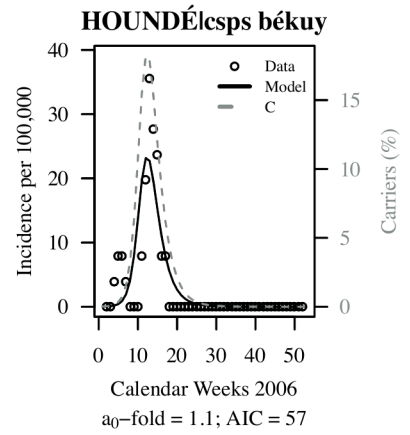
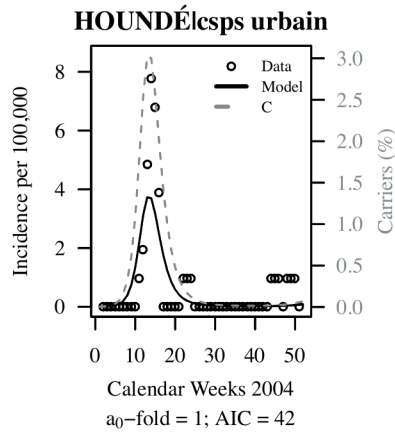
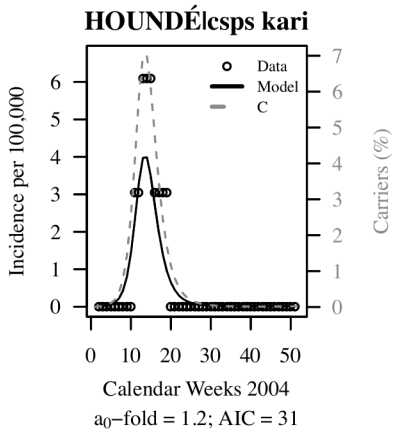


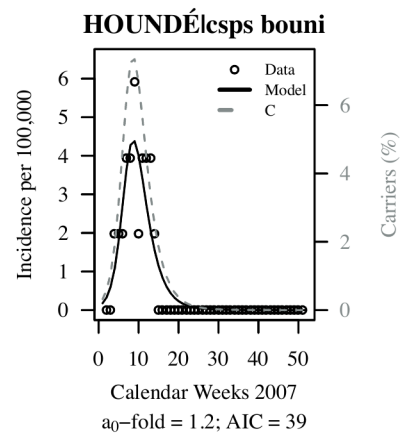
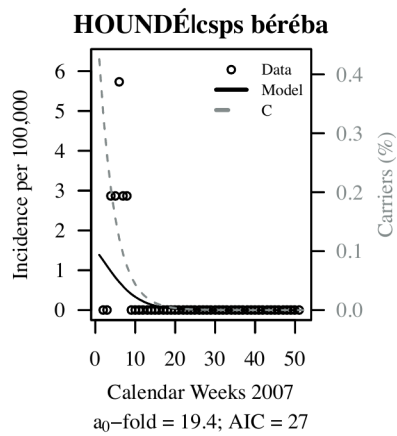
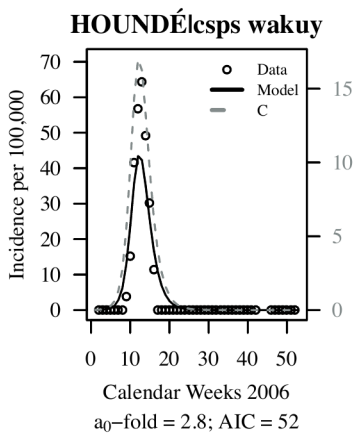
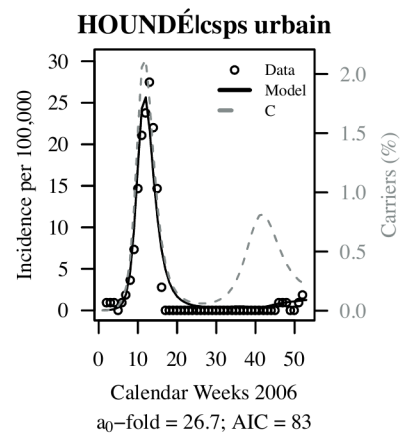
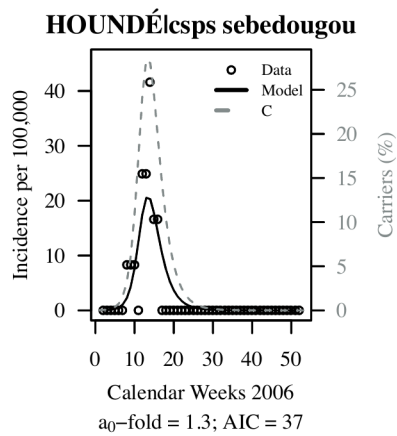
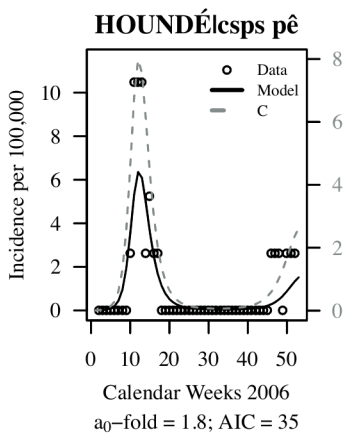
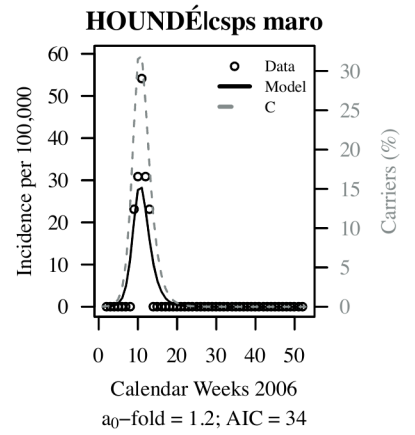
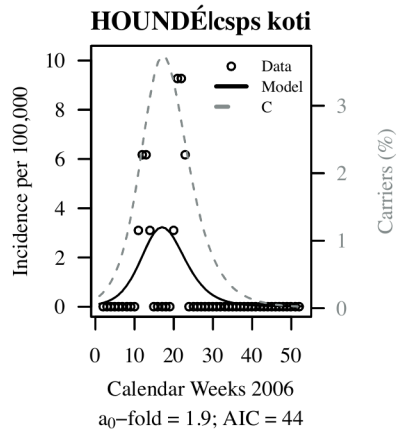
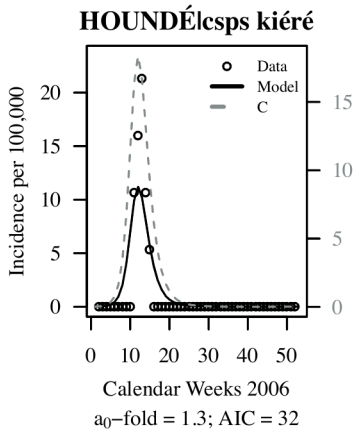
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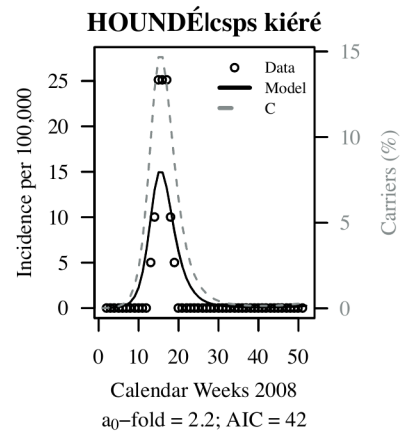
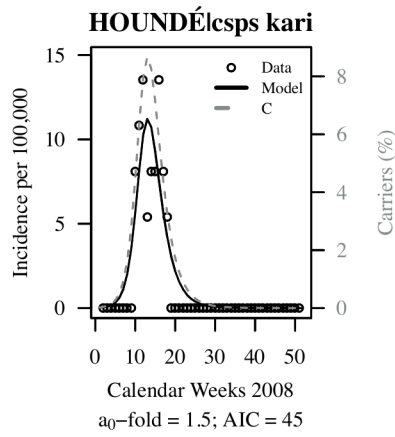
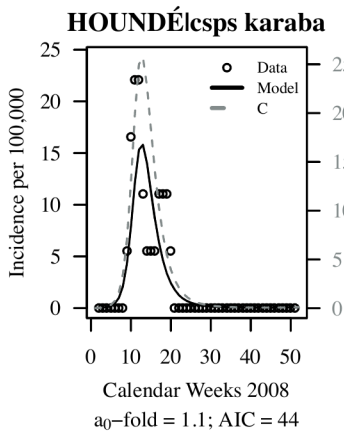
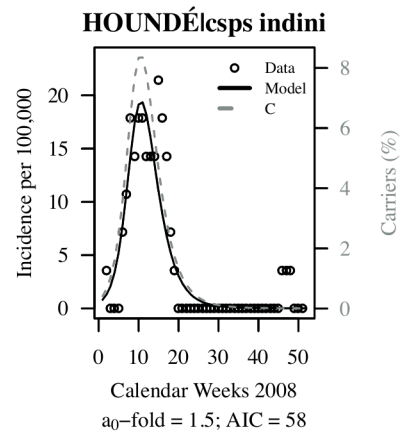
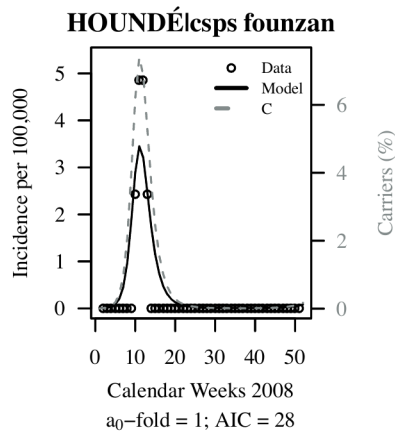
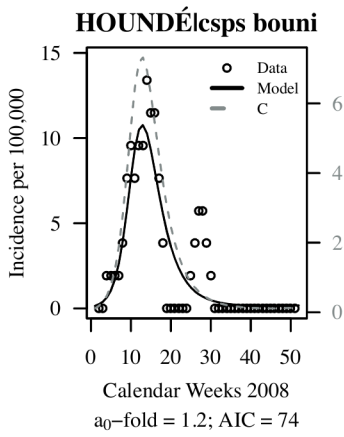
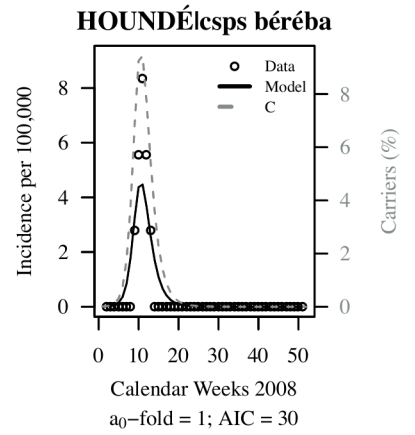
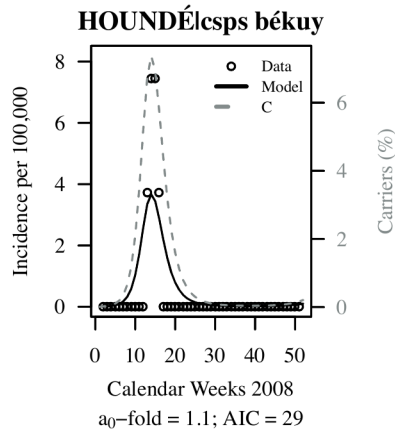
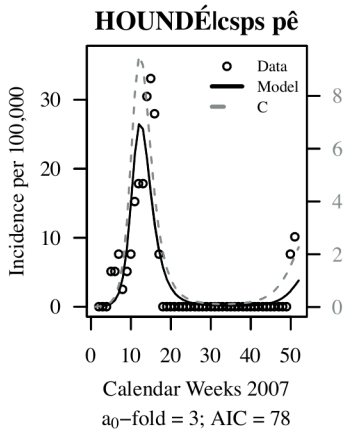


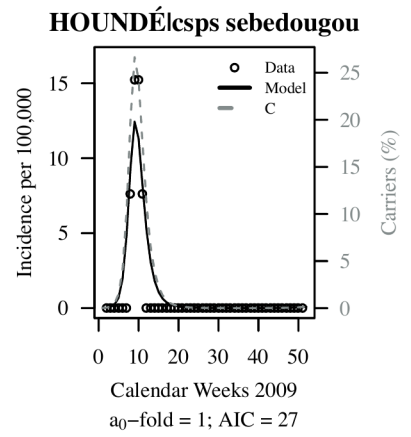
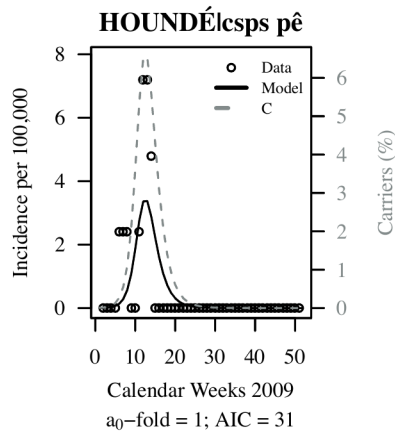
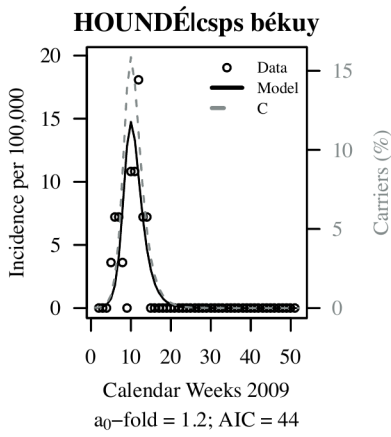
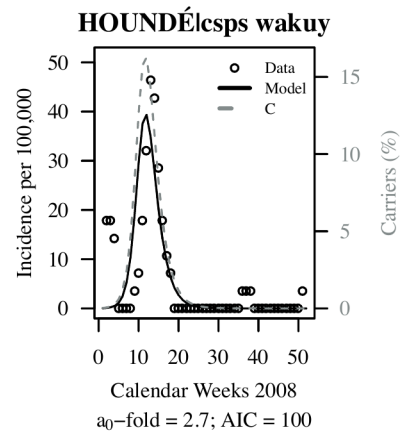
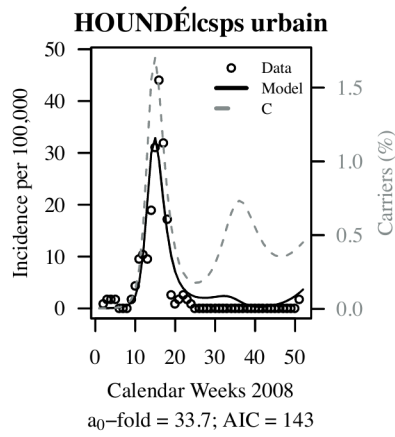
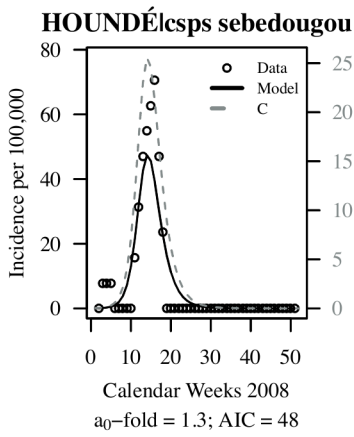
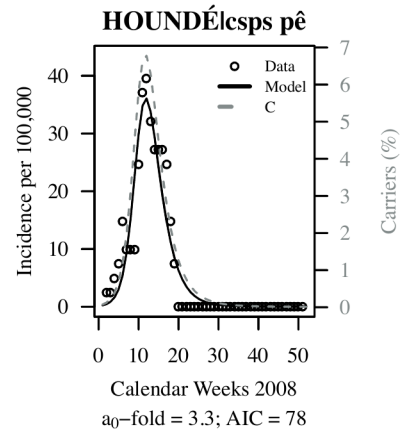
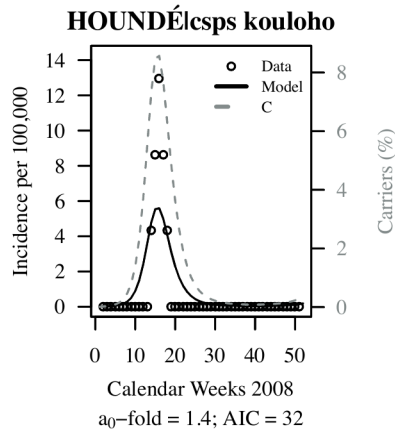
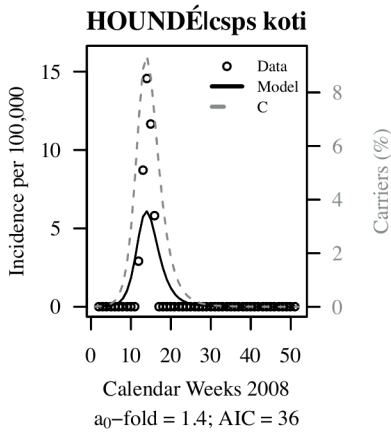
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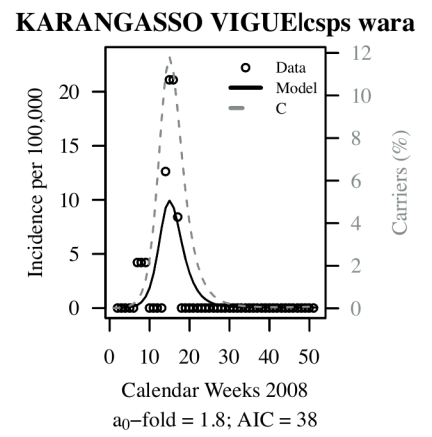
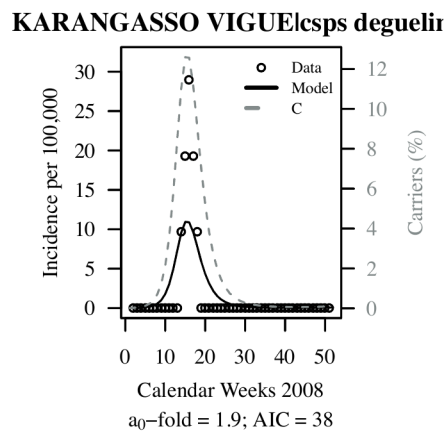
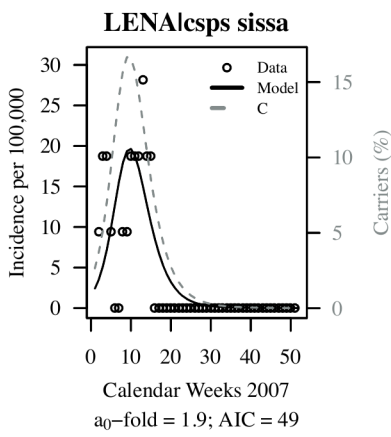
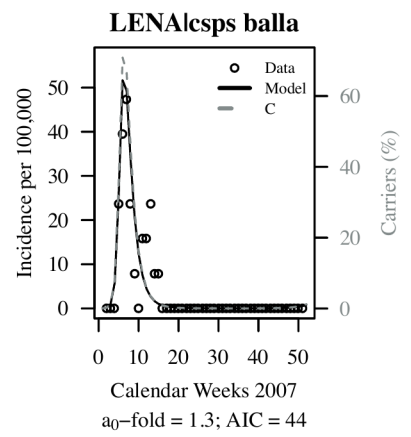
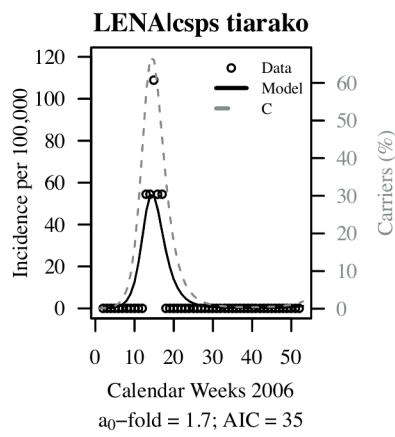
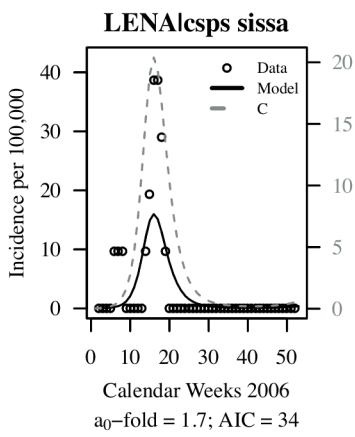
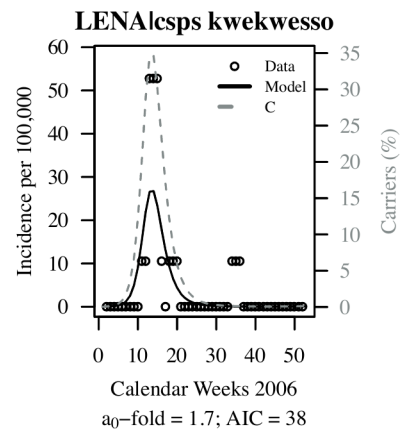
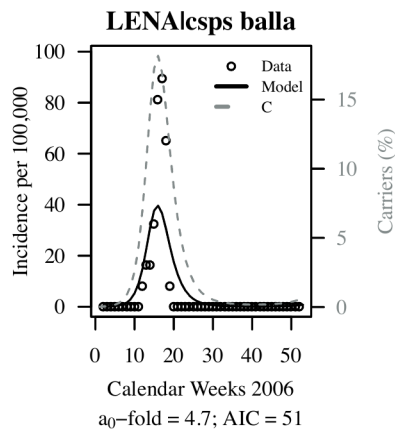
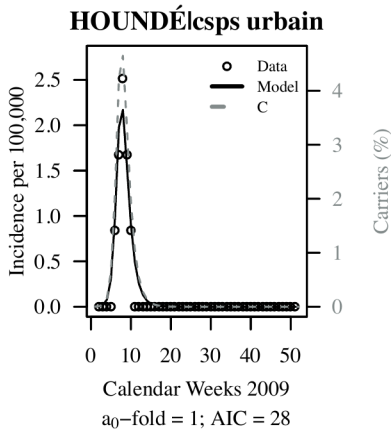




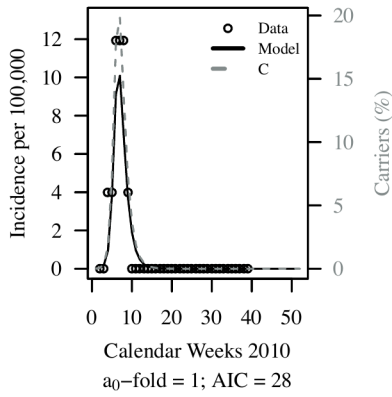




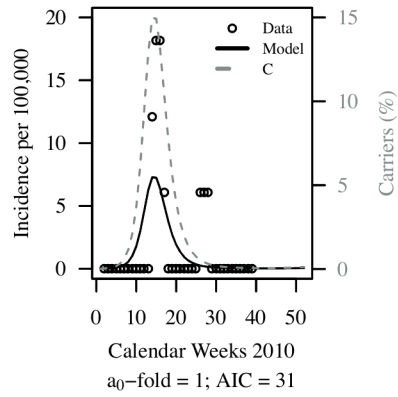




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S3 Fig 2. Model2-"transm" trajectories matching plots of simulated (black curve) and observed (black dots) weekly data, for 64 health center-years with complete data, across four health districts of Burkina faso (2004–2010).

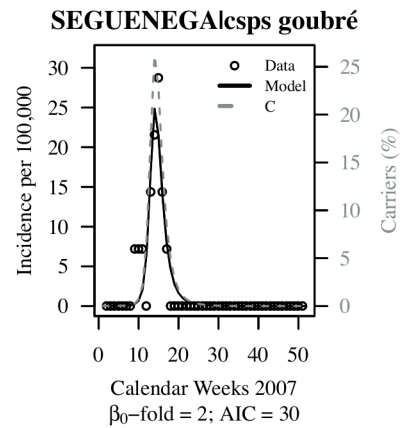
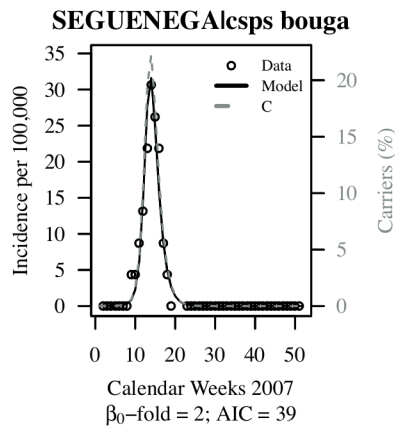
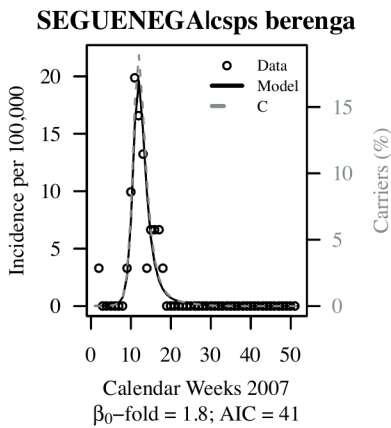
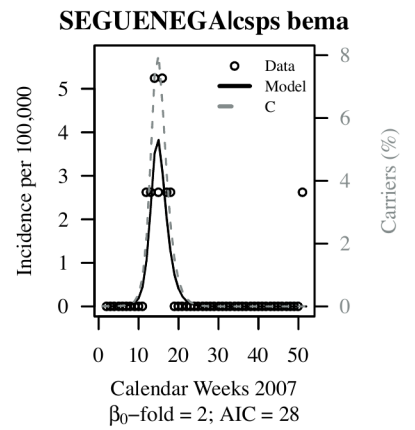
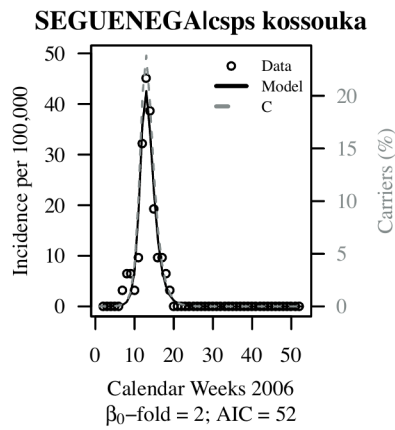
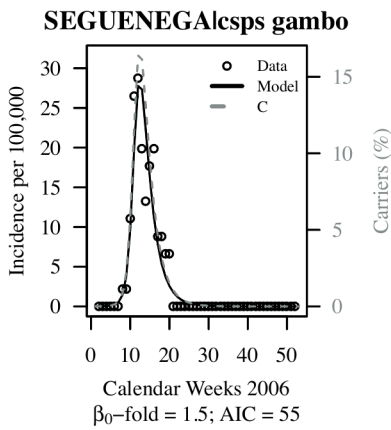
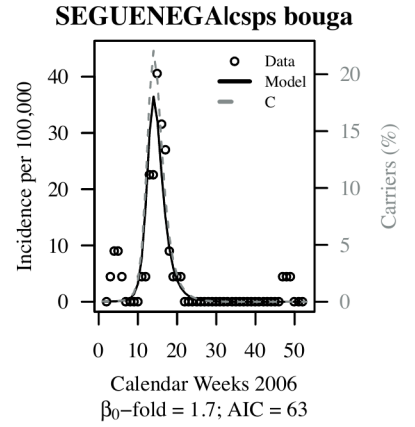
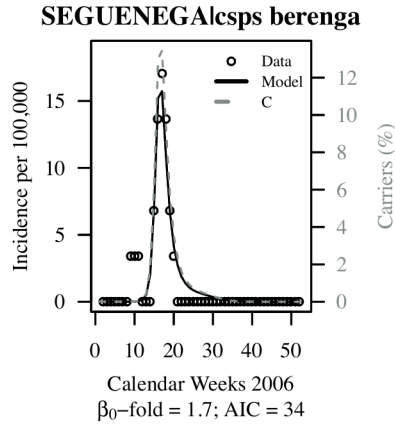
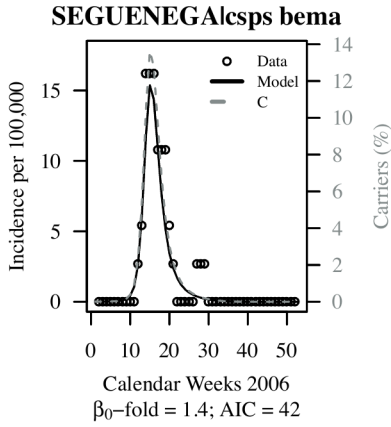
Dashed lines curve represents weekly carriage prevalence predictions. α_0 -fold and β_0 -fold indicate the fold increase of the invasion and transmission rate (respectively) from their baseline value. R^2 : The percentage of total variability in observed data explained by the model. Model2-"transm": seasonal forcing of the transmission rate alone.

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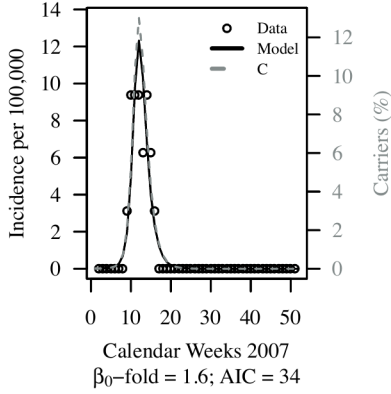
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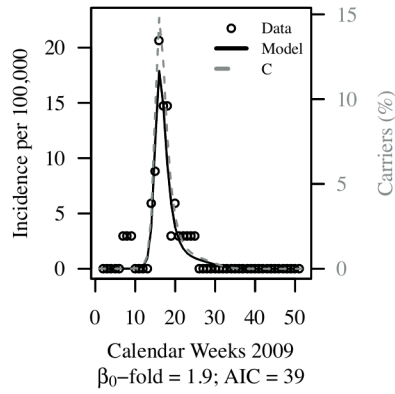
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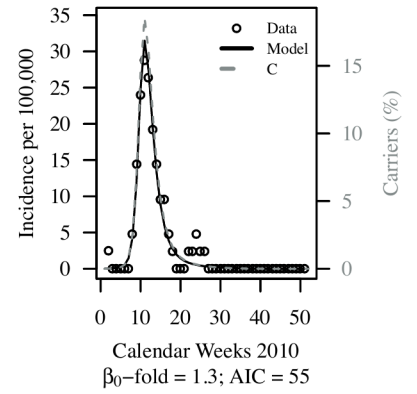
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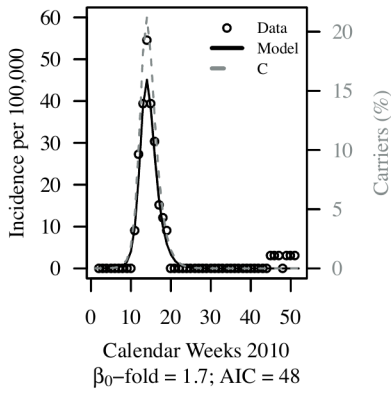
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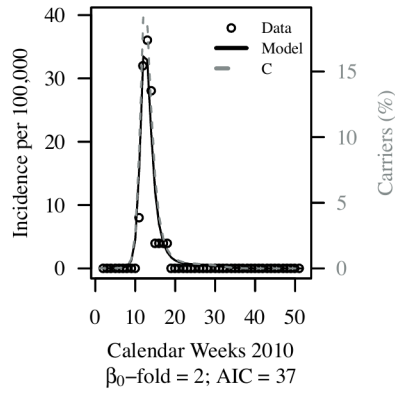
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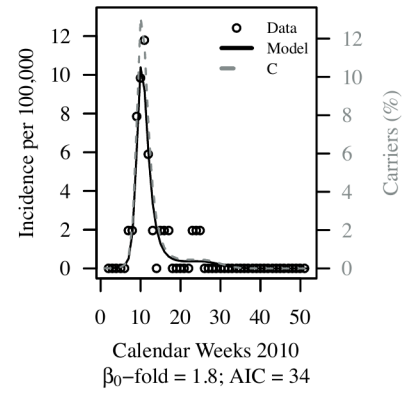
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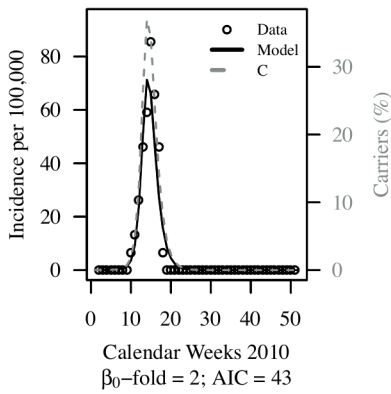
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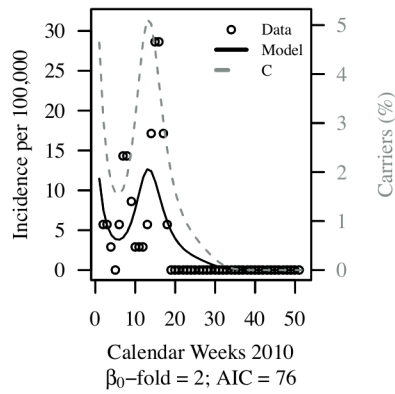
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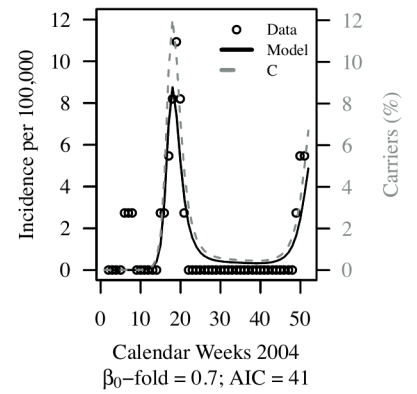
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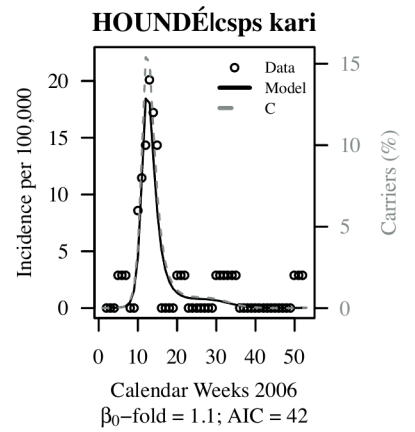
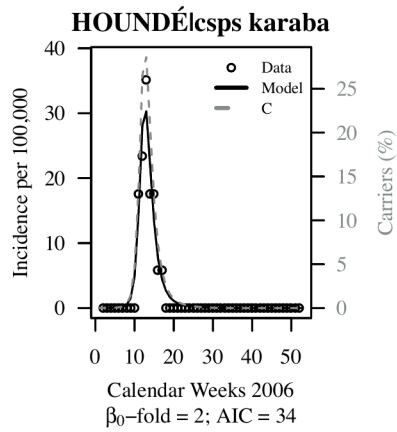
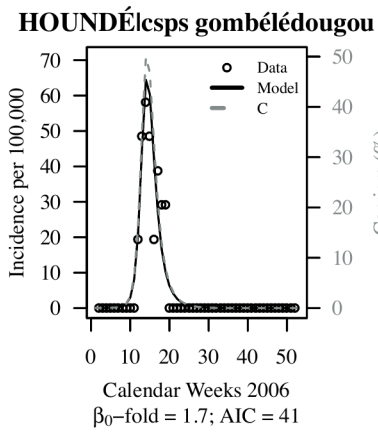
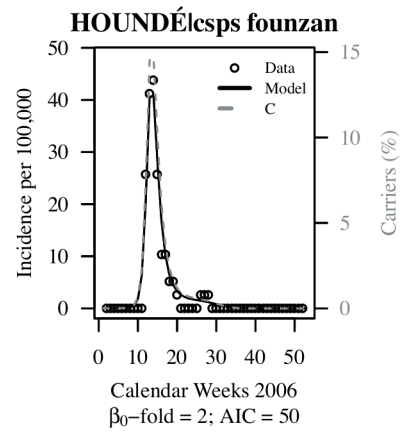
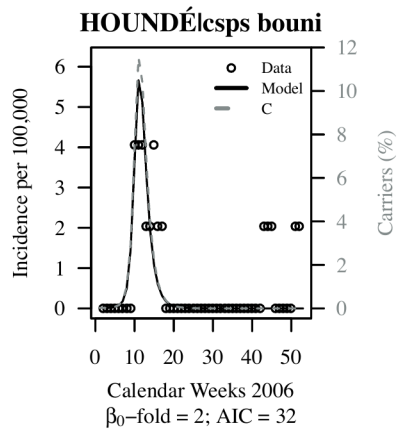
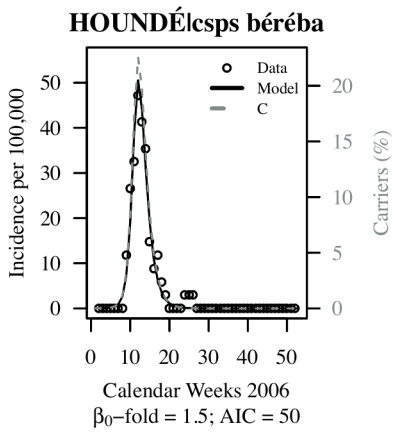
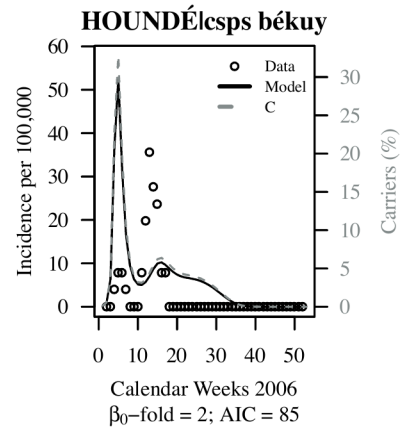
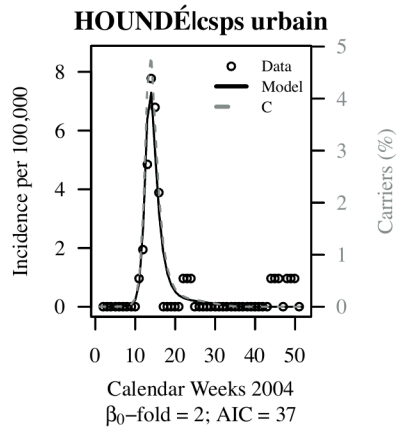
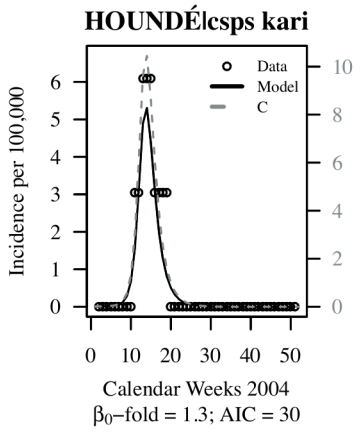


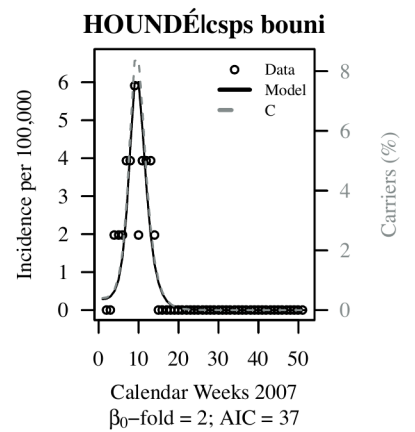
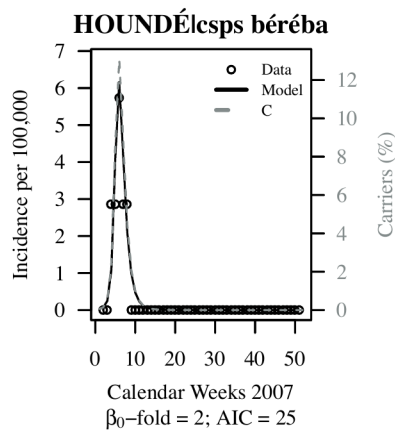
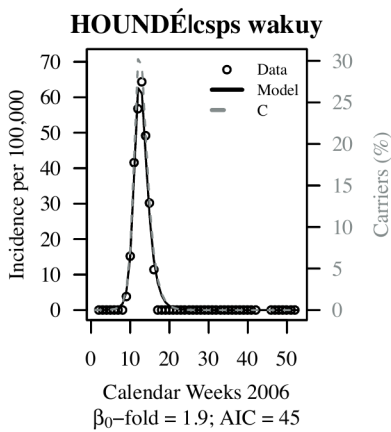
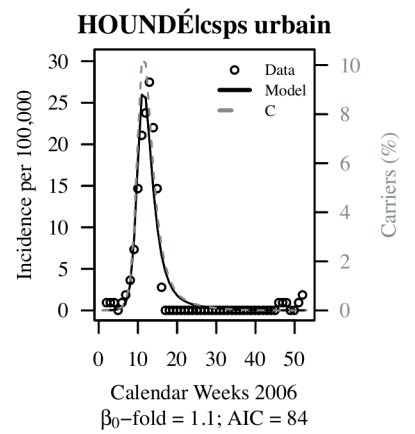
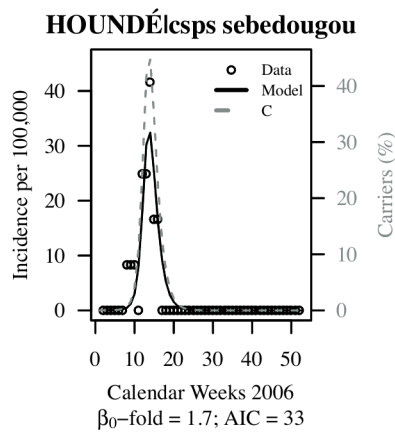
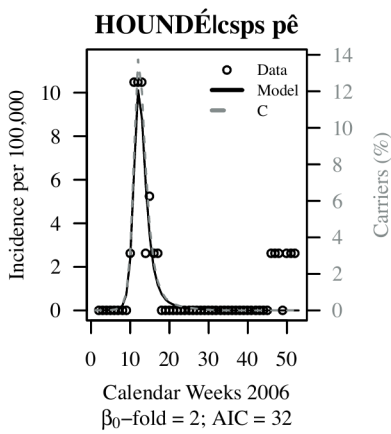
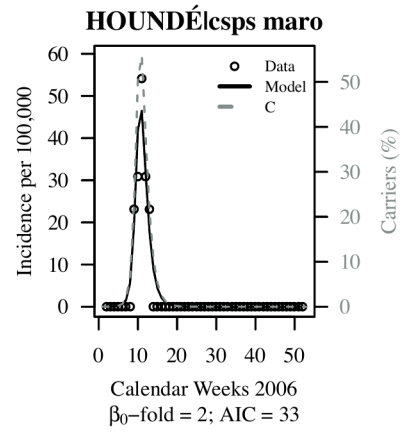
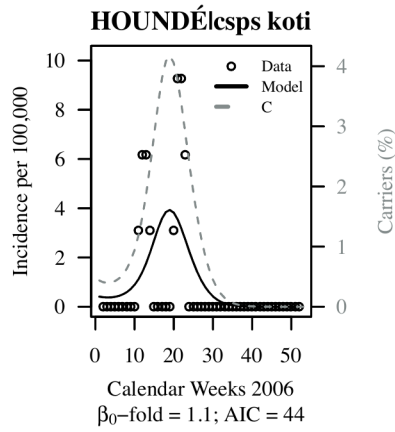
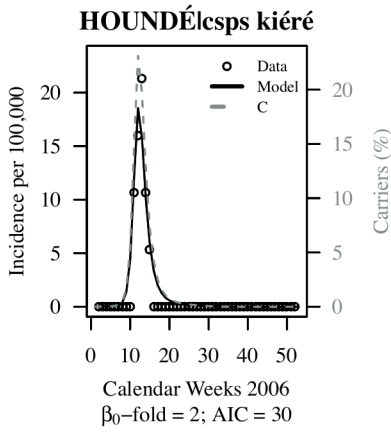
SEGUENEGAlcspss kossouka

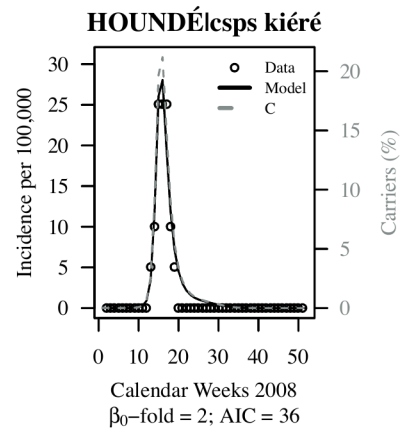
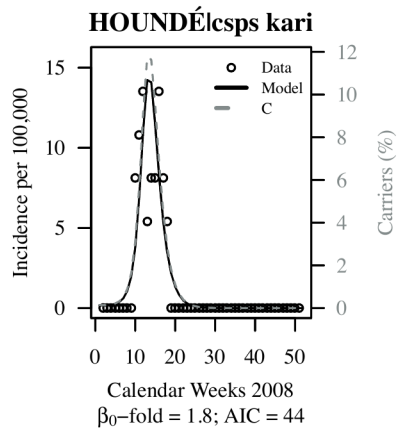
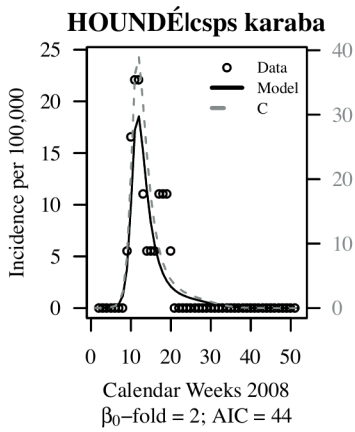
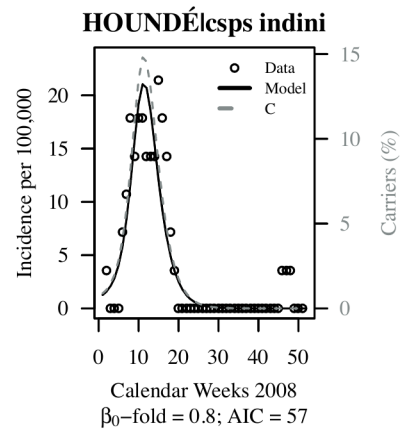
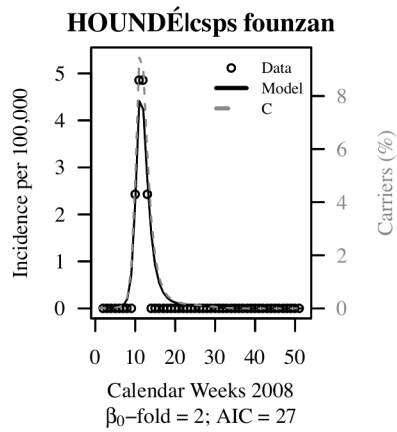
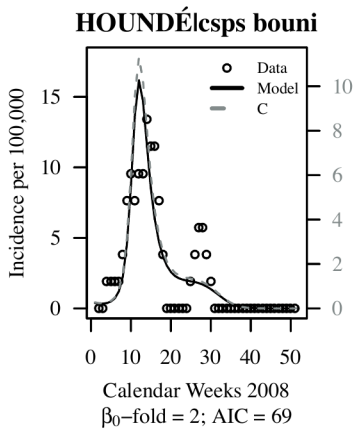
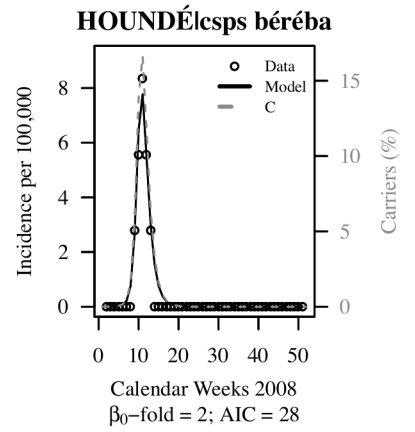
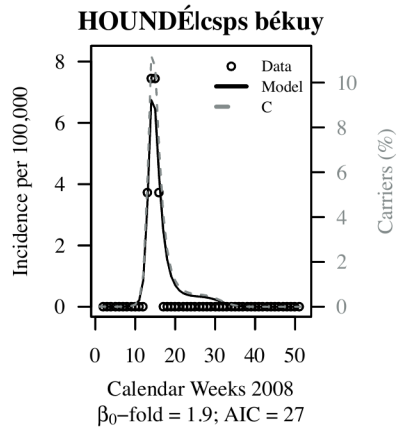
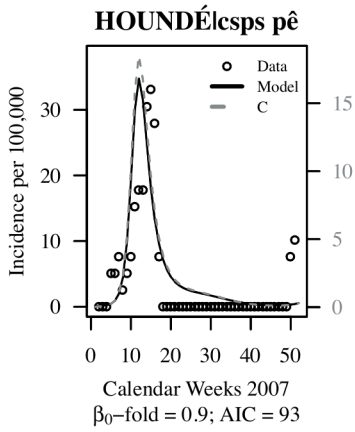


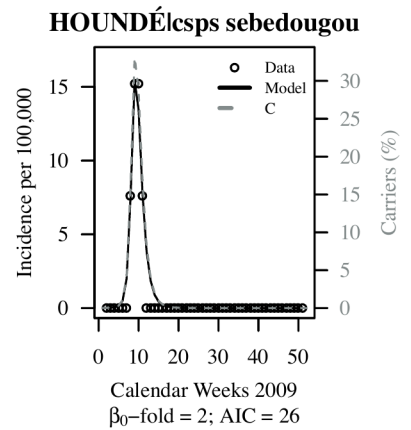
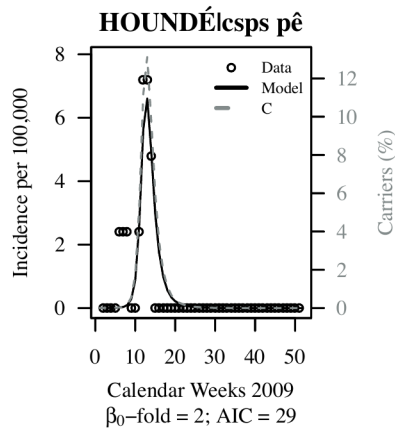
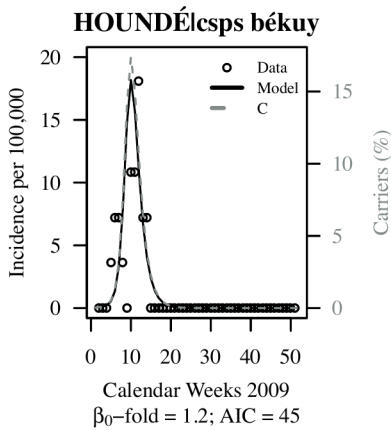
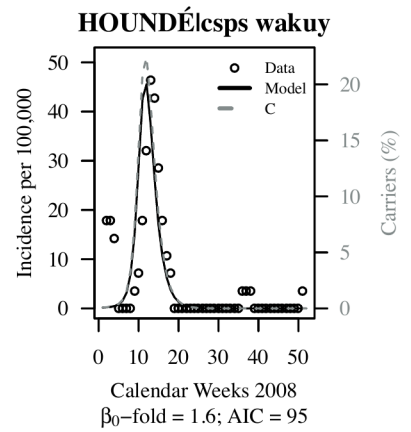
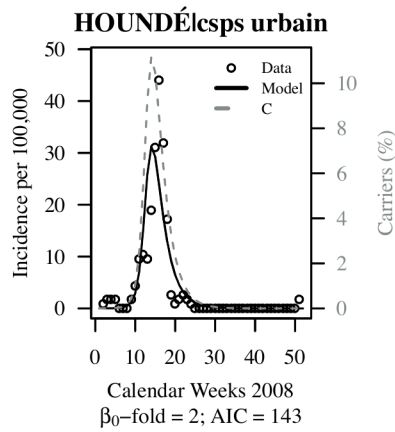
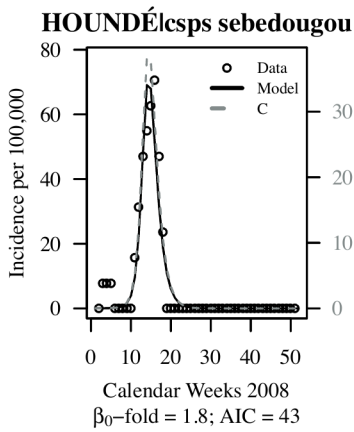
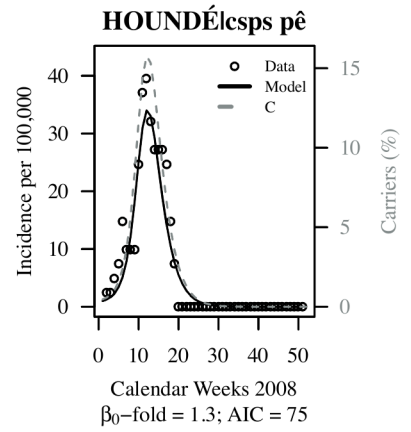
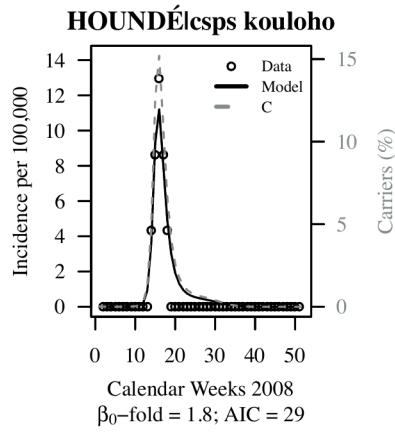
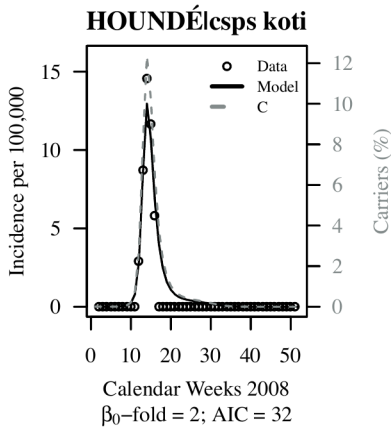
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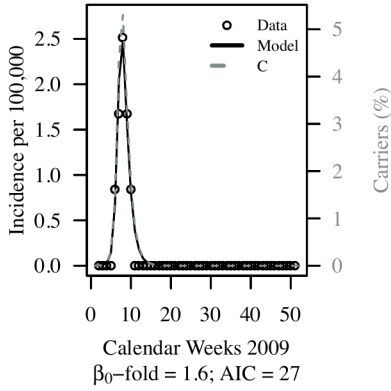




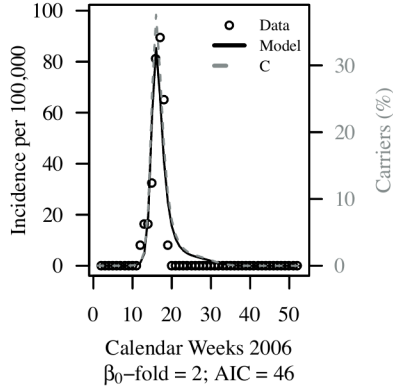




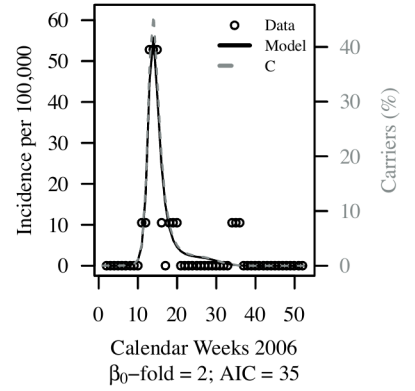
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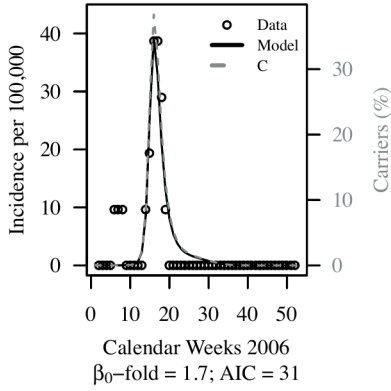
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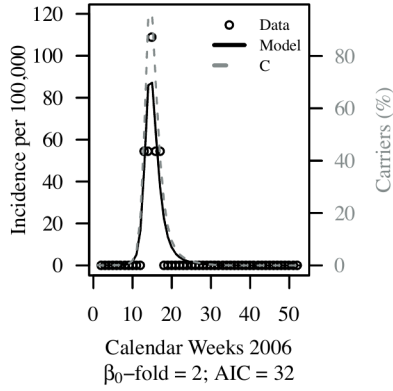
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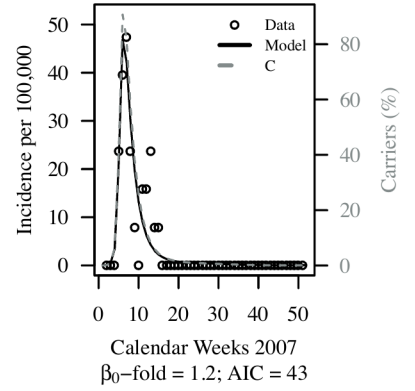
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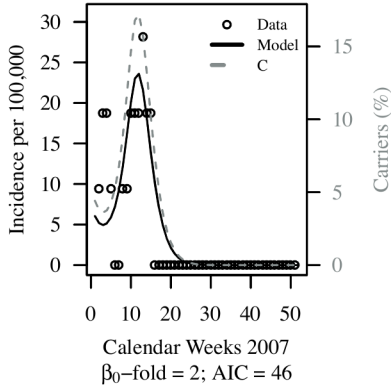
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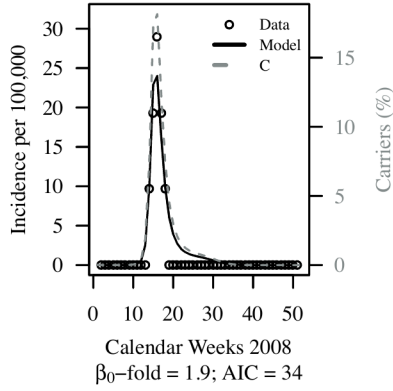
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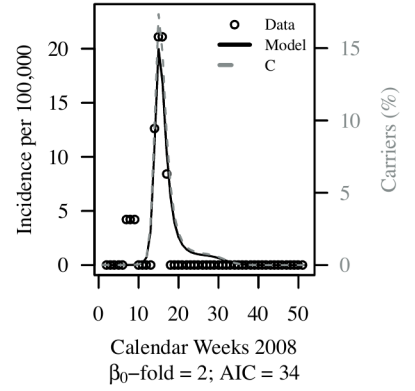
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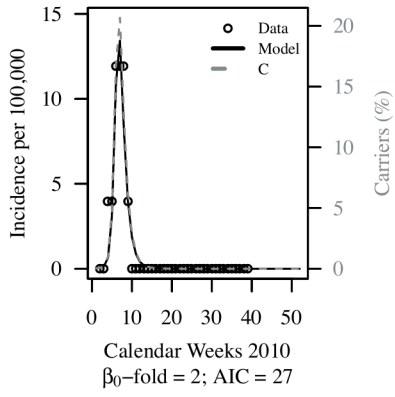
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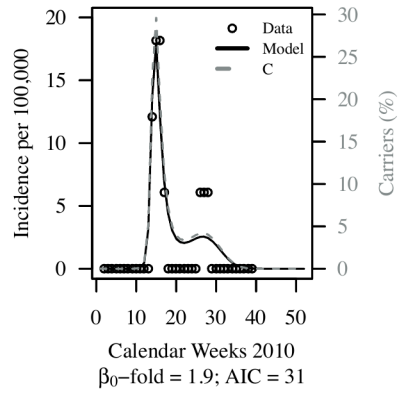
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KARANGASSO VIGUEldispe diosso



S3 Fig 3. Model3-"inv-transm" trajectories matching plots of simulated (black curve) and observed (black dots) weekly data, for 64 health center-years with complete data, across four health districts of Burkina faso (2004–2010).

Dashed lines curve represents weekly carriage prevalence predictions. α_0 -fold and β_0 -fold indicate the fold increase of the invasion and transmission rate (respectively) from their baseline value. R^2 : The percentage of total variability in observed data explained by the model. Model3-"inv-transm": seasonal forcing of the transmission and invasion rate.

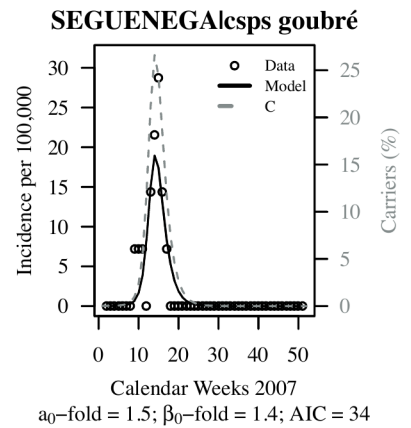
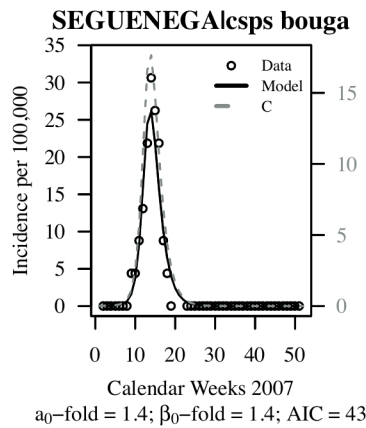
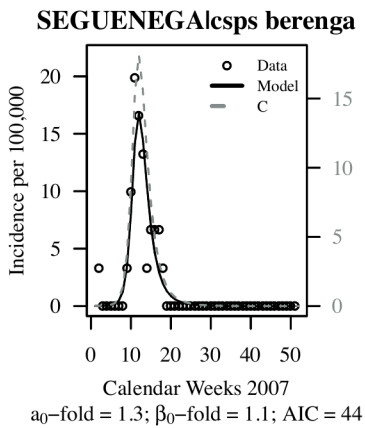
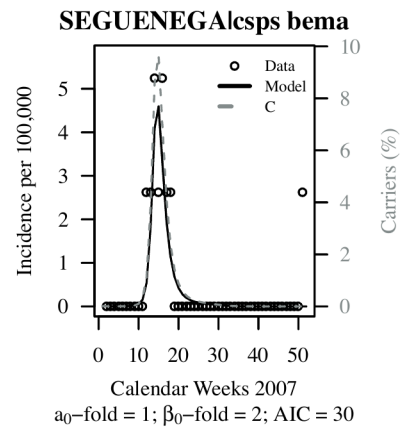
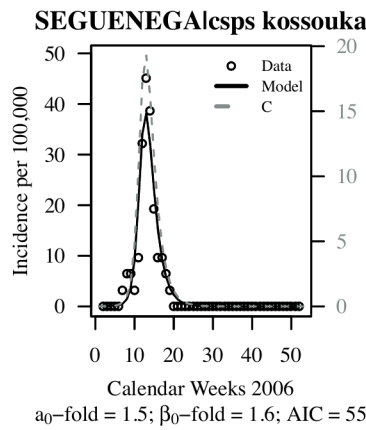
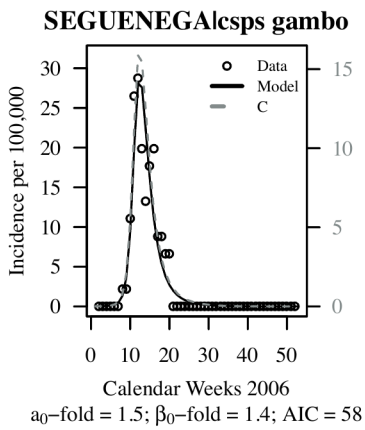
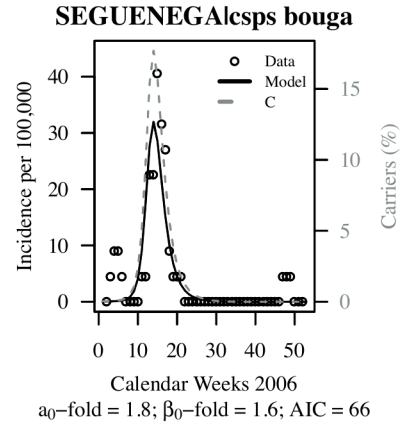
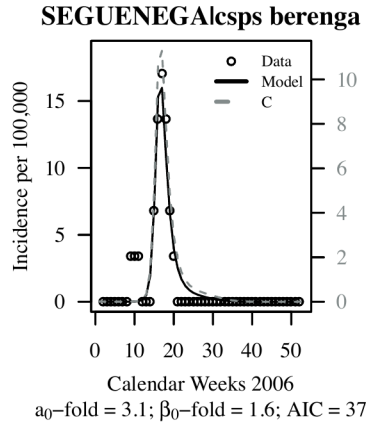
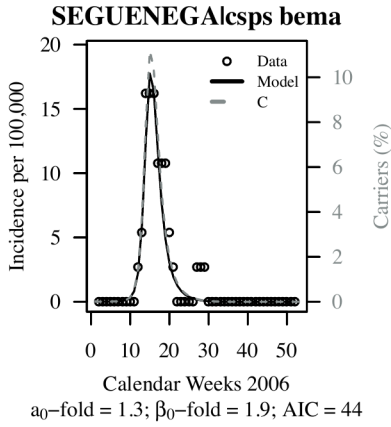
Epidemiology and Infection

Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt

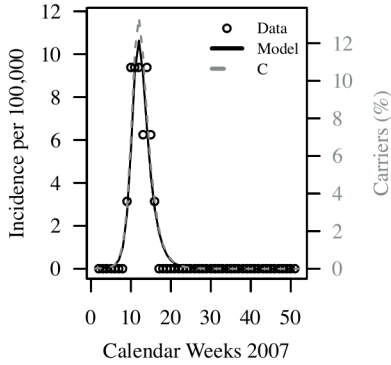
Thibaut KOUTANGNI, Pascal Crépey, Maxime Woringer, Souleymane Porgho, Brice Wilfried Bicaba, Haoua Tall, Judith E. Mueller

Supplementary Fig S3. Model3–"Inv-Transm" predictions and observed data in all 64 health centre years with complete data across four health districts of Burkina Faso (2004–2010). α_0 -fold and β_0 -fold indicate the fold increase of the invasion and transmission rate (respectively) from their baseline value. AIC is the Akaike information criterion.

In figures. "Model" stands for incidence prediction of the model, "C" stands for carriage prediction

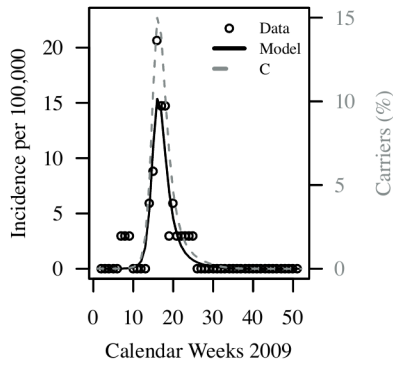


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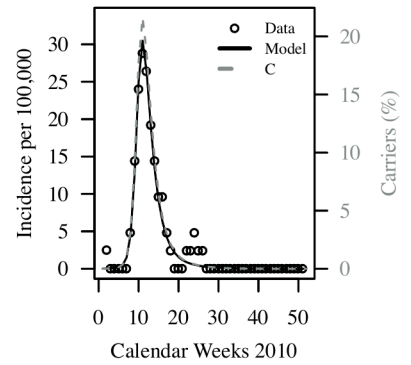
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SEGUENEGAlcspss kossouka



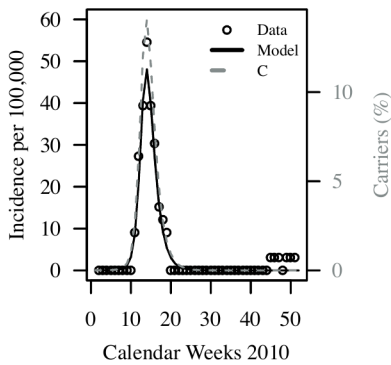
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SEGUENEGAlcspss bema



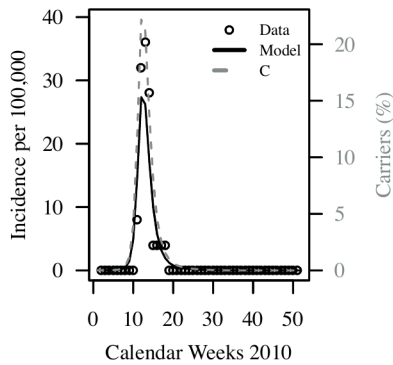
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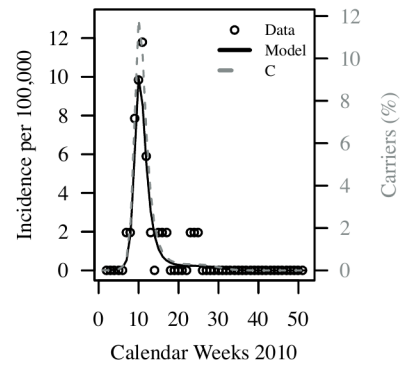
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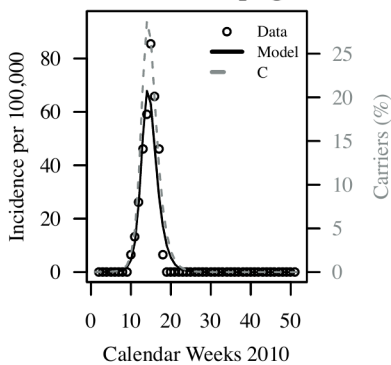
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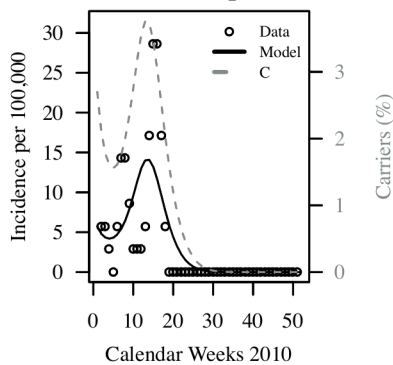
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SEGUENEGAlcspss goubré



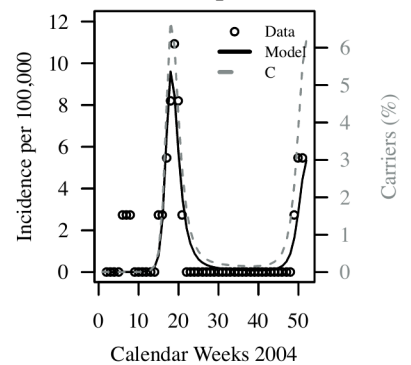
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SEGUENEGAlcspss kossouka

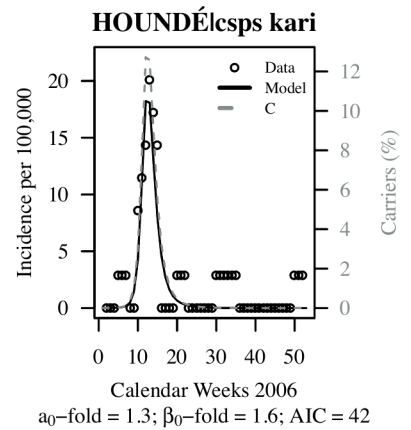
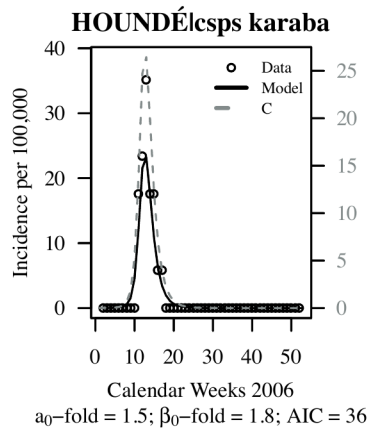
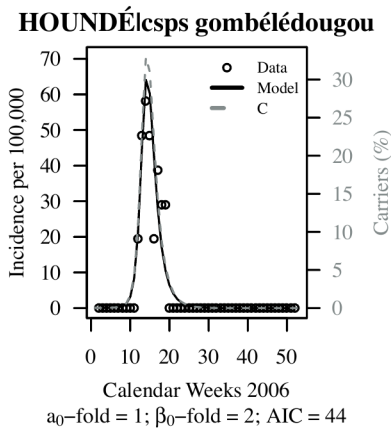
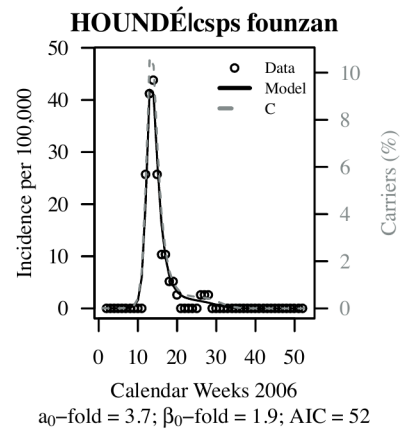
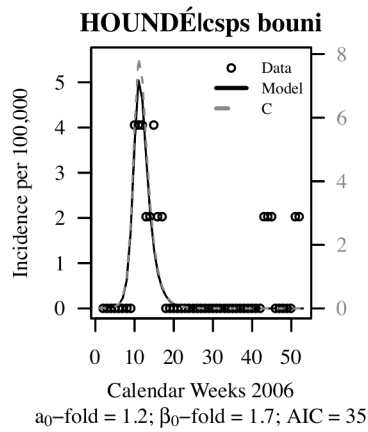
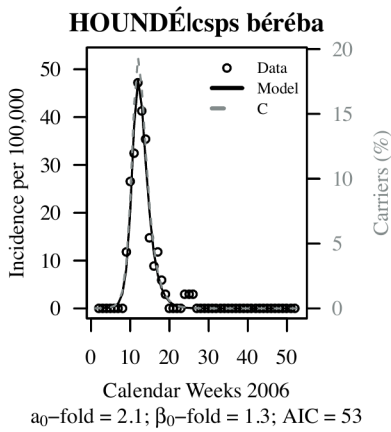
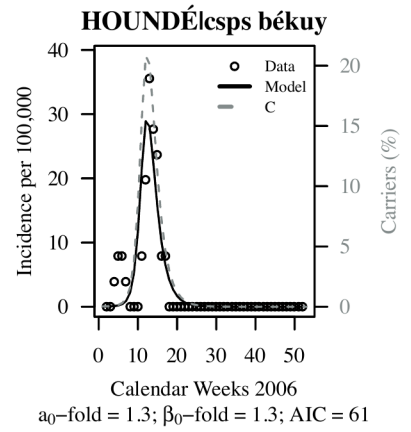
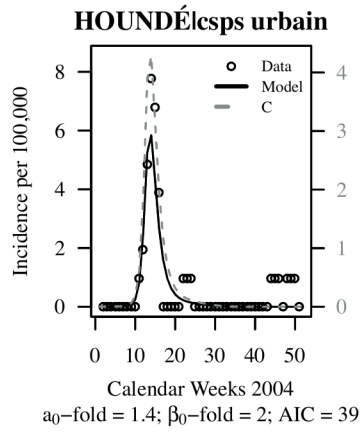
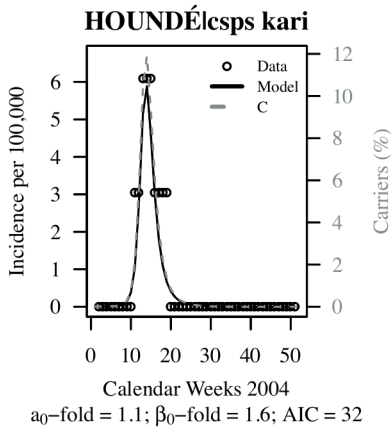


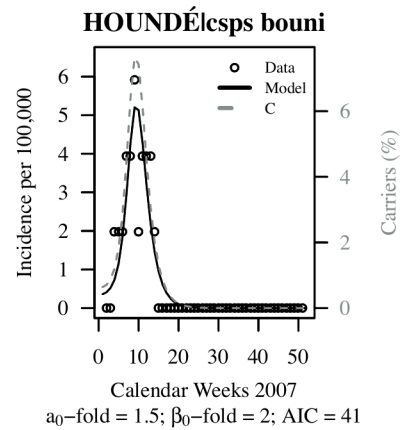
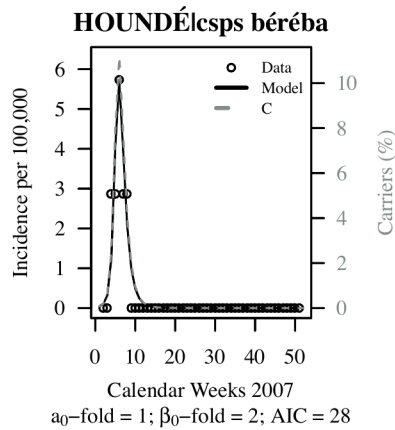
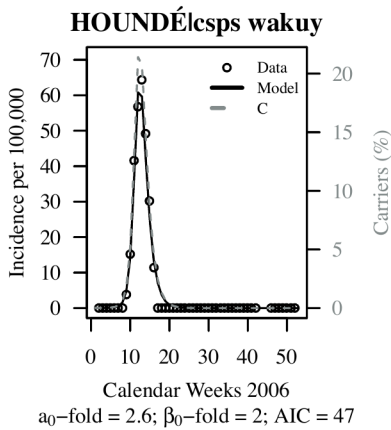
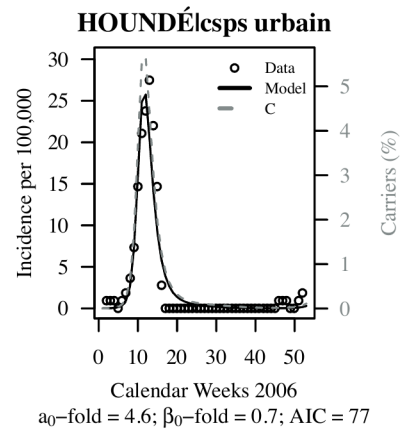
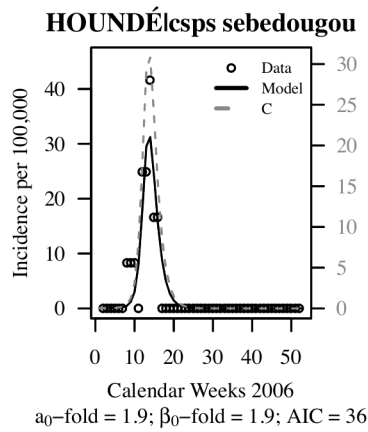
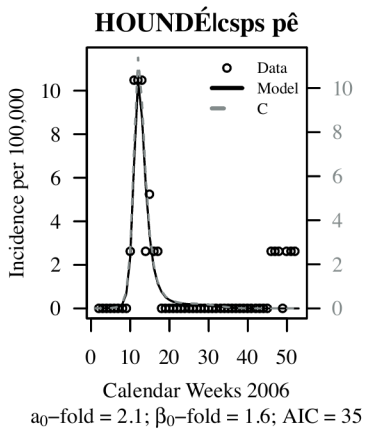
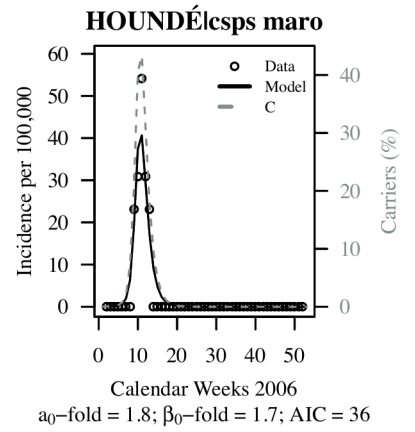
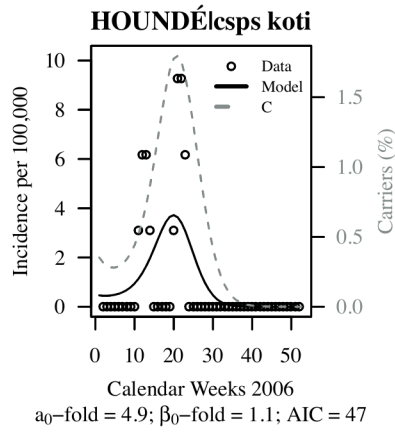
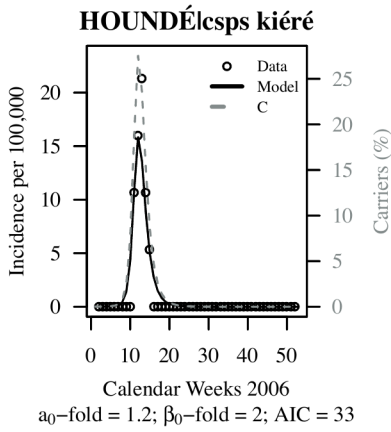
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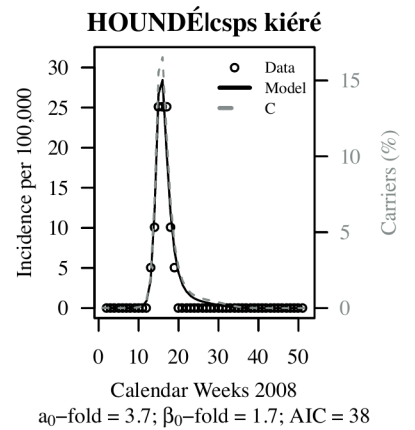
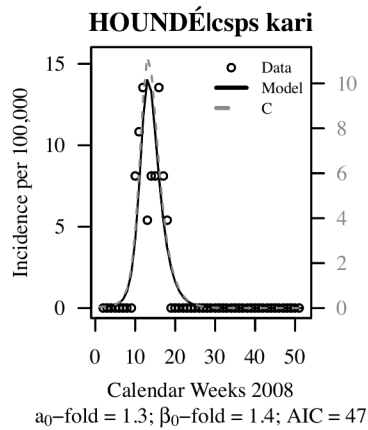
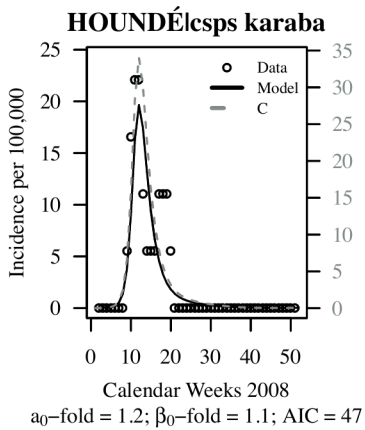
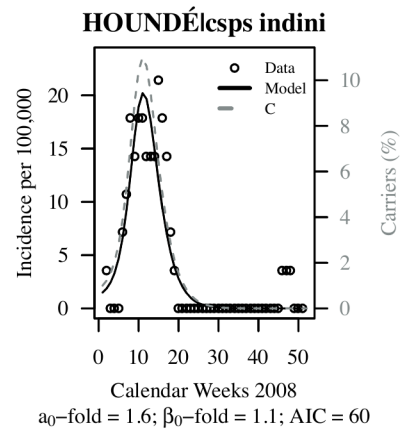
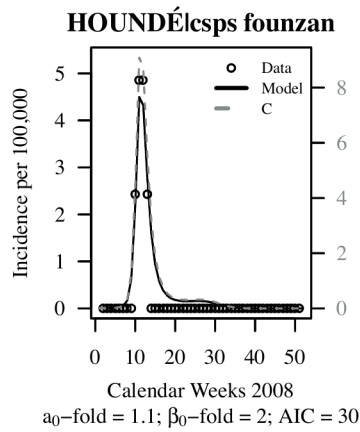
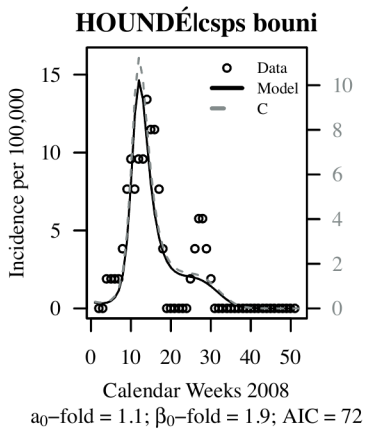
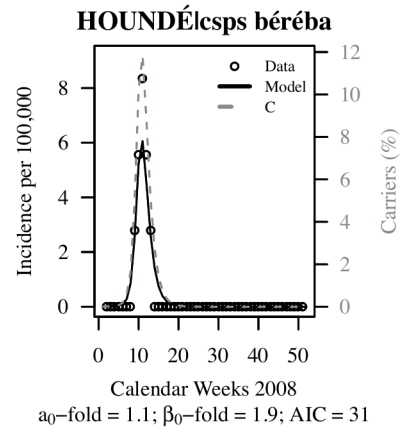
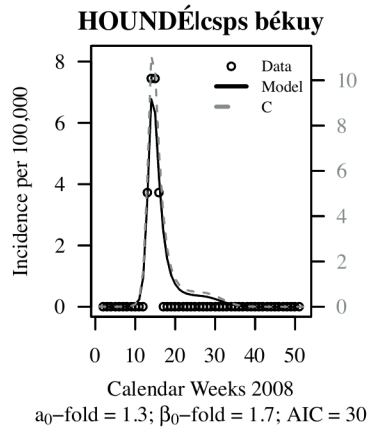
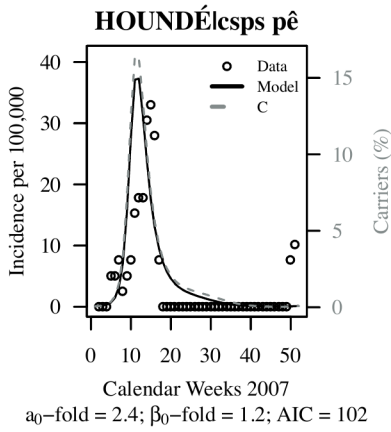
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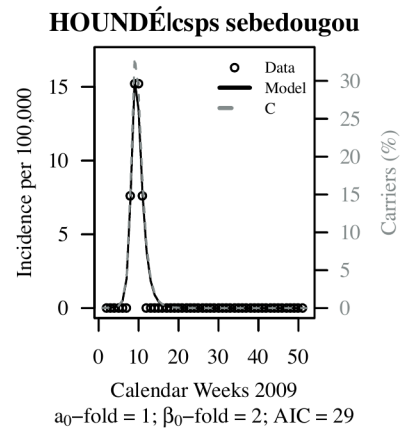
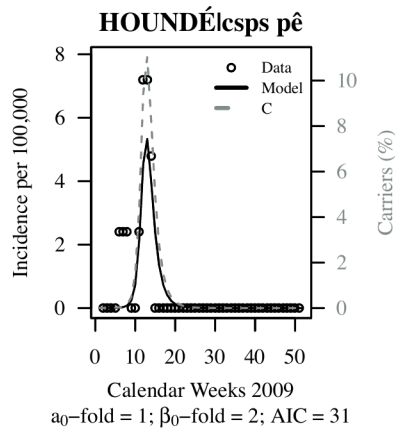
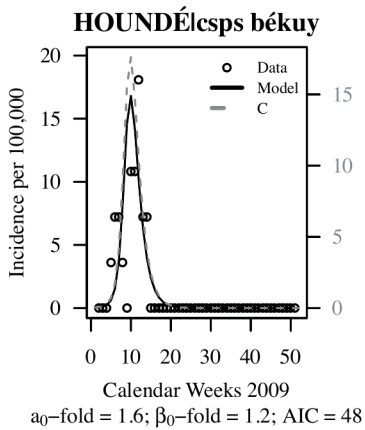
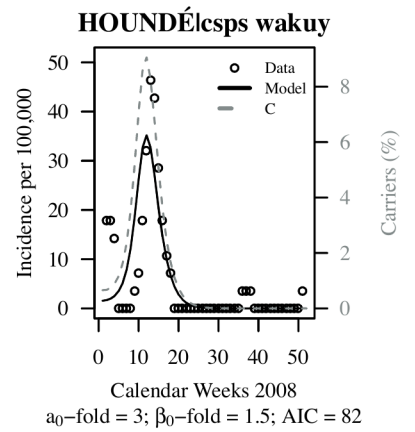
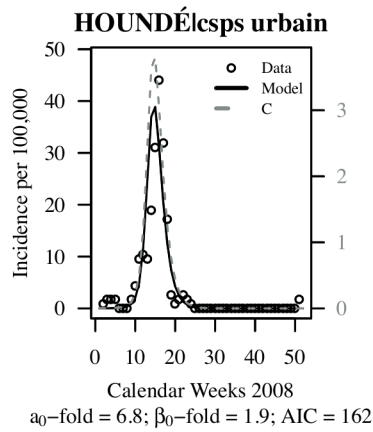
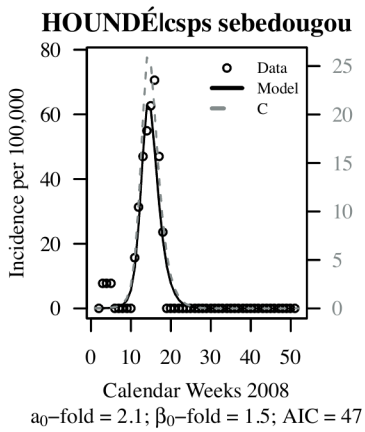
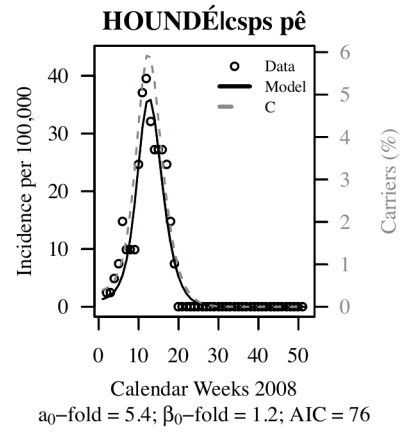
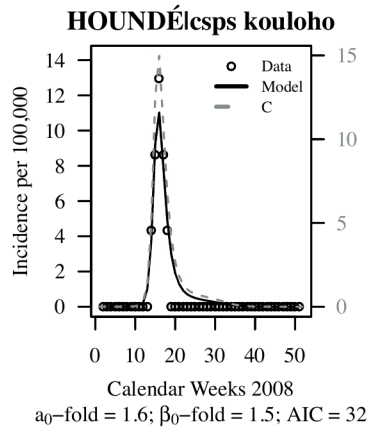
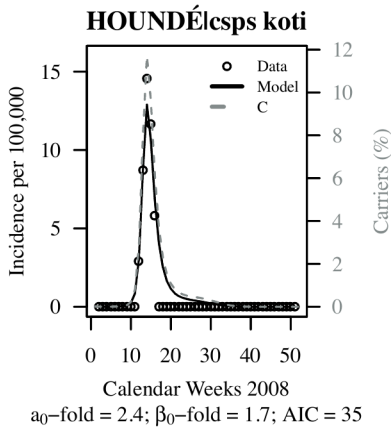


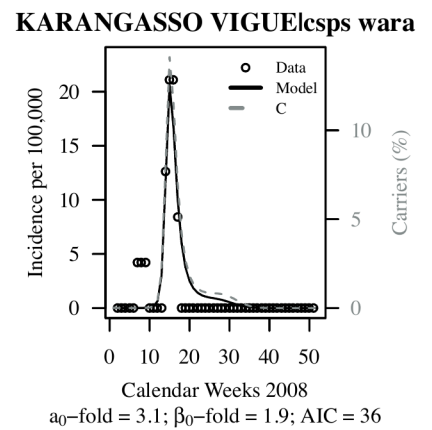
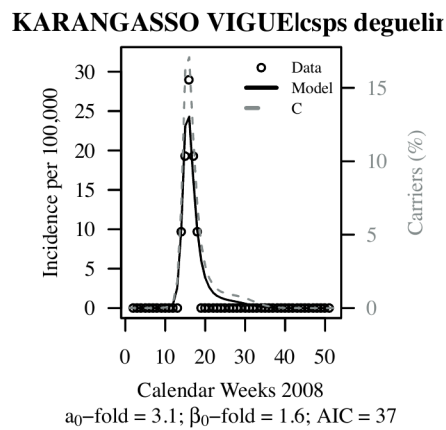
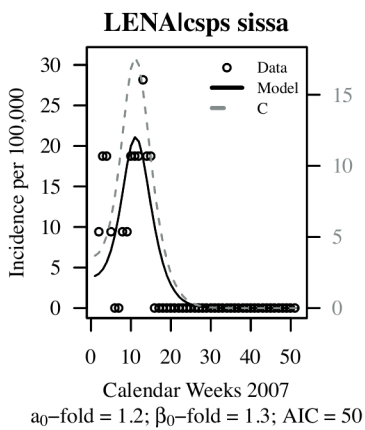
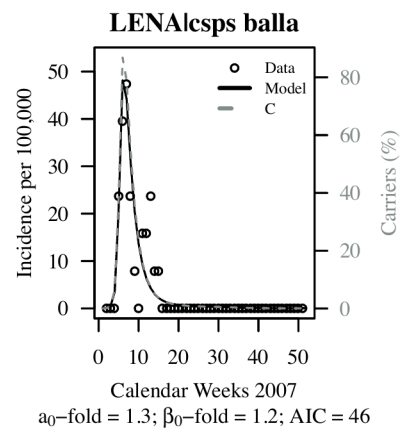
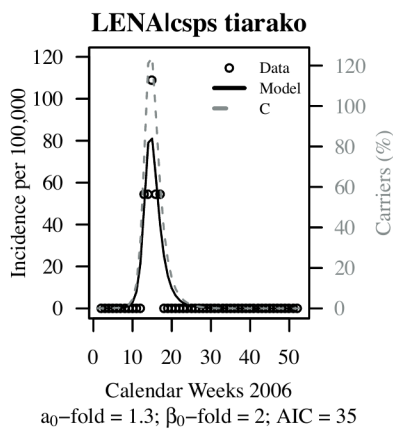
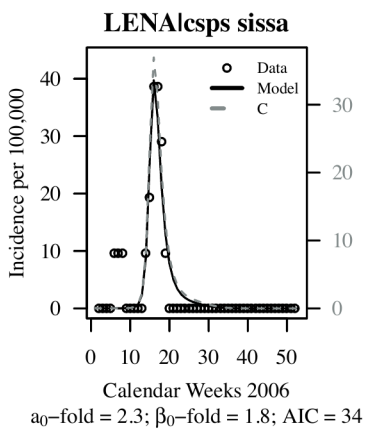
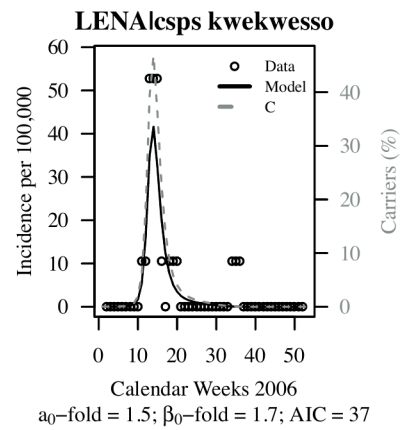
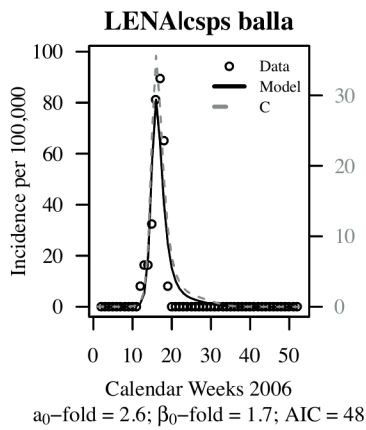
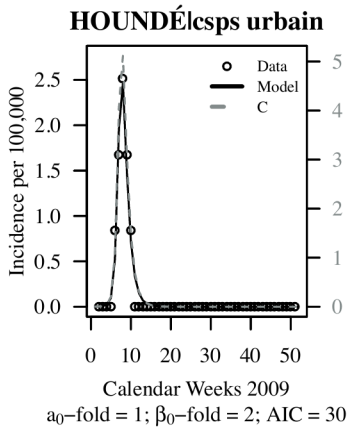
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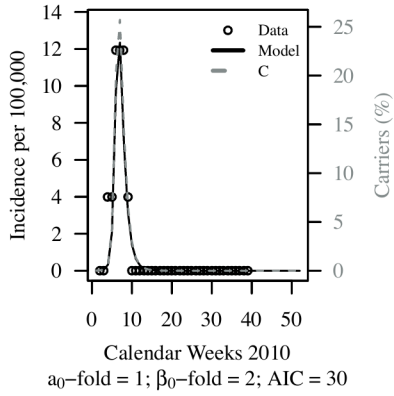




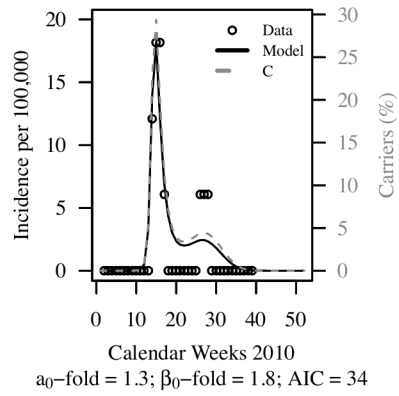




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Epidemiology and Infection

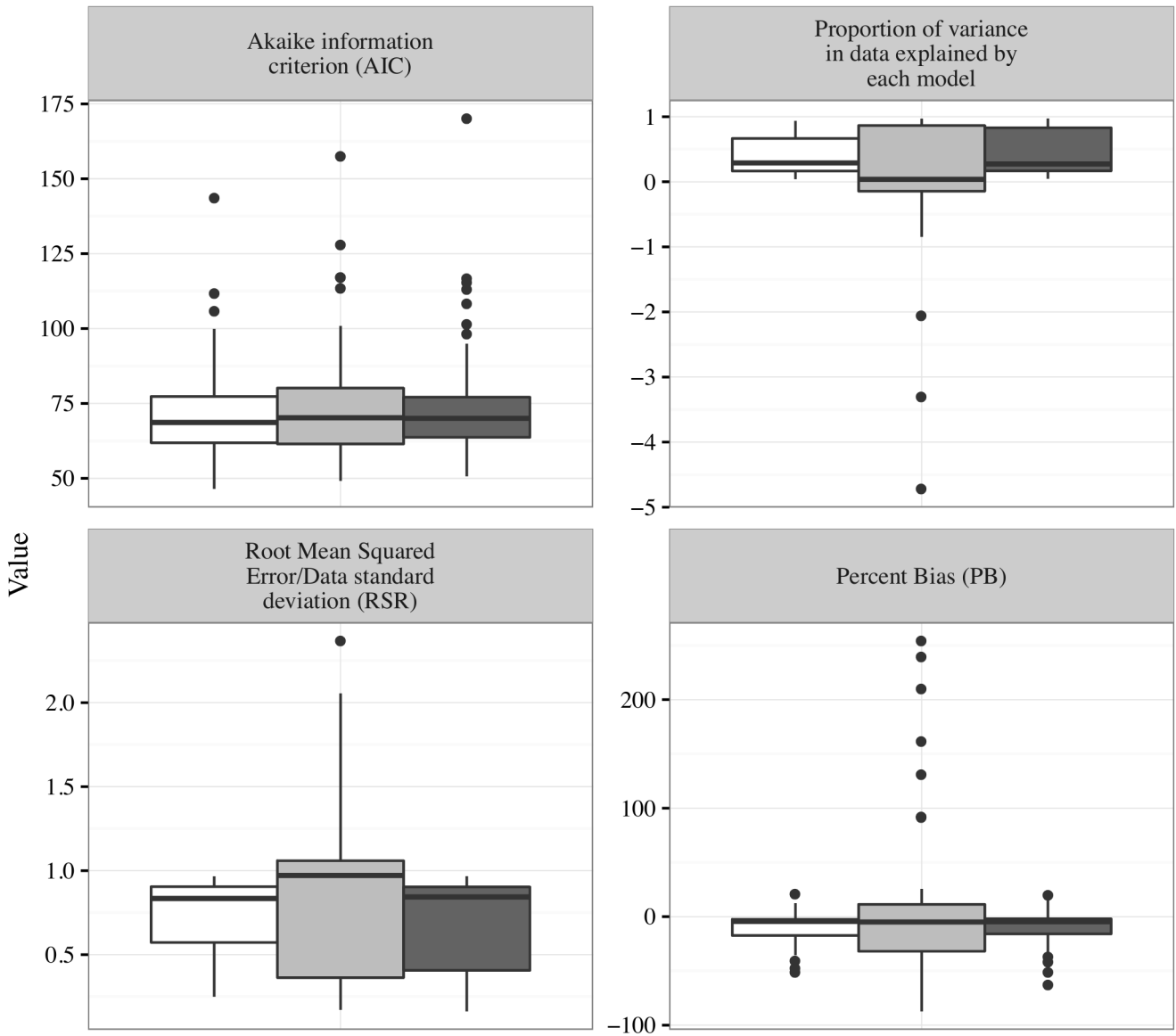
Compartmental Models for Seasonal Hyperendemic Bacterial Meningitis in the African Meningitis Belt

Thibaut KOUTANGNI, Pascal Crépey, Maxime Woringer, Souleymane Porgo, Brice Wilfried Bicaba, Haoua Tall, Judith E. Mueller

Supplementary Material S3. Results of simulations of the SCIRS age-structured models.

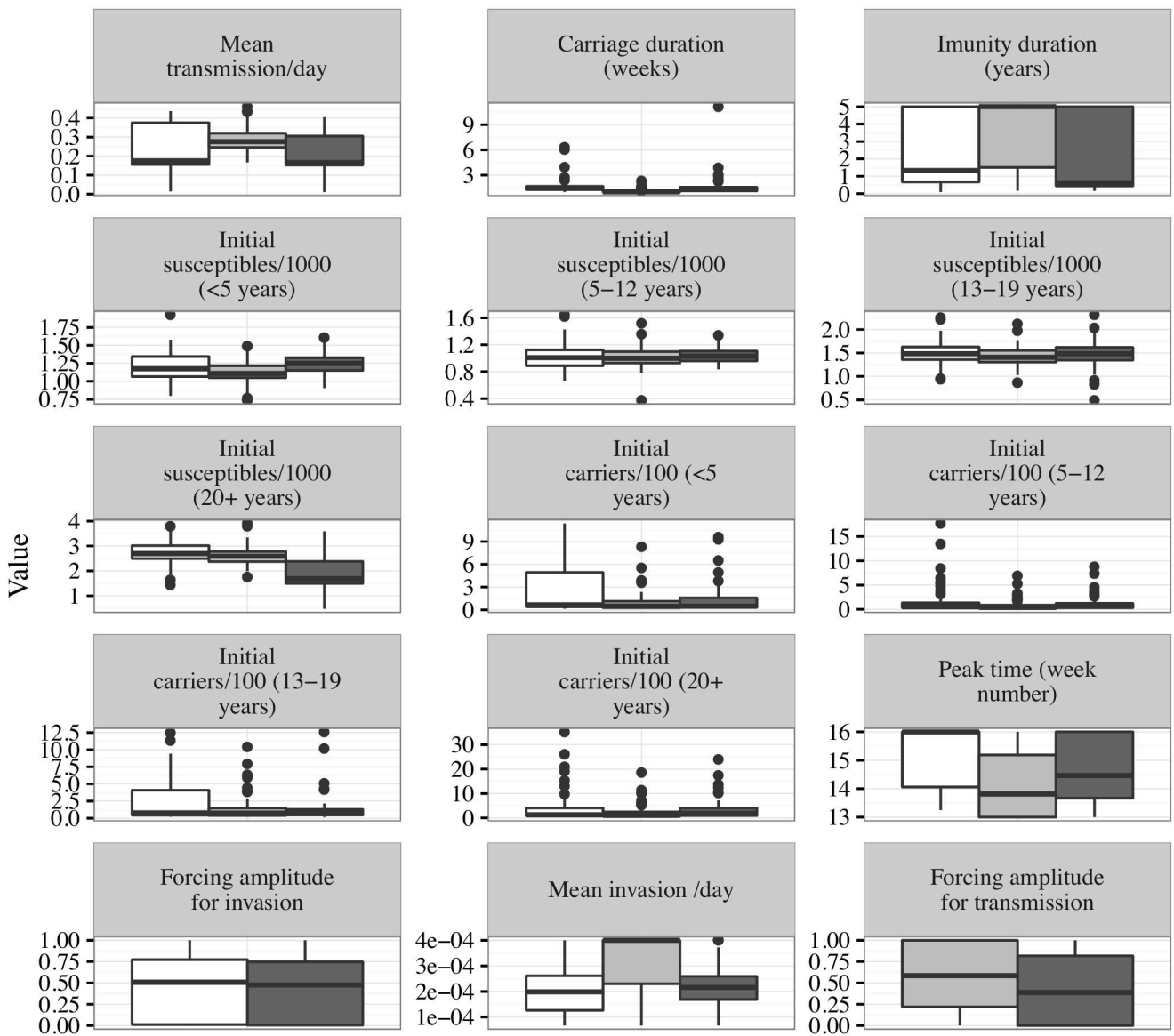
(A) Distribution of age-structured models performance stats

Model1-Inv Model2-Transm Model3-Inv-Transm



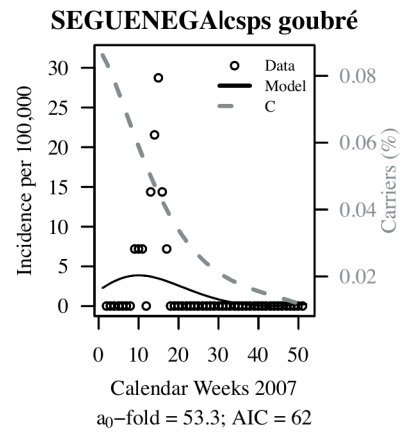
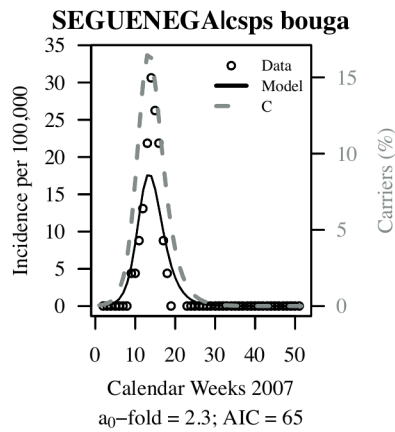
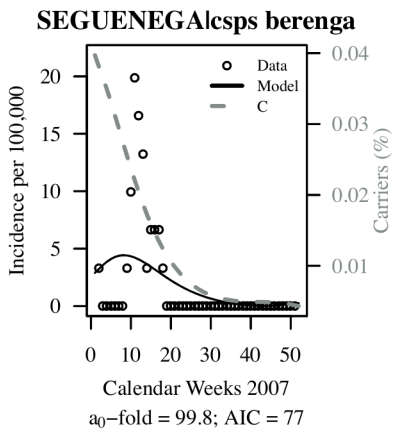
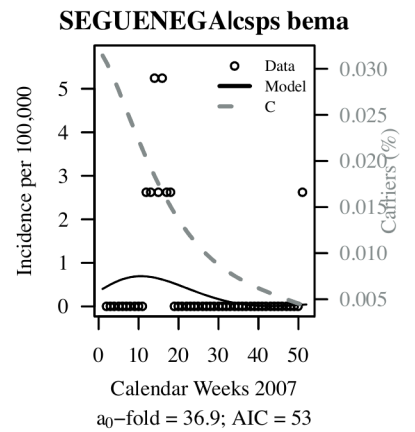
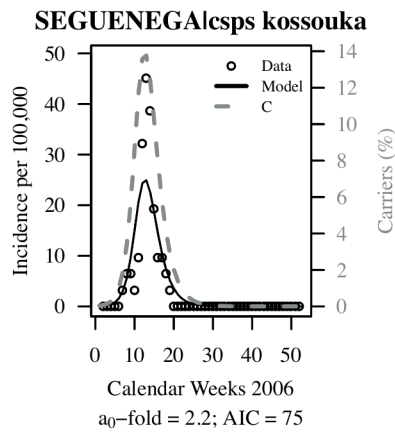
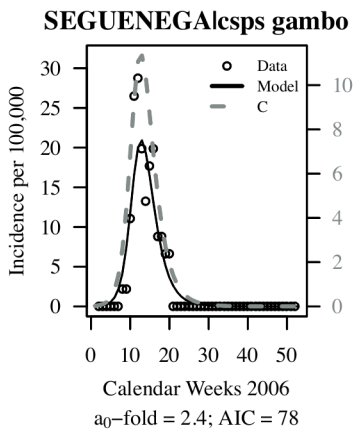
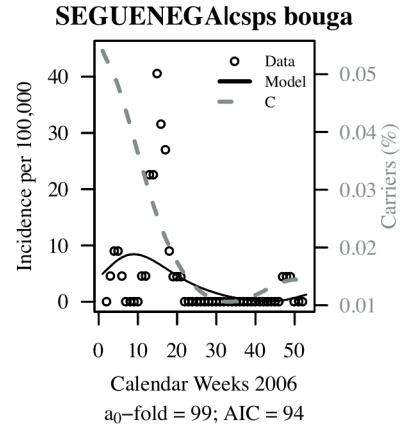
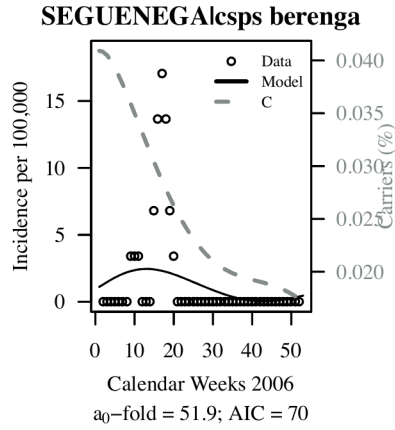
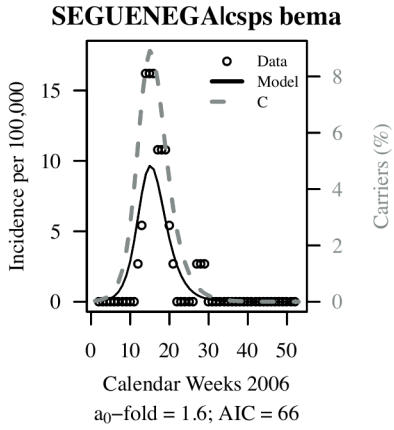
(B) Distribution of parameters estimates across all health center years

Model1-Inv Model2-Transm Model3-Inv-Transm

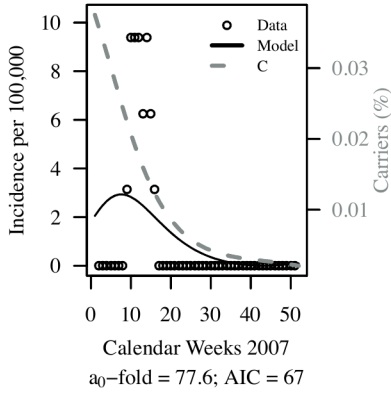


(C) Model1-"inv" trajectories matching plots of simulated and observed (weekly) data, for 64 health center-years with complete data, accross four health distrirts of Burkina faso (2004-2010).

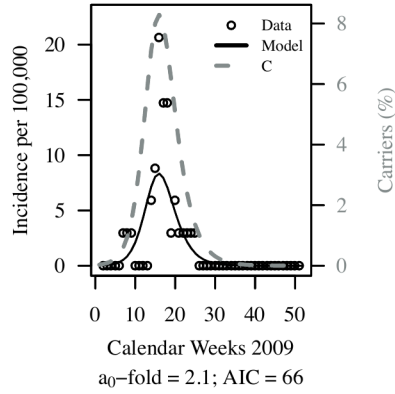
In figures. "Model" stands for incidence prediction of the model, "C" stands for carriage prediction



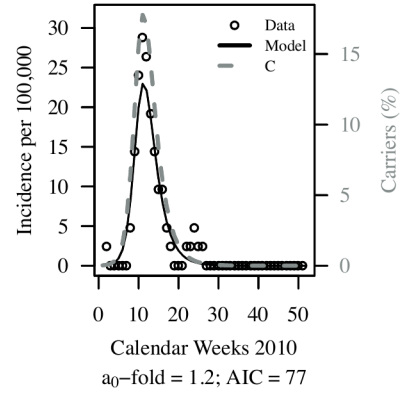
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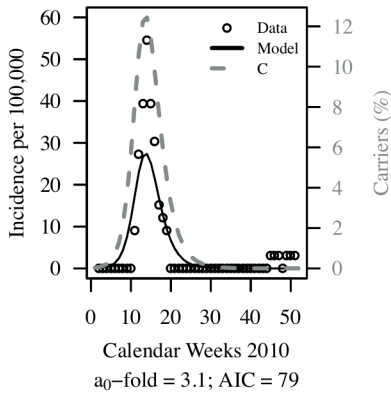
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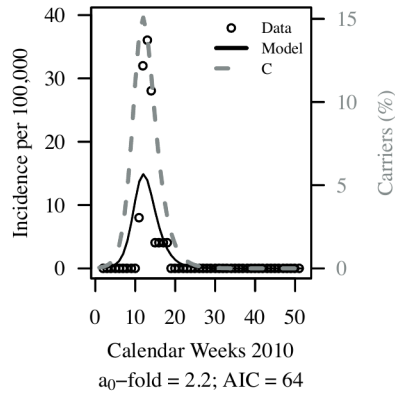
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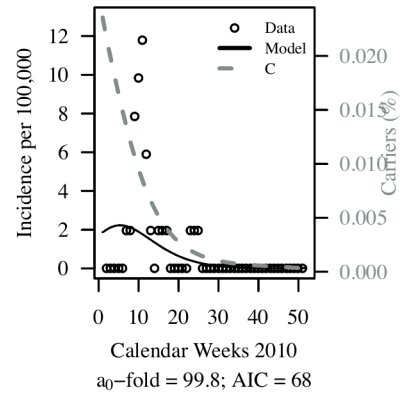
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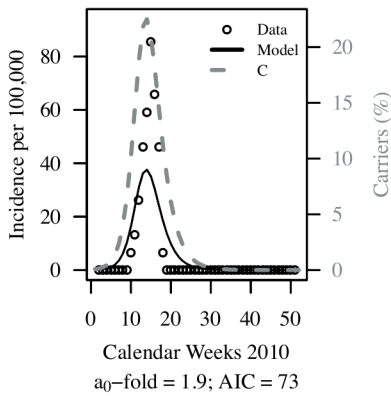
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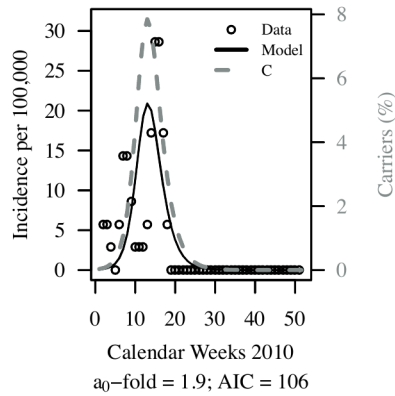
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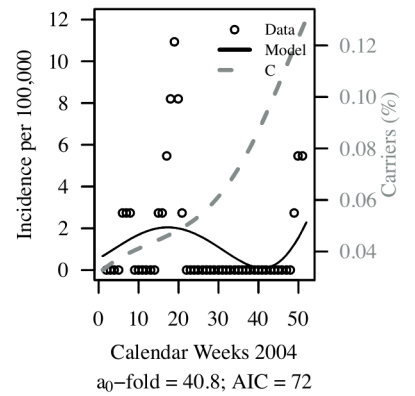
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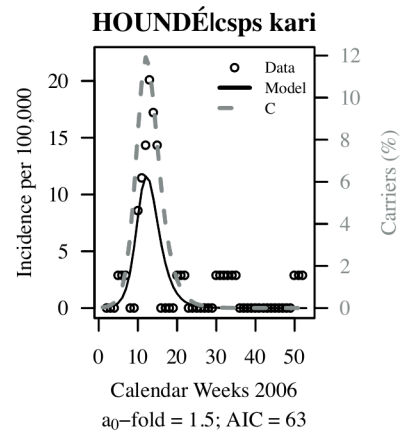
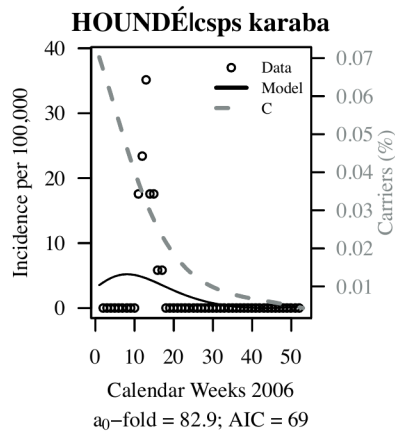
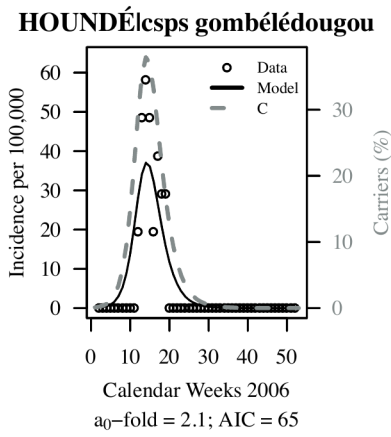
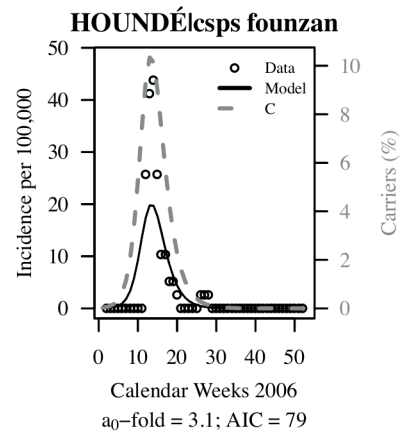
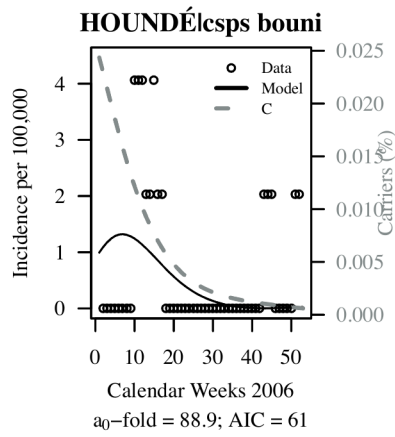
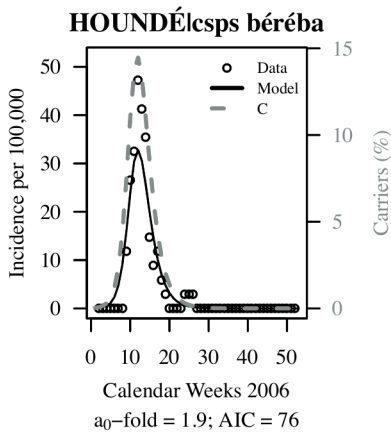
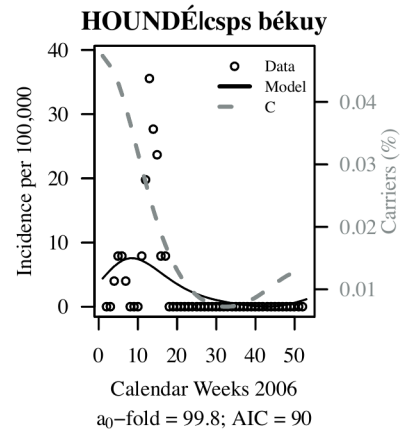
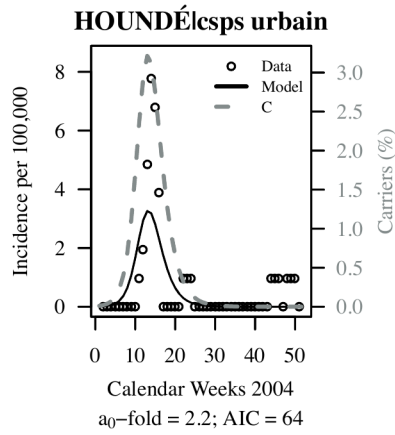
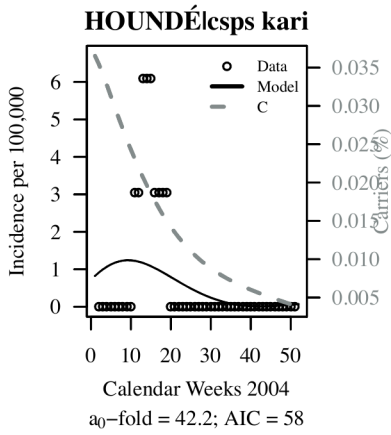


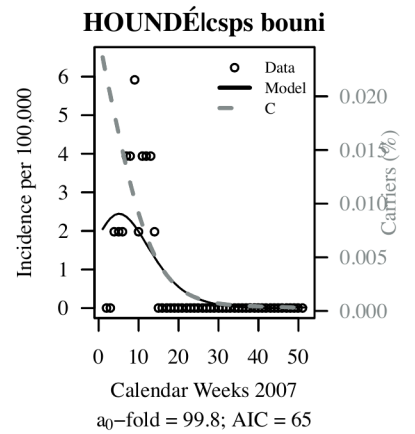
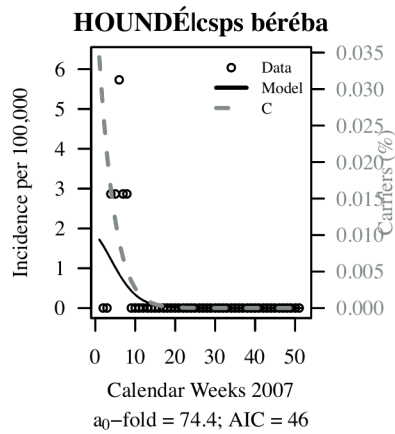
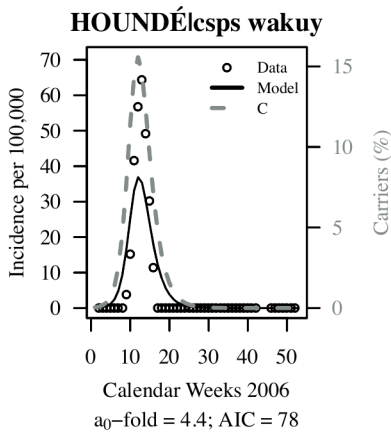
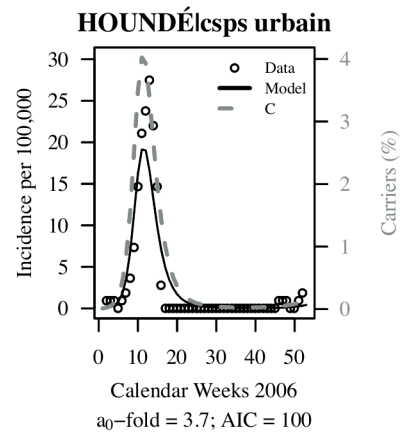
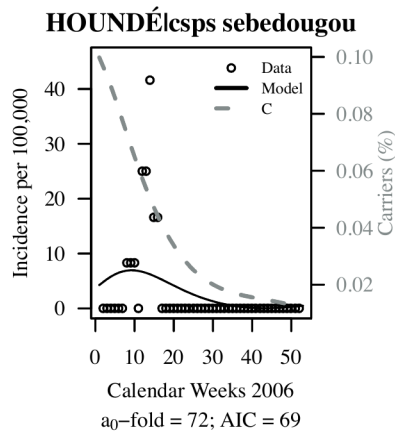
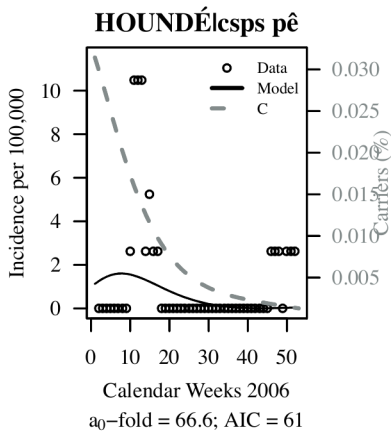
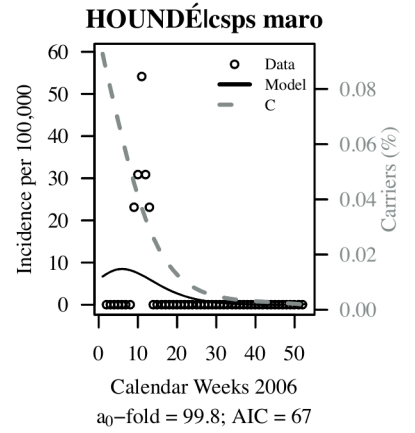
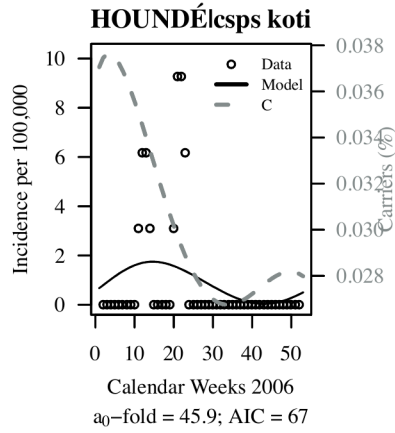
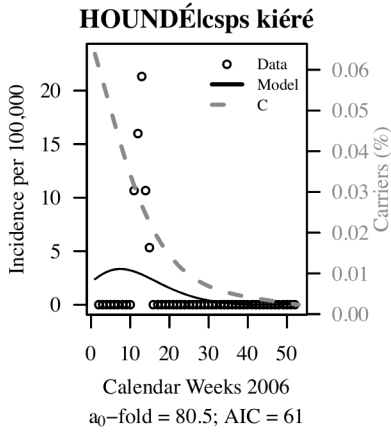
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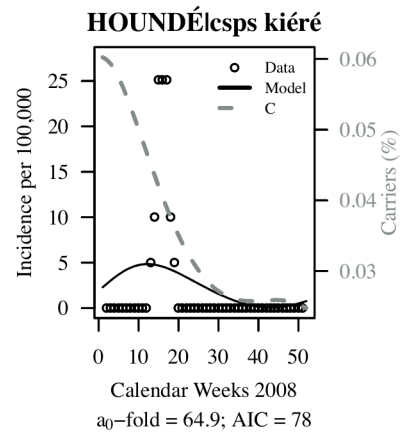
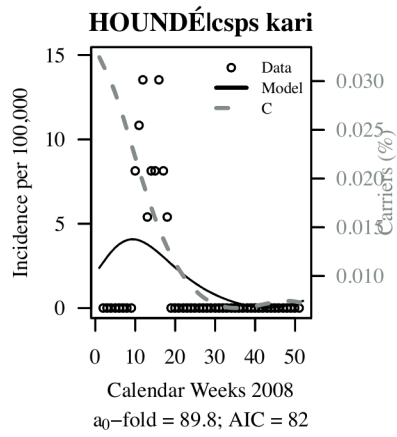
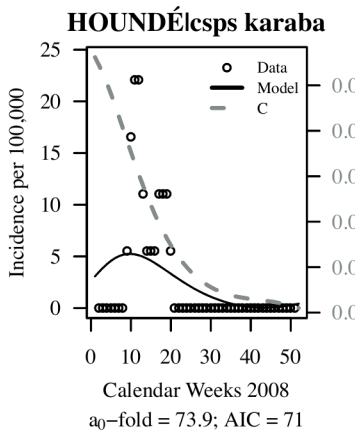
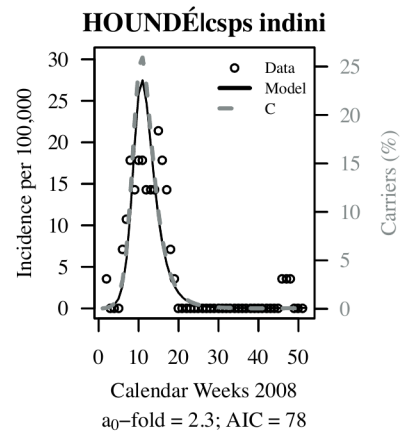
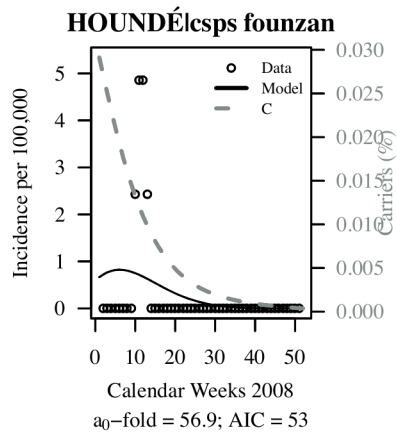
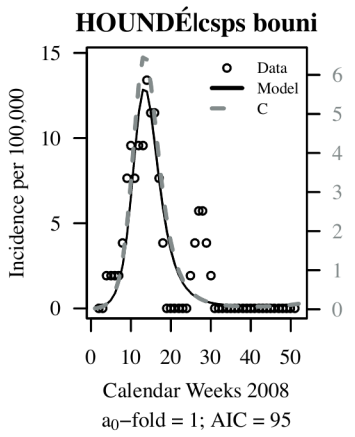
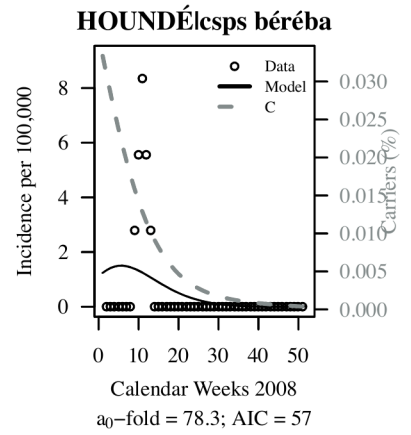
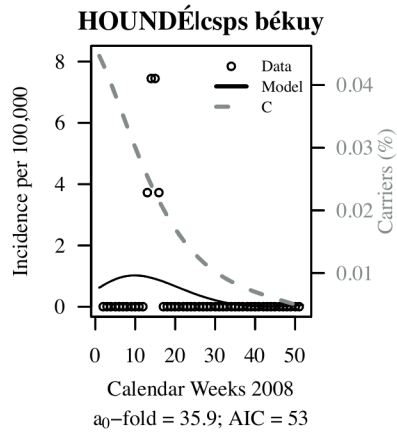
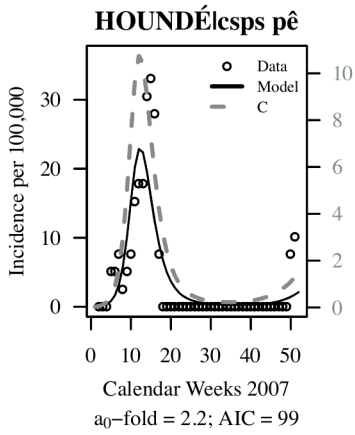


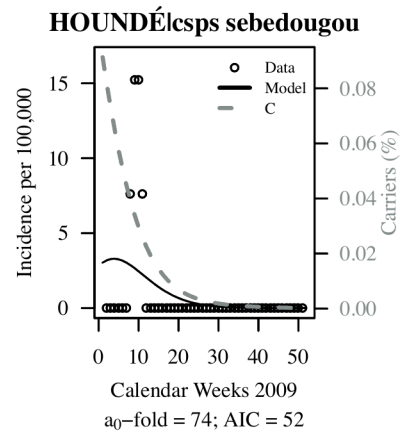
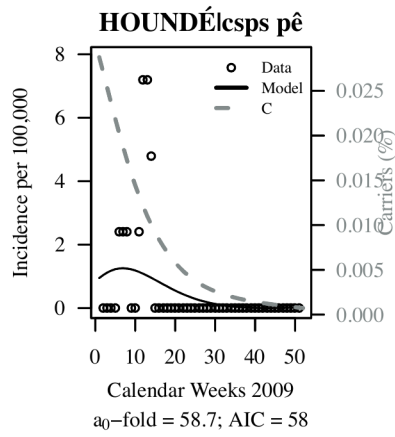
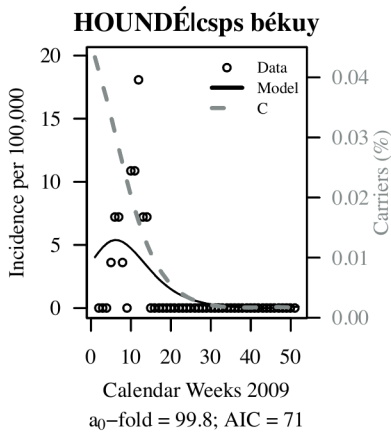
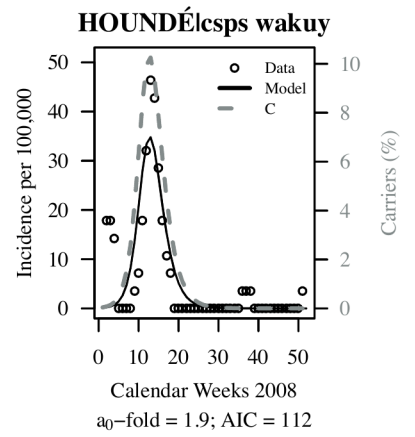
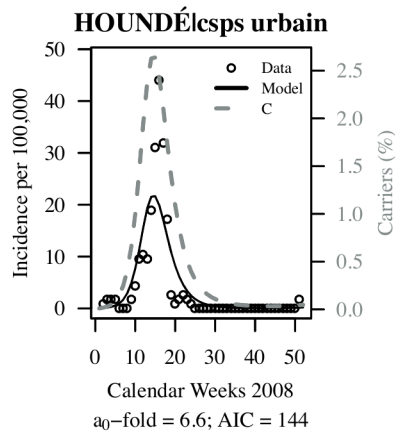
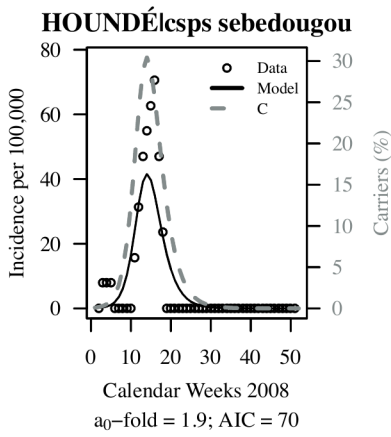
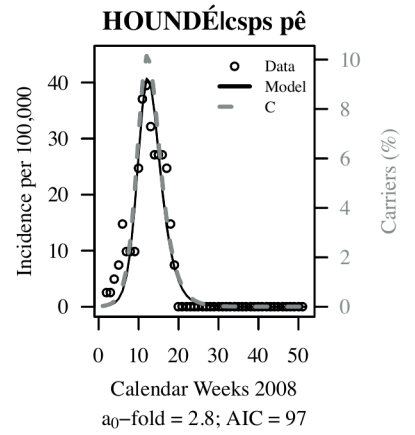
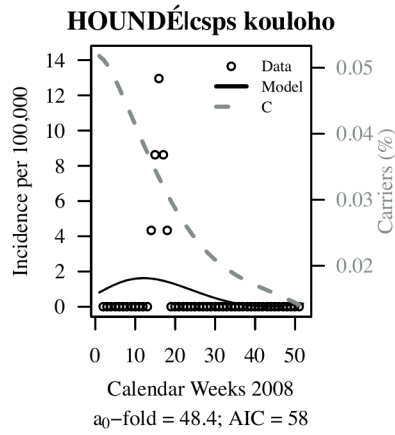
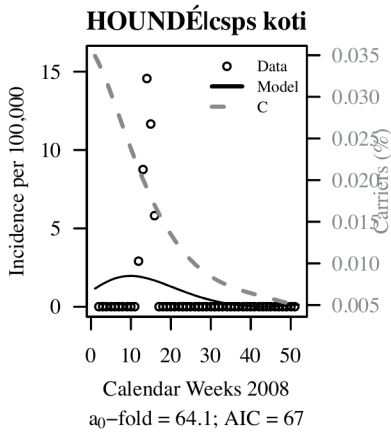
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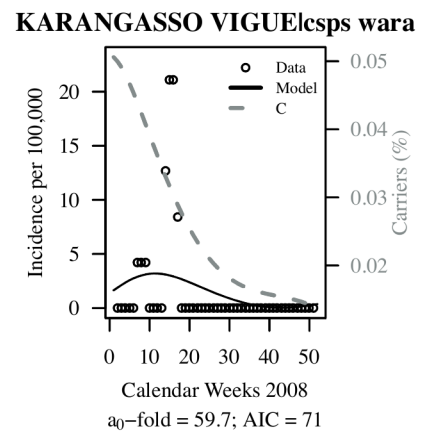
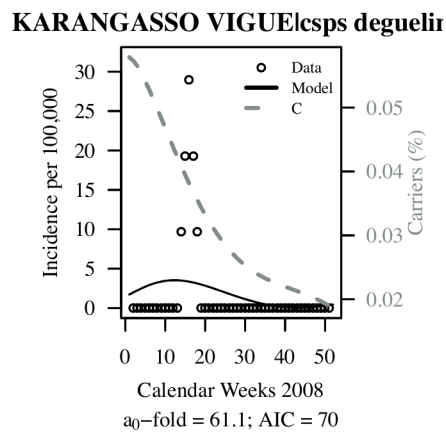
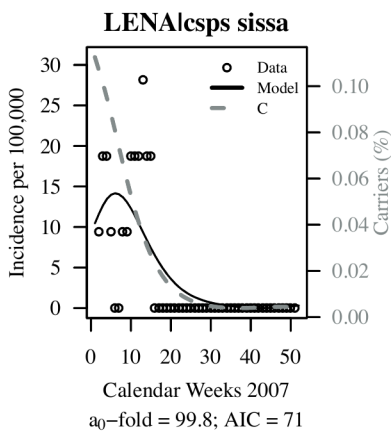
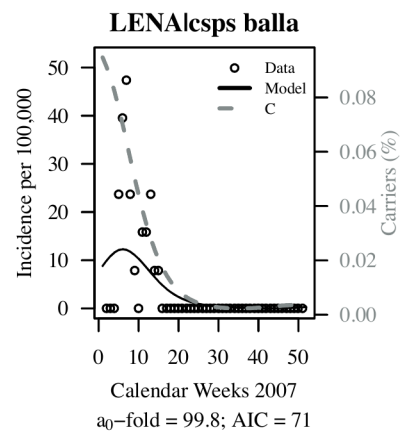
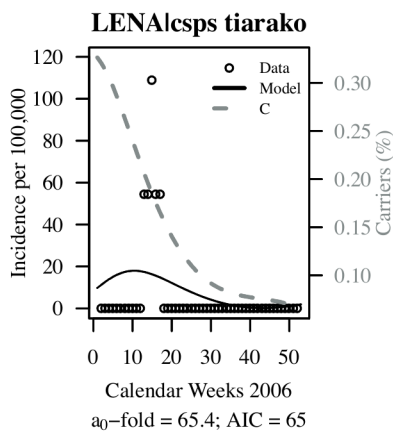
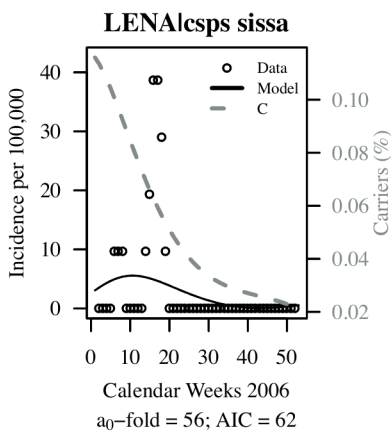
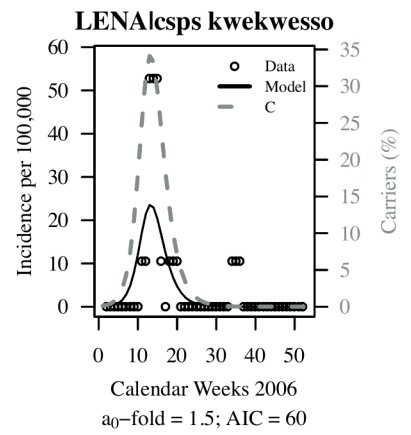
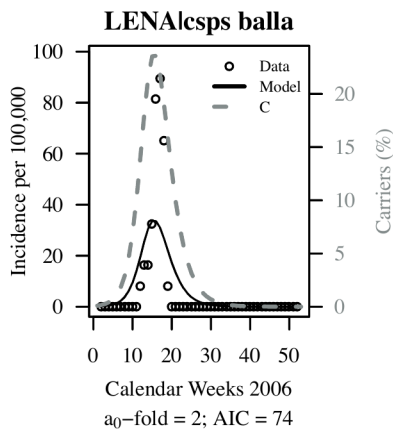
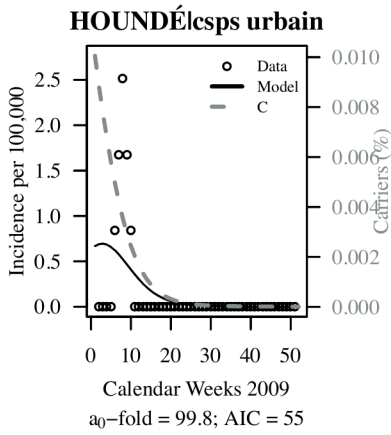




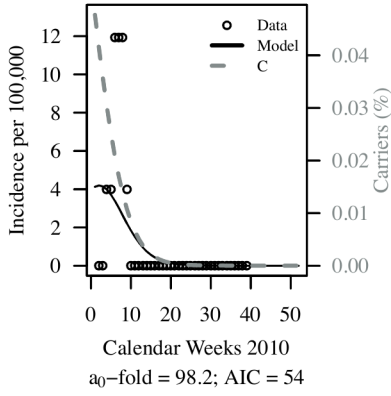




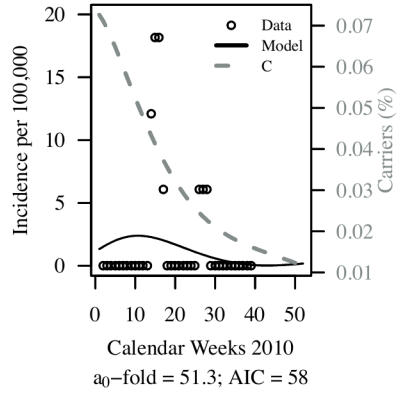




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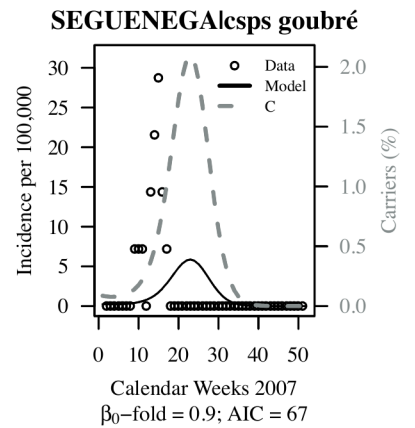
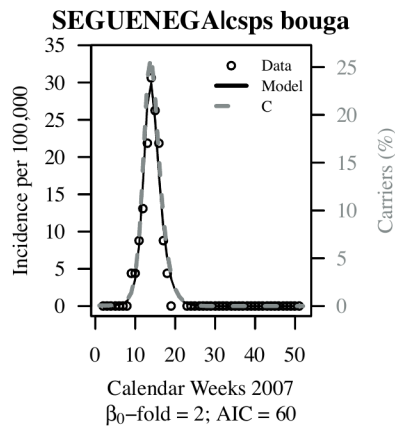
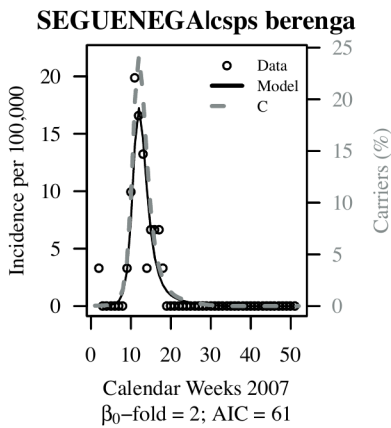
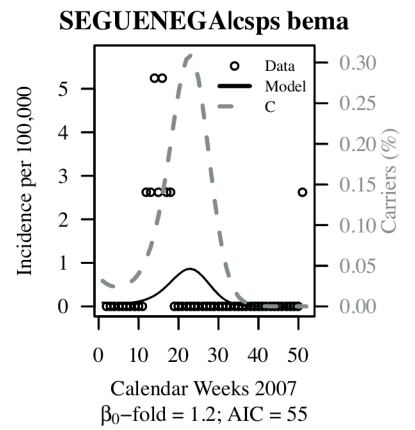
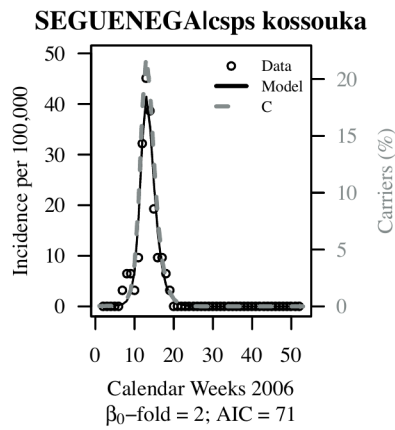
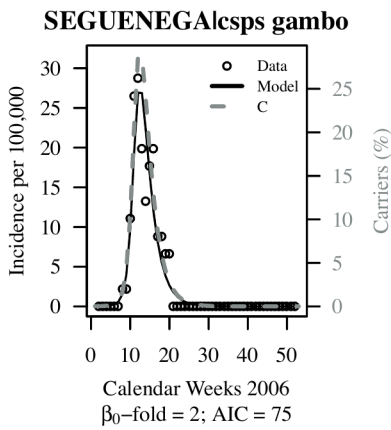
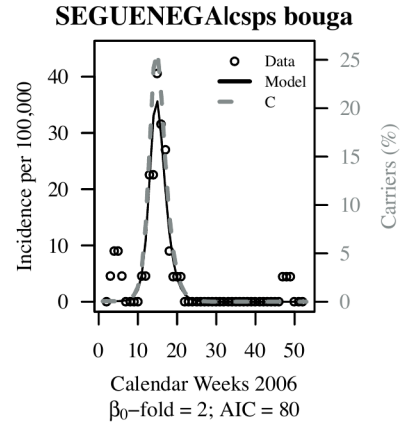
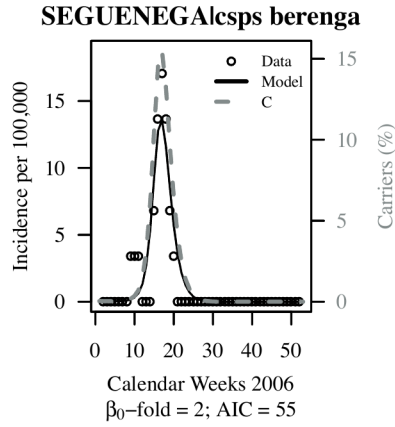
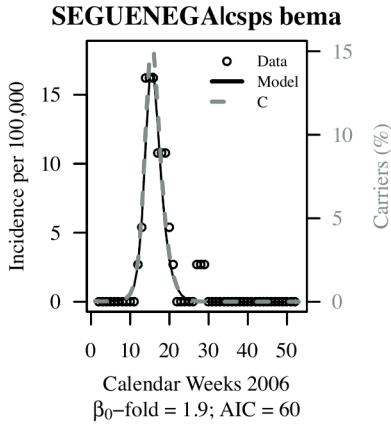


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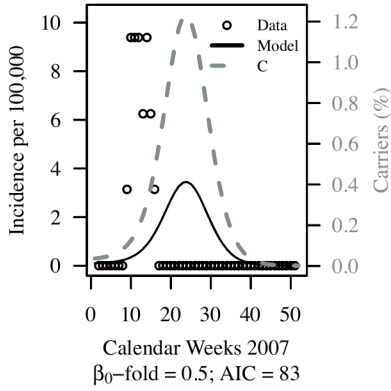


(D) Model2-"transm" trajectories matching plots of simulated and observed (weekly) data, for 64 health center-years with complete data, across four health districts of Burkina faso (2004-2010).

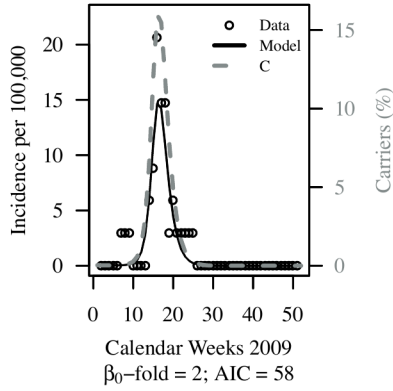
In figures. "Model" stands for incidence prediction of the model, "C" stands for carriage prediction



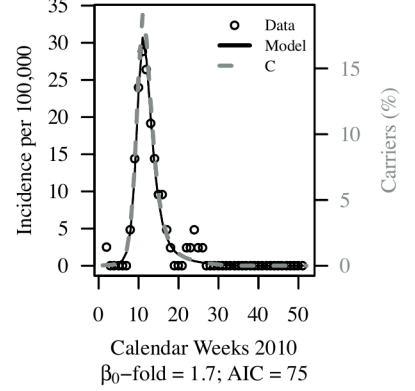
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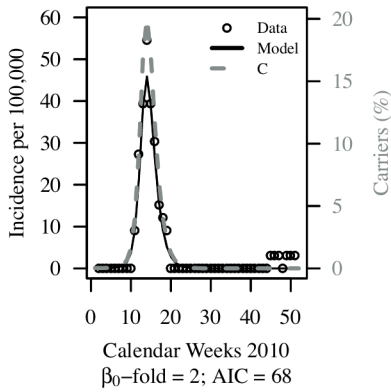
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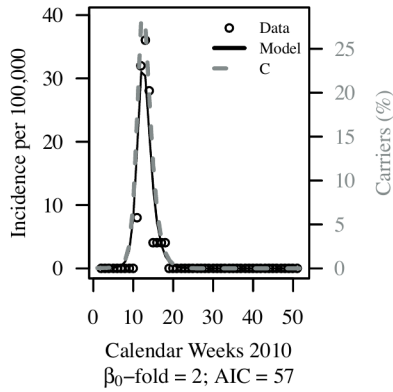
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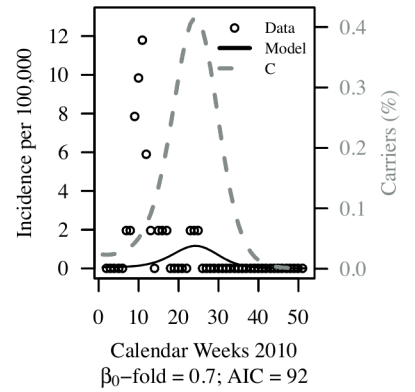
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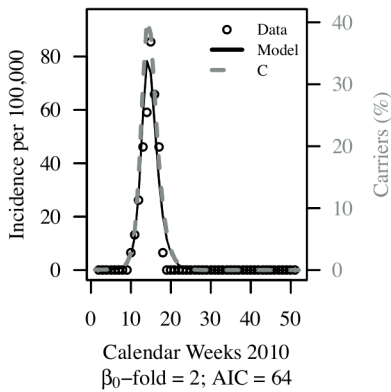
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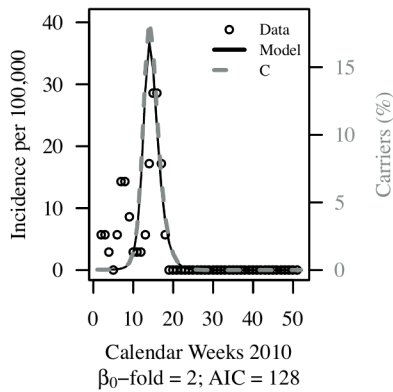
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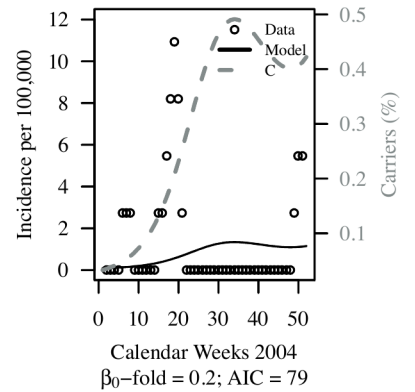
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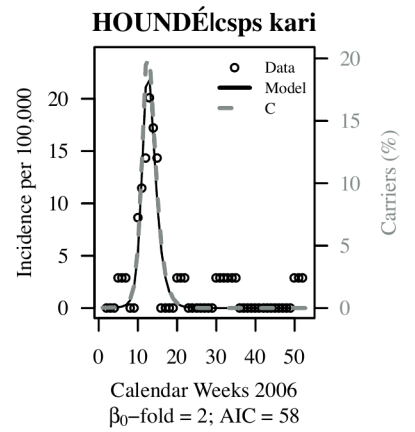
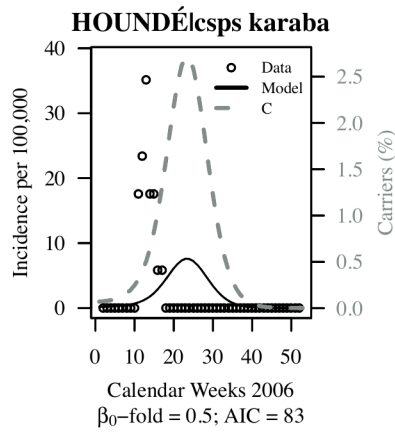
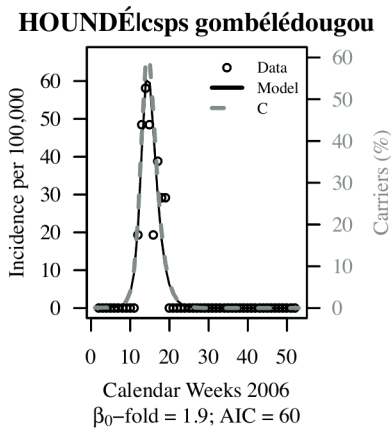
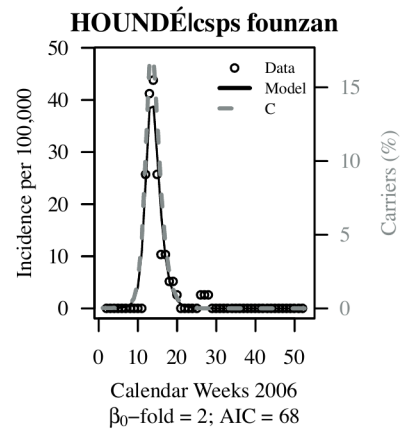
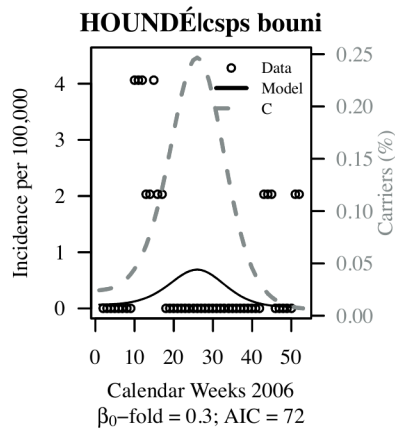
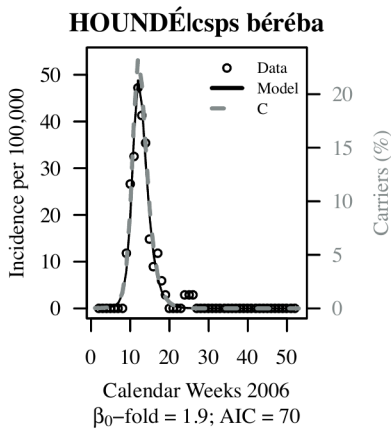
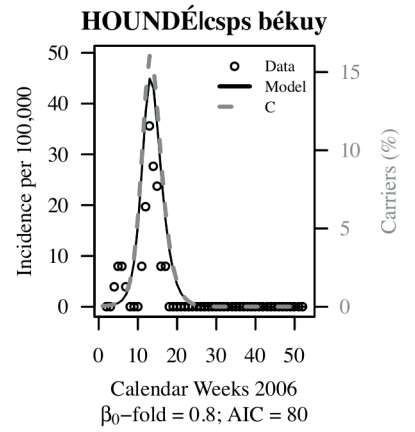
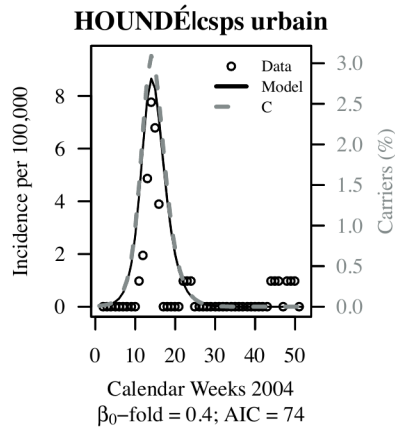
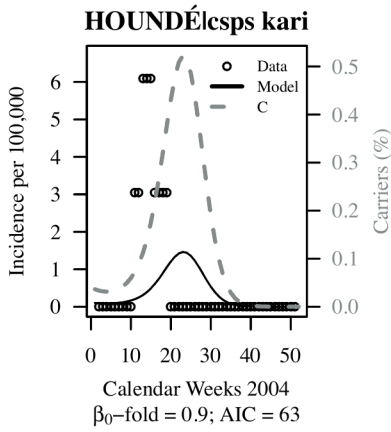


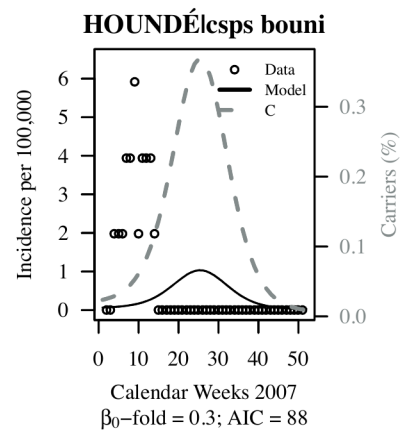
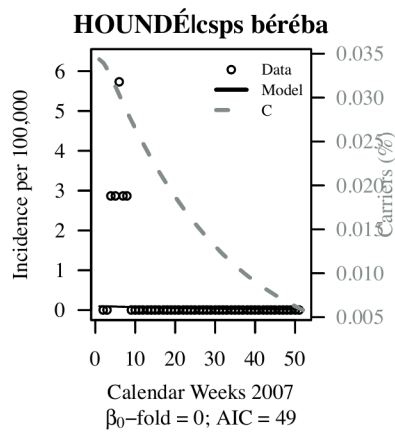
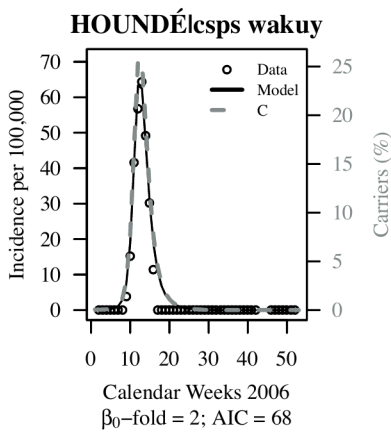
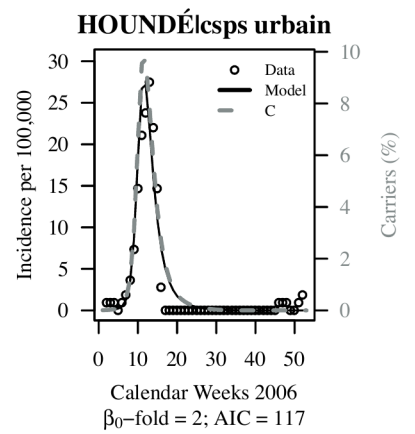
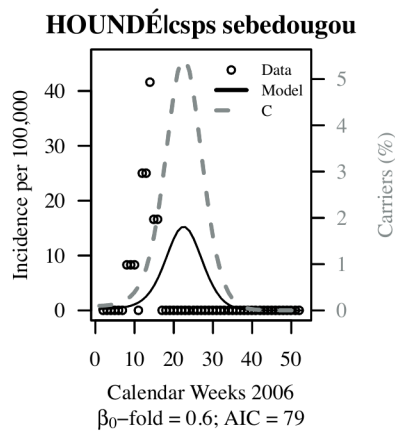
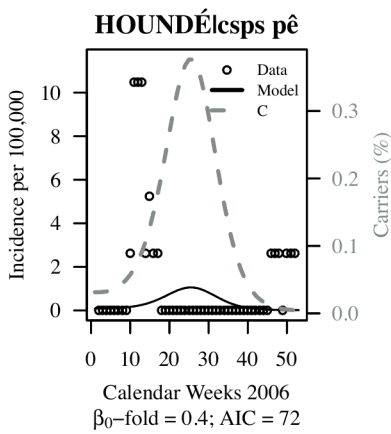
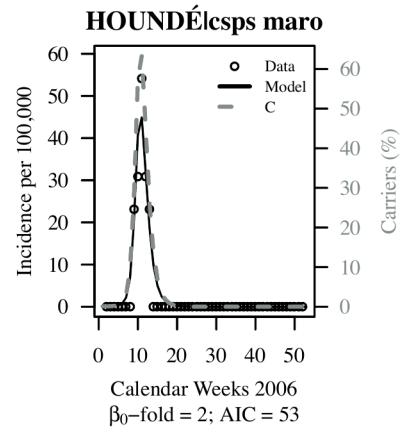
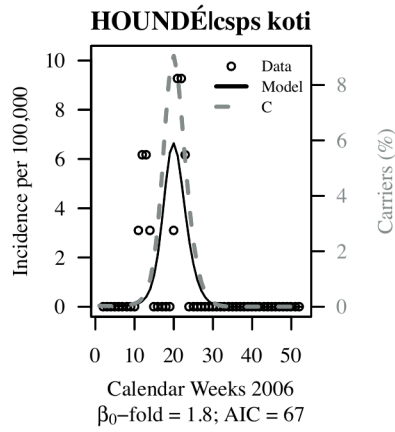
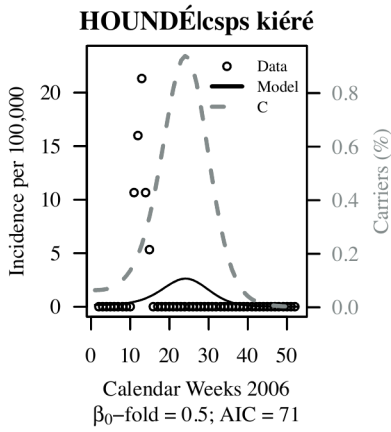
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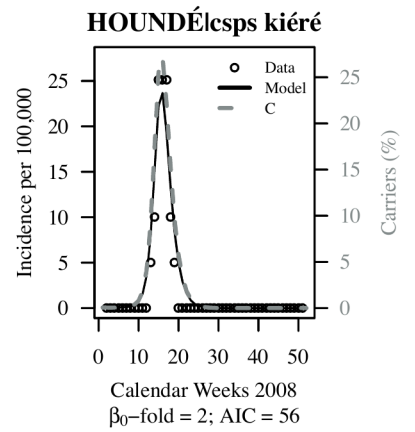
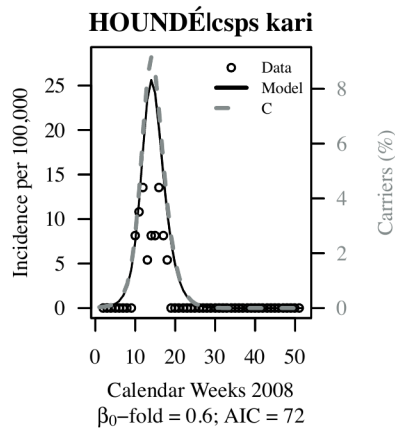
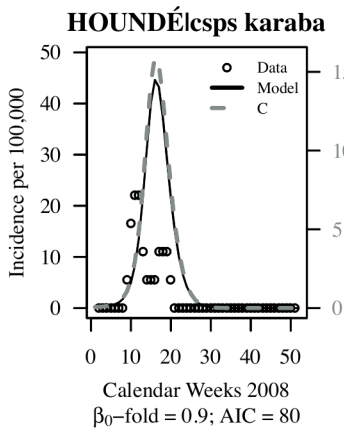
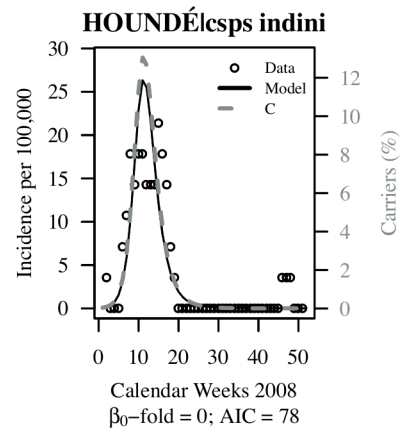
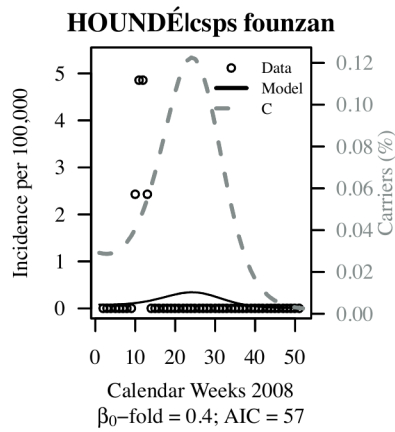
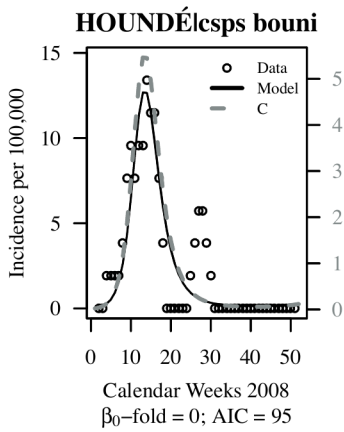
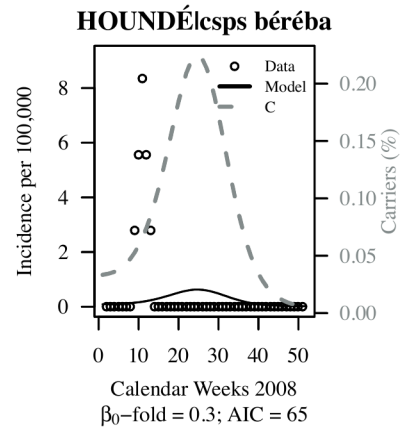
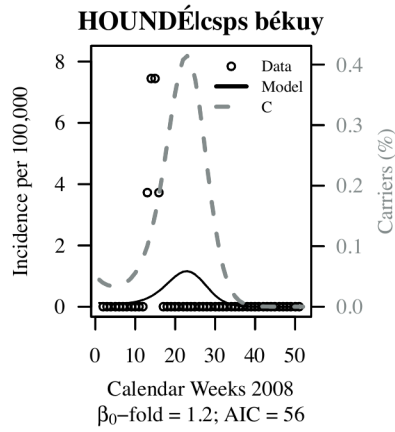
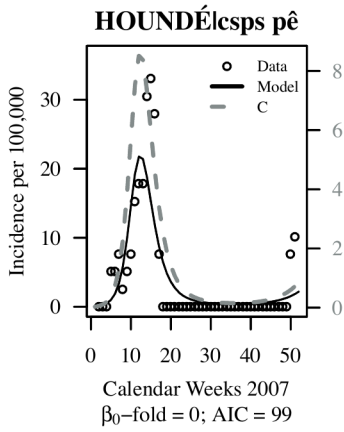


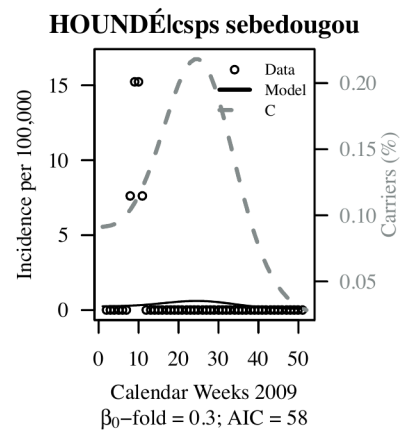
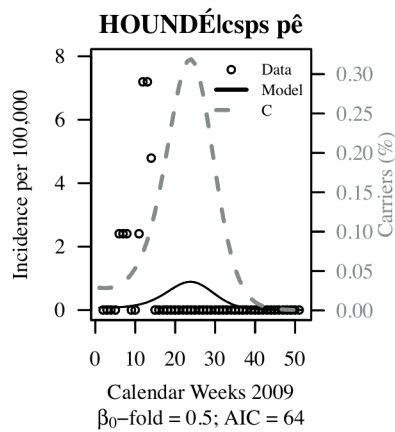
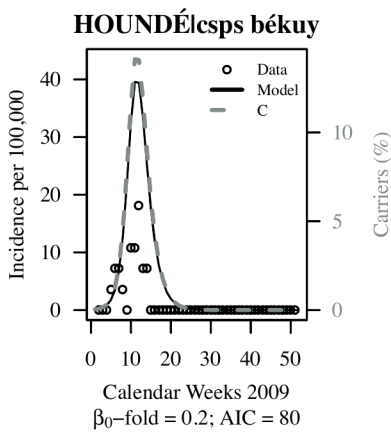
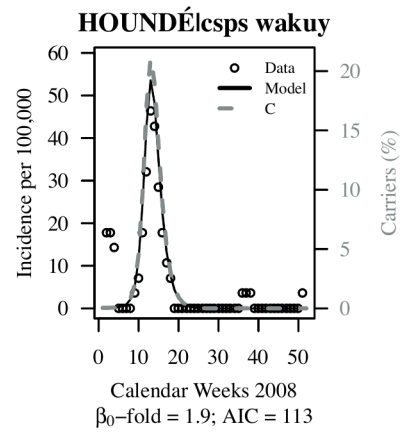
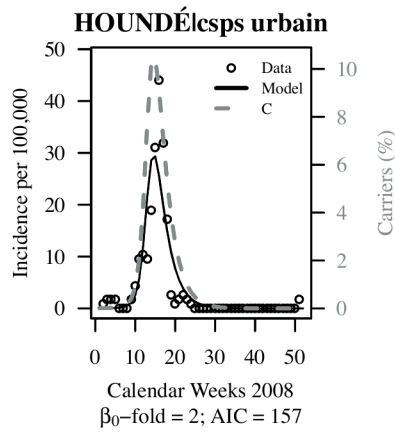
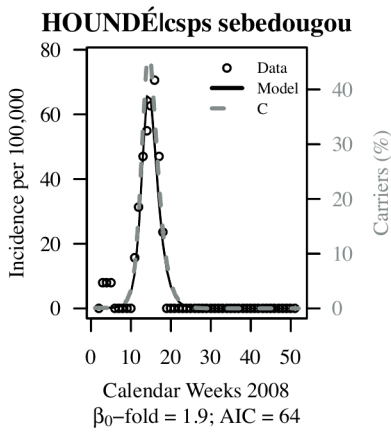
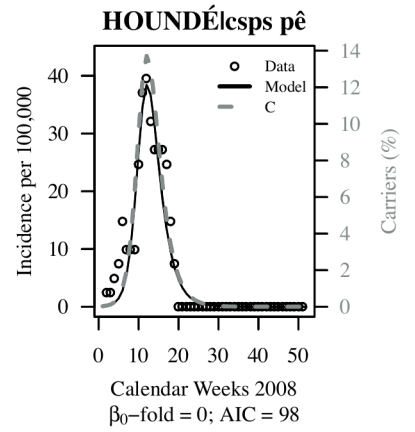
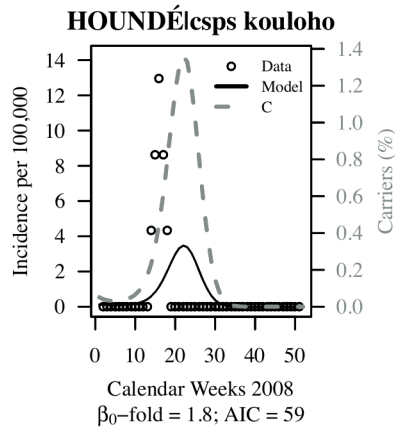
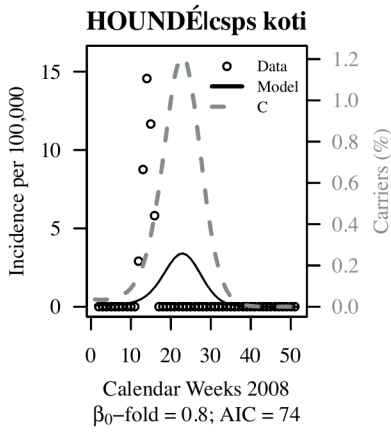
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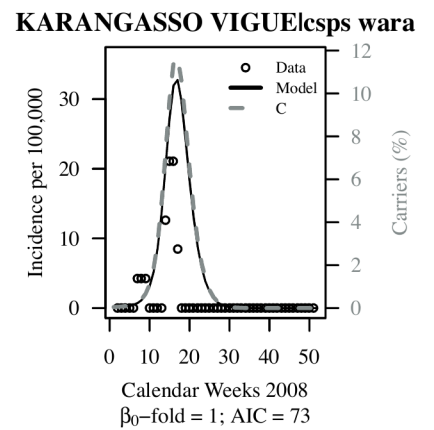
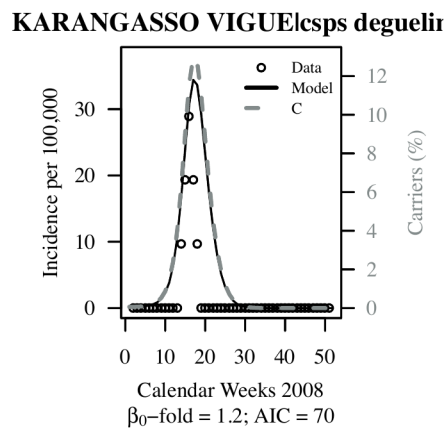
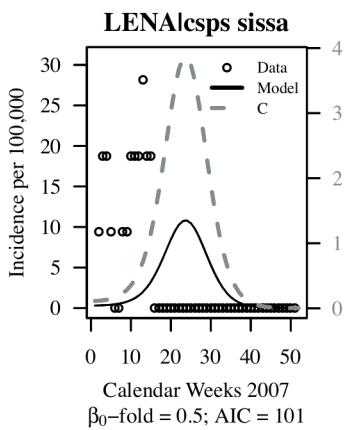
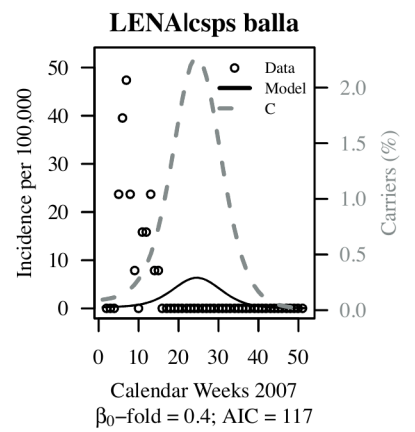
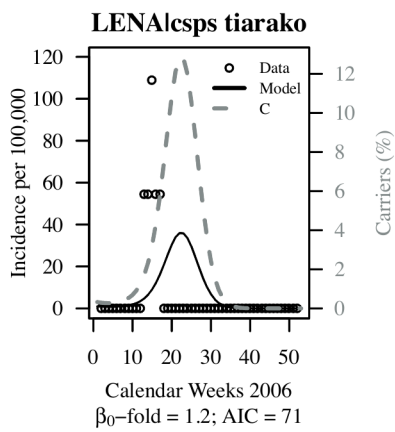
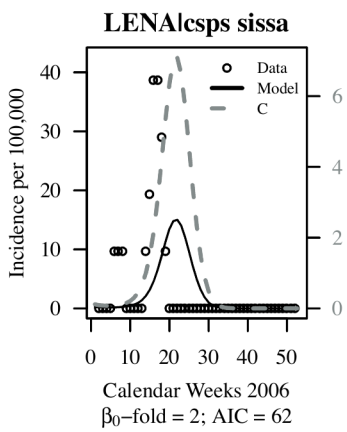
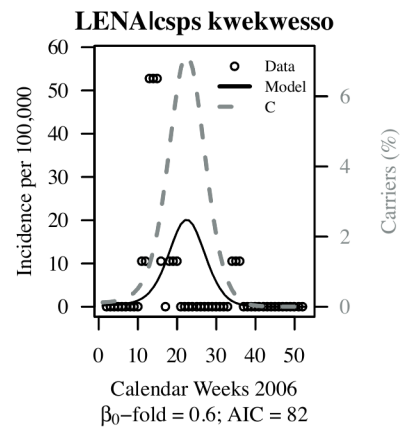
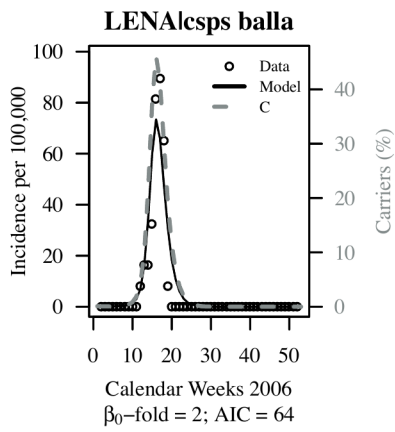
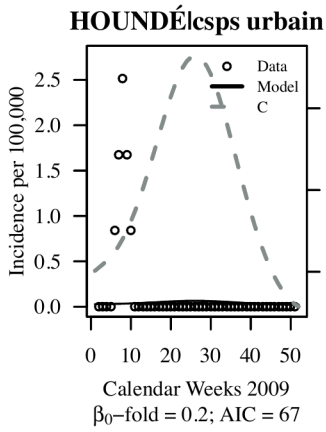




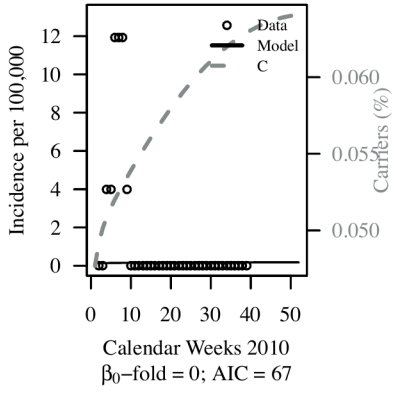




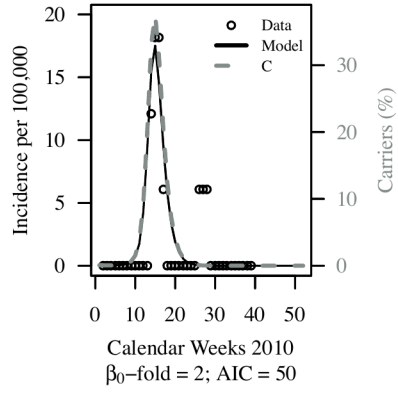




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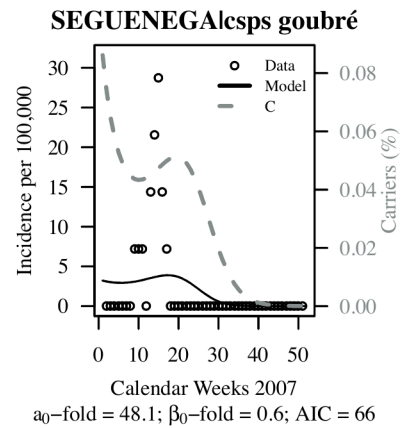
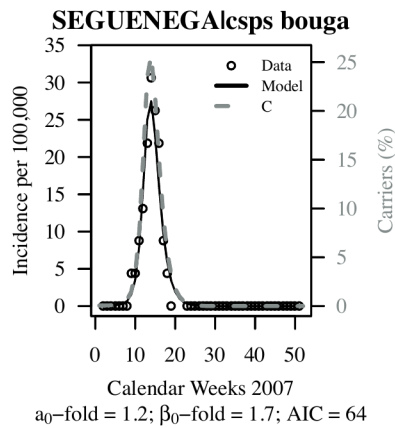
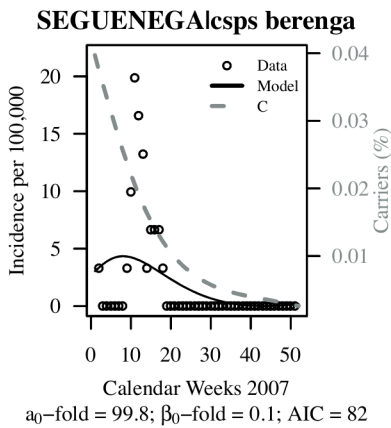
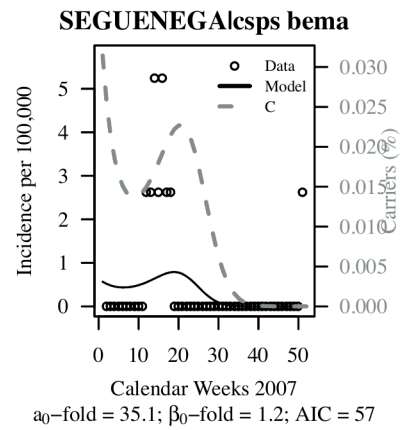
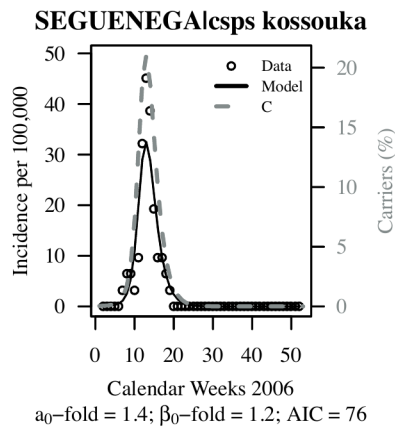
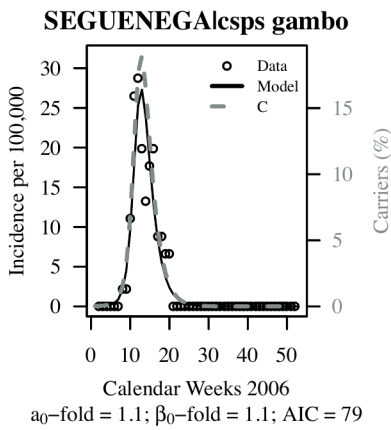
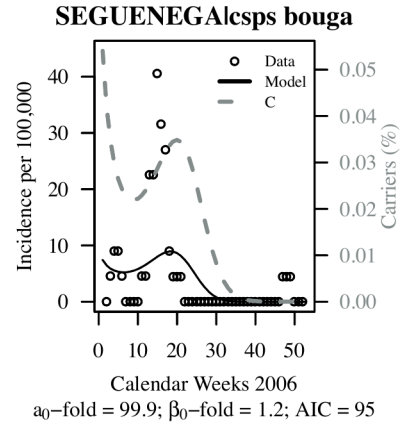
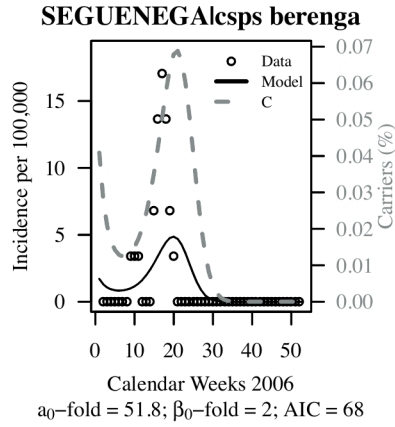
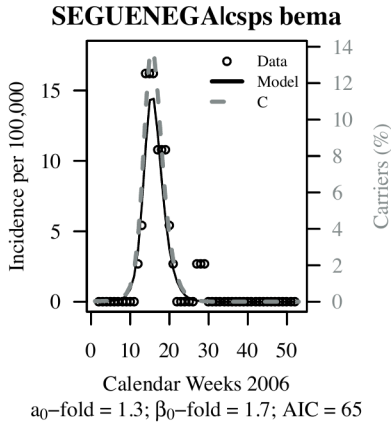


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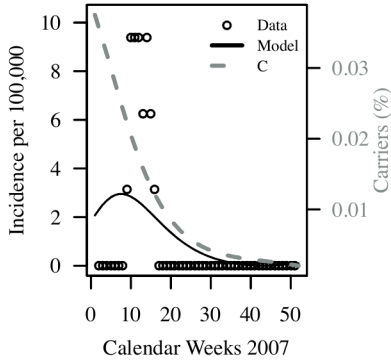


(E) Model3-"inv-transm" trajectories matching plots of simulated and observed (weekly) data, for 64 health center-years with complete data, across four health districts of Burkina faso (2004-2010).

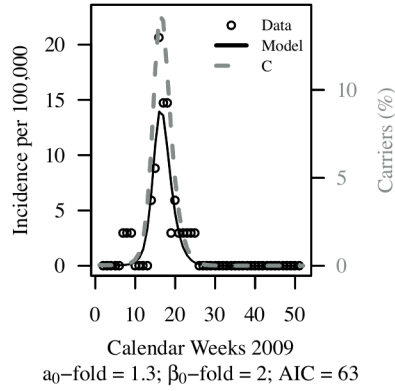
In figures. "Model" stands for incidence prediction of the model, "C" stands for carriage prediction



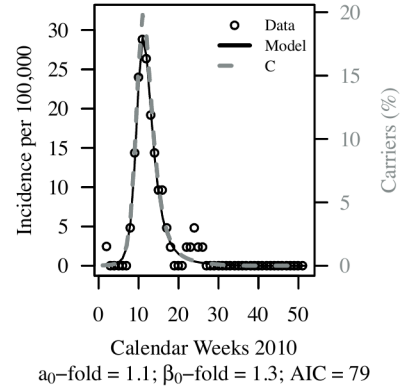
SEGUENEGAlcspss kossouka



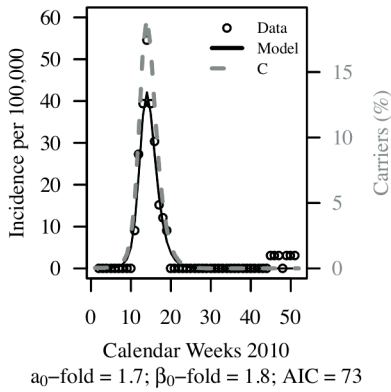
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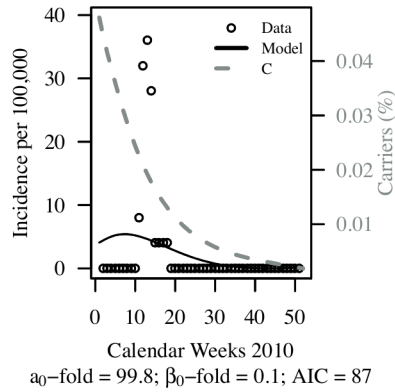
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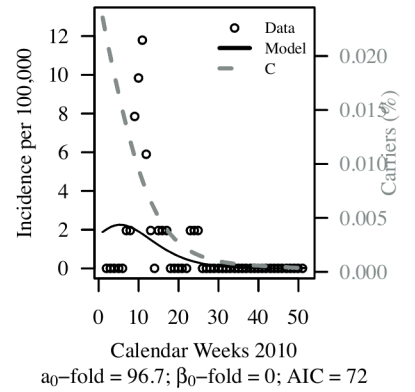
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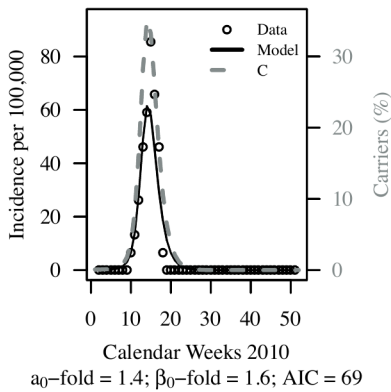
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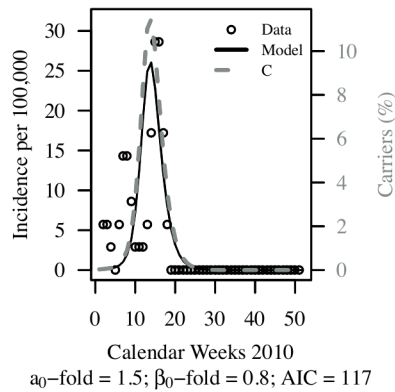
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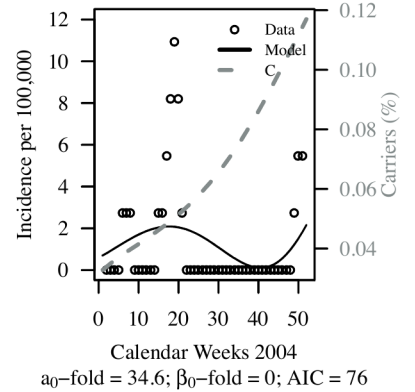
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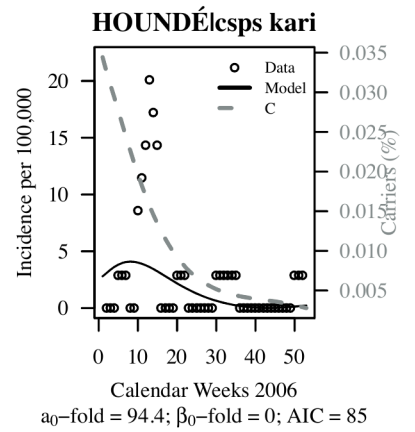
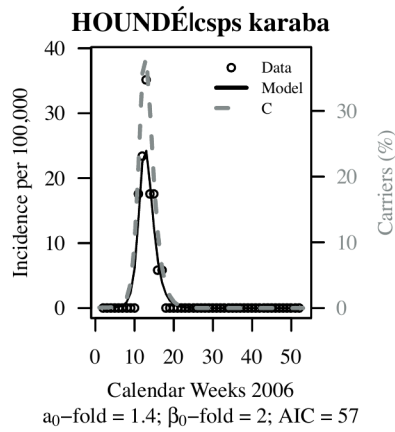
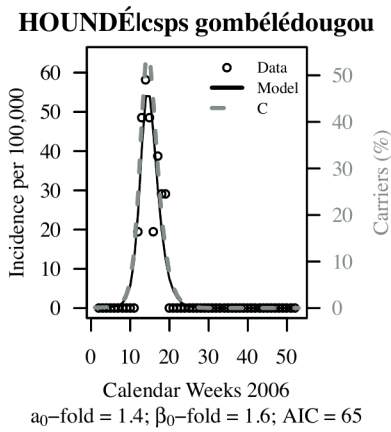
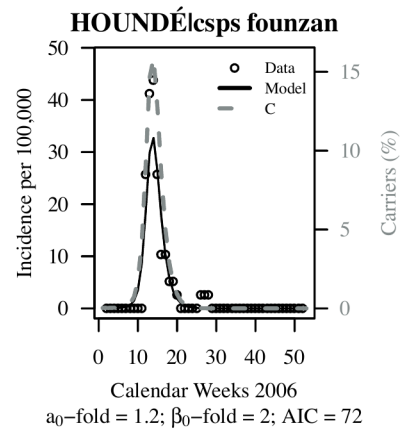
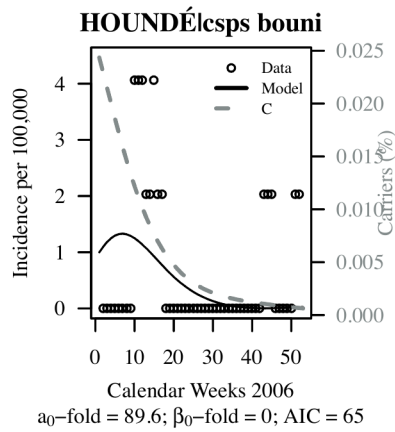
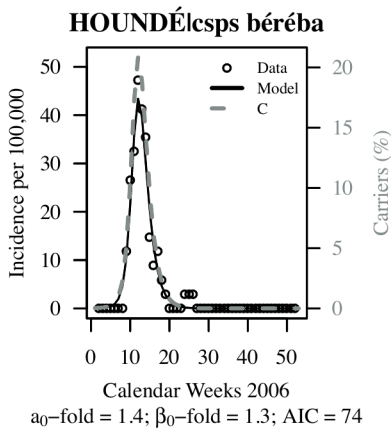
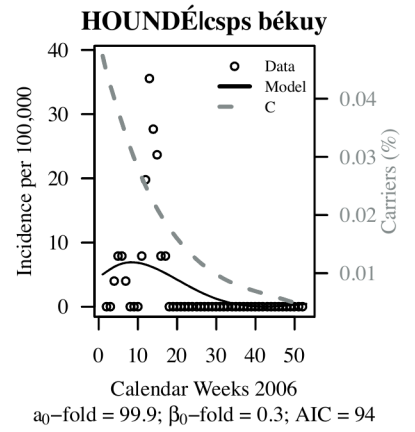
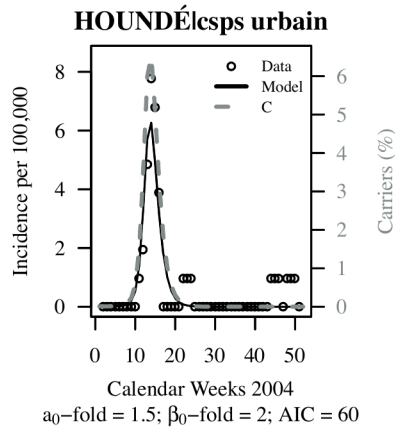
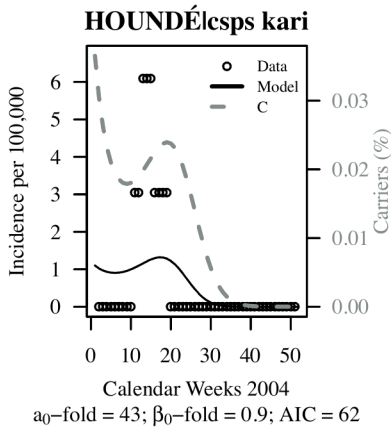


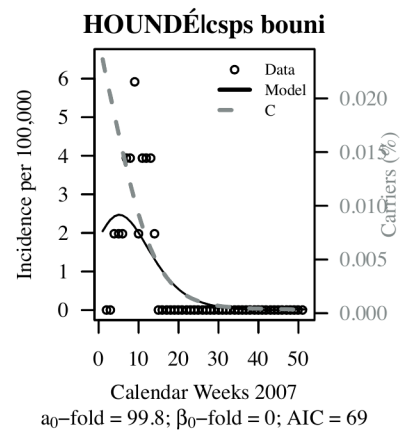
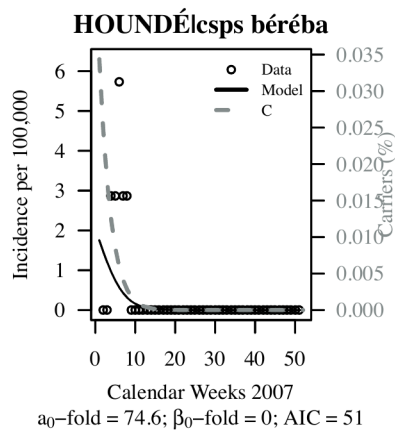
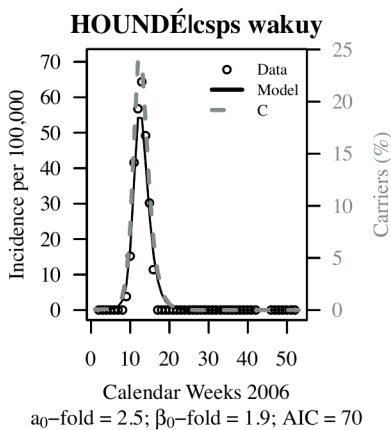
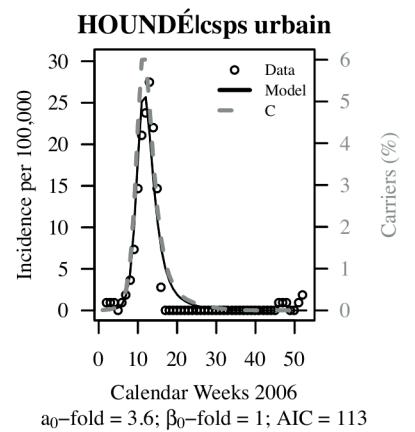
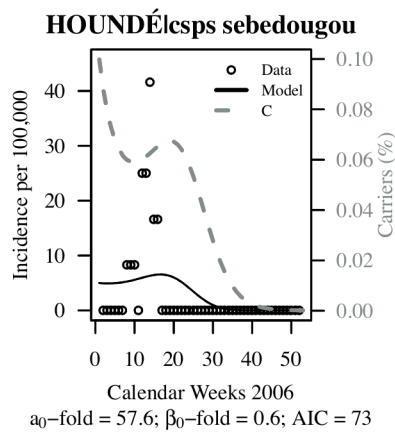
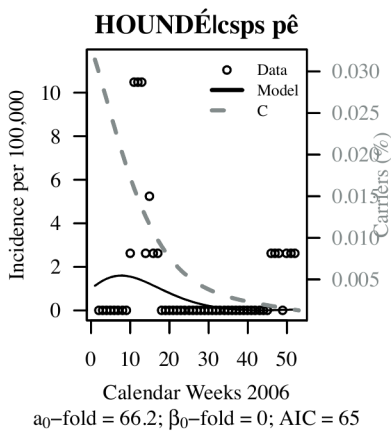
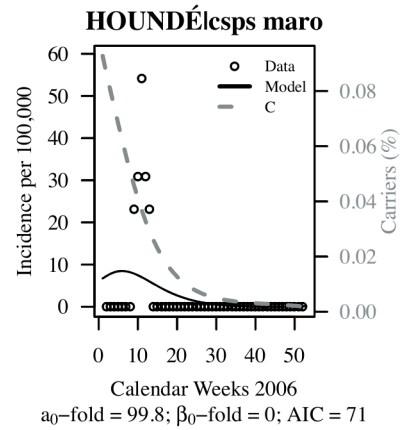
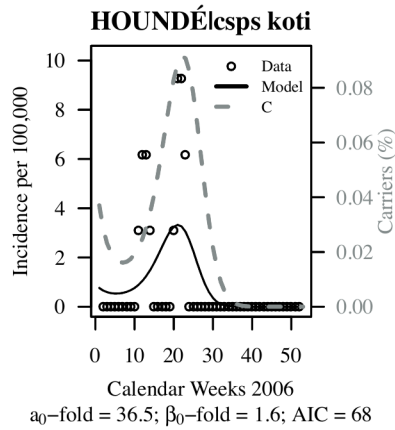
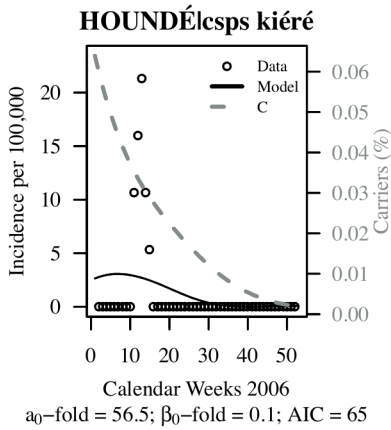
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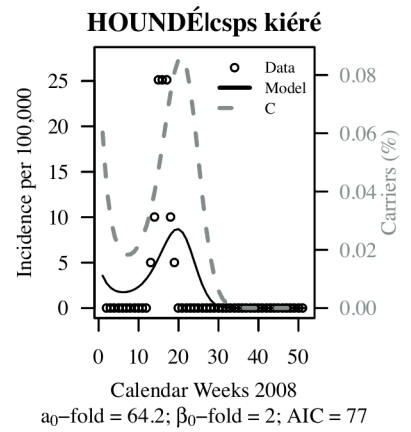
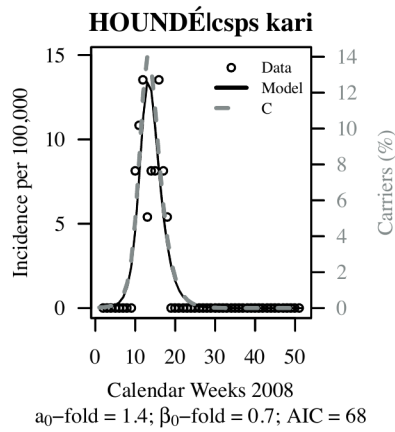
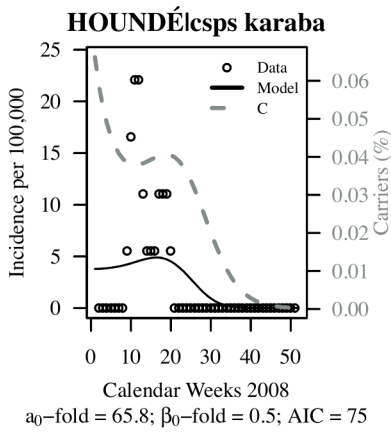
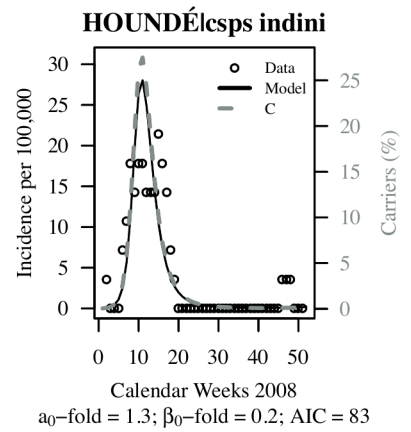
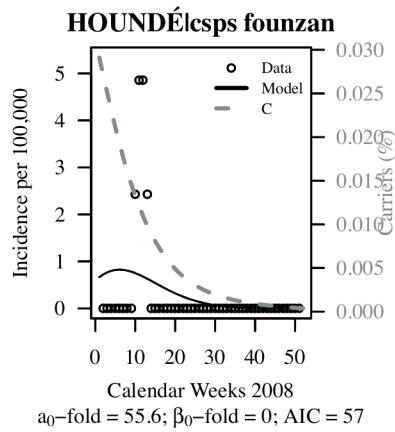
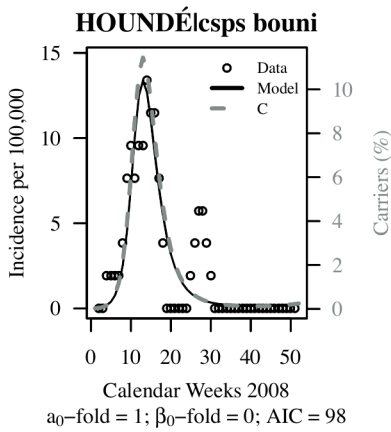
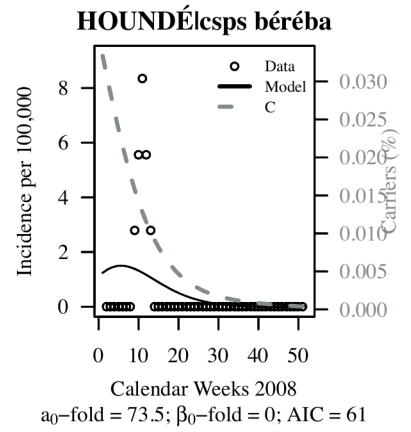
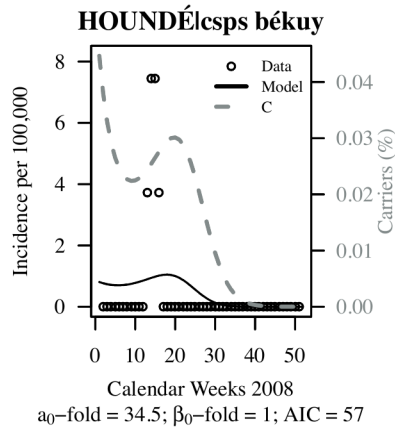
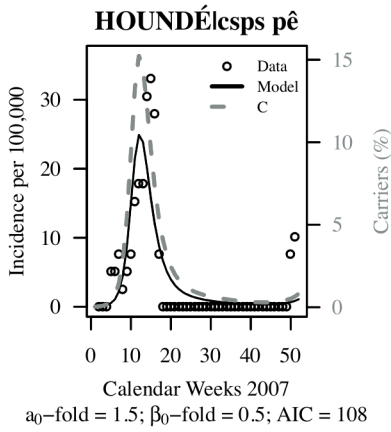


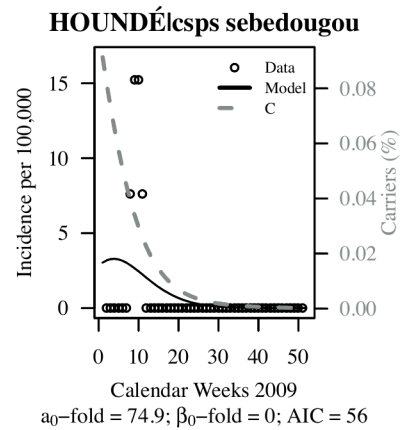
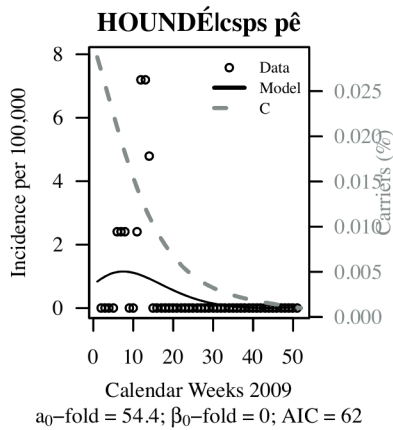
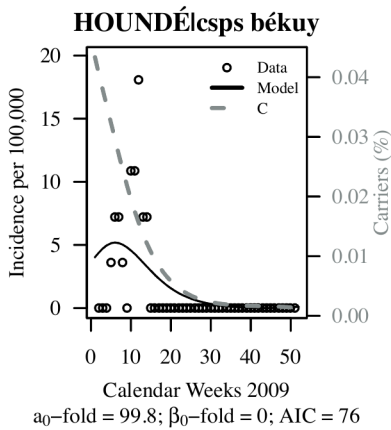
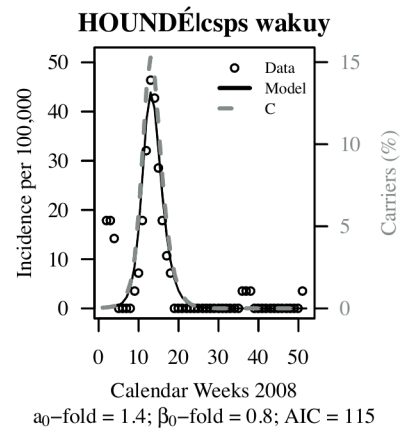
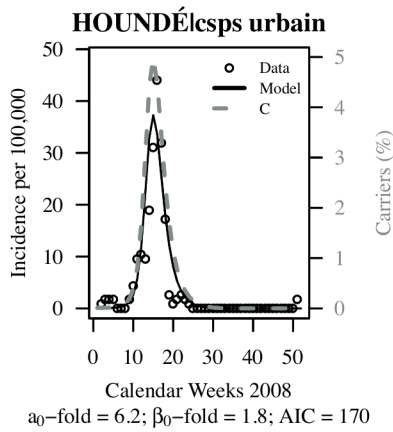
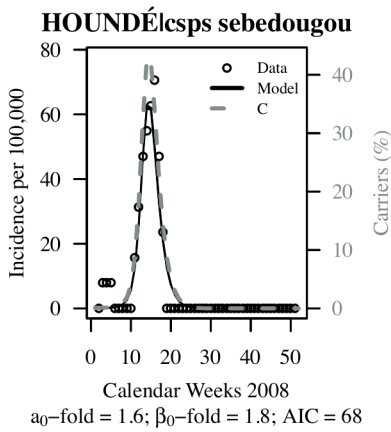
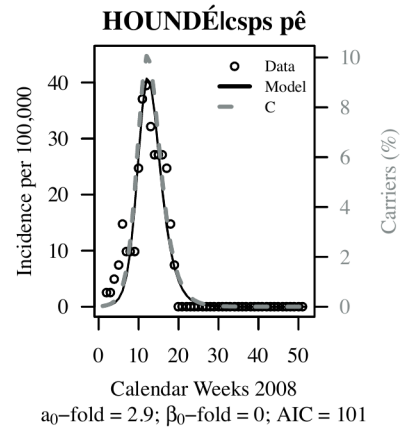
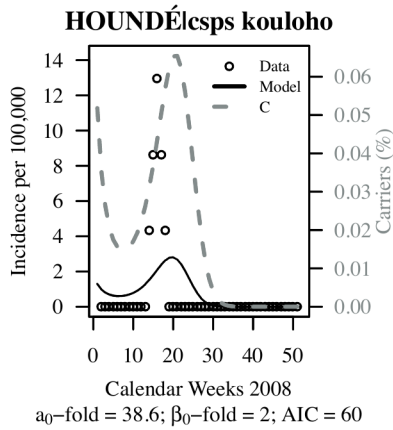
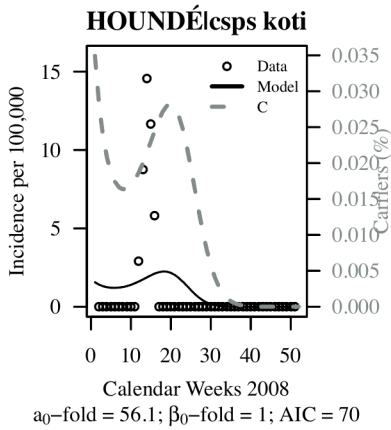
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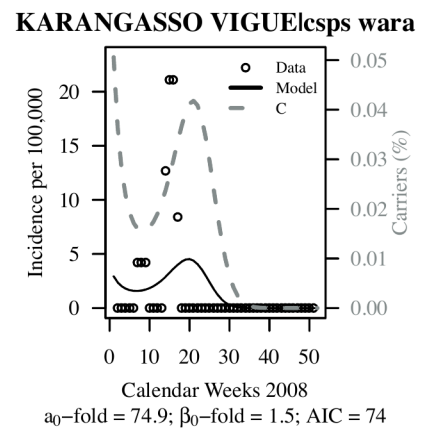
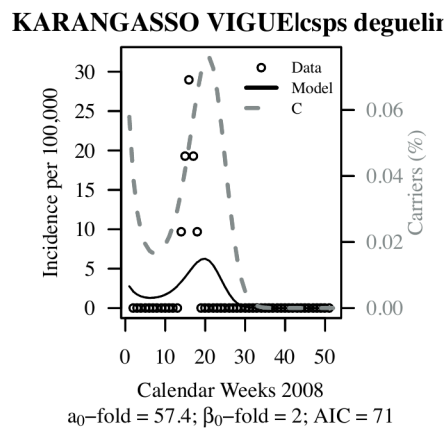
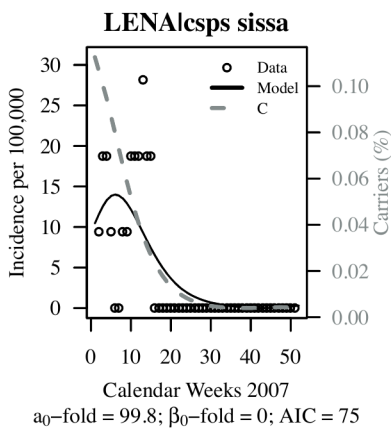
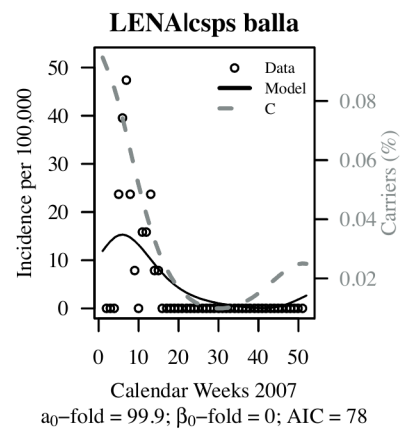
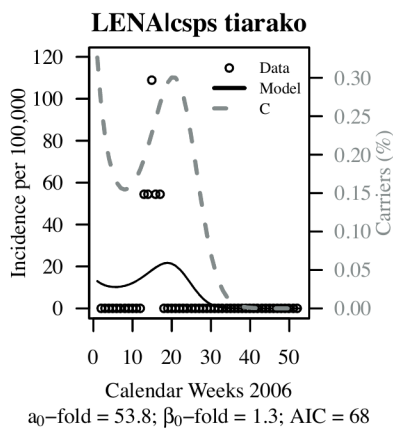
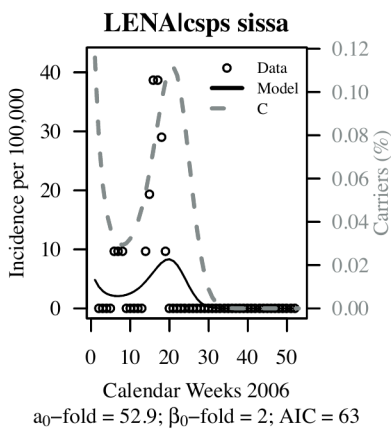
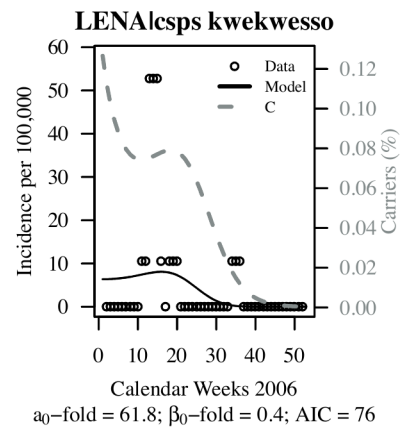
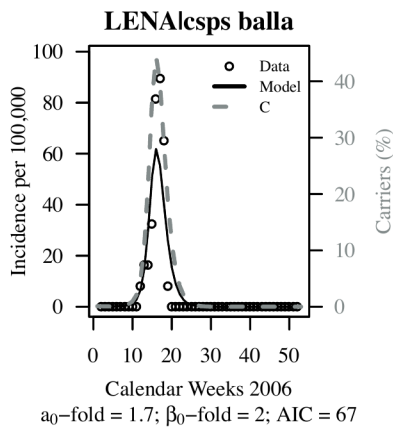
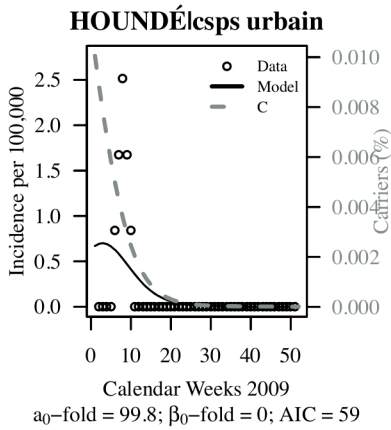




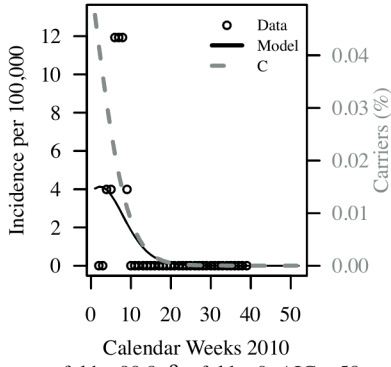




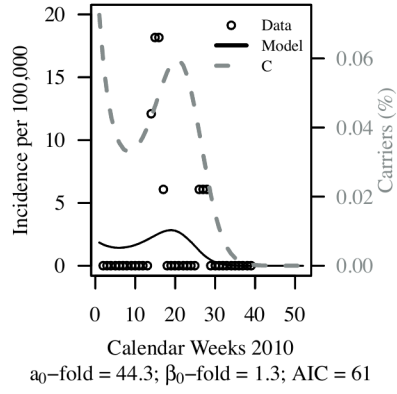




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Chapter 5: Summary, discussion, and conclusion

The previous two chapters reported the findings of this thesis and included a discussion for each of our findings. This final chapter will provide a synthesis of the key findings of this thesis and highlight a few points, limitations, and strengths that may have not been discussed in the aforementioned chapters or the published papers. It will also focus on the contributions of our findings to the scientific debate on the meningitis belt phenomenon and opens perspectives on future research on its exploration.

Summary of thesis and discussion

The striking epidemiology of bacterial meningitis in the African meningitis belt has been the focus of several research efforts over the past decades, in particular the contribution of the climate of the meningitis belt to the disease recurrent seasonality and epidemics. Previous research attempts to develop tools to forecast the disease incidence have tended to focus on the use of climatic variables and data (Sultan et al. 2005; Yaka et al. 2008). Several authors (Agier, a Deroubaix, et al., 2013; Sultan et al., 2005; Yaka et al., 2008; Agier et al., 2016; Paireau et al., 2016) have shown associations between climatic variables such as relative humidity, temperature, rainfall, dust, wind speed etc., but at the time of this thesis little is known about the potential mechanisms by which the climate of the dry season could impact bacterial meningitis incidence and seasonality. Several hypotheses and a hypothetical model were proposed (Moore, 1992b; Griffiths et al., 1987; Mueller & Gessner, 2010; Greenwood et al., 1984) in the scientific literature for how the climate of the dry season might contribute to the seasonal dynamic of bacterial meningitis and epidemics meningitis in the African meningitis belt.

The most discussed of these hypotheses for which consensus lacks are as follows: Firstly, meningitis incidence increases every year in the dry season in the meningitis belt because the low humidity and dusty climate of the dry season increases the risk of invasion of the bacteria among colonized individuals

(Molesworth et al., 2003; Greenwood et al., 1985; Martiny & Chiapello, 2013); for example, by damaging the mucosa of the nasopharynx. Secondly, the climate of the dry season would facilitate transmission of the bacteria and increase its carriage; for example, through changes in population mixing patterns. The peak of meningococcal disease coincides with respiratory viral illnesses during winter in developed countries, and some authors suggested that respiratory viral co-infections during the dry season in the meningitis belt could also contribute to increasing colonisation and invasive disease by weakening the host immune defences (Moore, 1999, Mueller et al., 2017). However, this mechanism would likely apply to epidemics meningitis (Mueller et al., 2017) rather than to meningitis regular seasonal hyperendemicity (Mueller & Gessner, 2010).

A characteristic feature of meningitis infection is that the bacteria often colonize the nasopharynx of the host before eventually causing disease (Doran et al., 2016). Most important, meningitis disease is a rare outcome of the infection outside the dry season (Koutangni et al., 2015), and asymptomatic carriage of all serogroups can still remain overall high (Trotter & Greenwood, 2007b; Diallo et al., 2016). This raises the question about whether increased transmission of the bacteria alone or increased invasion of the bacteria among colonized individuals in the dry season are determinants of meningitis recurrent annual seasonality in the meningitis belt. If so, would including these competing hypotheses in mathematical models of bacterial meningitis allow capturing the disease incidence and annual seasonality in the African meningitis belt accurately?

We addressed these hypotheses and questions during this thesis by analysing appropriate data from the meningitis belt using relevant and complementary methods.

Three main findings rose from our analyses. Firstly, serogroup A meningococcal meningitis case-carrier ratios (a proxy for the rate of meningococcal meningitis among asymptomatic carriers) is much higher on average in the dry season than in the wet season across the meningitis belt. This result is in favour of a seasonal change in the rate of meningococcal invasion among colonized individuals.

Secondly, from our analysis, there is no evidence supporting a systematic increase in serogroup A carriage prevalence between the wet and the dry hyperendemic season. Finally, including the two competing hypotheses in a mathematical deterministic modelling framework for bacterial meningitis reproduced well meningitis incidence and its annual hyperendemic seasonality.

The models cannot rule out some seasonal variations in the transmission rate during the dry season, however they have been useful in highlighting the potential importance of seasonal change of the invasion rate among colonized individuals.

When work was started on this thesis, there were limited published modelling studies on meningitis in the meningitis belt, each with their limitations and strengths.

Previous efforts either relied on a wide space of unknown parameter values instead of estimation (Irving et al., 2012), or used incidence data at a low spatial resolution (Tartof et al., 2013) and (Karachaliou et al., 2015) for model fitting, which likely does not allow differentiating between dry seasons with localized epidemics and dry seasons without localized epidemics, as localized epidemics can often only be seen at the health center level (Tall et al., 2012; Paireau et al., 2012). To improve this approach, we have developed a model in which unknown parameters are estimated based on surveillance data at a fine spatial (health center) and temporal (weekly) scale.

Irving et al work was the first published transmission model of meningitis in the meningitis belt. Despite being based on extensive work, it has the limitation of not using real data to parameterize and validate the model and thus was not able to assess the model accuracy in reproducing observed incidence in the meningitis belt quantitatively. The two subsequent works, by Karachaliou et al (building on Irving et al.), and Tartof et al., have used an age structured meningitis compartment models to evaluate long-term vaccination strategies with serogroup A conjugate vaccine. Both studies assumed seasonal changes of the transmission and invasion rate but did not aim to compare models including seasonal forcing of

transmission, risk of invasive disease or both with regard to fitting incidence data from hyperendemic years.

Based on their age-structured model of MenA transmission and disease designed to evaluate vaccine impact in the meningitis belt, Tartof et al. proposed that observed data trends could be explained in a model with variable force of infection but little seasonal variation in risk of disease given colonization. This conflicts with our modelling work results. While lack of age structure in our model may explain some of the differing conclusions, it is important to note that our respective approaches to modelling seasonality of transmission and risk of infection differs. Tartof et al. added seasonality of the two parameters as a discrete event with a value estimated for the rainy and dry season respectively. In our study we followed the same approach as (Irving et al., 2012) and (Karachaliou et al., 2015). We used sinusoidal functions to model seasonality of the two parameters, with a slight modification in our forcing function for the risk of meningitis given colonization, to account for plausible range of variations of the case-carriers ratios of meningitis estimated from our meta-analysis study in the meningitis belt.

Another aspect is the spatial resolution of analyses. We aimed to evaluate specifically the seasonal changes between endemic and hyperendemic situation, by excluding all health center years with localized epidemics. By contrast, Tartof et al. included all observations and categorized them as epidemic and non-epidemic, which at the district or country level would correspond to epidemic waves (according to the hypothetical model by Mueller & Gessner) – in fact epidemic years usually come in groups of 2 or 3, as shown in Figure 4 of the Tartof et al. article (Tartof et al., 2013). An interpretation could be that Tartof's model actually captures epidemic events, during which then increased transmission (localized epidemics) and population immunity (epidemic waves) may be the key drivers (Irving et al., 2012). However, our efforts to discard health centres-year with localised epidemics from our model analysis may have its own limitations as the clear distinction between hyperendemic and epidemic incidence might not always be straightforward as suggested by the hypothetical explanatory model for meningitis in the meningitis belt (Mueller & Gessner, 2010).

This interpretation is supported by results from our systematic review and meta-analysis of carriage prevalence, incidence and case-carrier ratios of MenA in the meningitis belt (Koutangni et al, 2015), which suggest that hyperendemicity was related to an increased risk of disease given carriage (and not increased carriage prevalence), while localized epidemics was mainly related to a systematic increase in carriage, and to a lesser extent to increased risk of invasive disease. While our model including seasonal forcing of the transmission rate alone also fitted the data reasonably well, it required on average a high constant risk of meningitis given colonization.

Our models explicitly include natural immunity from carriage or disease but not vaccine induced immunity. We aimed in the first instance, to evaluate the competing assumptions or hypotheses regarding seasonality of the invasion or/and transmission rate at first. Moreover, we parameterized our models on data prior to the introduction of the serogroup A conjugate vaccine (assuming that plain polysaccharides vaccines had little or no effect on the recurrent annual seasonal pattern of bacterial meningitis). This is supported by findings by Paireau et al. who found in ecological analyses that vaccination campaigns with plain polysaccharide vaccines in the previous year were not a protective factor against experience of high meningitis incidence.

In addition to assessing the model performance in predicting observed incidence, we also considered whether season specific carriage prevalence predictions from the evaluated models were realistic compared to meningococcal carriage estimates from studies in the meningitis belt (Trotter & Greenwood, 2007a; Koutangni et al., 2015). Though our models were not fitted to carriage data (which were not available for the individual catchment areas of the health centres), the proposed model indeed predicted carriage prevalence in the range of those reported by carriage studies during the wet and dry season (Koutangni et al., 2015; Trotter & Greenwood, 2007b). The carriage prevalence estimates from the model likely reflect carriage of all meningococcal serogroups combined, but most important, it is the seasonal variations of the carriage prevalence estimates, which is of interest for the proposed model interpretation. Furthermore, the proposed model could also apply to pneumococci, which can cause a substantial part of the reported

suspected bacterial meningitis cases during endemic and hyperendemic period, and which are known to be commonly carried in the meningitis belt in all age groups, including children adolescents and adults (Mueller et al., 2012). The carriage prevalence decreases with increasing age (Usuf et al., 2014).

Sinusoidal terms, used in chapter 4 to describe seasonal variation of the bacteria transmission and invasion rates (perhaps representing climatic variation), have been widely used in other models of seasonal disease. A more realistic approach would be to integrate data on the actual factors which correlates well with this seasonality, such as aerosol load, relative humidity, temperature, and rainfalls data. However, access to high quality data on any of these climatic variables is important but was not available to us at the time of this thesis.

In addition, seasonal population movements and changes in mixing patterns could be demographic factors to consider when exploring seasonal variations in the bacteria transmission rate. However, the later has not yet been firmly established as important factor responsible for the regular seasonality of meningitis incidence seen in the meningitis belt. Therefore, such approach is not necessarily justified given the current state of knowledge on the role of these demographic factors on meningitis seasonality in the meningitis belt. Future research should closely investigate the contributions of these demographic factors to meningitis seasonal dynamics and epidemics in the meningitis belt.

The proposed model is able to predict, with relatively good accuracy, the annual seasonality and incidences of suspected meningitis cases observed at high spatial and temporal resolution (community health centres and weekly incidences). It will further be relevant to parameterize the model with laboratory confirmed cases and serogroup specific data and to include age-structure data. The model can then serve to assess the short- and long-term impact of controls interventions on meningitis incidence at the communities' level. Interventions such as those aiming at humidifying the nasopharynx mucosa during the dry season (e.g. using nasal spray) could be assessed in combination with seasonal vaccination using such model structure. The proposed model could also serve as a building block for meta-populations model structure, allowing seasonal meningitis incidents cases predictions at both communities and districts levels. The meta-population model

structure would help design and evaluate efficiency of a range of vaccination strategies including targeted community vaccination.

The wide spread deployment of MenA conjugate vaccine through mass campaign vaccination in 2010 across countries of the meningitis belt targeting the 1-29 years age group and recommendations of its inclusion into the routine expanded program on immunization schedule (EPI)(World Health Organization, 2016) have important implication for the reduction and elimination of serogroup A carriage, and epidemics meningitis, in the following years (MenAfriCar consortium, 2015; Kristiansen et al., 2014; Mustapha & Harrison, 2018). However other meningococci serogroups (C, W and X) have the potential to cause epidemics (Greenwood, 2007; Delrieu et al., 2011) and it is uncertain what impact elimination of serogroup A meningococci will have on the frequency of outbreaks caused by these serogroups in the future (The MenAfriCar consortium, 2015). Emergence of serogroup C epidemics have been reported inside (e.g. Nigeria and Niger) and recently outside (Liberia) the traditional meningitis belt (Mustapha & Harrison, 2018; Sidikou et al., 2016; Bozio et al., 2018).

Following the recent (2015) introduction of pneumococcal conjugate vaccines in the EPI schedule, the older age groups representing the most susceptible population may not be sufficiently protected to reduce the disease burden (Agier et al., 2017). Until an effective and affordable conjugate multivalent Nm vaccine that provides protections against the main serogroups causing meningitis in the meningitis belt is available and pneumococcal vaccination protects all age groups, control and prevention strategies need to be adapted to the changing epidemiology of meningitis in the meningitis belt (Maïnassara et al., 2015). Mathematical models of meningitis transmission and disease can assist in such task. A better understanding of the determinants of the disease transmission and seasonal dynamics in the meningitis belt is needed in the first place. This was the focus of this thesis contribution.

Conclusion and perspectives.

Taken together, the results suggest that it may be too early at this stage of research to decide on the exact mechanism underlying the regular seasonality of bacterial meningitis in the meningitis belt. However, our findings did highlight the contribution of seasonal variations in the risk of invasion of the bacteria given colonization, to the recurrent annual seasonality of bacterial meningitis in the meningitis belt. This thesis work provides a modelling framework accessed both quantitatively and qualitatively, upon which complex models can be built, for predicting meningitis incidence (hyperendemic and epidemic), at both health centre and district levels in the meningitis belt (e.g. age-structured, meta-populations models), eventually adding vaccination.

The relative importance of transmission and invasion rates is an area identified by the results of our models as an important target for future studies. A possible mechanism by which transmission of the bacteria could be higher in the dry season than in the rainy season is that during the cooler nights (especial during the Harmattan), people may sleep inside, in close quarters (Greenwood, 1999). A study of contact patterns in the meningitis belt, similar to those conducted by Mossong et al. across 8 European countries (Mossong et al., 2008) would allow testing this hypothesis. Such a survey would also be useful to accurately parameterise the ‘Who acquired Infection from Whom (WAIFW)’ matrices for use in age-structured models, and, therefore, to the planning of vaccination strategies with the MenA conjugate vaccine in the meningitis belt. In addition, the duration of meningococcal and pneumococcal carriage episodes has been poorly studied in the African meningitis belt although it may play an important role on the seasonal dynamic and epidemics of bacterial meningitis. A longitudinal pilot study of meningococcal carriage conducted within 116 households (including 202 residents) in Bamako (Mali) prior MenA conjugate vaccine introduction reported carriage duration of 2.9 months (95% CI: (1.6, 5.4)) (Basta et al., 2018). Additional longitudinal carriage studies specifically designed to monitor the temporal evolution of meningococcal and pneumococcal carriage prevalence are needed including meningococcal disease-causing serogroups other than Men A which carriage prevalence have been more investigated since the implementation

of MenA conjugate vaccine (Greenwood, 2013; Balmer et al., 2018). These carriage studies should ideally assess carriage at a much shorter interval and throughout a year and monitor inter-season and inter-annual variations of the carriage prevalence for different serogroups in different epidemiological context (endemic, hyperendemic, epidemic) within the same population. These studies should also ideally be coupled with seroprevalence studies to better identify correlate of protection against carriage and disease. Implementation of this type of study can be costly and practically challenging, but would worth advancing our understanding of the role of carriage and natural immunity duration on the dynamics of bacterial meningitis in the meningitis belt.

Our findings highlighted the contribution of seasonal variations in the risk of bacterial invasion given colonization, to the annual seasonality of meningitis.

Building on this thesis work and the proposed model framework, the mechanisms underlying localised epidemics meningitis could be further investigated. A stochastic framework may be relevant to consider given the irregular pattern of localized epidemics. To further improve the approach, the model structure evaluated in this thesis can serve as building block for the development of metapopulation models, making it possible to explicitly model the interactions between populations at the community level and to predict disease incidence at the community and district level. The meta-population approach could be useful for reproducing and predicting the distribution of localized epidemics in space and time, and would provide new insights into localized epidemics processes in the meningitis belt. Evaluation of control strategies including vaccination and / or meningitis treatments could be included in this type of model to identify the most effective and / or efficient strategy for controlling the disease and epidemics meningitis in the meningitis belt.

Paper 1 (as published)

RESEARCH ARTICLE

Incidence, Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Citation: Koutangni T, Boubacar Maïnassara H, Mueller JE (2015) Incidence, Carriage and Case-Carrier Ratios for Meningococcal Meningitis in the African Meningitis Belt: A Systematic Review and Meta-Analysis. PLoS ONE 10(2): e0116725. doi:10.1371/journal.pone.0116725

Academic Editor: Cristina Costa, University Hospital San Giovanni Battista di Torino, ITALY

Received: June 26, 2014

Accepted: December 12, 2014

Published: February 6, 2015

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: TK was financially supported by EHESP School of Public Health during a Master internship and by Université Pierre et Marie Curie (Paris 6) through a doctoral contract. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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

Abstract

Background

To facilitate the interpretation of meningococcal meningitis epidemiology in the “African meningitis belt”, we aimed at obtaining serogroup-specific pooled estimates of incidence, carriage and case-carrier ratios for meningococcal meningitis in the African meningitis belt and describe their variations across the endemic, hyperendemic and epidemic context.

Methods

We conducted a systematic review and meta-analysis of studies reporting serogroup-specific meningococcal meningitis monthly incidence and carriage in the same population and time period. Epidemiological contexts were defined as endemic (wet season, no epidemic), hyperendemic (dry season, no epidemic), and epidemic (dry season, epidemic).

Findings

Eight studies reporting a total of eighty pairs of serogroup-specific meningococcal meningitis incidence and carriage estimates were included in this review. For serogroup A, changes associated with the transition from endemic to hyperendemic incidence and from hyperendemic to epidemic incidence were 15-fold and 120-fold respectively. Changes in carriage prevalence associated with both transitions were 1-fold and 30-fold respectively. For serogroup W and X, the transition from endemic to hyperendemic incidence involved a 4-fold and 1•1-fold increase respectively. Increases in carriage prevalence for the later transition were 7-fold and 1•7-fold respectively. No data were available for the hyperendemic-epidemic transition for these serogroups. Our findings suggested that the regular seasonal variation in serogroup A meningococcal meningitis incidence between the rainy and the dry season could be mainly driven by seasonal change in the ratio of clinical cases to subclinical infections. In contrast appearance of epidemic incidences is related to a substantial increase in transmission and colonisation and to lesser extent with changes in the case-carrier ratio.

Conclusion

Seasonal change in the rate of progression to disease given carriage together with variations in frequency of carriage transmission should be considered in models attempting to capture the epidemiology of meningococcal meningitis and mainly to predict meningitis epidemics in the African meningitis belt.

Introduction

The epidemiology of bacterial meningitis in the African meningitis belt is characterized by regular hyperendemicity during one single dry season (approximately November–May), which alternates with endemic incidence during the rainy season (June–October). [1, 2] Epidemics of meningococcal meningitis occur on the community level irregularly, but always limited to the second half of the dry season. In cycles of 7–10 years, epidemics form waves that span larger regions and consecutive dry seasons. Until the introduction of a meningococcal serogroup A conjugate vaccine (MenAfriVac) in the meningitis belt from 2010 on, these epidemics were mostly due to serogroup A *Neisseria meningitidis* (NmA), but since then, no NmA epidemics have occurred. However, since 2000, serogroups W (NmW) and X (NmX) have repeatedly caused epidemics, sometimes with local incidence rates comparable to NmA epidemics. [3] The factors leading to epidemics remain hypothetical [4], but their identification would help to better predict epidemics and designing control strategies, including vaccination.

Several hypotheses exist as to why seasonality and seasonal epidemics occur [5–8], but apart from modelling studies of meteorological information and some opportunistic studies during outbreaks, no hypothesis-driven research has occurred. In a conceptual model for meningococcal epidemics in the meningitis belt, Mueller & Gessner [4] suggested that the transitions from endemicity (during the wet season) to seasonal hyperendemicity and sporadic epidemics (during the dry season) are two distinct phenomena caused by different mechanisms. These mechanisms would include increased risk of invasion given pharyngeal colonisation during the dry season, and surges in colonisation leading to epidemics.

Building on this model, we aimed at exploring how colonisation and susceptibility to meningitis given colonisation change over seasons and epidemics. Dynamics of colonisation can be estimated in carriage studies. The case-carrier ratio (CCR) is an ecological proxy for the risk of meningitis given colonisation and can be estimated by dividing meningitis incidence by concurrent carriage prevalence. We therefore conducted a systematic review with meta-analysis to provide best evidence on how serogroup-specific incidence, carriage and case-carrier ratio vary according to epidemiological context (endemicity, hyperendemicity and epidemic) in the African meningitis belt.

Methods

This review was conducted based on an elaborated systematic review and meta-analysis protocol (S1 Text). Reporting is done according to the PRISMA 2009 checklist (S1 PRISMA Checklist). We aimed at including studies that (1) reported serogroup-specific meningococcal carriage and laboratory-confirmed meningococcal meningitis cases over the same time period in the same population; (2) were conducted in populations within the African meningitis belt; (3) included a representative sample of the general population for carriage evaluation (at least cluster sampling

free of coverage bias) and enrolled suspected meningitis cases in exhaustive way; (4) were conducted from 1969 onward. Studies targeting children and/or young adults attending schools were also eligible provided that school attendance was common. We included only studies conducted after 1969, when the distinction between *N. meningitidis* and *N. lactamica* was possible. [9] We searched MEDLINE, Academic Search Complete via EBSCOhost and the African Index Medicus for medical subject headings and text words representing the concepts meningococcal meningitis, colonisation and African meningitis belt countries (S2 Text). Databases searches were initially performed in February 2012 and last updated in December 2013. Our selection criteria included publications in English and French languages. We hand searched references lists of included papers, relevant reviews and contacted relevant research groups to identify unpublished data. After a first screening based on titles and abstracts of retrieved records by one reviewer, two reviewers conducted full text screening and data extraction. Study and participants' characteristics, as well as relevant meningococcal serogroup-specific data were extracted from eligible studies by one reviewer (Table 1, S1 Table). We used Graph Extract v2.5 (QuadTech Associates) for data extraction from graphs in two studies. [10, 11]

Eligible articles were scrutinized to identify additional information required, which then was sought from the articles' authors, using data collection sheets. This concerned the number, over specific time periods, of confirmed Nm cases by serogroup, suspected case reporting and age-stratified data. A pair of incidence and carriage estimates during a given month in a given community was called "Case Carrier Observation Unit" (CCOU)" and was described by size of the surveyed population, carriage study sample size, serogroup-specific number of confirmed cases and carriers, and monthly incidence and carriage prevalence with measures of variance (standard errors or deviation). Each CCOU was categorised according to season (wet/dry) and epidemiological context (endemic, hyperendemic, or epidemic). The categorisation was conducted by two reviewers based on information provided by authors in the article, weekly incidence rates of suspected meningitis cases relating to the follow up period if available, and meteorological data as provided by authors or available on tutitempo.net following an algorithm (Fig. 1). Mean daily Relative Humidity (MRH) in the study area in the two weeks preceding study onset was the main criteria for season assignment. When only the month of study was reported, this was considered for MRH. Meteorological situations with $MRH > 40\%$ and $MRH < 40\%$ were defined wet and dry, respectively. If $35\% < MRH < 45\%$, the mean precipitation (mm) during the two weeks preceding the study was taken into account. Within dry seasons with no reported epidemic, weekly incidence rates of suspected cases less than ten per 100,000 populations were classified as hyperendemic. [12, 13] Based on authors' information, we assigned a causal serogroup to epidemics, and classified study populations as "vaccinated" if they have received a meningococcal mass vaccination against the relevant serogroup one week to three years prior to the study onset.

We evaluated the risk of bias in studies using the following criteria: (1) appropriateness of reported inclusion and exclusion criteria, (2) appropriateness of carriage study sampling design, (3) described bacterial identification protocol in accordance to World Health Organization (WHO) standards [14], (4) diagnostic criteria for meningitis diseased in accordance to WHO standards [15], (5) appropriateness of reported swabbing protocol, and (6) whether swabs were plated on site during population based carriage surveys.

Serogroup-specific case-carrier ratios (CCR) were computed for each CCOU as:

$$CCR = \frac{ncases/npopulation}{ncarriers/nsample}$$

Table 1. Summary characteristics of included studies reporting meningococcal serogroup-specific incidence and carriage prevalence of the same population and time period.

First author. Year [Reference]	Settings	Age range (years)	Sampling time point/ Follow-up	Study participants	Vaccination status of study population (date of vaccine campaign) [¶]	Epidemiological context of study / Season
Boisier et al. 2006 [25]			May 2003			Hyperendemic / post-epidemic (first rains mid-May, humidity <40% until end of May)
	Djinguinis, Azao, Fardak and Dallé villages (Tahoua region, Niger)	2–65		Residents of villages referring to Illela health centre and having registered at least one NmW case during March and April 2003 in the district of Illela.	No	
			February 2004			Hyperendemic / Dry
Hamidou et al. 2006 [26]			February 2003			Hyperendemic / Dry
	Primary schools in Niamey (Niger)	7–16	March 2003	Primary schools children in Niamey	Yes (2001/2002)	Hyperendemic / Dry
			May 2003			Hyperendemic / Dry (first rains mid-may humidity <40% until end of May)
Hassan-King et al. 1987 [11]	Farafeni (Gambia)	2–20	January to April 1983	Residents living in two villages in the centre of the Farafeni study area.	No	Serogroup A epidemic / Dry
Leimkugel et al. 2007 [10]	Kessena Nankana district (Ghana)		April from 1998 to 2005			Endemic / Wet
		< 5–50+		Inhabitants of Kessena Nankana district	Yes (1997/2005 yearly campaigns)	
			November from 1998 to 2005			Hyperendemic / Dry
Mueller et al. 2011 [23]			March 2006	Residents of Kofila and Konkourouna	No	Serogroup A epidemic / Dry
	Lena, Kofila, and Konkourouna villages (Burkina Faso)	1–39				
			March 2006	Residents of Lena	Yes (March 12–15, 2006)	Serogroup A epidemic / Dry
Mueller et al. 2006 [22]	Urban Bobo-Dioulasso (Burkina Faso)	4–29	February, March, and April 2003	Residents of the urban area of sanitary districts Secteur 15 and Secteur 22 as of Feb-June 2003 (urban Bobo-Dioulasso)	Yes (2002)	Hyperendemic / Dry
Sié et al. 2008 [24]	Nouna district (Burkina-Faso)	not reported	April 2006	Resident of the Nouna Demographic Surveillance System Area	No	Hyperendemic / Dry
Trotter et al. 2013 [21]	Urban Bobo-Dioulasso (Burkina Faso)	0–59	February to March 2008	Residents of the urban area of Bobo-Dioulasso	No	Hyperendemic / Dry

[¶] Yes, if the study population have been vaccinated within 2 weeks to 3 years prior to the onset of carriage and surveillance studies, using a vaccine against one or several meningococcal serogroups. All campaigns were conducted using serogroup A/C meningococcal polysaccharide vaccines.

doi:10.1371/journal.pone.0116725.t001

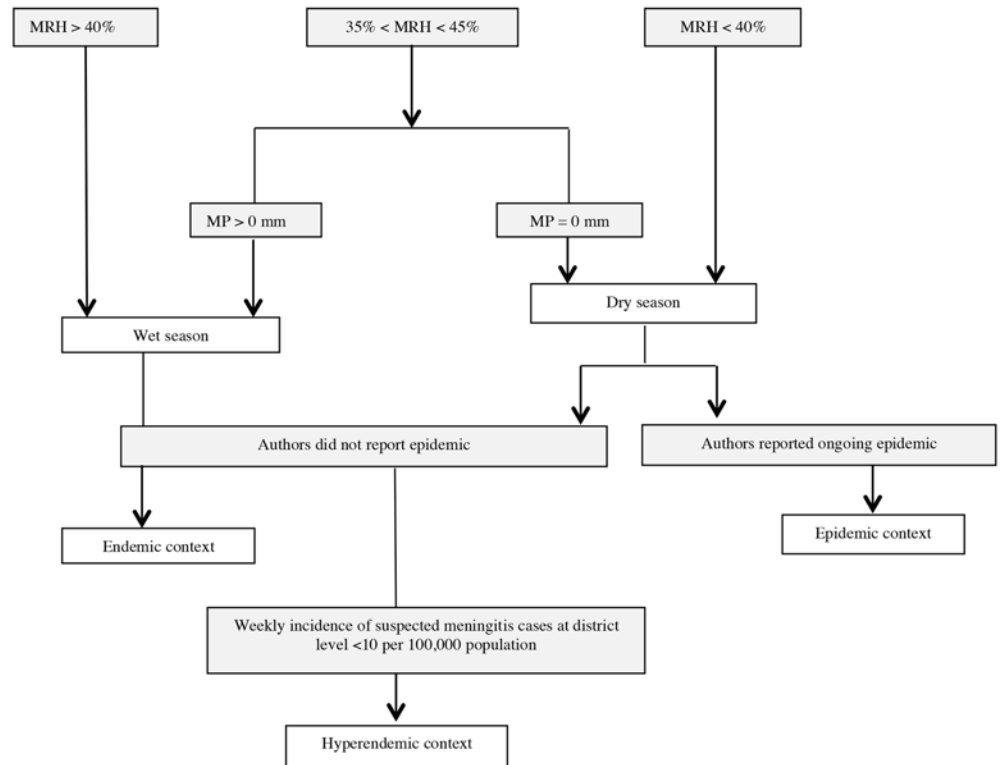


Figure 1. Algorithm for the definition of season and epidemiological context of case-carrier observation units reported by publications. MRH = Mean daily relative humidity in the two weeks preceding study onset or MRH of the study month (when only month of study was reported). MP: Mean daily precipitation amount (mm) during the two weeks preceding the study.

doi:10.1371/journal.pone.0116725.g001

Haldane’s continuity correction [16] was applied on CCOUs if cases, but no asymptomatic carriers have been identified. Using the Delta method [17], the variance of the natural logarithm of the CCR was calculated as:

$$Var = \frac{n_{population} - n_{cases}}{(n_{population})(n_{cases})} + \frac{n_{sample} - n_{carriers}}{(n_{population})(n_{cases})}$$

Where *n* denotes numbers. For each epidemiological context, pooled serogroup-specific meningitis incidence, carriage prevalence, and CCR were estimated with 95% confidence intervals (95%-CI) using the inverse-variance random-effects model. This approach uses the inverse-variance weighting method to combine study-specific estimates into a weighted average estimate. Prior to combining study results, each study-specific estimate is weighed in inverse proportion to its variance. Inconsistency among CCRs of the same epidemiological context was quantified as the inconsistency index (*I*²): *I*² > 50% was considered substantial heterogeneity and *I*² < 50% moderate inconsistency. The *I*² statistics computed based on the Q statistics of the Cochran’s Q test has the advantage of not inherently depending on the number of studies included. Analyses were performed using STATA 11.2 (StataCorp LP) and The R foundation for statistical computation software v. 3.0.1.

Results

We retrieved 367 records from the initial search of which ten were eligible based on full text screening (Fig. 2). Three studies were excluded from the review because we failed to obtain

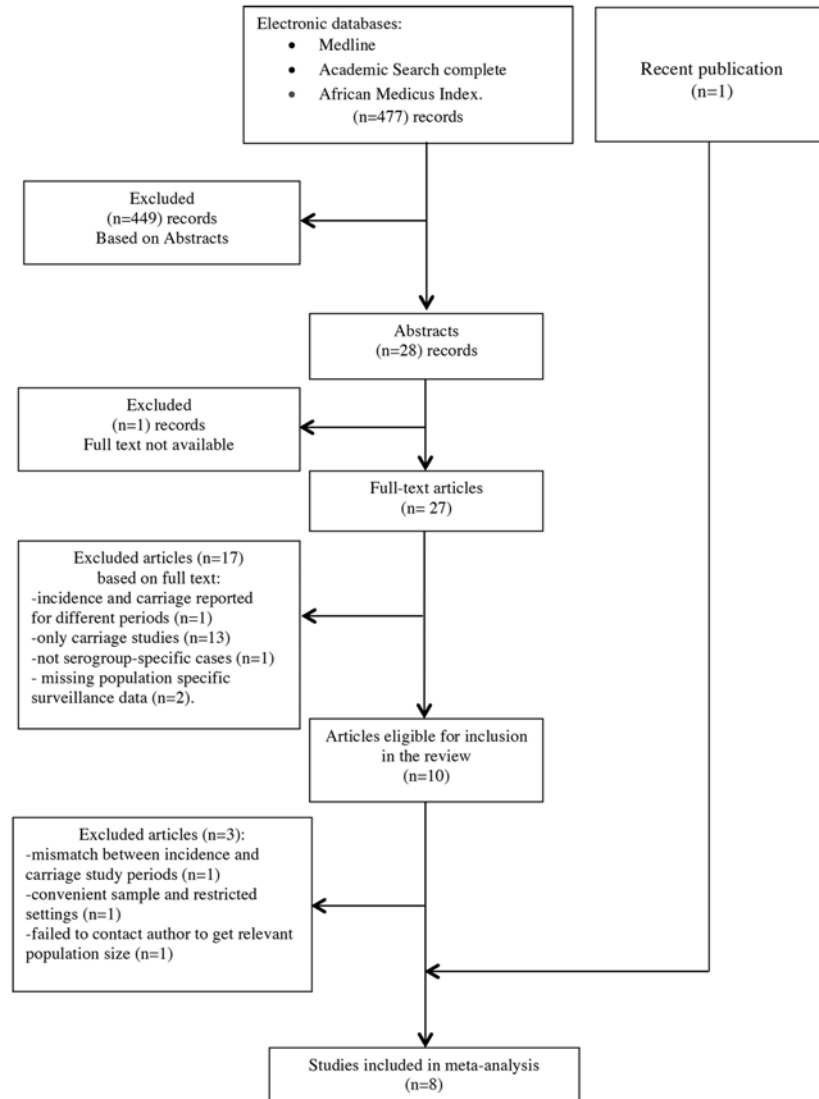


Figure 2. Flow diagram of study identification and inclusion in the systematic review on meningococcal case-carrier ratios in the African meningitis belt.

doi:10.1371/journal.pone.0116725.g002

information from authors on study population size [18], because the carriage study carried on a convenience sample [19], and because there was a mismatch between the time periods of meningitis surveillance and carriage survey, respectively. [20] The search update yielded 477 records with one recently published eligible study identified. [21] Overall, eight studies (Table 1) reporting 29 eligible CCOUs were available for meta-analysis on NmA, seven (27 CCOUs) on serogroup W and six (24 CCOUs) on serogroup X (S1 Table). Four studies were conducted in Burkina Faso [21–24] (eight CCOUs for NmA, eight for NmW), two in Niger [25, 26] (five for NmA, five for W, two for NmX) one in Ghana [10] (14 CCOUs for NmA, 14 for NmW, 14 for NmX) and one in the Gambia [11] (two CCOUs for NmA). One of the two NmA CCOUs in the Gambian study [11] was lately excluded from meta-analysis after contact with the main author, because neither requested information nor meteorological data was available to allow classification into the appropriate season and epidemiological context. For two studies [11, 24], confirmed cases in the hyperendemic context could only be obtained

for 4- and 7-month periods, and we approximated monthly incidence as the average incidence. For NmA, four eligible CCOUs corresponded to the dry/epidemic context, 18 to the dry/hyperendemic context, and six to the wet/endemic context. For NmW, six CCOUs corresponded to wet/endemic context, and 21 to the dry/hyperendemic context. For NmX, six and 18 CCOUs corresponded to wet/endemic and dry/hyperendemic respectively.

Two studies [11, 25] had an unclear risk of bias with regards to their carriage study sampling design. One of these two studies was conducted in 1983 and was missing diagnostic criteria for meningitis cases. Another study [26] was subject to potential selection bias even though authors considered that the participants were representative of the target population (S1 Fig.). Age-specific estimates were accessible only for 7 CCOUs, all from studies conducted in Burkina Faso (three in epidemic context and four in hyperendemic context); in consequence, we did not conduct age-stratified analyses.

The pooled estimate of NmA carriage prevalence was similar in the endemic and hyperendemic context [0.53% (95%-CI, 0.09%–1.31%) and 0.50% (0.17%–0.98%), respectively], but 30-fold higher in the epidemic context [15.28% (8.58%–23.48%)]. Corresponding NmA meningitis monthly incidence rates per 100,000 were 0.17 (0.01–0.58), 2.64 (0.90–5.30) and 319 (150–549), respectively (Fig. 3). The resulting CCRs were 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2}) for endemic, 0.5×10^{-2} (0.2×10^{-2} – 1.2×10^{-2}) for hyperendemic, and 2.0×10^{-2} (1.3×10^{-2} – 3.3×10^{-2}) for epidemic situations (Fig. 4). Heterogeneity between CCOUs was low for the endemic ($I^2 = 0.0\%$, $P = 0.903$), substantial for the hyperendemic ($I^2 = 69.5\%$, $P = 0.000$) and moderate for the epidemic context ($I^2 = 46.8\%$, $P = 0.131$).

The heterogeneity of the hyperendemic estimate was reduced by stratification by vaccination status (14 CCOUs were observed 1 week to 3 years after serogroup A meningococcal polysaccharide vaccine campaigns) (S2 Fig. and S3 Fig.). For the endemic situation, CCR was now

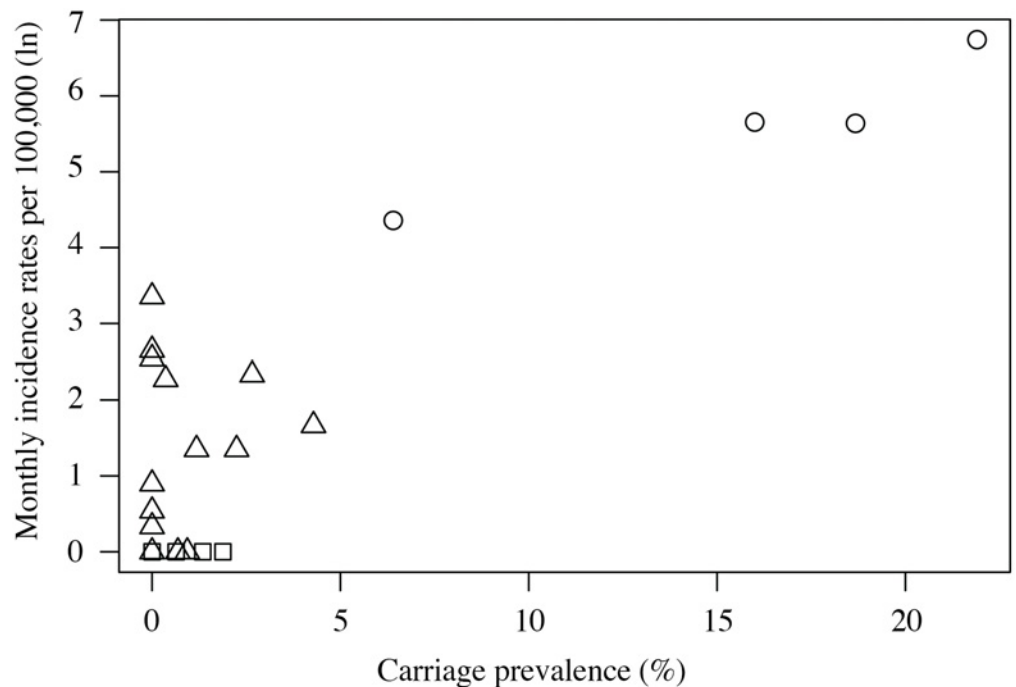


Figure 3. Scatterplot of meningococcal serogroup A monthly incidence rates and carriage prevalence across case carrier observation units. Squares show data points in endemic context; triangles show data points in hyperendemic context, and hallow circle show data points in epidemic context.

doi:10.1371/journal.pone.0116725.g003

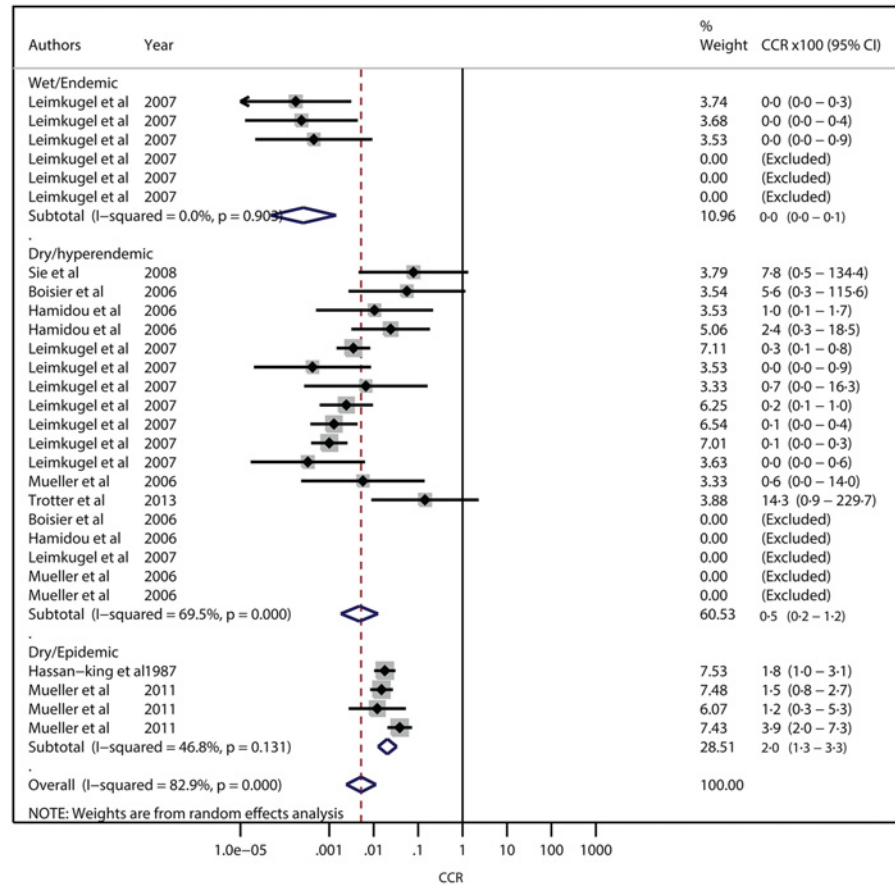


Figure 4. Forest plot for meta-analysis of serogroup A meningococcal meningitis case-carrier ratios according to epidemiological context in the African meningitis belt.

doi:10.1371/journal.pone.0116725.g004

0.1×10^{-2} (95%-CI, 0.0×10^{-2} – 0.1×10^{-2} ; $I^2 = 0.0\%$, $P = 0.903$; $N = 6$) among vaccinated, while no data were available for unvaccinated populations. For the hyperendemic context, CCR was 0.2×10^{-2} (0.1×10^{-2} – 0.5×10^{-2} ; $I^2 = 37.9\%$, $P = 0.106$; $N = 14$) among vaccinated and 8.8×10^{-2} (1.7×10^{-2} – 46.0×10^{-2} ; $I^2 = 0.0\%$, $P = 0.899$; $N = 4$) for unvaccinated populations. For the epidemic context, CCR was 1.5×10^{-2} (0.8×10^{-2} – 2.7×10^{-2} ; $N = 1$) among vaccinated and 3.3×10^{-2} (1.2×10^{-2} – 4.4×10^{-2} ; $I^2 = 52.7\%$, $P = 0.120$; $N = 3$) among unvaccinated populations. We could not identify any other factor of heterogeneity. For NmW, the pooled carriage prevalences in endemic and hyperendemic contexts were 0.15% (0.02–0.37%) and 1.08% (0.46–1.95%), respectively. Corresponding monthly incidence rates per 100,000 were 0.18 (0.01–0.58) and 0.73 (0.26–1.43), respectively. No carriage and incidence data was available for the epidemic context with serogroup W. The CCR was 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2} (only one CCOU provided information) and 0.1×10^{-2} (0.1×10^{-2} – 0.2×10^{-2} ; $I^2 = 37\%$, $P = 0.103$) for endemic and hyperendemic contexts, respectively. No carriage and incidence data was available for the epidemic context.

Pooled carriage prevalence of NmX was 1.40% (0.07–4.34%) in the endemic and 0.78% (0.15–1.90%) in the hyperendemic context. Corresponding monthly incidence rates per 100,000 were 0.18 (0.01–0.58) and 0.19 (0.06–0.39), respectively. The resulting CCR was 0.0×10^{-2} (0.0×10^{-2} – 0.1×10^{-2} ; $I^2 = 7.4\%$, $P = 0.373$) for the endemic context, and had an upper 95% confidence limit below 0.0005 for the hyperendemic context (the software did not specify

the central estimate at the fourth decimal below 0.000). No carriage and incidence data was available for epidemic context with serogroup X.

Discussion

This is the first study that systematically reviews and synthesizes available serogroup-specific incidence and carriage data of meningococcal meningitis in the meningitis belt. The substantially higher CCR during non-epidemic dry seasons, compared to wet season suggests that seasonal hyperendemicity of NmA meningitis appears related to an increased risk of meningitis given asymptomatic colonisation, but not related to an increase in transmission and colonisation. In contrast, the occurrence of NmA epidemics appears related to a substantial increase in meningococcal transmission and colonisation, and to a lesser extent with increased risk of meningitis given carriage. These results lend force to some hypotheses on the causation of seasonal hyperendemicity and epidemics and inform others.

In pooled analyses, meningococcal carriage prevalence of NmA, NmW and NmX did not increase substantially from endemic (wet season) to hyperendemic context (dry season). NmW did show a significant difference, however, its magnitude (0.15% vs. 1.08%) probably is not important from a biological standpoint: using a recently published model for meningococcal meningitis epidemics [27], for a fixed rate of progression from carriage to disease, seasonal oscillations of disease incidence with magnitudes as observed (10–100-fold) could be produced by seasonal variations of carriage prevalence between <1% and 40%. A review of carriage studies in the meningitis belt concluded that changes in the prevalence of carriage are not linked to season in any consistent way. [28] Minor variations have been described in series of cross-sectional studies [29], but should not be interpreted as systematic seasonal variation. They likely correspond to long-term strain variations rather than a seasonal phenomenon. In consequence, seasonal differences in bacterial transmission e.g. mediated by improved pathogen survival [30] or different social mixing patterns, should be dismissed as explanation for seasonality of meningococcal meningitis. [31]

Statistical analyses only allowed an approximation of fold-increase in CCR from wet to dry season between >5 to infinite. This was due to endemic incidences being close to zero, with an endemic CCR of 0.00. Given that carriage prevalence was the same for endemicity and hyperendemicity, but incidence differed 15-fold, we can assume the increase in CCR being around 15-fold. Meteorological modelling studies suggest that relative humidity below 40% in combination with high aerosol load strongly correlates with hyperendemicity of meningococcal meningitis in the meningitis belt. [32] No demonstrated pathophysiological explanation exists on how dry and dusty air can facilitate meningitis, but it could be intuitive that such exposure can weaken the nasopharyngeal mucosa and therefore facilitate meningococcal invasion into tissues and bloodstream. Meningococcal septicaemia is rarely observed in the meningitis belt, suggesting that facilitated meningococcal invasion may not typically involve invasion into the blood stream. In addition, meningococcal invasion of olfactory nerve structures mounting towards the meninges has been found in mice. [33] In this scenario, environmental damage of the mucosa would lead to facilitated direct meningeal invasion by meningococci. In theory, increased meningitis incidence also could be attributed to reduced immune function during the dry season, but no data are available to inform this hypothesis. In any case, this around 15-fold seasonal increase in invasion is one of the strongest impacts that usual meteorological variations have on health. Upcoming climate changes may increase the proportion of the world's population exposed to such prolonged dry seasons and high aerosol load, and may increase the resulting global burden of disease. Pneumococcal meningitis, a major cause of morbidity and mortality in the African meningitis belt, also shows a 10-fold increase in incidence during dry

seasons, [34] and similar mechanisms may be involved. Measures to prevent this seasonally increased risk of invasive disease given asymptomatic bacterial infection could be developed, in addition to pathogen-specific vaccines.

As opposed to constant NmA carriage between endemicity and hyperendemicity, we found 30-fold increased NmA carriage prevalence during epidemics, which may be causal for, or a consequence of epidemics. Meningitis patients do not transmit meningococci substantially more frequently than healthy persons, as disease-specific spreading behaviour such as vomiting occurs after disease onset, when patients are already bound to bed. It is therefore more likely that increased acquisition and transmission contribute to the occurrence of epidemics. If the dry season environment greatly facilitated invasion of colonising meningococci, an increase in colonisation would simply lead to proportionally increased meningitis incidence. However, the estimated 30-fold increase in NmA carriage prevalence suggests that the carriage increase is not sufficient to explain on its own the 130-fold increase in incidence, as postulated in the hypothetical model by Mueller & Gessner. According to our results, a further slight increased risk of invasion given colonisation occurs during epidemics (4-fold increase in CCR). Respiratory virus infections could play such a double role, as they probably facilitate meningococcal adhesion to the mucosa or increase transmission via coughing and sneezing, and also temporarily reduce immune defence against bacterial disease by disrupting the immune response against encapsulated bacteria. [35] This is supported by observations during NmA meningococcal epidemics, where carriage was associated with respiratory infection symptoms [36, 37] and participants reporting recent flu-like symptoms were at increased risk of subsequently presenting with confirmed or purulent meningitis. [23]

Although the hypothetical model by Mueller&Gessner concentrated on climatic factors to explain the variation between endemic and hyperendemic situation, in principal, seasonal variations of viral co-infections, or other intermediary factors, could contribute to increase risk of meningococcal invasion (but not transmission, given our results)

Our analyses stratifying by vaccination status suggest that polysaccharide vaccination against serogroup A related to a reduced risk of meningitis given colonisation, possibly more in hyperendemic (where there was a significant difference in CCR between vaccinated and unvaccinated populations) than epidemic situations. However, interpretation by epidemiological situations may be inappropriate due to the small number of relevant observations for unvaccinated populations and potential heterogeneity between studies.

We cannot provide clear evidence on the question whether NmW behaves similar to NmA, as no data for the epidemic context were available. Both incidence and CCR increased from endemic to hyperendemic context, although to lesser extent than NmA. We did not observe a clear seasonality for NmX meningitis. Leimkugel et al. observed periods of substantially increased NmX carriage during hyperendemicity (prevalence 17%), but outside epidemics, NmX meningitis incidence usually remained low at levels comparable to endemic periods of NmA and NmW. The risk of meningitis given colonisation appears to be substantially lower compared to NmA. [10] It is unclear whether this is due to better natural immunity or a lesser capacity for invasion. Combined carriage and surveillance studies during periods with strong serogroup X or W incidence and epidemics are needed to better understand the epidemic behaviour of these serogroups.

There are some limitations to our analysis. The estimated CCRs are imprecise, as surveillance systems unlikely achieve complete case identification and carriage studies probably underestimate colonisation prevalence. [38] Furthermore, except for one study performing repeated assessments, [10] we cannot follow the CCR variation of incidence-carriage pairs across epidemiological contexts, but are limited to group comparison. Methodological differences between studies may have led to over- or underestimating CCR changes between

epidemiological contexts; e.g. the series of CCOUs reported by Leimkugel et al. [10] generally showed lower CCR. Finally, we did not analyse age-specific CCRs, due to difficulties in re-analysing original data collected up to 20 years ago. Such age stratification would provide insight into the high incidence among teenagers, but its omission unlikely biases our results. In this study, we cannot evaluate the association between specific meteorological features, such as humidity or aerosol load, and changes in meningococcal meningitis epidemiology. To identify the mechanism through which dry season is associated with higher meningitis incidence, correlation studies between meteorological and incidence data are more appropriate.

The most important limitation is that we transfer results from an ecological analysis to the individual level of susceptibility for disease, which will only be a further step in evaluating a hypothesis and does not have the validity of clinical evidence.

In conclusion, this study provides orientation on how risk of bacterial invasion and transmission or colonisation may interact to produce the particular epidemiology of the African meningitis belt. The findings will be useful for developing models to evaluate vaccination strategies, to develop further relevant research. They leave room to hypothesis that other diseases, such as pneumococcal meningitis and pneumonia, may be concerned by a complex interaction between climatic environment, bacteria, potentially co-infections, and human mucosal and immune defence.

Supporting Information

S1 PRISMA Checklist. PRISMA 2009 checklist.
(DOC)

S1 Fig. Risk of bias summary for included studies.
(TIF)

S2 Fig. Forest plot for meta-analysis of serogroup A meningococcal meningitis case-carrier ratios in vaccinated populations according to epidemiological context in the African meningitis belt.
(TIF)

S3 Fig. Forest plot for meta-analysis of serogroup A meningococcal meningitis case-carrier ratios in unvaccinated populations according to epidemiological context in the African meningitis belt.
(TIF)

S1 Table. Summary of serogroup-specific Case Carrier Observation Unit by epidemiologic context.
(DOCX)

S1 Text. Protocol for Systematic Review and Meta-analysis.
(PDF)

S2 Text. Search Strategy.
(DOCX)

Acknowledgments

We are grateful to Dr. Trinquart Ludovic for advice with meta-analysis and to Dr. Boisier Pascal and Dr. Musa Hassan-King for providing additional information on their publications.

Author Contributions

Conceived and designed the experiments: TK JEM. Performed the experiments: TK. Analyzed the data: TK. Contributed reagents/materials/analysis tools: HBM. Wrote the paper: TK JEM.

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Paper 2 (as published)

Original Paper

Cite this article: Koutangni T, Crépey P, Woringer M, Porgo S, Bicaba BW, Tall H, Mueller JE (2018). Compartmental models for seasonal hyperendemic bacterial meningitis in the African meningitis belt. *Epidemiology and Infection* 1–11. <https://doi.org/10.1017/S0950268818002625>

Received: 6 October 2017

Revised: 3 July 2018

Accepted: 22 August 2018

Key words:

Meningitis; mathematical model; African meningitis belt; hyperendemicity; seasonality

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Compartmental models for seasonal hyperendemic bacterial meningitis in the African meningitis belt

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Abstract

The pathophysiological mechanisms underlying the seasonal dynamic and epidemic occurrence of bacterial meningitis in the African meningitis belt remain unknown. Regular seasonality (seasonal hyperendemicity) is observed for both meningococcal and pneumococcal meningitis and understanding this is critical for better prevention and modelling. The two principal hypotheses for hyperendemicity during the dry season imply (1) an increased risk of invasive disease given asymptomatic carriage of meningococci and pneumococci; or (2) an increased transmission of these bacteria from carriers and ill individuals. In this study, we formulated three compartmental deterministic models of seasonal hyperendemicity, featuring one (model1-‘inv’ or model2-‘transm’), or a combination (model3-‘inv-transm’) of the two hypotheses. We parameterised the models based on current knowledge on meningococcal and pneumococcal biology and pathophysiology. We compared the three models’ performance in reproducing weekly incidences of suspected cases of acute bacterial meningitis reported by health centres in Burkina Faso during 2004–2010, through the meningitis surveillance system. The three models performed well (coefficient of determination R^2 , 0.72, 0.86 and 0.87, respectively). Model2-‘transm’ and model3-‘inv-transm’ better captured the amplitude of the seasonal incidence. However, model2-‘transm’ required a higher constant invasion rate for a similar average baseline transmission rate. The results suggest that a combination of seasonal changes of the risk of invasive disease and carriage transmission is involved in the hyperendemic seasonality of bacterial meningitis in the African meningitis belt. Consequently, both interventions reducing the risk of nasopharyngeal invasion and the bacteria transmission, especially during the dry season are believed to be needed to limit the recurrent seasonality of bacterial meningitis in the meningitis belt.

Introduction

Africa has the highest contribution to the global burden of bacterial meningitis, a severe disease with up to 30% case fatality despite timely antibiotic treatment and 20% of survivors living with psychomotor sequelae [1–4]. In the African meningitis belt spanning the Sahel from Senegal to Ethiopia [5], meningococcal and pneumococcal meningitis incidence displays a seasonal pattern during the dry season (December through May) with a 10- to 100-fold increase of weekly incidences at local health centre, district and national levels, which subsides with the onset of the rainy season [6, 7]. This seasonal increase in the disease incidence in the dry season is observed every year and consistent across countries of the so-called African meningitis belt: a situation commonly described as ‘ubiquitous seasonal hyperendemicity’. In addition, localised epidemics of meningococcal meningitis occur unpredictably limited to one or few villages, with attack proportions beyond 1% [1]. Despite introduction of effective and affordable conjugate vaccines against meningococcal serogroup A (in December 2010) [8] and 10–13 pneumococcal serotypes (in 2013) [9] through mass vaccination campaigns and infant routine immunisation, respectively, this pattern continues, mainly due to the persistence of other epidemic meningococcal serogroups and high adult pneumococcal meningitis incidence.

A distinction between the mechanisms underlying meningitis ubiquitous annual seasonality (hyperendemicity) and localised epidemics would have implication on how the disease is mathematically modelled and how control strategies are designed in the meningitis belt [1, 6, 7]. A better understanding of the mechanisms behind this epidemiology is therefore needed,

along with appropriate mathematical models allowing the identification of optimised preventative vaccination strategies.

Previous modelling efforts relied on a wide range of unknown parameters values [10] given the lack of surveillance data from which parameters could be estimated. Others have used incidence data for model fitting at low spatial resolution, mainly data aggregated at district level [11, 12]. This does not allow differentiating between dry seasons with localised epidemics and dry seasons without localised epidemics, as localised epidemic usually can be seen at the health centre level only [13, 14]. To go further from these previous efforts, we have developed a model in which unknown parameters values are estimated based on meningitis surveillance data at a fine spatial (health centre) and temporal (weekly) scale. This study focuses on modelling the regular seasonal hyperendemicity, observed during all dry seasons across the meningitis belt and used surveillance data from Burkina Faso for parameters estimation and model validation. Burkina Faso lies within the meningitis belt with an enhanced surveillance system for bacterial meningitis.

Two main explanations have been suggested for the hyperendemic incidence increase during the dry season. First, the climatic conditions such as low relative air humidity and high aerosol load experienced across countries of the meningitis belt during the dry season (November through May) could damage the nasopharyngeal mucosa and thus facilitate invasion of meningococci and pneumococci into nasopharyngeal tissues, which results in meningitis [15]. The second hypothesis suggests that these climatic conditions or related behavioural changes could facilitate the bacterial transmission in the population and thus proportionally increase disease incidence [15]. Mueller and Gessner's hypothetical explanatory model builds on the first hypothesis (increased invasion rate) [16].

In a systematic review and meta-analysis of published data from the meningitis belt [7], seasonal hyperendemicity of meningococcal meningitis was associated with a seasonal increase of the case-carrier ratio, while the prevalence of meningococcal carriage assessed in cross-sectional carriage studies did not change with season, thus supporting the first hypothesis. However, in a multi-site series of cross-sectional meningococcal carriage studies, Kristiansen *et al.* [17] reported minor but statistically significant changes in serogroup A meningococcal carriage prevalence between the rainy and dry season (from 0.24% to 0.62%), a finding supporting the second hypothesis (increased transmission rate). The present study aimed at using mathematical models to assess which of these competing hypotheses or their combination best explained observed hyperendemic incidence pattern of suspected bacterial meningitis in Burkina Faso.

Methods

Study setting and surveillance data

In countries of the meningitis belt, suspected cases of bacterial meningitis (as defined by the WHO) are systematically notified from the peripheral level (local health centres) to the intermediate (district) and central (national) levels since the establishment of an enhanced meningitis surveillance network in 2003 across the meningitis belt with the support of the WHO. Suspected meningitis cases are notified from the local health centres on a weekly basis and the number of cases must be reported even when there is zero case at all levels. Burkina Faso is one of the countries entirely located within the meningitis belt for which we had access

to weekly counts of suspected bacterial meningitis cases at the health centres level. In the country, prior to 2010, suspected meningitis case notification was often supplemented by laboratory investigation of a subset of the notified cases; especially when epidemic threshold defined at the district level is crossed, to guide epidemic preparedness and choice of polysaccharide vaccine. Acute bacterial meningitis in the meningitis belt is most commonly caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* and, since introduction of a conjugate vaccine, to a lower extent *Haemophilus influenzae* Type b [18, 19]. Suspected and laboratory-confirmed cases correlate well usually [20] and suggest a relatively good performance of the surveillance system and appropriateness of the data for epidemiologic studies. Until 2010, and before the introduction of serogroup A meningococcal conjugate vaccine in December 2010, meningitis epidemics were predominantly caused by *N. meningitidis* across the belt. Pneumococcal meningitis contributes to meningitis hyperendemicity and mimics the seasonality of meningococcal meningitis across the meningitis belt [21]. In this study, to estimate the unknown parameter values and to evaluate our models performances, we used data from routine surveillance of suspected acute bacterial meningitis cases recorded from 2004 through 2010 in health centres in Burkina Faso (a period preceding introduction of the MenAfrivac serogroup A meningococcal vaccine). While data aggregated at the district level are available in routine surveillance reports, this database of original weekly health centre data had been compiled in a collaborative effort between the Direction de la Lutte contre la Maladie (DLM) of the Ministry of Health of Burkina Faso, EHESP French School of Public Health, and the Agence de Médecine Préventive (AMP), Paris, France. We selected four health districts (Houndé, Lena, Karangasso Vigué and Séguénéga) for the completeness of data, providing 126 health centre years. Seasonal hyperendemicity and localised epidemics are two distinct phenomena involving potentially different mechanisms [16]. Therefore, we separated health centre years with localised epidemics from those with usual hyperendemic incidences, using the threshold definition of 75 weekly cases per 100 000 maintained during at least two consecutive weeks [13]. Thus, only hyperendemic health centre year curves are used for models' analysis in this study. Seasonal hyperendemicity of bacterial meningitis is a regular phenomenon observed every year in the belt. Localised meningitis epidemics are irregular in the meningitis belt. Therefore, we considered a deterministic framework as a reasonable first step over a stochastic framework in modelling hyperendemic meningitis in the belt. Overall, 64 hyperendemic health centre years (out of the 126) identified based on the defined threshold were used in the primary analysis (Supplementary Fig. S1–S3).

A second threshold of 50 weekly cases per 100 000 maintained during at least two consecutive weeks was used for sensitivity analyses. This sensitivity analysis was performed to assess the efficiency of the model when using a lower incidence threshold definition of hyperendemic incidence excluding health centre years with outlier peak incidence from the primary analysis. Fifty-seven out of the initial 64 hyperendemic health centre years were then identified and used in the sensitivity analysis. We smoothed incidence time series using a simple moving average on a 3-week window to reduce random noise in the data and the influence of instable estimates of incidence potentially due to delays in reporting. We used the SMA function in the TTR R package to achieve this.

Model structure

Similar to Irving *et al.* [10], we used a compartmental deterministic Susceptible–Carrier–Ill–Recovered–Susceptible (SIRS) model, which divides the population into four mutually exclusive groups (Fig. 1): individuals susceptible to infection (S); asymptomatic carriers (C) who can transmit the bacteria (meningococci or pneumococci) to susceptibles; individuals ill from meningitis (I) following contagion and who are also infectious; and individuals who have recovered (R) from asymptomatic carriage or meningitis. Recovered individuals have developed temporary immunity and become susceptible once immunity has waned [22]. Transition rates include rates for birth, natural death and death from meningitis (Table 1). The system of ordinary differential equations defining the model dynamic is as follows:

$$\frac{dS}{dt} = \varphi R + b - \beta_t S(C + I) - \mu S \quad (1)$$

$$\frac{dC}{dt} = \beta_t S(C + I) - a_t C - \alpha C - \mu C \quad (2)$$

$$\frac{dI}{dt} = a_t C - \rho I - (\mu + \gamma) I \quad (3)$$

$$\frac{dR}{dt} = \rho I + \alpha C - (\varphi + \mu) R \quad (4)$$

$$a_t = a_0 \left[\left(\frac{\varepsilon_a}{2} \right) \cos \left(2\pi \left(t - \frac{\theta}{365} \right) \right) + \left(1 + \frac{\varepsilon_a}{2} \right) \right] \quad (5)$$

$$\beta_t = \beta_0 \left[1 + \varepsilon_b \cos \left(2\pi \left(t - \frac{\theta}{365} \right) \right) \right] \quad (6)$$

Variables S , C , R , and I are proportions of the total population at time t in the respective compartments of the model. The models' parameters are described in Table 1.

Seasonality

To represent the two hypotheses of increased invasion or transmission rate during the dry season, we included seasonal forcing of the transition rate to invasive disease given carriage (model1-‘inv’), or the bacterial transmission rate (model2-‘transm’), or both (model3-‘inv-transm’). The invasion and transmission parameters (a_t and β_t) were represented with periodic sinusoidal functions (equations 5 and 6). Based on the explanatory model by Mueller and Gessner [16], and the systematic review of season-specific case–carrier ratio in the meningitis belt [7, 16], the case–carrier ratio (a proxy for the risk of invasive meningitis given colonisation) could increase up to 100-fold during the dry season. We included this information by parameterizing the periodic function of the invasion rate such that variations of up to 100-fold are possible in the dry season depending on the seasonal forcing amplitude (ε_a) estimate which can take on values from 0 to 100. The seasonal forcing amplitudes ε_a and ε_b dictate the

magnitude of seasonal variation of the invasion and transmission rate, respectively (equations 5 and 6).

Model assumptions

The model structure assumed a steady and well-mixed population with frequency-dependent transmission. Age structure of the population was deliberately not included in this proof of concept. However, the potential effects of heterogeneous mixing were explored in complementary analyses. Immunity from asymptomatic carriage and disease was assumed temporary. We assumed immunity provided by carriage and disease to be of similar duration, and asymptomatic carriers are as likely as ill individuals to transmit the infection to a susceptible. Ill individuals may be at a greater risk to transmit only from vomiting but are usually bound to bed.

Parameterisation

We obtained parameters values including natural death rate, death rate from meningitis, recovery rate after bacterial meningitis and birth rate from the scientific literature (Table 1). Case fatality rates of 10–15% were reported during serogroup A epidemics meningitis in the meningitis belt [1]. We inferred natural death rate as the inverse of life expectancy at birth (average life expectancy was 54 years in Burkina Faso) [26], and the average recovery rate as the inverse of duration of acute phase of meningitis (acute phase of bacterial meningitis would last a week on average) [27] (Table 1). Parameters that are not available in the literature were estimated using suspected bacterial meningitis cases report data from Burkina Faso; a country within the meningitis belt. The data consist of weekly counts of new suspected cases of bacterial meningitis recorded at health centres of four districts of the country from 2004 to 2010 together with the population sizes covered by each health centre. The estimated parameters were: the average meningococcal transmission and invasion rates, the amplitudes of seasonal forcing of transmission and invasion rates, the rate at which asymptomatic carriers and ill individuals recover, the duration of temporary immunity and the timing of weekly incidence peak relative to January 1. Initial susceptibles and carriers population size at the start of calendar years were also estimated for each health centre year hyperendemic's curves, as they could not be inferred directly from the literature. We limited the space of potential parameters values to be tested to plausible values according to the published literature if possible (Table 1). For example, we used the 95% confidence interval of the meningococcal case–carrier ratio estimate during the dry hyperendemic season in the meningitis belt [7] as plausible values range for the average bacterial invasion rate (a_0). We estimated all unknown parameters values using a maximum likelihood approach. For each model, parameters values were selected to maximise the Poisson likelihood of observed bacterial meningitis incident cases. We used the COBYLA algorithm, a derivative-free optimisation algorithm, implemented in the R package nloptr for parameters optimisation routine [28]. We chose this algorithm as it is relatively fast, it allows good convergence of the coefficients estimated on our data and it supports optimisation constraints such as parameter range. Several initial values were tested, and best-fit parameters estimates were obtained after 40 000 iterations. Implementations details of the optimisation routine are provided in Supplementary Material S1. In the complementary exploratory analysis investigating heterogeneous mixing of the population age

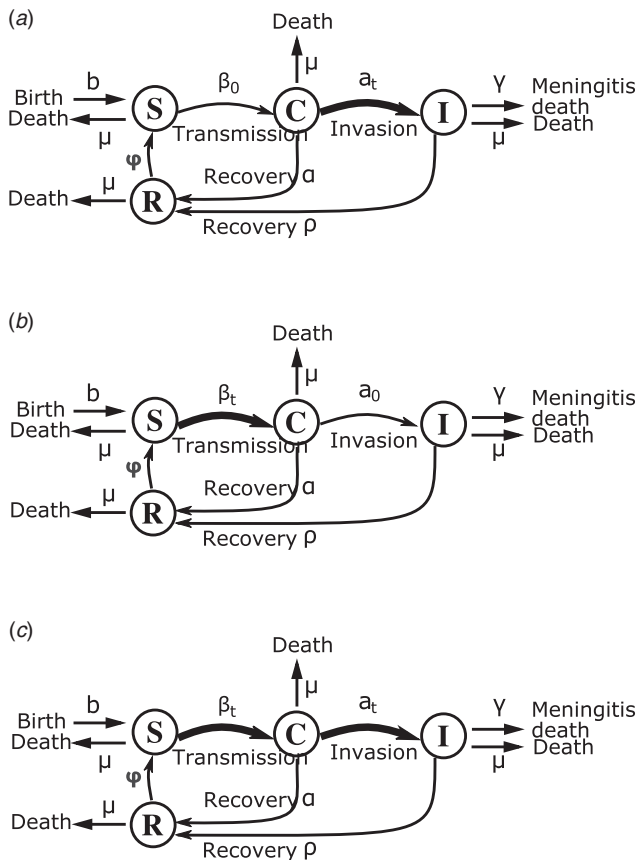


Fig. 1. Flow chart of state progression of individuals between the different epidemiological classes of the SCIRS models. Thick black arrows indicate parameters with seasonal forcing. (a) Model1-'inv': seasonal forcing of the invasion rate alone, (b) model2-'transm': seasonal forcing of the transmission rate alone, (c) model3-'inv-transm': seasonal forcing of the transmission and invasion rate.

groups in the models, we inferred the effective contact matrix from age-specific force of infection estimates in dry season with 'minor epidemics' as reported by Tartof *et al.* [11] in Burkina Faso.

Model simulation and evaluation

We implemented and simulated the models using R statistical computing software [29], and the lsoda function (deSolve package) for numerical integration of the ordinary differential equations with 1-day time step. We computed weekly incidence as:

$$\int_t^{t+(1/52)} a_t C dt, \quad (7)$$

with $a_t C$, the proportion of asymptomatic carriers who becomes ill at time t .

We quantitatively assessed the models' performance accuracy using the coefficient of determination (R^2), the per cent bias (PB), and the ratio of the root-mean-squared-error (RMSE) to observation standard deviation (RSR) (Supplementary Material S1). These three statistics quantify errors in models' predictions. PB computes the average absolute bias in model predictions of

observations. It gives an indication on whether the model results are consistently under- or overestimated compared with the observations [30]. The optimal value of PB is 0.

RSR standardises the RMSE using the observations standard deviation. It incorporates the benefits of error index statistics and includes a scaling/normalisation factor, so that the resulting statistic can be compared across data with different variance. The lower RSR, the better the model simulation performance. We also compared carriage prevalence predicted by the models with carriage prevalence reported by series of meningococcal carriage studies and a review of carriage during wet endemic and dry hyperendemic seasons in the meningitis belt [7, 17, 31]. We assessed the models' performance qualitatively by visual inspection of trajectories matching plots of model predictions of weekly incidence and observed data, and the ability of the models to fit data across all health centre years with a relatively good accuracy, i.e. capture both the seasonal trend in data, as well as timing and amplitude of observed seasonal peaks. Finally, the three models were compared based on their Akaike Information Criteria (AIC) to account for model complexity associated with the number of input parameters. The lower the model's AIC, the better and an absolute difference in AICs between 0 and 2 was considered weak to distinguish two models.

Uncertainty and parameter sensitivity analysis

The Latin Hypercube Sampling (LHS) uncertainty technique [32] was used to assess the model robustness to varying fixed and estimated parameters values (uncertainty analysis). Primarily, we evaluated the effect of parameters estimates uncertainty on predictions of the annual cumulative meningitis incidence and the annual average asymptomatic carriage prevalence. The estimates of these two models' state variables were obtained from the results of uncertainty analyses, and their distribution described for each model. Probability distribution functions (pdfs) of the estimated parameters were unknown. Therefore, we set the parameters pdfs to the uniform distribution. We also set the minimum and maximum values of the uniform distributions to be the 1st and 3rd quartiles of each of the estimated parameters distribution per model. Models were simulated with each of 1000 sets of parameters values sampled based on the LHS schema. We sampled a large number of values (1000) without replacement, within the boundaries of each parameter space to ensure that a great number of plausible parameters values combinations were explored. We calculated partial rank correlations coefficients (PRCC) between each of the estimated parameters and the sensitivity outcome variable: the annual cumulative incidence of meningitis cases. Scatterplots (of each input parameter against the sensitivity outcome variable) were generated to check that the assumption of monotonicity was satisfied. The sign of the PRCC identifies the specific qualitative relation between each of the estimated parameters and the sensitivity outcome variable. We used the PRCC to identify key parameters that contributed the most to the models' predictions imprecision.

Results

Model fit

The three models reproduced the weekly incidence of meningitis cases across the 64 health centre years with a good accuracy. Median R^2 over all health centre years was 0.72, 0.86 and 0.87

Table 1. Fixed and unknown parameters values and ranges for calibration of the models of seasonal hyperendemic bacterial meningitis in the African meningitis belt

Parameter	Short description	Plausible range	Initial value ^a	Unit	Comments and sources
Unknown parameters					
β_0	Meningococcal mean transmission rate	>0	0.5	Day ⁻¹	Unknown. Only positive values
α_0	Meningococcal mean invasion rate given carriage	0.002–0.012	0.007	Month ⁻¹	Inferred from case–carrier ratios estimated in a systematic review, specific for season and epidemiological context [7]
α	Rate of loss of carriage	1–52	12	Year ⁻¹	Unknown, carriage duration between 1 week and 1 year, range inferred from [20, 23]
φ	Rate of loss of natural immunity	0.2–12	4	Year ⁻¹	Unknown, persistence of natural immunity of between 1 month and 5 years, range inferred from [20, 24]
ε_a	Amplitude of seasonal forcing of invasion rate	0–100	50		An amplitude of 0 means that the baseline invasion rate remains constant across seasons; of 100 means it increases up to 100-fold
ε_b	Amplitude of seasonal forcing of meningococcal transmission rate	0–1	0.5		An amplitude of 0 means that the baseline transmission rate remains constant across seasons, and values up to 1 means presence of seasonality
θ	Calendar day of maximal invasion rate	91–112	97		Assuming correlation with aerosol load during period of relative humidity <40% (calendar week 13 through 16) [25]
S_0	Proportion of initial susceptibles in the population	0–1	0.5		The proportion of susceptible at the beginning of the calendar year (1 January)
C_0	Proportion of initial carriers in the population	0–1	0.01		The proportion of carriers at the beginning of the calendar year (1 January)
Fixed parameters values					
γ	Death rate from meningitis	5.2		Year ⁻¹	Case fatality = 10% [1]
μ	Natural death rate	0.02		Year ⁻¹	Life expectancy = 54 years [26]
ρ	Recovery rate	52		Year ⁻¹	Acute phase of bacterial meningitis disease lasts a week on average [27]
b	Birth rate	$b = \mu + \gamma I$		Year ⁻¹	Scaled to keep total population size constant

^aValues used as initial values for parameters optimisation routine.

for model1-‘inv’, model2-‘transm’ and model3-‘inv-transm’, respectively (Table 2). On average, model1-‘inv’ underestimated observed values, namely the peak incidence values (highest weekly incidence in the year) by 2%, while model2-‘transm’ and model3-‘inv-transm’ overestimated observed incidences by 5% and 1%, respectively. The error rates of the three models were relatively low but model 1-‘inv’ had an error rate (RSR = 0.52) that is about 40% higher than for model2-‘transm’ and model3-‘inv-transm’ (Table 2). Adding annual seasonality of the transmission parameter to seasonality of the invasion rate (model3-‘inv-transm’) improved the weekly incidence predictions of model1-‘inv’ overall (R^2 and error rate RSR improved). However, the gain in prediction accuracy was marginal when comparing model3-‘inv-transm’ to model2-‘transm’ performances (Table 2).

The AIC of the three models were on average similar, suggesting that the models cannot be distinguished based on their quantitative performance alone (mean AIC = 46, standard deviation S.D. = 19 for model1-‘inv’; mean AIC = 44, S.D. = 20 for model2-‘transm’ and mean AIC = 46, S.D. = 20). Trajectories matching plots between the models predictions of weekly incidences and

data at each health centre year suggested that seasonal trends in data were captured well by the three models, but model2-‘transm’ and model3-‘inv-transm’ captured annual peaks of disease incidence better than model1-‘inv’ in some health centre years (Fig. 2, Supplementary Figs S1–S3).

Model1-‘inv’ involved an average 2.9-fold increase, S.D. = 5.5 of the baseline invasion rate, while model2-‘transm’ involved an average 2.0-fold increase, S.D. = 0.3, of the baseline transmission rate. When both seasonality of the invasion and transmission rate is included (model3-‘inv-transm’), an average 2.0-fold increase, S.D. = 1.2 of the invasion rate is involved vs. an average 1.6-fold increase of the transmission, S.D. = 0.3.

The weekly carriage prevalence predicted by all three models during endemic wet season were <1% and in agreement with meningococcal serogroup A carriage prevalence studies outside epidemic periods in the meningitis belt [7, 17]. During the dry season, the median value of weekly carriage prevalence peaks (across all 64 health centre years) was 12% (1st, 3rd quartile = 7%, 18%) for model1-‘inv’, 17% (1st, 3rd quartile = 13%, 26%) for model2-‘transm’ and 11% (1st, 3rd quartile = 15%, 25%) for model3-‘inv-transm’. Including age structure in the models did

Table 2. Quantitative performances (goodness of fit) of the three compartmental models in predicting annual seasonal hyperendemic incidence of 64 health centre years in four health districts of Burkina Faso during 2004–2010

Models	R^{2a}		PB (%) ^b		RSR ^c	
	Median	1st, 3rd quartile ^d	Median	1st, 3rd quartile	Median	1st, 3rd quartile
Model1-‘inv’	0.72	0.62, 0.83	−2.30	−11.10, 4.20	0.52	0.41, 0.61
Model2-‘transm’	0.86	0.78, 0.92	0.50	−7.10, 1580	0.37	0.28, 0.47
Model3-‘inv-transm’	0.87	0.78, 0.92	4.96	−10.20, 11.20	0.36	0.28, 0.46

^a R^2 : coefficient of determination. Refers to the variance in observed data explained by the model.

^bPB: per cent bias (%). Average tendency of the simulated values to be larger or smaller than their observed ones.

^cRSR: ratio of root-mean-square error (RMSE) to standard deviations of observations.

^d1st, 3rd quartiles refers to: first and third quartiles of the estimates distribution.

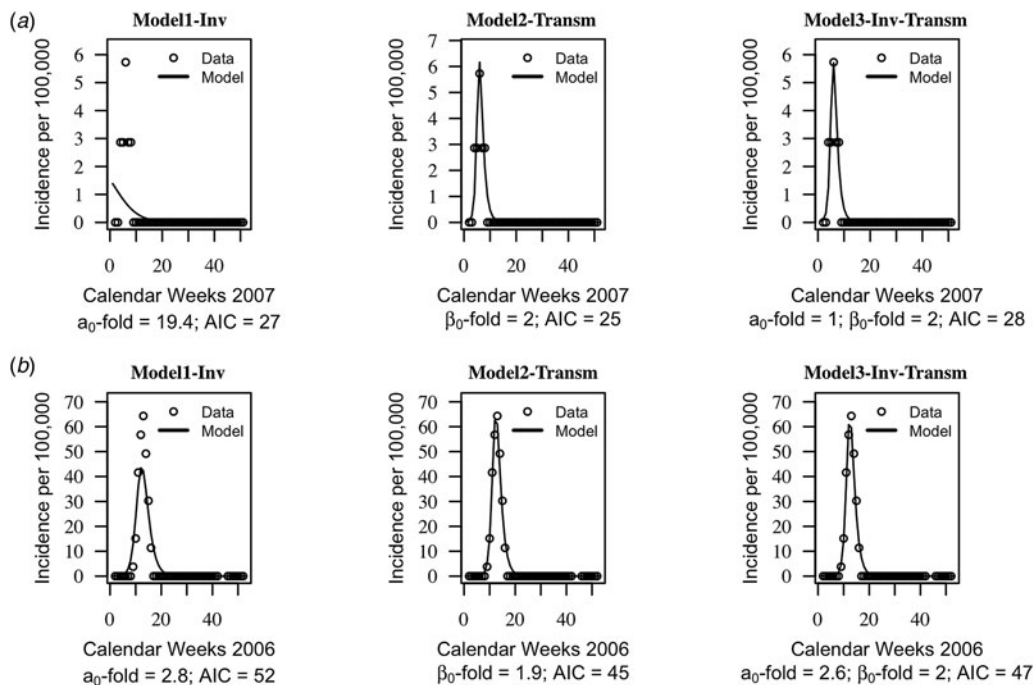


Fig. 2. Trajectory matching plots of observed weekly incidence data and models' predictions. Data (hallow circles) and models predictions (black solid line). (a) Health centre year with the poorest fitted data. (b) Health centre year with the best-fitted data. a_0 -fold and β_0 -fold indicate the seasonal fold increase of the invasion and transmission rate (respectively) relative to their baseline or average value. Model1-‘inv’: seasonal forcing of the invasion rate alone, model2-‘transm’: seasonal forcing of the transmission rate alone, and model3-‘inv-transm’: seasonal forcing of the transmission and invasion rate. Trajectory matching plots for all 64 health centre years are provided in Supplementary Figs S1–S3. Simulations are based on best-fit estimates of the parameters.

not improve the models fit to data nor significantly change the results. This complementary analysis and the fits results are presented in Supplementary Material S2.

Parameter estimation

Estimates of the baseline transmission rate were similar in the three models, as were estimates of the average duration of immunity, the timing of weekly incidence peak, and the initial susceptibles population size in model2-‘transm’ and model3-‘inv-transm’. However, with model1-‘inv’, duration of immunity tended to be longer, and the initial susceptibles population size larger (Fig. 3, Table 3). The average invasion rate estimated by model2-‘transm’ was fourfold higher than that of model1-‘inv’ and model3-‘inv-transm’. Overall, parameter estimates with model3-‘inv-transm’ had smaller between-health centres variances than with

model1-‘inv’ and model2-‘transm’ (Fig. 3, Table 3). Sensitivity analyses with hyperendemic health centre years defined as 50 weekly cases per 100 000 maintained during at least two consecutive weeks did not yield substantially different results (data not shown).

Uncertainty and parameters sensitivity

Uncertainty analysis results (Table 4) show that the prediction precision of the three models is low due to high degree of estimation uncertainty for the baseline values of the estimated parameters. Model2-‘transm’ has the higher prediction imprecision with a larger variance of the predicted annual cumulative incidence: 6346 compared with 439 for model1-‘inv’, and 731 for model3-‘inv-transm’. Uncertainty in estimating five of the nine estimated parameters was most critical in affecting the prediction precision of the three models. The five most critical parameters

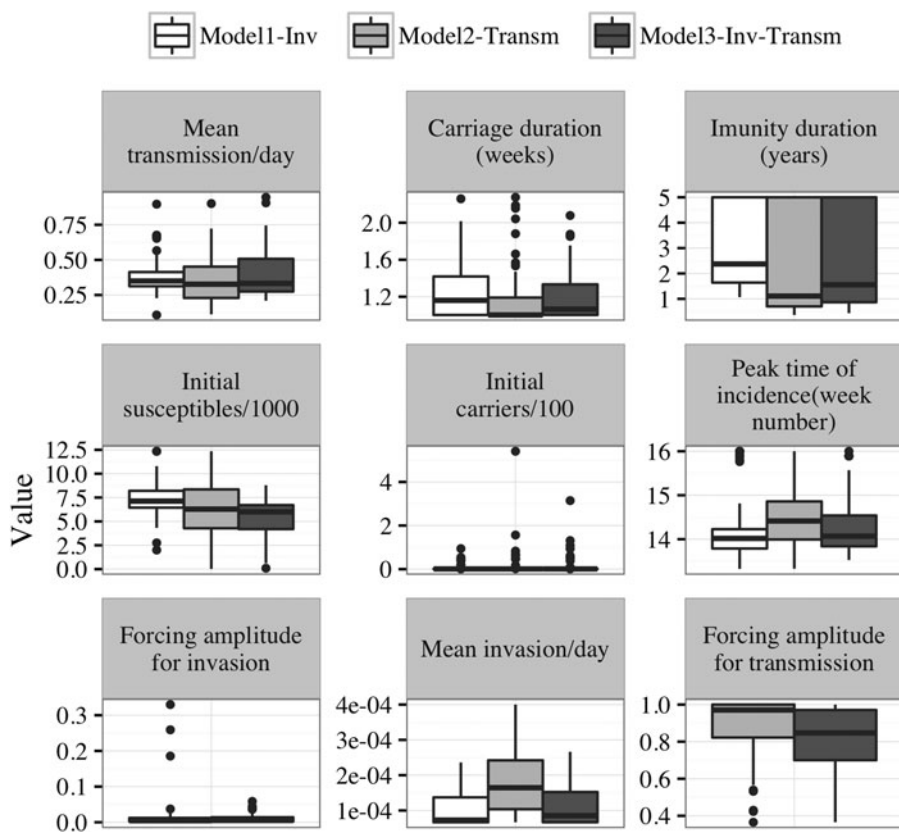


Fig. 3. Boxplot showing the distribution of parameter estimates across all health centres years per model. The boxes include 50% of the distribution, and dots represent outliers' values. Tick horizontal lines in the boxes represent the median value of the estimates. Values below the boxes are less than the 25th percentile and values above the boxes are greater than the 75th percentile of the distributions. Initial susceptibles and carriers' populations estimates are reported as proportion of the population as of 1 January of the calendar years. Model1-'inv': seasonal forcing of the invasion rate alone, model2-'transm': seasonal forcing of the transmission rate alone, and model3-'inv-transm': seasonal forcing of the transmission and invasion rate.

were the baseline transmission and invasion rates, average duration of asymptomatic carriage, the duration of immunity to infection and disease and the initial susceptibles population size (Table 5). The effect of uncertainty of carriage duration on prediction imprecision was more important with model1-'inv', than with model2-'transm' and model3-'inv-transm'. Parameter sensitivity ranking based on the PRCCs indicates that with model1-'inv', the baseline invasion rate was the most sensitive parameter, followed by the duration of asymptomatic carriage. With model2-'transm', the most sensitive parameters were duration of immunity to infection and disease, and the baseline invasion and transmission rate. With model3-'inv-transm', the baseline transmission and population immunity were the first two most critical parameters. However, initial proportion of carriers at the beginnings of the dry season also appears critical for the later (Table 5).

The positive value of the PRCC for the majority of the estimated parameters values implies that when the values of these input parameters increase, the future number of meningitis cases will increase. As immunity wanes quickly, the future number of meningitis cases is likely to increase. One possible way this can occur is by fast replenishment of the pool of susceptible individuals. With higher pool of susceptible individuals and lower population level immunity, comes increased likelihood of effective transmission of infection.

Discussion

This modelling study is a first attempt to fit compartmental models based to surveillance data of suspected bacterial meningitis at a fine spatial (health centre) and temporal (weekly) scale in the African meningitis belt. Two publications, by Karachaliou *et al.*

[12] (building on Irving *et al.* [10]. work), and Tartof *et al.* [11] used meningitis compartment models to evaluate long-term vaccination strategies with serogroup A conjugate vaccine. Both studies included seasonal change of the transmission and invasion rate in an age-structured model, but did not aim at comparing models with different types of seasonal forcing with regard to the transition from endemic to hyperendemic situation. Our study aimed at investigating the pathophysiology of the seasonal hyperendemicity of bacterial meningitis in this region at a fine scale, which is extraordinarily pronounced with a 10- to 100-fold increase observed every year in all districts [6, 7]. We found that compartmental models using seasonal forcing of risk of invasive disease given carriage, transmission or both, all produced seasonal disease incidence patterns consistent with the observed data, while models containing a seasonal effect on transmission improved the fit of seasonal incidence peaks. The latter finding appears to be somewhat in contrast with the hypothetical model presented by Mueller and Gessner [16]. While the three models required similar estimates of the endemic transmission rate to reproduce the observed disease incidence, the model including seasonality of transmission only (model2-'transm') involved a 2–4 times higher endemic invasion rate. This suggests that it is not sufficient to have higher transmission in the dry season to accurately reproduce the observed hyperendemicity, the level of meningitis disease risk given colonisation is important as well. Also, we found that seasonal change occurred in both the transmission and invasion rate in the model including seasonality of these two parameters. Our findings seem to conflict with the results from Tartof *et al.* [11] who published an age-structured model of MenA in the meningitis belt showing that observed data trends could be explained by a model with varying infection rates, but little

Table 3. Quantiles of the distributions of parameters estimated across the 64 health centre years per model

Parameters	Model1-inv			Model2-trans			Model3-inv-trans		
	25%	50%	75%	25%	50%	75%	25%	50%	75%
Quantiles									
Baseline transmission/day (β_0)	0.312	0.349	0.413	0.229	0.326	0.451	0.274	0.332	0.507
Carriage duration (weeks) (α)	1.002	1.1611	1.4187	1.0027	1.0027	1.190	1.0027	1.0658	1.3336
Immunity duration (years) (φ)	1.640	2.374	5.000	0.701	1.108	5.000	0.866	1.554	5.000
Initial susceptibles (S_0)	6443.310	7128.267	8205.869	4282.658	6289.297	8356.209	4199.00	6002	6712
Initial carriers (C_0)	1.000	1.000	1.251	1.000	1.000	1.558	1.000	1.000	1.201
Peak time (week number) (θ)	13	14	14	14	14	15	13	14	14
Seasonal forcing of invasion (ε_a)	0.002	0.004	0.012	-	-	-	0.002	0.005	0.013
Baseline invasion (σ_0)	1×10^{-4}	1×10^{-4}	1×10^{-4}	1×10^{-4}	2×10^{-4}	2×10^{-4}	1×10^{-4}	1×10^{-4}	2×10^{-4}
Seasonal forcing of transmission (ε_b)	-	-	-	0.822	0.970	1.000	0.700	0.847	0.970

seasonal variation in the risk of disease given colonisation. Adding a similar age-specific contact pattern to our models did not significantly change our results nor improve the fit to the data (Supplementary Material S3). The age-specific contact matrix (Supplementary Material S2) for this complementary analysis was extrapolated from Tartof *et al.*'s [11] paper and its supplementary materials, which may have its own limitations. However, discrepancies with the Tartof *et al.*'s study may be explained by differences in the spatial scale and scope of data analyses. Tartof *et al.* used data aggregated at the district or national level and aimed at explaining the occurrence of larger epidemic clusters or epidemic waves spanning several consecutive years. In contrast, our exercise aimed at studying the transition from endemic to hyperendemic situations, excluding localised epidemics detected based on high-resolution data (health centre level). The two models therefore differ in aim and spatial scale. Their use of larger scale data, i.e. district or national while we use local health centres, may prevent from accurately discriminating epidemic from regular hyperendemic events, thus mixing two distinct disease spreading mechanisms. Until appropriate contact pattern data from the meningitis belt population become available, our complementary analysis of the models including an age-structured model of transmission (Supplementary Material S2 and S3) should be considered exploratory.

The average annual carriage prevalence estimates from our models' uncertainty analysis exceeded 1% (1.9%). Carriage prevalence studies conducted in the meningitis belt show that, outside of epidemics, MenA carriage prevalence rarely exceeds 1%. Lack of serogroup-specific surveillance data for our model estimation may explain this behaviour, and the obtained carriage estimates represent both meningococci and pneumococci, all serogroups and type combined. Carriage studies using classical swabbing and culture inoculation techniques may have also underestimated the prevalence of nasopharyngeal carriage [6, 33–35]. Seasonal variations of the transmission rate in each health centre year appear to mirror the small or absent seasonal variations of carriage prevalence observed in available epidemiological studies [17, 31].

The model including only seasonal forcing of invasion (model1-'inv') required a substantially longer persistence of natural immunity following carriage or disease (median = 2.5 years vs 1 and 1.5 years), where the few serological studies available suggest rather shorter immunity persistence [20, 24]. An additional limitation of model1-'inv' was its lower accuracy in reproducing annual peaks of data in several health centre years, which was improved by an additional forcing of the transmission rate. An explanation for this could be that some health centre years incidence curves were classified as hyperendemic incidence based on the epidemic threshold definition used but were small-localised outbreaks resulting essentially from an accelerated transmission of the bacteria in the community as explained in the explanatory model suggested by Mueller and Gessner. However, sensitivity analyses with a lower epidemic threshold (50 weekly cases per 100 000) did not impact the models' results.

The fold increase of the transmission rate was not systematically higher than that of the invasion rate. It appears that both pathophysiological mechanisms are relevant and may reflect the impact that climatic conditions have on bacterial meningitis.

This study builds on the model published by Irving *et al.* [10] who investigated how well simple deterministic models were able to qualitatively reproduce the meningitis epidemiology in the African meningitis belt. Their study was limited to larger

Table 4. Description of predicted annual incidence and weekly carriage prevalence (averaged over the year) using 1000 combinations of parameters values from the Latin Hypercube Sample (uncertainty analysis)

Values	Annual incidence per 100 000 inhabitants			Average weekly carriage prevalence (%)		
	Model1	Model2	Model3	Model1	Model2	Model3
Minimum	28.70	0.06	0.28	0.90	0.00	0.01
Maximum	125.4	355.0	139.0	3.8	3.7	3.5
Mean	67.0	115.0	59.0	1.9	1.6	1.8
Median	62.3	105.0	54.0	1.8	1.5	1.7
Variance	439.9	6346.0	731.0	0.3	0.7	0.6
5th percentile	37.70	1.50	18.00	1.10	0.02	0.70
95th percentile	108.8	273.0	110.0	2.7	3.1	3.2

Table 5. Partial rank correlation coefficients (PRCC) between the Latin Hypercube Samples of estimated parameters and the annual cumulative incidence of meningitis (sensitivity analysis)

Parameter	Short description	Model1-'inv'		Model2-'transm'		Model3-'inv-transm'	
		PRCC ^a	95% Confidence interval	PRCC	95% Confidence interval	PRCC	95% Confidence interval
β_0	Meningococcal mean transmission rate	0.76***	0.68–0.84	0.80***	0.75–0.86	0.91***	0.88–0.96
α_0	Meningococcal mean invasion rate	0.90***	0.86–0.96	0.84***	0.76–0.94	0.81***	0.75–0.89
α	Rate of loss of carriage	–0.89***	–0.93 to –0.86	–0.49***	–0.65 to –0.31	–0.63***	–0.75 to –0.54
φ	Rate of loss of natural immunity	0.80***	0.73–0.88	0.87***	0.82–0.93	0.90***	0.87–0.95
θ	Calendar day of maximal invasion rate	0.18	–0.01 to 0.36	0.03	–0.17 to 0.27	–0.04	–0.26 to 0.19
ϵ_a	Seasonal forcing amplitude of invasion rate	–0.15	–0.34 to 0.05	NA	NA	–0.025	–0.25 to 0.22
ϵ_b	Seasonal forcing amplitude of meningococcal transmission rate	NA ^b	NA	0.18	0.03–0.37	–0.11	–0.31 to 0.11
S_0	Initial susceptibles' proportion	0.86***	0.81–0.93	0.73***	0.66–0.84	0.81***	0.74 to 0.90
C_0	Initial carriers' proportion	0.09	–0.08 to 0.33	0.11	–0.095 to 0.28	0.22*	0.04 to 0.40

^aPartial rank correlation coefficients estimates are significantly different than 0 at 0.05 level (*), and $<10^{-10}$ level (***) two-sided *P* values. They quantify the statistical relationship between each parameter and the model output.

^bNA stands for not applicable to the model.

epidemic waves that are observed every 7–10 years at the national level and did not use surveillance data for parameterisation or evaluation of model performance. The authors found that the model captured the irregular pattern of meningitis epidemics qualitatively and concluded, under the assumption of an increased bacterial transmission during the dry season, that the dynamics of population immunity could explain disease dynamics. Our study focused on hyperendemic incidences during the dry season, and results from the two studies should be considered as complementary, in particular as; as suggested by Mueller and Gessner [16], hyperendemicity, localised epidemics and epidemic waves may be distinct phenomena with distinct pathophysiological and epidemiological mechanisms. However, it appears essential to use surveillance data for parameterisation and quantitative evaluation. The availability of such data at high spatial (health centre) and temporal (weekly) resolution will allow adapting our model to reproduce the occurrence of localised epidemics, epidemic waves and meningitis incidence at the regional level

using meta-populations models. Eventually integrating immunisation interventions, such models will serve to develop optimised vaccination strategies against meningococcal and pneumococcal meningitis. We identified key parameters for which more data from clinical and epidemiological studies are needed to improve prediction, in particular duration of immune protection and carriage episodes, rates of invasion and transmission of the bacteria, and their variation by season.

Our study has some limitations inherent to the deliberately simple model structure and assumptions. We assumed that mixing among individuals was homogeneous. Meningococcal carriage and disease affect different age groups at different rates [31] and it is expected that contacts will be more intense between individuals in the same age group, in particular for older children and young adults. Limitations inherent to our extrapolation of age-specific contact pattern from Tartof *et al.*'s paper may have prevented our age-structured model from achieving better fit to the data than the simpler model. Similarly, we assumed only

one level of protection against carriage and disease, given the sparsity of evidence, while models evaluating vaccination strategies will require more distinct assumptions.

We used sinusoidal functions to force the seasonality of the transmission and invasion parameters, while an improved approach could consist in modelling these two parameters as a function of climatic variables, such as mean aerosol load, that are known to correlate well with seasonal meningitis incidence [36–38]. In some health centres with small population size, we had to limit the effect of random noise in the data by smoothing the time series to focus on the underlying seasonal trend. Chance variations of some unknown parameters, in particular the extent of climate conditions changing from year to year, was not explicitly included in the model structure. We addressed this in part by fitting the parameters on a yearly basis rather than using a single multiple year time series. However, stochastic models may be more appropriate when these fluctuations are important. Stochastic models shall be explored in the future for they appear to be particularly relevant when modelling localised epidemics. We used a model structure of overall meningococcal carriage and infection. The epidemiology of carriage likely differs between meningococcal and pneumococci meningitis but the limited knowledge about both bacteria dynamics made it challenging to adapt the proposed model to include pneumococci carriage data. Finally, our analysis carried on hyperendemic bacterial meningitis, i.e. both meningococcal and pneumococcal meningitis, assuming similar pathophysiologic mechanisms [39]. This assumption may not hold with regard to a variety of factors, including age structure of carriage, duration of carriage and immunity. However, given the lack of pathogen-specific meningitis surveillance data over a long period and in a large area, our approach appears justified, while it should be improved as appropriate surveillance data become available.

Despite these limitations, our findings suggest that the ubiquitous hyperendemicity of bacterial meningitis during the dry season in the African meningitis belt occurs due to a combination of increased risk of meningitis given asymptomatic carriage and meningococcal transmission. Despite the description of this phenomenon by Lapeyssonie [40] more than 50 years ago, the biological mechanisms for this pronounced seasonality remain largely unknown and little is known about the impact of aerosols and low air humidity on the human mucosal structures, immune system and interaction with the bacteria.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0950268818002625>.

Acknowledgements. We acknowledge the staff of health centres in Burkina Faso who participated in the meningitis surveillance, the Ministry of Health of Burkina Faso, The Ecole des Hautes Etudes en Santé Publique, Rennes, France and the Agence de Médecine Préventive, Ouagadougou, Burkina Faso for their collaborative effort in combining and making the surveillance data available for use in this study.

Financial support. This work was supported by the Université Pierre et Marie Curie, Paris 6.

Conflict of interest. None.

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Abbreviations

N.m.	<i>Neisseria meningitidis</i>
S.p.	<i>Streptococcus pneumoniae</i>
Hib	<i>Haemophilus influenzae</i> type b
WHO	World Health Organization
Men A	Meningococcal serogroup A
MenAfriVac A	Serogroup A meningococcal conjugate vaccine
NmX	<i>Neisseria meningitidis</i> serogroup X
NmA	<i>Neisseria meningitidis</i> serogroup A
NmW	<i>Neisseria meningitidis</i> serogroup W
CCR	Case Carrier Ratio
CCOUs	Case Carrier Observation Units
PRCC	Pairwise Rank Correlation Coefficient
LHS	Latin Hypercube Sampling
Pdfs	Probability density functions

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