UNIVERSITÉ — PARIS-EST

Ecole Doctorale de Santé Publique

THESE DE DOCTORAT

Université de Paris-Est

Ecole doctorale de santé publique (EDSP-570)

Discipline : Santé publique

Spécialité : Epidémiologie

Approche intégrée de la veille sanitaire : importance de la pluridisciplinarité dans le cadre du développement de méthodes pour la collecte et l'analyse de données sanitaires

---

Présentée et soutenue par

Alizé MERCIER

le 18 décembre 2020

Composition du jury :

Pr. Nathalie BAREILLE	Oniris, France	Rapportrice
Pr. Maguelonne TEISSEIRE	Inrae, France	Rapportrice
Dr. Arnaud TARANTOLA	Institut Pasteur, France	Examinateur
Pr. Nadia HADDAD	Ecole nationale vétérinaire de Maisons-Alfort, France	Examinatrice
Dr. Gina ZANELLA	Anses, France	Directrice
Dr. Julien CAUCHARD	Anses, France	Co-encadrant

Approche intégrée de la veille sanitaire : importance de la pluridisciplinarité dans le cadre du développement de méthodes pour la collecte et l'analyse de données sanitaires

Thèse présentée pour obtenir le grade de

Docteur de l'Université Paris-Est

Ecole doctorale de santé publique (EDSP-570)

Discipline : Santé publique

Spécialité : Epidémiologie

Alizé MERCIER

2020

ANSES :
Unité d'épidémiologie
Laboratoire de santé animale
ANSES Maisons-Alfort, France

CIRAD :
UMR Animaux, santé, territoires, risques et écosystèmes (ASTRE)
Campus international de Baillarguet
CIRAD Montpellier, France

Remerciements

Un grand merci à mes deux encadrants de l'ANSES, Julien Cauchard et Gina Zanella, d'avoir accepté d'embarquer avec moi dans cette aventure. Qu'ils trouvent ici, chacun, l'expression de ma reconnaissance de la confiance et de la liberté qu'ils m'ont accordées.

Merci à Nathalie Bareille, Arnaud Tarantola, Maguelonne Teisseire et Nadia Haddad d'avoir accepté de participer à mon jury de thèse.

Je suis reconnaissante aux membres de la Plateforme ESA, et plus particulièrement Céline Dupuy et Yves Lambert, pour leur soutien. Merci également à Didier Calavas et Pascal Hendrikx qui ont encouragé et soutenu ce travail. Leur engagement en faveur du développement des capacités d'épidémiosurveillance en santé animale est exemplaire. Merci au GS VSI pour ce beau travail d'équipe. Merci aussi à Laura Gonzalez Tapia pour son expertise en communication et illustration.

I'd like to thank Dr. Paul White for his contagious passion for epidemiology and GIS. It has been a pleasure and a privilege to work by your side at SPC, through the good and the bad. Your dedication is a true source of inspiration.

Mes remerciements vont ensuite à Mathieu Roche pour son soutien sans faille, sa bienveillance, sa disponibilité et les échanges scientifiques très enrichissants (et pluridisciplinaires pour le coup) que nous avons pu avoir concernant l'interface informatique/fouille de texte et épidémiologie. Ton attention aux détails, ta vision claire et ta capacité à avoir une vue d'ensemble m'ont été indispensables tout au long de cette thèse.

Un grand merci à mon père EI, Thomas Mollet, et à Bertrand Sudre de l'ECDC pour leur confiance, leur pédagogie et leur bonne humeur. C'est un réel plaisir, une chance et une véritable source d'inspiration que de pouvoir travailler à vos côtés dans le cadre de nos projets.

Je tiens également à remercier tous les collègues qui ont contribué aux travaux présentés dans cette thèse,notamment les collègues de l'IPNC (Myrielle Dupont-Rouzeyrol et Laurent Gillaumot) et de la CPS (Adam Roth et Christelle Lepers) pour leurs informations précieuses et leur expertise en lien avec les arboviroses dans le Pacifique, merci aux collègues de l'IRD (Morgan Mangeas, Christophe Menkes, Marc Despinoy, Magali Teurlai) pour cette première expérience en épidémiologie.

Merci aux collègues du Cirad, et plus particulièrement Facundo Munoz pour sa patience et sa pédagogie, Marion Bordier et Aurélie Binot pour leur expertise en sciences sociales, les autres doctorantes (Claire, Sarah, Mariline, Marie-Jeanne), ainsi qu'Elena Arsevska et Francesca Frangadini, pour leur soutien et leurs encouragements, les collègues de la VSI et le secrétariat d'Astre pour son aide. Merci également aux collègues du LIRMM pour leur confiance.

Enfin, je remercie JB, Carine et ma famille pour leur soutien sans faille. Merci de m'avoir permis de garder ma santé mentale tout au long de ce projet. Pas évident de ramasser les paniers cassés et de sortir des chantiers battus.

Title in English

"An integrated approach to epidemic intelligence: the importance of pluridisciplinary collaborations in the framework of the development of methods to collect and analyze health data"

Summary

In response to the growing threat of emerging infectious diseases, several countries have implemented epidemic intelligence activities to complement traditional surveillance systems. Epidemic intelligence is the process of early detection, verification, analysis and reporting of health events in order to recommend publish health measures. In addition to indicator-based surveillance, it also relies on event-based surveillance and the use of both official and unofficial information sources to improve the early detection of potential health threats.

Through two case studies of tool development (PADI-web and OpenESSENCE), I illustrate examples of pluridisciplinary collaborations between computer scientists, epidemiologists and local health agencies to ensure the co-design of automated data collection and analysis tools in the context of the online media monitoring for animal health in France (PADI-web) and the enhanced electronic surveillance for human mass gatherings in the Pacific (OpenESSENCE). These developments aimed to mobilize generic and automated tools in a pluridisciplinary and One Health approach to improve the early detection and alerting of health threats.

Through two case studies analyzing epidemic intelligence data (spatio-temporal analysis and spread rate modelling), I highlight the integration of expert knowledge and innovative methodologies to better characterize disease threats and inform risk analyses using a pluridisciplinary approach. Strengthening the links between epidemic intelligence and risk analysis provides real-time data on the epidemiological situation and improves disease knowledge to adapt and target epidemic intelligence systems.

With the emergence of three novel coronavirus in the past two decades, there is a strong need for an integrated approach to epidemic intelligence involving cross-border collaborations in a One Health context to promote the pooling of pluridisciplinary data, expertise and tools through a common strategy. The monitoring of weak signals and genetic information can help improve the timely detection of the emergence of unknown pathogens.

The integration of new sources of information and innovative technologies into existing epidemic intelligence systems can form the basis for an enhanced risk detection, monitoring and assessment platform. Mathematical models can identify environmental and socio-economic drivers of disease emergence and spread to facilitate the surveillance and prediction of future outbreaks. The implementation of an integrated approach should extend beyond scientific disciplines to bring together scientists, health professionals, governmental agencies and private stakeholders to implement contextualized and collaborative actions that foster a pluridisciplinary culture across human and animal interfaces.

Keywords: *epidemic intelligence, early detection, infectious diseases, integration, pluridisciplinary*

Résumé

Malgré une amélioration des systèmes de surveillance et des avancées technologiques et scientifiques, la menace des maladies infectieuses émergentes continue de s'accroître. Dans le contexte actuel de changements globaux et de mobilité accrue des personnes, animaux et des biens, les systèmes de surveillance traditionnels basés sur la surveillance d'indicateurs ne suffisent plus pour assurer une détection précoce des émergences et de la propagation de foyers infectieux, particulièrement dans le cas d'agents pathogènes inconnus. Pour faire face à cette menace, de nouvelles approches telles que la veille sanitaire et l'intégration des données non-officielles ont été développées pour améliorer la performance des systèmes de surveillance et permettre aux autorités d'anticiper les menaces liées aux maladies infectieuses émergentes.

La veille sanitaire (également appelée intelligence épidémiologique d'après la traduction du terme anglais « epidemic intelligence ») est le processus de collecte, de vérification, d'analyse et de communication de toute information permettant la détection, la vérification, l'évaluation et l'investigation de dangers sanitaires dans un but d'alerte précoce (source : OMS).

La veille sanitaire intègre des informations provenant de deux composantes complémentaires : la surveillance basée sur des indicateurs (SBI) et la surveillance basée sur des évènements (SBE). La SBI est fondée sur la surveillance en continu d'informations structurées récoltées par des systèmes de surveillance routiniers. La SBE se base sur la détection d'évènements sanitaires inhabituels à travers le suivi de sources d'information non structurées qui peuvent être officielles ou non-officielles (ex : médias, communication personnelle).

Le processus de la veille sanitaire comprend cinq étapes : la collecte, le tri, la vérification, l'analyse et la communication d'informations concernant de potentielles menaces sanitaires afin d'alerter les autorités sanitaires et de pouvoir fournir des recommandations de mesures de lutte efficace. Chaque étape de ce processus se fait en étroite collaboration avec un réseau pluridisciplinaire d'experts nationaux et internationaux, pour assurer la vérification et l'interprétation des évènements sanitaires détectés.

Un exemple de système de veille sanitaire est le dispositif « Veille sanitaire internationale » (VSI) de la Plateforme d'épidémiosurveillance en santé animale (ESA), que j'ai animé en réseau avec d'autres acteurs de la santé animale en France dont l'Anses. La Plateforme ESA a été créée en octobre 2011 et associe les principaux acteurs de la santé animale : Etat, scientifiques, organisations d'éleveurs, de chasseurs, de vétérinaires et de laboratoires d'analyse. Cette plateforme vise à améliorer l'efficience de la surveillance à travers notamment la mise en place de synergies entre recherche et surveillance, ainsi que le développement, l'amélioration et la promotion de différents dispositifs de surveillance.

La veille sanitaire internationale (VSI), et notamment la détection précoce de l'émergence et de la propagation d'agents pathogènes au niveau mondial, est l'un des maillons permettant de prévenir l'introduction en France de dangers sanitaires. L'intégration de la nouvelle thématique VSI au sein du programme d'activité de la Plateforme ESA a ainsi été décidée en janvier 2013. La VSI a pour objectif la détection, la vérification et l'interprétation d'événements inhabituels au niveau international pouvant diffuser et présenter un caractère de gravité pour la santé animale en France. Elle produit des informations sanitaires validées et interprétées à des fins d'évaluation

du risque, de gestion du risque et d'information des professionnels de santé. Les signaux sanitaires détectés et analysés par la VSI proviennent de sources officielles (ex : bases de données de notifications et rapports de l'OIE, la Commission européenne et de la FAO), mais aussi des sources non officielles, de natures diverses, telles que les médias ou des communications obtenues à travers un réseau d'experts nationaux et internationaux. La VSI participe également au développement d'outils permettant d'améliorer la performance du dispositif à travers, par exemple, la collecte automatisée d'informations à partir de médias sur internet ou la modélisation de la vitesse de propagation d'agents pathogènes infectieux.

Dans le cadre de problématiques de santé qui sont à la fois complexes et trans-sectorielles, la pluridisciplinarité est un enjeu majeur de la veille sanitaire qui permet d'adopter une approche globale et intégrée de la surveillance des risques sanitaires. Elle permet de disposer de visions complémentaires et polyvalentes de la problématique pour en assurer une meilleure compréhension. L'intérêt d'une approche pluridisciplinaire est illustré dans ce manuscrit par quatre cas d'étude répartis en deux chapitres, l'un basé sur l'amélioration de la collecte de données pour alerter et l'autre sur l'analyse de données pour caractériser et prédire.

Les deux premiers cas d'étude (chapitre 3) présentent deux outils, PADI-web et OpenESSENCE, développés dans le cadre d'une approche pluridisciplinaire visant à améliorer la détection et l'alerte précoce de dangers sanitaires dans des contextes de santé animale et de santé humaine.

L'outil PADI-web (« Platform for Automated extraction of animal Disease Information from the web ») est un outil de veille automatisée des médias électroniques qui se base sur des techniques innovantes de fouilles de texte. L'outil identifie des articles de médias en ligne en utilisant une liste prédéfinie de mots clés qui peuvent être spécifiques (nom de maladies) ou non spécifiques (liste de syndromes ou d'hôtes). PADI-web a été développé pour la VSI de la Plateforme ESA afin d'améliorer la détection précoce d'évènements sanitaires à partir de données non officielles et non structurées disponibles sur internet. Les experts en veille sanitaire de la VSI ont été inclus dès les premières étapes du développement au groupe comprenant des chercheurs en sciences informatiques et en épidémiologie, afin d'assurer une co-conception de l'outil pour qu'il réponde aux besoins des utilisateurs et que ces derniers puissent se l'approprier plus facilement et durablement.

Dans le contexte de crise sanitaire et de mobilisation d'outils existants, PADI-web a été utilisé pour identifier les premiers articles médias traitant de l'émergence de la COVID-19 en Chine en décembre 2019, et en comparant cette détection précoce à deux autres outils de biosurveillance que sont HealtMap et ProMED. Outre la précocité de la première détection, les termes utilisés dans ces premiers articles médias ont été analysés pour mieux caractériser le vocabulaire en lien avec des phénomènes émergents encore inconnus. Cette étude a montré que l'outil PADI-web était tout aussi efficace que d'autres outils de biosurveillance internationaux et donc suffisamment générique pour pouvoir être utilisé dans un contexte One Health. Les résultats ont aussi permis d'identifier le vocabulaire le plus adapté à détecter un phénomène de nouvelle émergence d'un agent pathogène inconnu. En intégrant ce nouveau vocabulaire, les outils de

biosurveillance seront un atout considérable dans la détection précoce de nouvelles menaces sanitaires, en complément des systèmes traditionnels basés sur la surveillance d'indicateurs.

L'outil OpenESSENCE est un outil dont l'utilisation s'inscrit dans le cadre du programme mis en place par la Communauté du Pacifique (CPS) afin de renforcer la surveillance syndromique mise en place lors de rassemblements de masse organisés dans le Pacifique. Ces évènements (religieux, socio-culturels, sportifs ou autre) rassemblent un nombre important de personnes et risquent de peser lourdement sur les ressources du système sanitaire local en termes de planification et d'action. A travers les fortes densités de personnes qu'ils génèrent, ces évènements augmentent considérablement le risque d'introduction et de propagation d'agents pathogènes infectieux, ainsi que leur exportation dans d'autres régions au retour des participants dans leur lieu de résidence. La surveillance électronique des maladies permet de réduire les délais en termes de collecte, d'analyse et de communication d'information sanitaire, particulièrement dans des contextes de ressources limitées, et d'améliorer ainsi l'alerte précoce et le contrôle des maladies infectieuses. L'outil OpenESSENCE, développé en collaboration avec des chercheurs de l'Université de Johns Hopkins, permet la collecte, l'analyse et la consolidation de rapports de manière centralisée et électronique, donc un gain de temps significatif dans la production journalière de rapports pour les autorités sanitaires et organisateurs de l'évènement. Le deuxième cas d'étude présente l'utilisation de cet outil pour le renforcement de la surveillance pour les Jeux de la Micronésie qui ont eu lieu à Pohnpei en juillet 2014. L'outil a été adapté à l'évènement par une équipe composée d'informaticiens, de programmateurs, d'épidémiologistes et d'experts en veille sanitaire, et des autorités gouvernementales locales, permettant ainsi la formation du personnel de santé, l'appropriation de l'outil par les autorités sanitaires locales, et le renforcement durable des capacités locales en veille sanitaire.

Ces deux cas d'étude illustrent l'intérêt de l'automatisation des méthodes utilisées à différentes étapes du processus de veille sanitaire, de la collecte à l'analyse et la conception de rapports permettant la dissémination d'information validée et analysée. Toutefois, l'intervention humaine demeure indispensable pour valider et interpréter ces informations afin de mieux formuler les recommandations de mesures de contrôle qui pourraient en découler. L'intégration pluridisciplinaire peut concerner différentes disciplines scientifiques dans le cadre de la recherche, mais également l'inclusion des utilisateurs tels que les professionnels de santé en charge de l'opérationnalité des systèmes de veille sanitaire. Au-delà des professionnels de santé, inclure les parties prenantes et les décideurs permet de donner un appui plus solide à la prise de décision des politiques et de les sensibiliser aux enjeux.

Dans le chapitre 4, l'importance d'une démarche pluridisciplinaire est à nouveau illustrée par deux cas d'étude présentant des méthodes d'analyse de données de veille sanitaire visant à caractériser les dangers sanitaires pour alimenter les analyses de risque et les modèles de prédiction.

La première étude présente l'analyse spatio-temporelle de la circulation de la dengue, du chikungunya et du Zika dans les pays et territoires insulaires du Pacifique de 2012 à 2014. Cette étude a été réalisée par la CPS avec des données de circulation de dengue, chikungunya et Zika dans le Pacifique de janvier 2012 à septembre 2014, dans le but d'analyser une possible évolution de l'épidémiologie de ces arboviroses dans la région. A travers une série temporelle et une carte

de la localisation des épidémies et de circulation (= lorsque des cas sont déclarés sans qu'il n'y ait de mention d'une épidémie par les autorités locales) des trois arboviroses, l'étude a confirmé l'intensification de la circulation des trois arboviroses à l'échelle régionale, avec la réémergence du chikungunya en 2011 et l'émergence du Zika en 2013 dans la région, ainsi qu'une augmentation de la co-circulation de plusieurs sérotypes de virus de la dengue. Cette dernière constatation représente un changement dans l'épidémiologie de la dengue dans le Pacifique, qui était jusque-là marquée par la circulation d'un sérotype dominant ensuite remplacé par un nouveau sérotype introduit et se propageant à travers la région sous forme de vague épidémique. Cette propagation en vagues épidémiques est caractéristique d'une épidémiologie insulaire, marquée par un isolement géographique, une importante mobilité et la présence de plusieurs espèces de vecteurs d'arboviroses, ce qui augmente le risque d'épidémie. L'étude présente aussi une carte de distribution des principales espèces vectrices de moustiques *Aedes* présentes dans la région. Cette étude a été réalisée dans une démarche pluridisciplinaire rassemblant des épidémiologistes, des microbiologistes et des entomologistes afin de mobiliser plusieurs expertises complémentaires pour mieux caractériser et comprendre la circulation des arboviroses à l'échelle régionale.

La deuxième étude présente la modélisation de la vitesse de propagation de la dermatose nodulaire contagieuse bovine (DNCB) dans les Balkans de 2015 à 2016. Cette étude, que j'ai menée lorsque j'étais en poste au CIRAD, se base sur des donnés de foyers de DNCB dans les Balkans de mai 2015 à décembre 2016, extraites de bases de données de la Commission européenne et de la FAO. Le modèle utilise la date et la géolocalisation de foyers de DNCB pour en extraire et interpoler la semaine de première invasion sur toute la zone d'étude. La vitesse de propagation (km/semaine) est estimée à partir de l'inverse d'un indice de friction (semaine/km), correspondant à la résistance de l'environnement à la propagation du virus. La vitesse médiane de propagation de la DNCB dans les Balkans a été estimée à 7,3 km/semaine. La saisonnalité de la DNCB semble marquée par une augmentation du nombre de foyers de mai à août, ce qui correspond à des températures plus élevées et favorables à l'activité d'insectes vecteurs. Les résultats de l'étude nous ont permis d'identifier deux processus de diffusion distincts. Le premier processus, caractérisé par de faibles vitesses de propagation (inférieures à 15 km/semaine), correspond à une diffusion locale de la maladie essentiellement due à la transmission vectorielle ou un contact entre animaux malades et sains. Le deuxième processus est marqué par des vitesses de propagation de plus de 15 km/semaine (dont un maximum observé de 544 km/semaine) et correspond plutôt au transport d'animaux malades ou de produits contaminés, ce qui expliquerait ce « bond » de plusieurs centaines de kilomètres. Nous prévoyons d'incorporer des variables explicatives dans le modèle afin d'expliquer ces différences de vitesse observées. Une des limites du modèle est qu'il ne tient pas compte des campagnes de vaccination qui ont été mises en place à travers la région et qui ont permis de ralentir et au final d'arrêter la progression de la maladie à d'autres régions d'Europe.

L'adaptation et l'application de ce modèle d'estimation de la vitesse de propagation ont été mises en place grâce à un effort pluridisciplinaire regroupant des épidémiologistes et des modélisateurs, permettant aux épidémiologistes de comprendre les processus sous-jacents du modèle et de mieux en interpréter les résultats. Un package R appelé « spreadrate » a été développé pour faciliter l'utilisation du modèle par les experts de la VSI pour caractériser d'autres dangers sanitaires surveillés par la VSI. Ces deux cas d'étude présentent des exemples d'analyses rapides à mettre en place, menées par des équipes de veille sanitaire, permettant ainsi d'optimiser la

caractérisation des dangers sanitaires détectés et l'information des autorités sanitaires. Les résultats de ces analyses peuvent aussi être utilisés pour des analyses de risque plus détaillées. Le renforcement du lien entre la détection, la caractérisation et l'analyse du risque associé à des dangers sanitaires permet d'effectuer des analyses de risque avec des informations mises à jour en temps réel par la veille sanitaire, et de pouvoir cibler les systèmes de veille sanitaire en fonction des résultats des analyses de risque.

Mes contributions aux quatre cas d'étude présentés se décline à deux niveaux. Le premier niveau correspond à une contribution méthodologique, visant à proposer des méthodes innovantes et des ajustements techniques d'outils de veille permettant d'en faciliter l'utilisation pour les utilisateurs. Le deuxième niveau est un méta-niveau qui se base sur l'intégration des connaissances d'experts afin de s'assurer que les outils développés répondent aux besoins, à la fois théoriques et techniques, des utilisateurs, favorisant ainsi une appropriation et utilisation durable par la communauté d'utilisateurs.

Il existe de nombreuses variantes à la définition de la veille sanitaire (ou intelligence épidémiologique), et je suis en accord avec celles fournies par l'ECDC et l'OMS. Contrairement à l'ECDC et à l'OIE par exemple, je considère que la veille sanitaire inclut la détection et la caractérisation du danger sanitaire, mais n'inclut pas l'étape de quantification et d'estimation du risque qui requiert une expertise différente, liée à la maladie, à l'agent pathogène et au mode de transmission. Cependant, la détection et l'analyse de risques sanitaires font partie d'un processus continu, qui nécessite donc de renforcer les liens entre la veille sanitaire et les analyses de risque. Ce lien peut varier à l'échelle internationale en fonction du mandat de l'institution, de l'expertise des différents experts et des ressources disponibles.

La mise en œuvre d'une approche pluridisciplinaire et intégrée des différents processus de la veille sanitaire est essentielle pour améliorer la performance des systèmes à travers la mise en place d'outils et de méthodes innovantes. L'intégration de diverses disciplines scientifiques et l'implication des acteurs impliqués dans le processus de développement de ces méthodes permet d'avoir une vision globale de la problématique, de mieux comprendre les principes sous-jacents et d'en interpréter les résultats, mais aussi de plus facilement s'approprier les outils et méthodes développés. La crise COVID-19 est le dernier exemple en date du besoin de collaborations pluridisciplinaires et entre acteurs, avec la mobilisation du secteur de la santé animale et la mise à disposition de matériels, équipements et experts.

Au-delà de l'intégration de plusieurs disciplines et du renforcement des liens entre la détection et l'analyse du risque, l'intégration intersectorielle entre la santé humaine et animale est aussi essentielle afin de mutualiser les données, connaissances, ressources et outils dans le but d'améliorer la détection précoce de nouvelles émergences, qui se situent souvent à l'interface homme-animal. L'intégration des différents niveaux géographiques permet aussi une vision globale des enjeux et stratégies, ainsi qu'une remontée d'information et de problématiques depuis le niveau local. Elle promeut l'inclusion des différents acteurs locaux, nationaux et internationaux.

Dans le cadre de la modélisation du phénomène infectieux, l'inclusion de variables explicatives environnementales ou socio-économiques permet de mieux comprendre et de prédire les phénomènes d'émergence et de transmission des maladies infectieuses. Ceci est notamment

prévu pour le modèle d'estimation de la vitesse de propagation. Avec l'expansion de l'internet et les récentes avancées technologiques, de nouvelles sources de données et de nouvelles technologies sont disponibles. L'intégration d'informations provenant des réseaux sociaux, de blogs, de forums et de requêtes sur internet, ainsi que la mise en place d'échanges d'informations avec les citoyens via des applications téléphoniques, peuvent permettent d'étendre le champ de surveillance des systèmes de veille et ainsi améliorer la précocité de la détection de dangers sanitaires.

Comme l'illustrent les trois émergences de nouveaux coronavirus ces deux dernières décennies, la menace de nouveaux agents pathogènes inconnus (correspondant à la « maladie x » désignée par l'OMS) est bien réelle et nécessite un renforcement de la surveillance de signaux faibles dans les systèmes de veille sanitaire. Cela peut passer par l'intégration de mots clés spécifiques aux émergences, tels qu'identifiés dans notre étude sur la COVID-19 avec PADI-web, au sein des outils de biosurveillance afin d'améliorer la SBE. Comme l'illustre la crise sanitaire COVID-19, il est indispensable de pouvoir mieux anticiper ces menaces en mobilisant une grande diversité d'expertises, pratiques autant que théoriques, et aborder la préparation et la prévention de manière plus proactive.

Mots clés : *veille sanitaire, détection précoce, maladies infectieuses, intégration, pluridisciplinaire*

Table of contents

List of associated publications

International peer-reviewed journals

Mercier A., Lancelot R., Hendrikx P., MacKinnon L., Madoff L., Lambert Y., Calavas D. and Cauchard J. (2020). The French Epidemic Intelligence System: comparing disease surveillance at national and international levels using the Program for Monitoring Emerging Diseases (ProMED) data. *OIE Scientific and Technical Review.* 39(3), in press. Available at: www.oie.int/fileadmin/Home/eng/Publications_%26_Documentation/docs/pdf/revue_plurithematique/2020/01042020-00162-EN_Mercier_ANG.pdf

Valentin S., **Mercier A.**, Lancelot R., Roche M. and Arsevska E. (2020). Monitoring online media for the early detection of unknown diseases: insights from a retrospective study of COVID-19 emergence. *Transboundary and Emerging Diseases*. in press. doi:10.22541/au.158766858.80343558.

Valentin S., Arsevska E., Falala S., de Goër J., Lancelot R., **Mercier A**., Rabatel J. and Roche M. (2020). PADI-web: a multilingual event-based surveillance system for monitoring animal infectious diseases. *Computers and Electronics in Agriculture*. 169, 105163, doi:10.1016/j.compag.2019.105163.

Mercier A., Arsevska E., Bournez L., Bronner A., Calavas D., Cauchard J., Falala S., Caufour P., Tisseuil C., Lefrançois T. and Lancelot R. (2018). Spread rate of lumpy skin disease in the Balkans, 2015–2016. *Transboundary and Emerging Diseases*, 65(1): 240-243. doi:10.1111/tbed.12624.

White P., Saketa S., Johnson E., Gopalani S., Edward E., Loney C., **Mercier A.**, Toatu T., Wojcik R., Lewis S. and Hoy D. (2018). Mass gathering enhanced syndromic surveillance for the 8th Micronesian Games in 2014, Pohnpei State, Federated States of Micronesia. *Western Pacific Surveillance and Response Journal*, 9(1): 1-7. doi:10.5365/wpsar.2016.7.4.001.

White P., Saketa S., Durand A., Vaai-Nielsen S., Leong-Lui T., Naseri T., Matalima A., **Mercier A**., Lepers C. and Lal V. (2017). Enhanced surveillance for the Third United Nations Conference on Small Island Developing States, Apia, Samoa, September 2014. *Western Pacific Surveillance and Response Journal,* 8(1): 15-21. doi: 10.5365/WPSAR.2016.7.4.002.

Roth A., **Mercier A.**, Lepers C., Hoy D., Duituturaga S., Benyon E., Guillaumot L. and Souares Y. (2014). Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012–2014. *Euro surveillance,* 19(41) : 1-8. doi:10.2807/1560-7917.ES2014.19.41.20929.

National peer-reviewed journals

Munoz F., **Mercier A.**, Cauchard J. and Lancelot R. (2020). Estimation de la vitesse de propagation de la PPA en Belgique. *Bulletin épidémiologique en santé animale*. 90, in press. doi:10.5281/zenodo.4036288.

Cauchard, J. **Mercier A.**, Falala S., Bronner A., Lancelot R. and Calavas D. (2018). Dermatose nodulaire contagieuse bovine : situation épidémiologique dans les Balkans et en Turquie au 30 novembre 2017. *Bulletin épidémiologique en santé animale.* 82: 1-5.

Arsevska A., Bronner, A., Calavas A., Cauchard J., Caufour P., Falala S., Hamon M., Hendrikx P., Lancelot R., **Mercier A.**, Rautureau S. and Tisseuil C. (2016). Dermatose nodulaire contagieuse des bovins : état de connaissances et situation épidémiologique dans les Balkans au 31 juillet 2016. *Bulletin épidémiologique santé animale*. 75: 20-24.

Book chapters and conference abstracts

Valentin S., Arsevska E., **Mercier A**., Falala S., Rabatel J., Lancelot R. and Roche M. (2020). PADI-web: an event-based surveillance system for detecting, classifying and processing online news. In Post-Proceedings of 8th Language & Technology Conference, LTC 2017, *Lecture Notes in Computer Science / Lecture Notes in Artificial Intelligence* - Springer, 2020, in press.

Munoz F., **Mercier A.**, Lancelot R. and Cauchard J. (2019). Estimation of the spread-rate of epidemics. The case of African Swine Fever in wild boar populations from Belgium. Symposium de l'Association d'Epidémiologie et de Santé Animale, Liège, Belgique, 6 May 2019, 5 p.

Perazzo Ferreira J., Leal-Neto OB., Hoy D., **Mercier A.** and Saketa S. (2016). Participatory surveillance for mass-gatherings. In *Disease Surveillance: Technological Contributions to Global Health Security*, p.172-176.

Hoy D., **Mercier A.**, White P., Saketa S., Roth A., Souares Y., Lepers C., Wojcik R., Katz A., Campbelle T. and Patel S. (2015). Using SAGES OpenESSENCE for Mass Gathering Events. *Online Journal of Public Health Informatics*, *7*(1). doi: 10.5210/ojphi.v7i1.5800.

Oral communications

Mercier A., Arsevska E., Cauchard J., Caufour P., Falala S., Bronner A., Bournez L., Ettore F., Peiffer B., Lefrançois T., Gilbert M., Tisseuil C., Hendrikx P., Calavas D. and Lancelot R. (2018). Modelling the spread of emerging infectious diseases in animal health: case study of Lumpy Skin Disease in the Balkans, 2015-2016. Innovations in Health Surveillance (InnovSur) Conference, 14 – 18 May 2018, Montpellier, France.

Mercier A., Arsevska E., Cauchard J., Caufour P., Falala S., Bronner A., Bournez L., Ettore F., Peiffer B., Lefrançois T., Gilbert M., Tisseuil C., Hendrikx P., Calavas D. and Lancelot R. (2017). Modelling the spread of emerging infectious diseases in animal health: case study of Lumpy Skin Disease in the Balkans, 2015-2016. 3rd International Conference on Animal Health Surveillance (ICAHS), 20 April – 5 May 2017, Rotorua, New Zealand.

Mercier A., Cauchard J. and Hamon M. (2016). Dermatose nodulaire contagieuse bovine – ou comment articuler la veille à l'international et une surveillance nationale. Journée Plateforme ESA, 22 November 2016, Paris, France.

List of acronyms

ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
Adilva	Association française des directeurs et cadres des laboratoires vétérinaires publics d'analyses
ADNS	Animal Disease Notification System
AFR	Acute fever and rash
ASF	African swine fever
BD	Boundary displacement
CAC	Codex Alimentarius Commission
CaribVet	Caribbean animal health network
CDC	Center for Disease Control and Prevention
CESPA	Centre d'épidémiologie et de santé publique des armées
CHIKV	Chikungunya virus
CIRAD	Centre de coopération internationale en recherche agronomique pour le développement
ComMod	Companion modelling
COVID-19	Coronavirus disease 2019
CPS	Communauté du Pacifique (anciennement Communauté du Pacifique Sud)
DENV	Dengue virus
DGAL	Direction Générale de l'alimentation (Ministère de l'Agriculture)
DHF	Dengue hemorrhagic fever
DIVA	Differentiating Infected animals versus Vaccinated Animals
DNCB	Dermatose nodulaire contagieuse bovine
EBS	Event-based surveillance
ECDC	European Centre for Disease Prevention and Control
ECSA	East/Central/South Africa (CHIKV strain)
EI	Epidemic intelligence
EID	Emerging infectious disease
EIOS	Epidemic intelligence from open sources
ESA	Plateforme d'épidémiosurveillance en santé animale/ Animal health epidemiological surveillance
ESSENCE	Electronic Surveillance System for the Early Notification of Community-based Epidemics
ESS	Enhanced syndromic surveillance
ESV	Plateforme d'épidemiosurveillance en santé végétale
FAO	Food and Agricultural Organization of the United Nations
FEIS	French epidemic intelligence system
FMD	Foot-and-mouth disease
FNC	Fédération nationale des chasseurs
FSM	Federated States of Micronesia
FYROM	Former Yugoslav Republic of Macedonia (now North Macedonia)
GDS	Groupement de défense sanitaire
GHSI	Global Health Security Initiative
GLM	Generalized linear model
GLS	Generalized least squares
GOARN	Global Outbreak, Alert and Response Network
GPHIN	Global Public Health Intelligence Network
H2020	Horizon 2020
HIV	Human immunodeficiency virus

IBS	Indicator-based surveillance
IHR	International Health Regulations
ILI	Influenza-like-illness
INRAE	Institut national de recherche pour l'agriculture, l'alimentation et l'environnement
IRD	Institut de recherche pour le développement
ISID	International society for infectious diseases
JHU-APL	Johns Hopkins University applied physics laboratory
LSD	Lumpy skin disease
MERS-CoV	Middle East respiratory syndrome coronavirus
MOOD	Monitoring outbreak events for disease surveillance in a data science context
OE	OpenESSENCE
OFB	Office français de la biodiversité
PADI-web	Platform for automated extraction of disease information from the web
PCA	Principal component analysis
PCR	Polymerase chain reaction
PH	Public health
PHD	Public health division of SPC
PHEIC	Public health emergency of international concern
PICT	Pacific island countries and territories
PPHSN	Pacific public health surveillance network
ProMED	Program for monitoring emerging diseases
PSSS	Pacific syndromic surveillance system
REI	Research, evidence and information program of the PHD of SPC
RNA	Ribonucleic acid
RRA	Rapid Risk Assessment
RSS	Really simple syndication feed
SAGES	Suite for automated global electronic biosurveillance
SARS	Severe acute respiratory syndrome
SCA	Plateforme d'épidémiosurveillance de la chaîne alimentaire
SEGA	Réseau de surveillance épidémiologique et gestion d'alertes
ULB	Université libre de Bruxelles
SBE	Surveillance basée sur les évènements
SBI	Surveillance basée sur les indicateurs
SIDS	Small island developing states (United Nations Conference)
SNGTV	Société Nationale des Groupements Techniques Vétérinaires
SOP	Standard operating procedure
SPC	the Pacific Community (formerly Secretariat for the Pacific Community)
TPSR	Thin plan spline regression
TRL	Technology readiness levels
TSA	Trend surface analysis
VSI	Veille sanitaire international
WAHIS	World animal health information system
WHO	World health organization
ZIKV	Zika virus

Glossary of main terms

Alert: an event that requires the implementation of control or prevention measures by health authorities

Emerging infectious diseases (EID): diseases that have newly appeared in a population or have existed previously but are rapidly increasing in incidence or geographic range

Epidemic intelligence (EI): discussed in the discussion (section 6.2)

Event-based surveillance (EBS): the organized collection, monitoring, assessment and interpretation of mainly unstructured *ad hoc* information regarding health events or risks, which may represent a risk to human health. The information collected for EBS originates from multiple, often not-predetermined sources both official and unofficial, including rumors reported by the media or *ad hoc* reports from informal networks (source: WHO)

Event: a signal that has been selected (i.e. represents a potential threat according to criteria defined by health authorities) and verified (i.e. to confirm the veracity of the information using official sources)

Health hazard: pathogenic agent that could produce adverse consequences on populations (also referred to as health threat)

Health risk: the probability of the occurrence of a health event with adverse consequences

Indicator-based surveillance (IBS): the systematic and routine collection, monitoring, analysis, and interpretation of structured data, i.e. indicators, produced by a number of well-identified, predominantly health-based official sources. (source: WHO)

Interdisciplinary: involving several disciplines to build common strategies through collaborative conception and implementation of research questions, methods and tools, and results

Multidisciplinary: involving several disciplines working individually, in parallel, to contribute to the topic, with no collaboration between disciplines

Outbreak: the occurrence of one or more epidemiologically-linked cases of a disease within an epidemiological unit

Pluridisciplinary: involving more than one discipline (see also multi-disciplinary, inter-disciplinary and trans-disciplinary)

Risk analysis: discussed in section 5.1 – includes risk assessment, risk estimation and risk evaluation

Signal: a health-related information that could potentially impact the target population

Transdisciplinary: involving several disciplines working on a research topic that is co-constructed through collaborative and participatory methods, and includes strong involvement of social science stakeholders

Zoonotic disease: a disease in animals that creates a potential for a disease in humans as a result of human exposure to the animal source (or vector) (source: WHO)

List of illustrations

List of tables

Chapter 1

Introduction

1.1. Objectives

Epidemic intelligence is defined as the process of early detection, verification, assessment and reporting of health events to inform health control measures (Paquet *et al.*, 2006). It is key to anticipate and prevent the introduction and spread of health threats. Although it is a relatively novel concept, epidemic intelligence activities are thriving with the increasing global threat of emerging infectious diseases. This highlights the need for event-based surveillance to complement traditional surveillance systems and improve early detection and alerting.

I became aware of the importance and the transversal role of epidemic intelligence during my experiences in human and animal health, in the Pacific and in Europe, in research centers and in intergovernmental agencies. These experiences came from working as an epidemiologist at the French Research Institute for Development (IRD), the Pacific Community (SPC) and the French Agricultural Research Center for International Development (CIRAD) from 2013 to 2020. These experiences taught me the importance of connectivity between each step of the epidemic intelligence process, from data collection to reporting, from methodological tool design to operational implementation and sustainable use, from the local detection of an unusual event to national reporting and recommendation of control measures. I discovered similarities in methods, challenges and procedures between human health and animal health relating to epidemic intelligence, even though the geographical or disease scopes of my experiences were different. I noticed gaps in existing systems and aimed to improve these systems while adopting and promoting a pluridisciplinary approach.

The objective of this thesis is to describe and draw from different experiences the importance of adopting an integrated pluridisciplinary approach when implementing epidemic intelligence activities, from the early detection and alerting of health threats to their characterization and prediction, spanning across geographic scales, sectors and disciplines.

Following a brief introduction of the context of emerging infectious diseases, a first section presents the concepts and steps of epidemic intelligence, illustrated with the example of the French animal health epidemiological surveillance platform and its epidemic intelligence system (Mercier *et al.,* 2020). I then proceed with several case studies of pluridisciplinary collaborations

in the context of tool development (to improve early detection and alerting of health threats) and the analysis of epidemic intelligence data (to better characterize and predict health threats). The case studies presented are the following:

- For the development of tools to improve data collection and early detection:
    o An automated tool to collect health-related information from online media articles in order to detect the emergence of the novel coronavirus in China in 2019
    o An electronic data collection tool to enhance disease surveillance during mass gatherings in the Pacific (Hoy *et al.*, 2015; White *et al.*, 2018)
- For the analysis of epidemic intelligence data to characterize health threats:
    o The analysis of the circulation of dengue, chikungunya and Zika viruses in 2012-2014 in the Pacific (Roth *et al.*, 2014a)
    o The estimation of the spread rate of lumpy skin disease in 2015-2016 in the Balkans (Mercier *et al.*, 2018)

Finally, the main ideas of this thesis are summarized and discussed, and I conclude with perspectives of future developments and strategies.

1.2 Context

Risk of disease emergence

Global changes including globalization, high mobility of people and goods, land-use changes, and climate change have favored the (re-)emergence of known and unknown infectious diseases (Morens *et al.*, 2004; Rodríguez-Prieto *et al.*, 2015). Emerging infectious diseases (EIDs) are "infections that have newly appeared in a population, or have existed previously but are rapidly increasing in incidence or geographic range" (Morse, 2001). A literature review conducted in 2005 revealed that 13% of the 1 407 known pathogens infecting humans were considered as emerging or re-emerging (Woolhouse *et al.*, 2005). EIDs are mainly of animal origin (60% are zoonoses, i.e. diseases that can transmitted from animals to humans), and their incidence has significantly increased over time placing an additional burden on human and animal health services (Morens *et al.*, 2004; Jones *et al.*, 2008). They are characterized by their unpredictability and instability in terms of occurrence, evolution and impact (health, social or economic), which makes them difficult to predict and prevent. Infectious pathogens are constantly evolving, and human actions can impact these pathogens, their epidemiological cycle and the interactions between pathogen, host and environment, and hence potentially increase the risk of outbreaks (Desenclos *et al.*, 2007).

International air travel has improved connectivity between endemic/epidemic and non-affected regions, thereby increasing the risk of rapid spread of infectious diseases across the world. Infectious diseases are not only spreading faster, they appear to be emerging more quickly. Since the 1970s, one or more new emerging diseases have been identified each year (World Health Organization, 2007). In Europe, the risk of introduction and spread of new infectious diseases has increased over the past 20 years along with the movements of humans and animals between Member States mainly due to the expansion of the European Union, the increase in population, and the promotion of 'open trade' between countries (Rodríguez-Prieto *et al.*, 2015).

Of 335 EID events recorded between 1940 and 2004, 54% were caused by bacteria (e.g. *Bacillus anthracis* causing anthrax or *Leptospira interrogans* causing leptospirosis) – keeping in mind the role of antibiotic resistance for which the availability of quantitative information remains limited –, 25% by viral or prion pathogens, 11% by protozoa (e.g. *Plasmodium falciparum* causing malaria or *Toxoplasma gondii* causing toxoplasmosis), 6% by fungi (e.g. *Penicillium marneffei* or *Candida albicans* infections), and 3% by helminths (e.g. *Trichinella spiralis* causing trichinellosis or the *Taenia solium* tapeworm) (Jones *et al.*, 2008). Viruses play an important role in disease emergence. Although they were not responsible for the majority of emergence events, the most devastating recent emergences (e.g. human immunodeficiency viruses – HIV, influenza H1N1, Ebola, coronaviruses) have involved ribonucleic acid (RNA) viruses, which can replicate in many host species and have high mutability potential. About a third of the viruses that have recently emerged are arboviruses (transmitted by arthropods, most often mosquitoes). The term 'disease' will be used in this manuscript to refer to infectious diseases, often of viral nature.

Examples of recent disease emergences

In a global economy with open markets and frequent exchanges of goods and animals over long distances, the unprotected and crowded farm animal population in Europe provides an ideal context for the (re-)emergence of exotic animal infectious diseases (Sobrino & Domingo 2002). Previous outbreaks have underlined the sensitivity of European animal populations to EIDs, such as the introduction of foot-and-mouth disease (FMD) in the United Kingdom in 2001, responsible for over 1 000 outbreaks and a sub-sequent spread to France and the Netherlands, or the 2015-2016 emergence of lumpy skin disease in seven countries of the Balkans following an introduction in Greece in 2015 (Sobrino *et al.*, 2001; Mercier *et al.*, 2018). Several new highly pathogenic avian influenza viruses have also been reported such as the H5N8 virus that emerged in Europe in 2016, affecting over 21 countries including France (Guinat *et al.*, 2018). Another example is African swine fever (ASF), which was introduced in Europe in 2007 from Russia, and has since been reported in more than ten Eastern European countries (European Food Safety Authority, 2020). In September 2018, ASF emerged in wild boar populations in Belgium, probably introduced by human action (e.g. transport of animals or animal products), and led to 833 cases reported in the South of the country as of 28th September 2020 according to the European Commission's database. ASF then emerged in Germany in September 2020, with 37 cases notified to the European Commission as of 29th September.

There have also been several emergences of human diseases, notably caused by arboviruses (e.g. dengue, chikungunya, Zika), but also coronaviruses. There have been three emergences of new coronaviruses causing large outbreaks in the past two decades. In 2002-2003, an outbreak of Severe Acute Respiratory Syndrome (SARS) affected 29 countries and resulted in more than 8 000 cases and 750 deaths reported (World Health Organization, 2003). Since its emergence in September 2012, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) has caused over 2 494 cases and over 800 deaths in 27 countries (World Health Organization, 2019). The recent emergence of the SARS-CoV-2 virus responsible for coronavirus disease 2019 (COVID-19) pandemic is the latest example. Following the detection of its emergence in Wuhan, China, the virus rapidly spread worldwide with 31 091 469 cases and 961 352 deaths reported as of 21st September 2020 (European Centre for Disease Prevention and Control, 2020).

Importance of anticipating health threats

New emergence and spread of diseases are impossible to predict accurately. We can, however, anticipate these risks by improving disease surveillance to detect early signals of emergence (Desenclos *et al.*, 2007). Anticipating health threats is crucial to mitigate the impact of a potential emergence of an infectious disease in a previously unaffected area. A recent example is the emergence of ASF in wild boar populations in Belgium in September 2018. Following this first detection of ASF in Belgium, a neighboring country, French animal health authorities rapidly implemented measures to prevent the introduction of ASF in France. These measures included:

- enhancing surveillance at the French-Belgian border,
- a multi-national taskforce was created between Belgium, Luxemburg and France to facilitate the timely exchange of information and prevention/control strategies between countries,
- building fences at the French-Belgian border to avoid the crossing of potentially infected wild boars from Belgium to France,
- raising awareness among health professionals, and
- collaborating with hunters to eradicate wild boars in a defined perimeter near the border.

Due to the timely implementation of these prevention measures, France remained free from ASF more than a year after the emergence of the disease just several kilometers from the French-Belgian border. This example illustrates the importance of anticipating health risks and implementing prevention measures instead of waiting for the introduction of the disease to set up control measures. It also stresses the need for cross-border surveillance and collaborations. The level of anticipation depends on whether the disease spread was diffusive and progressive (e.g. Germany, near the Polish border), or if there was a significant jump in the spatial distribution linked to the movement of infected animals or animal products (e.g. Belgium).

These last few years, surveillance systems have improved and outbreak information is communicated more widely and rapidly through information channels such as online media (Desenclos *et al.*, 2005). The integration of epidemic intelligence activities has improved the timely detection and reporting of health threats to alert health authorities. This is particularly important given the significant consequences and costs of delayed detection of a novel disease spreading through a naïve population. For example, the FMD outbreak in the United Kingdom in 2001 was estimated to have cost 1.1 billion GBP in compensation costs alone, and the Ebola outbreak in Western Africa in 2014-2016 was estimated to have caused 53 billion US dollars in economic costs, including indirect and social costs (Thompson *et al.*, 2002; Huber *et al.*, 2018). Early alerting allows health authorities and professionals to prepare, for instance by setting up awareness campaigns, stocking up on vaccines and medical equipment, or enhancing surveillance in high-risk areas or potential entry points (e.g. borders, airports).

Improving surveillance

Recent disease emergence such as the novel 2009 influenza A (H1N1) outbreak and the COVID-19 pandemic in 2020 have demonstrated how rapidly pathogens can spread worldwide. The threat of EIDs, combined with a concern over intentional biological or chemical events, motivated the

World Health Organization (WHO) to update its International Health Regulations (IHR) in 2005 (World Health Organization, 2008b). The 2005 updated IHR, a legally binding instrument for all 194 WHO member countries, significantly expanded the scope of reportable conditions to help prevent and respond to global public health threats. In the revised 2005 IHR, WHO clearly expressed that the reporting requirement for countries is no longer based exclusively on a list of infectious diseases with epidemic potential, but rather consists of the obligation to report any event that may constitute a Public Health Emergency of International Concern (PHEIC) (World Health Organization, 2008b).

Surveillance and response are two key elements to control EIDs. The timely detection and reporting of health threats, along with the rapid implementation of control measures, are crucial to limit the spread of the disease and mitigate the impact on populations and the subsequent health, social and economic costs, as is illustrated in Figure 1 with the breaking of the epidemic curve which limits the spread of the disease.
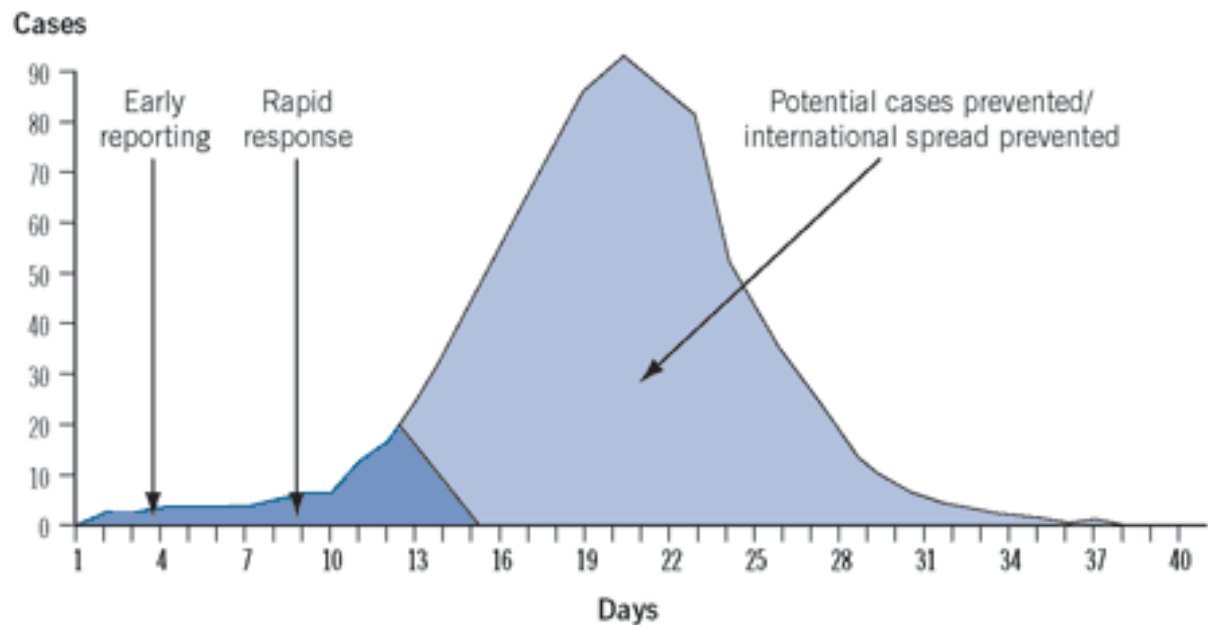
Figure 1. Impact of early detection and rapid response measures on the epidemiological curve of an outbreak (source: ECDC)

European Member States have long-established disease surveillance systems that provide traditional surveillance based on formal indicators. In May 2006, Member States committed to comply with WHO's 2005 revised IHR and have developed and/or strengthened their epidemic intelligence activities (World Health Organization, 2008b). Countries have had to improve their detection and response capacities to control the emergence and spread of infectious diseases. Some countries have strengthened existing surveillance systems by setting up epidemic intelligence activities.

Chapter 2

Epidemic intelligence

2.1. Definition

According to the European Centre for Disease Prevention and Control (ECDC), epidemic intelligence (EI) activities focus on the early identification, verification, assessment and investigation of potential health hazards in order to recommend control measures (Paquet *et al.*, 2006). WHO also defines EI as the early detection, verification, assessment and communication of health threats (World Health Organization, 2014).

EI provides countries with a conceptual framework to complement traditional surveillance systems and help adapt them to face the challenges of emerging infections. The aim of EI is the early detection and monitoring of health threats. It does not focus on the long-term monitoring of trends or morbidity.

EI focuses on the detection, monitoring and assessment of health threats, but does not intervene in the implementation of control measures and risk management. Depending on the institution's mandate, EI might not be in charge of large-scale communication through the media, but EI communicates information relating to detected alerts and notifies health authorities.

Early detection surveillance can focus on the emergence of a known disease in a previously unaffected area (e.g. FMD in the United Kingdom), the emergence of a new and previously unknown disease (e.g. COVID-19 pandemic) or an unusual increase in the frequency of occurrence of a known and circulating disease (e.g. influenza). In this manuscript, I will focus mainly on the first two objectives which are the most important for the early warning of known and unknown threats in order to avoid potentially high costs and burden on health infrastructures.

2.2. Elements of language

Some elements of language need to be clarified in order to ensure the comprehension of the EI process.

2.2.1 Risk and hazard

The World Organization for Animal Health (OIE) defines a health hazard as "any pathogenic agent that could produce adverse consequences on populations" (World Organisation for Animal Health, 2019b).

A risk is defined as "the possibility of an unfortunate occurrence" (Aven *et al.*, 2018).

A hazard is something with the potential to cause harm, whereas a risk refers to the probability or likelihood of an occurrence, as well as the magnitude of the consequences. In this manuscript, I will use the term "health threat", which corresponds to health hazard i.e. a health-related event, most often an outbreak or a disease emergence, representing a potential threat for a target population.

An outbreak corresponds to the occurrence of one or more epidemiologically-linked cases of a disease within an epidemiological unit (Cameron *et al.*, 2020). The epidemiological unit considered by the surveillance system needs to be clearly defined, and can correspond to an animal or an individual, or a specific population depending on the scope of the system (e.g. herd, farm, village, district, country).

2.2.2 Indicator and event-based surveillances

EI integrates both indicator-based surveillance (IBS) and event-based surveillance (EBS) (Figure 2).

IBS refers to structured data collected through routine and traditional surveillance systems, such as official notifications made by health authorities to WHO or OIE. These notifications usually contain epidemiological, geographic and clinical information relating to a specific disease outbreak (e.g. location, date of detection and confirmation, virus, host, control measures implemented). Traditional disease surveillance systems rely on IBS for the monitoring of health indicators from a range of sources, such as mortality, morbidity, clinical data, laboratory reports, surveys, animal or vector studies, hospital statistics and disease registries, over-the-counter drug sales, or school and work absenteeism. Traditional indicator-based systems have, however, demonstrated weaknesses in terms of early detection of health threats due to large amounts of data leading to delays in disease verification, analysis and reporting.

EBS focuses on the *ad hoc* collection and interpretation of real-time unstructured data gathered from heterogeneous sources that are not predefined and include non-official sources, such as electronic media, communications from field experts and social networks.

The use of EBS can improve early detection, but unofficial information (i.e. not officially validated) still needs to be verified by local health authorities because they could stem from false rumors (Khan *et al.*, 2012). Unofficial sources can help overcome limitations of traditional surveillance sources, including delays in detection and reporting, inconsistent population coverage and poor sensitivity in terms of early detection of emerging diseases (Khan *et al.*, 2012). They can increase the sensitivity of surveillance systems but, because the information is not verified, they can also increase the detection of false signals. The aggregation of several unofficial sources and the

verification of the signal by local health authorities can help avoid wasting resources to investigate and respond to false signals.

The 2005 IHR emphasize the importance of both event-based and indicator-based components of EI for the early detection of health threats (Figure 2) (Barboza *et al.*, 2013).

Figure 2. Indicator-based and event-based components of epidemic intelligence (Barboza, 2014)

2.2.3 The process of epidemic intelligence: from data collection to reporting

To detect health threats in a timely manner and monitor their evolution, EI activities are based on the systematic review of a variety of information sources, both official and unofficial.

The EI procedure is divided into several steps: data collection (including screening and filtering), verification, analysis and communication to health authorities and decision-makers (Figure 3). These steps are usually formalized through an SOP (standard operating procedure). Depending on

the situation, these steps can take time, particularly the validation and interpretation of the signal as they might involve several experts who might not be available to react instantly. Despite the number of steps in the EI procedure and the many people it might involve, the goal is to validate all the steps from data collection to reporting rapidly in order to ensure timely detection and communication of health threats to authorities and, in turn, timely action.
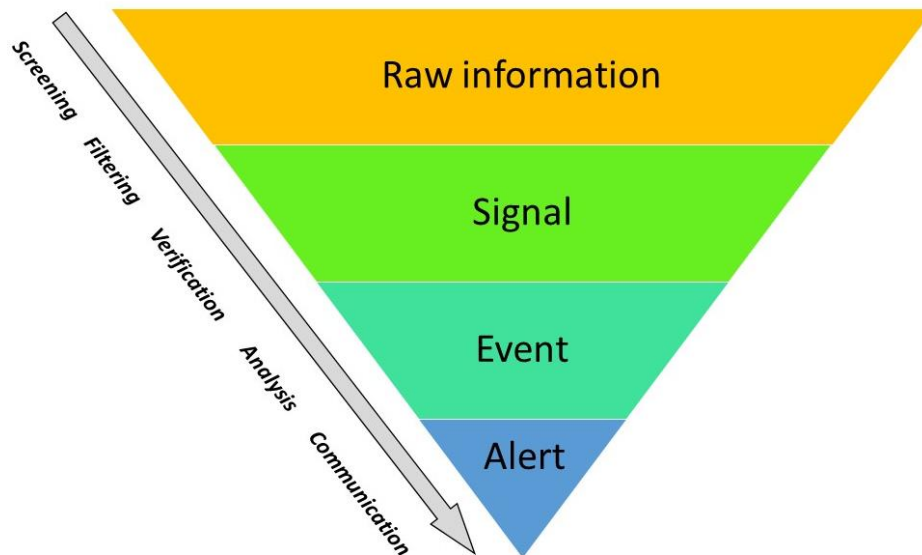
Figure 3. Epidemic intelligence framework

A signal is defined as any health-related information collected by the EI system, which could potentially impact human or animal populations (depending on the scope of the system).

An event is a signal that has been selected (i.e. represents a potential threat according to criteria defined by health authorities) and verified.

Different definitions exist for a signal and an event. I choose to use the terms as currently defined by ECDC and WHO, and not the definitions from Paquet *et al.* which are inversed, i.e. a signal corresponds to a verified event.

If the event is analyzed and judged to require the implementation of control or prevention measures by health authorities, it becomes an alert.

2.2.3.1   Data collection

When setting up EI activities, it is important to define the mandate and the scope of the system by determining the risk group. In the case of the French epidemic intelligence system (FEIS) which I led for four years, the EI team monitors any health-related event that could have a potential impact on the animal population in France, with a main focus on livestock (poultry, cattle) but also including wild animals, pets and other domestic animals.

Health-related information can be collected from many different information sources, both official and unofficial. Considering multiple sources of information, particularly combining unofficial and official sources, has been shown to improve the timeliness of the detection and the accuracy of the information collected (Yan *et al.*, 2017a). For animal health, the main official sources of

information for international EI activities are the Empres-I database from the Food and Agriculture Organization (FAO), the World Animal Health Information System (WAHIS) of the OIE and the Animal Disease Notification System (ADNS) of the European Commission. For human health, some examples of official information sources are the WHO, the ECDC and the Center for Disease Prevention and Control (CDC). Official information sources also include national or sub-national governmental health agencies, whether for veterinary or human health. Examples of unofficial sources for both veterinary and human health include media articles, rumors and unstructured personal communications from experts. The scope of sources monitored remains flexible and can rapidly and easily be adapted to the epidemiological context, for instance by strengthening EBS and monitoring local media outlets more closely for a country where a suspected outbreak has been detected.

Once the data has been screened, it is reviewed and filtered in order to detect new or updated information concerning potential health-related threats. Relevant information regarding health events are for example the occurrence of an outbreak of an EID, a significant increase in the endemic circulation of a known infectious disease, reports of high mortality or morbidity in animals with an unknown etiological cause, or epidemiological updates on ongoing EID outbreaks. Data filtering allows experts to discard information out of the surveillance scope (e.g. benign or non-infectious diseases), false rumors and duplicates in the collected data. This step is closely linked to the mandate of the institution and the scope of the EI system.

2.2.3.2   Data verification

The information collected is verified (or validated) in order to confirm its authenticity and veracity of its content.

Information gathered through IBS must be checked for possible surveillance biases and errors in reporting. For EBS, the verification of the information is particularly important when the information is collected from unofficial sources such as media articles or online blogs. Indeed, some information can generate false signals such as a false positive to a diagnostic test or a significant increase in reported cases with confirmation dates spanning over several months.

The information can be verified by corroborating the information with reliable sources of information such as health authorities (national or international), an expert (either a disease expert or a geographic expert in-country) or through networks of health professionals.

Signals are checked to verify the reliability of the information source, the veracity of the information, the clinical and epidemiological description of the event (e.g. clinical signs compatible with the suggested diagnosis) and elements of context such as control measures or biological confirmation (Bitar *et al.*, 2011). This can be done through a review of scientific literature or networking with disease experts and health professionals.

The step of data verification also presents an opportunity to gather complementary information to provide context, which is useful for verification, but also for analysis and interpretation.

2.2.3.3   Data analysis

For the FEIS, data analysis consists of gathering context information to provide useful information to stakeholders regarding the potential risk of the event (e.g. historical trends, date of last

outbreak in the region, neighboring countries affected, control measures implemented). For animal health, historical data can be gathered from official databases such as OIE's WAHIS, FAO's Empres-I or the European Commission's ADNS. If limited official information is available due to underreporting or endemic circulation, scientific literature can be consulted for information on past and current outbreaks.

Reference laboratories can be consulted to provide an interpretation of the event in its context.

Other types of information can be used to describe the context such as weather data, distribution data for insect vectors or mobility data relating to animal movements or human air travel.

Depending on the institution's mandate, the data can be further analyzed for risk assessment purposes. This includes gathering information relating to the pathogen, the host and the environment in order to better characterize the risk factors and the potential for evolution. This can be complemented by the use of epidemiological models to predict the importation of the pathogen, possible scenarios of spread, or to model the impact of different control and prevention measures (Bitar *et al.*, 2011).

2.2.3.4 Data reporting

Once the event is analyzed, the validated and interpreted information is communicated to health authorities and professionals. We can distinguish two levels of communication: internal communication (i.e. within an institution or national EI system) and external communication. External communication can target health professionals or, in a larger sense, the general population. The dissemination of information can be oriented towards the general public, in collaboration with or by health authorities. In any case, the content of the communication should be adapted to the targeted audience. When the communication targets the general public, technical vocabulary should be avoided and the message should be vulgarized in order to be understandable and clear to non-health professionals and civilians. This would apply to awareness campaigns, for example, to improve awareness and acceptability of prevention and control measures. It is important to inform without alarming, particularly during health crises such as the recent novel coronavirus pandemic.

2.2.4 Existing systems

Existing EI systems, whether at national or international level, rely on the different steps of the EI procedure (from data collection to reporting) to ensure timely detection and reporting of health threats to appropriate authorities in charge of risk management.

Some **international organizations** have set up EI systems, such as ECDC, WHO, OIE or the FAO. These international systems aim to timely detect and monitor disease outbreaks at the international level. The geographic scope of the diseases monitored varies depending on the mandate of each organization. ECDC monitors disease threats for European Member States while WHO, OIE and the FAO have a more global scope.

Some **countries** have set up an EI system at national-level through national health agencies. Some examples of these countries include France for human health (Rotureau *et al.*, 2007) and animal health (Mercier *et al.* 2020), England for human health (Wilburn *et al.*, 2019) and animal health (Animal and Plant Health Agency, 2017), or the Netherlands for human health (Bijkerk *et al.*, 2017).

These systems can be centralized through a specifically dedicated team (e.g. animal health in France) or dispatched among several disease-specific units (e.g. human health in France). The EI system in place for animal health surveillance in France will be detailed in the following section.

A comprehensive review of existing EI systems in Europe, for both animal and human health, is currently being conducted in the framework of the Horizon 2020 (H2020) research project funded by the European Commission, entitled "Monitoring outbreak events for disease surveillance in a data science context" (MOOD). This detailed review will focus on both national level (five case study countries: France, Italy, Spain, Serbia and Finland) and international level (WHO, OIE, ECDC, FAO) EI systems. It will cover dataflow and workflow, organizational structure, SOPs, dedicated resources, tools and databases used. I am co-leading this activity with colleagues from the public health agency in Finland. Results should be available by early 2021.

2.2.5 Presentation of the French epidemic intelligence system for animal health

2.2.5.1 The French animal health epidemiological surveillance platform

In France, the main challenges in animal health have evolved in the past decades with recent emergences leading to significant economic losses. Examples include bluetongue serotype 8 in 2006 (Sailleau *et al.*, 2017), Schmallenberg virus in 2011 (Dominguez *et al.*, 2014), and highly pathogenic avian influenza H5N8 in 2016 (Guinat *et al.*, 2018). Thankfully, surveillance, prevention and control efforts have improved in the past years. Following the acquisition of a disease-free status for multiple contagious diseases (e.g. FMD or rabies), the focus of disease surveillance in France switched to vigilance. Instead of monitoring the evolution of diseases already present in the country, health authorities had to focus on the early detection of new and emerging diseases at the international level to anticipate new introductions of emerging health threats.

Existing surveillance systems needed to be adapted in order to face the new challenges of disease emergence. For example, setting up a non-disease-specific surveillance through the implementation of syndromic surveillance would cover a broader scope of diseases with similar clinical manifestations. Partly due to these considerations, the French Ministry of Agriculture suggested the creation of a national platform for epidemiological surveillance in animal health.

The French animal health epidemiological surveillance (ESA) platform[1] was set up in 2011 to improve the efficiency of epidemiological surveillance at national level (Figure 4).

The ESA Platform counts six founding members, with four additional members added by 2018. These members represent different sectors of animal health: the General Directorate for Food (DGAL, part of the Ministry of Agriculture), farmers (La Coopération agricole, GDS France), veterinarians (French society for veterinarian technical groups – SNGTV),

Figure 4. ESA Platform logo

scientific support organizations (the Agency for Food, Environmental and Occupational Health & Safety – ANSES, CIRAD and the National Research Institute for Agriculture, Food and Environment – INRAe), laboratories (French association of public veterinary laboratories

---

[1] https://www.plateforme-esa.fr/

– Adilva), hunters (National Hunters' Federation – FNC), and wildlife and biodiversity services (French Office for Biodiversity – OFB) (Figure 5).

Through its members, the ESA Platform provides scientific support to improve animal health surveillance efficiency through a public/private partnership.

Figure 5. Members of the French animal health epidemiological surveillance platform (ESA Platform)

The main objective of the ESA Platform is to ensure that animal health surveillance systems are efficient and are developed according to methodological standards for surveillance. It aims to develop, adapt and promote surveillance systems, conduct EI activities, provide reports on the current epidemiological situation of health hazards, participate in the development of synergies between surveillance and research, ensure a co-construction of surveillance modalities between animal health professionals, and understand the determinants of health events to elaborate adapted surveillance measures. More generally, the activities of the ESA Platform focus on:

- supporting the implementation and improving epidemiological surveillance systems,
- centralizing, analyzing and sharing health data, and
- contributing to the analysis and dissemination of health information.

The scope of the platform covers all health threats that have or could have an impact on animal health and/or human health (zoonoses) in France, and for which surveillance is required for animals.

The ESA Platform provides a common structure to bring animal health stakeholders together, around common strategies, methods and tools. It is organized in 20 working groups, most of which focus on a specific disease or animal group. These working groups are presented in relation to the main disease group and animal type they focus on (Figure 6).

Figure 6. Working groups of the ESA Platform

Since its implementation in 2011, the ESA Platform has demonstrated its utility and efficiency, particularly during animal health outbreaks such as highly pathogenic avian influenza, Schmallenberg virus or bluetongue. On 20th June 2018, a new national framework convention was signed, ensuring the continuation of the platform's activities for another ten years. In addition, two sister platforms were created in 2018, following the model of the ESA Platform, for plant epidemiological surveillance ("*plateforme d'épidemiosurveillance en santé végétale*", ESV) and food safety ("*plateforme d'épidémiosurveillance de la chaîne alimentaire*", SCA).

2.2.5.2   Scope and members

Figure 7. Logo of the French epidemic intelligence system

In 2013, to better anticipate the threat of EIDs, international animal health monitoring was integrated into the ESA Platform's activities with the creation of the French Epidemic Intelligence System (FEIS), or "*Veille sanitaire internationale*" in French (Figure 7). The FEIS is in charge of animal health EI for the French Ministry of Agriculture. Its main activity is to detect, monitor and report health events, at national and international level, that could potentially threaten animal populations in France, in order to inform French authorities. Some coordination and administrative work are necessary to ensure the system's optimal functioning, e.g. keeping the network active and updated on current activities by organizing regular feedback meetings with the different stakeholders.

Members of the FEIS include all members of the ESA Platform so that the FEIS can meet the needs of all relevant stakeholders involved in surveillance activities (from farmers to veterinarians, policy makers, scientists, risk assessment experts or experts in EI methodology) in terms of access to

updated, validated and interpreted information on animal health events. The FEIS team is led by CIRAD and ANSES.

Regarding surveillance for French overseas territories, the FEIS relies on regional surveillance networks such as the Caribbean animal health network (CaribVet) and the Public Health Surveillance, Alert and Response network SEGA ("*Surveillance Epidémiologique et Gestion d'Alertes*") in the Indian Ocean (Gongora *et al.*, 2008; Halm *et al.*, 2017).

International agencies have set up EI systems to monitor health risks worldwide (e.g. ECDC or the International Society for Infectious Diseases – ISID – with its Program for Monitoring Emerging Diseases – ProMED). Because the FEIS monitors animal health risks for France at the international level, it monitors the same signals as supra-national systems. However, the FEIS stands out by also monitoring other sources of information to include in its reports, in addition to country notifications, in order to provide detailed reports with interpreted and contextual information to decision-makers. The existence of the FEIS is also justified by the extra layer of filter, which allows tailoring animal health surveillance according to the national context. Indeed, needs in terms of animal health surveillance may vary from one country to another depending on strategies and priorities (e.g. priority given to caterogy-1 health hazards as defined by French animal health authorities) (Le Ministère de l'Agriculture, de l'Agroalimentaire et de la Forêt, 2013).

2.2.5.3   Epidemic intelligence activities

The FEIS combines IBS and EBS by monitoring both official (e.g. French animal health authorities, OIE, FAO, the European Commission) and unofficial (e.g. media, ProMED-mail, personal communication) sources of information relating to animal health. Once collected, the information is verified and analyzed with the FEIS' network of national and international experts (Figure 8). This allows the FEIS to analyze and interpret the event according to the context when writing a report, and include information relating to the viral strain, seasonality patterns, the previous occurrence or the historical circulation of the virus in the country. Information relating to different disciplines, such as epidemiology, virology or entomology, is also useful to provide context and a holistic view taking into account complementary perspectives. This reinforces the need for a pluridisciplinary approach to EI, which is why the FEIS team and expert network include experts from a wide range of disciplines such as epidemiology, informatics, entomology, virology, and many other specialties.
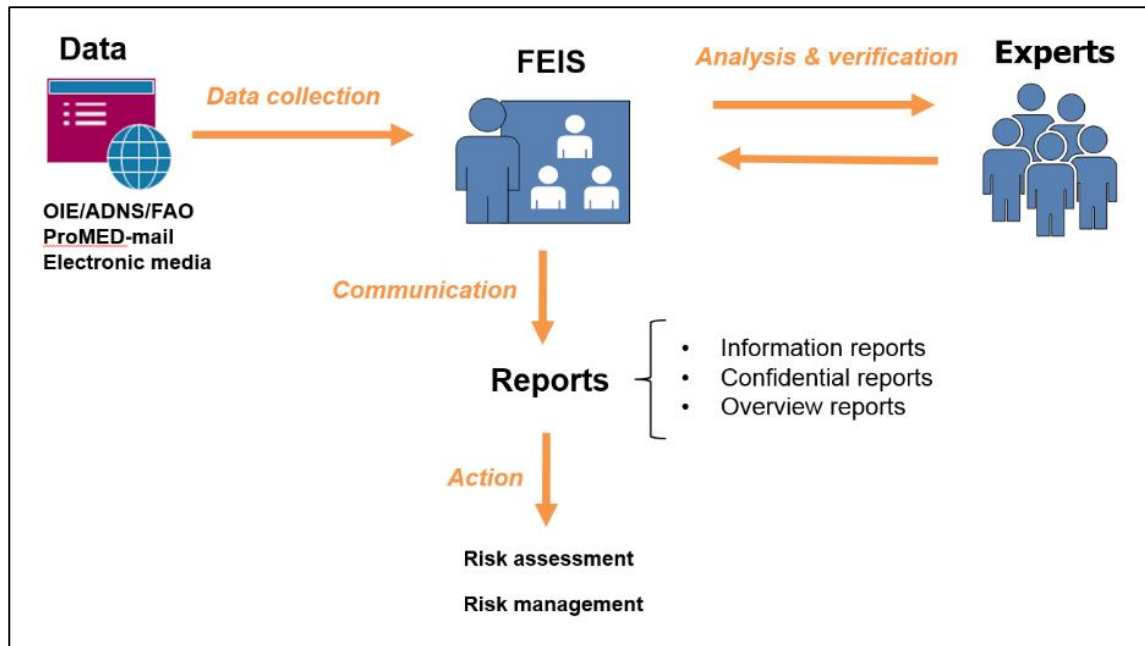
Figure 8. Process of the French epidemic intelligence system (Mercier *et al.*, 2020)

2.2.5.4   Reporting and publications

The FEIS publishes reports to inform animal health authorities and professionals of potential animal health risks. A report is published on a specific event when there is a quantitative or qualitative change in the epidemiological situation of the disease, i.e. re-emergence, geographic spread or increase in number of outbreaks. The dissemination of FEIS reports can be either public on the ESA Platform website or confidential (sent to the ESA Platform steering committee) depending on the source of the information it contains.

In addition to these reports, the FEIS produces a weekly EI bulletin named "*Bulletin hebdomadaire de veille sanitaire internationale en santé animale*", or BHVSI-SA. This bulletin includes various sections corresponding to specific diseases with, for example, sections for highly pathogenic avian influenza, ASF, West Nile or FMD. The bulletin is generally 5 to 15 pages long, depending on the global epidemiological situation. It is published online on the ESA Platform's website since October 2018.

2.2.5.5   Research activities

To further strengthen its EI activities, the FEIS is also involved in research projects. The FEIS plays a role in nurturing useful research questions which it then contributes to in order to find methodological solutions in line with its needs. These research projects aim to develop innovative tools and methods to improve the early detection and analysis of health threats. Data collection and analysis tools developed in the framework of the FEIS' participation in research collaborations include PADI-web, an online media monitoring tool, or a disease spread rate model that estimates the speed of spread of diseases. These two examples of tool will be described further in the manuscript (Sections 3.2 and 4.3). The FEIS is also actively involved in the H2020 MOOD project. The FEIS participated in the project proposal, and will be among the end-users consulted and interviewed as part of the comprehensive review of EI activities in Europe. The four-year project (2020-2024) operates on a budget of 15 million euros. The FEIS' involvement in this project will

set the stage for new research questions and future projects, aiming at further improving EI activities through the integration of different sources and types of information (e.g. environmental or molecular data), as well as new technologies.

2.3. Preliminary evaluation of the FEIS

The contribution of the FEIS to the EI process (data collection, verification, analysis and reporting) have been presented in a scientific article. After three years of leading and improving the FEIS, I decided to conduct a short study to evaluate if the FEIS detected and reported on all important events relating to animal health according to its scope, as a way to test its efficiency. To do so, I compared the reports produced by the FEIS to posts published by ProMED from 1st January 2016 to 31st December 2017, to identify if the system had missed any information. I set up a partnership with ProMED directors (based in the United States of America) and moderators in order to promote international collaborations through the bilateral exchange of information and discussions relating to methodology. The results of the analysis of the reports published by the FEIS from 2016 to 2017, and the comparison of these reports to ProMED alerts are presented in Mercier *et al.*, 2020.

2.4. Limitations and challenges

EI systems face several technical and organizational challenges that can hamper the exhaustiveness, timeliness and efficiency of these systems:

- Completeness of the collected information and its ability to reflect the current epidemiological situation is a main challenge. As mentioned, traditional surveillance systems relying on IBS to gather validated and official information in the form of indicators. However, this method may miss information in the early stages of disease emergence, and lacks timeliness and sensitivity in the detection of unusual events relating to emerging diseases. To overcome this challenge, some EI systems have set up an EBS component and use automated biosurveillance tools to monitor unofficial information sources such as online media reports or scientific publications.
- Timely verification of the information collected, particularly if the information originates from an unofficial source like the media or rumors, is another challenge. As previously stated, unofficial information can be validated using official sources or a network of experts. In the framework of the FEIS, this challenge was addressed by setting up an extensive network of national and international experts with different fields of expertise (e.g. epidemiology relating to both human and animal health, virology, entomology, farming systems). This network includes all of the French national reference laboratories for animal diseases as well as several European and OIE reference laboratories, which can be a very useful source of validation of information regarding the occurrence of an emerging disease.
- Timely reporting of health threats to authorities in charge of response can also be challenging. The internal hierarchical chain of validation of reports can delay the dissemination of information, particularly in the case of large institutions or agencies. To

address this issue, French animal health authorities have set up the ESA Platform to gather animal health professionals and stakeholders from different sectors (veterinary agencies, farmers, veterinarians, wildlife services, hunters, laboratories and research centers) and facilitate the exchange of information, methods and expertise.

International EI activities conducted by international organizations such as WHO, OIE or ECDC have their limits, but can be complemented by national-level EI systems. International systems provide a global coverage and monitor a large variety of information sources, which makes them very efficient at timely detection of health risks. The analysis of the threat, however, is very country-dependent. This is why some countries have set up an international EI system that uses international systems as information sources, but also provide an interpretation and analysis tailored to the country's needs. This means that health threats are filtered depending on the level of risk they represent for the specific country. This risk depends on several factors such as historical disease circulation, economic ties (e.g. trade, governance), travel access or geographical proximity. This challenge was addressed in France with the creation of a French international EI system as part of the French animal health epidemiological surveillance platform.

The integration of new methods, data sources or tools can be complicated by several factors. First, we should aim to improve and complement the existing systems already in place instead of creating new and independent tools, which can duplicate and complicate the work. Also, the developed methods or tools should fit the needs of end-users in order to ensure appropriation and sustained use of the tool. We are addressing these challenges in the framework of the H2020 MOOD project proposal by integrating a thorough review of existing activities, systems and tools, and adding a social science component in one of the work packages. This component aims to identify the main gaps and challenges relating to EI data and work flows within institutions of EI activities, and identify end users' needs in terms of data, tools and methods for the co-conception of solutions. The integration of social science processes such as participatory methods can facilitate interactions and communication in research projects involving many different stakeholders, disciplines and geographical scales.

Chapter 3

A pluridisciplinary approach to data collection in the context of tool development

3.1. Introduction

"Disciplines are the result of the artificial fragmentation of knowledge" (Choi *et al.*, 2006).

Some researchers, health professionals and policy-makers have a tendency to work individually, in silos, with limited interactions and collaborations. Information and tools often cross from one silo to another, but with limited sharing of knowledge and resources with a common goal. The development and implementation of tools to improve disease surveillance, for example, tend to be conducted unilaterally. This means tools are developed by researchers in informatics and computer sciences with limited consultation of end-users who might later have to implement and use a tool unfit for their needs or not practical to use. This can result in limited appropriation of the tool by end-users and limited sustainability of solutions for stakeholders.

Collaboration between experts from different disciplines is increasingly promoted in health research and services, particularly given the complex and interdisciplinary nature of current health issues (D'Amour *et al.*, 2005; Choi *et al.*, 2006). The term collaboration implies the notions of sharing and collective action towards a common goal. Teamwork involving several disciplines in the framework of tool development can be implemented at different levels. Several terms can describe such collaborations including multidisciplinary, transdisciplinary, interdisciplinary or pluridisciplinary. These terms are not always clearly defined and are sometimes used interchangeably. Here are a few definitions of pluridisciplinary approaches (involving more than one discipline) adapted from Schelling, 2016 and Darbellay, 2008 that I have chosen for this manuscript:

- A <u>multidisciplinary</u> approach involves several disciplines working individually, in parallel, to contribute to the topic, with no collaboration between disciplines.
- An <u>interdisciplinary</u> approach aims to build common strategies through collaborative conception and implementation of research questions, methods, tools and results.

- A <u>transdisciplinary</u> approach focuses on a research topic that is co-constructed through collaborative and participatory methods, and includes strong involvement of social science stakeholders.

Multidisciplinary (additive), interdisciplinary (integrative) and transdisciplinary (holistic) approaches reflect different degrees of collaborations along a continuum of pluridisciplinary work (Choi *et al.*, 2006).

In this section, I present two case studies based on my experience conducting EI activities in animal health in France (CIRAD, 2016-2020) and in human health in the Pacific (SPC, 2014-2016). These case studies describe examples of pluridisciplinary collaborations between researchers and end-users (in this context health professionals) in the framework of tool development to improve health surveillance activities.

In both of these studies, I actively contributed on two levels. The first is a meta-level to promote a global and generic approach based on a pluridisciplinary process and to identify the role of each stakeholder involved in the process, to ensure operationality. The second is a specific and technical level to suggest innovative methods and ensure the sustainable use of the tools by end-users. Both levels aim to place each type of stakeholder at the center of discussions to improve pluridisciplinarity. I acted as an intermediate link between end-users and tool developers, between research and surveillance, to allow the pluridisciplinary co-construction of tools.

3.2. Development of an automated media monitoring tool for animal health (PADI-web)

The first case study presents a pluridisciplinary collaboration to design an electronic media monitoring tool and use it to retrospectively detect the emergence of the novel coronavirus in China in December 2019 (Valentin *et al.*, 2020a).

3.2.1 Internet event-based surveillance

Internet biosurveillance, or digital disease detection, relies on unstructured information collected from a variety of online sources, and focuses on the early detection and alerting of health risks (Brownstein *et al.*, 2009; Hartley *et al.*, 2013). With increasing volumes of information and media outlets available online, internet biosurveillance has become a useful tool to monitor unofficial sources on the internet and complement traditional surveillance systems mainly relying on official sources.

Unofficial sources of information are important to consider and monitor in addition to official sources because their integration can improve the timeliness and sensitivity of disease surveillance systems (Yan *et al.*, 2017a). WHO has reported that more than 60% of initial disease outbreak reports originated from unofficial information sources (World Health Organization, 2016). In combination with the significant increase in internet use and accessibility worldwide, internet-based EBS has become an increasingly pertinent and useful tool for EI activities (Yan *et al.*, 2017a).

Several EBS systems exist to monitor unofficial sources from the web and detect occurrences of a wide range of health threats (Barboza *et al.*, 2013). Some examples include ProMED developed in 1994 by ISID in the United States of America (Carrion *et al.*, 2017), the Global Public Health Intelligence Network (GPHIN) developed in 1997 by the Public Health Agency of Canada (Dion *et al.*, 2015), and the MedISys tool developed in 2004 by the European Commission's Joint Research Center (Rortais *et al.*, 2010). These biosurveillance tools are developed independently and their functionalities may vary (e.g. number of languages, type of health threats monitored and scope). ProMED is based on a fully human-moderated process, while other systems are fully automated (MedISys, PADI-web) or include both automatic and manual processes (HealthMap, GPHIN). Figure 9 presents the main existing biosurveillance tools which include animal health threats in their scope, and compares their features and data processing techniques.

System name	ProMED	GPHIN	MedISys	HealthMap	IBIS	PADI-web
Owner	International Society of Infectious Diseases (USA)	Public Health Agency (Canada)	Joint research centre (European Union)	Boston Children's Hospital (USA)	University of Melbourne (Australia)	ESA Platform (France)
Year launched	1994	1997	2004	2006	2013	2016
Access policy	Public	Restricted	Public	Public	Public	Public
Threats covered[a]	A, H, P	A, H, P, E	A, H, P, E	A, H, P, E	A, P	A
Sources[b]	O, U	O, U	O, U	O, U	U	U
No. of languages	7	9	50	7	1	6
Translation	No	A, H	No	A	/	A
Data classification[c]	H	A (keyword-based)/ H	A (supervised classifier)	A (supervised classifier)/H	Not available	A (supervised classifier)
Interface						
Available data source[d]	Full text (NL)	Full text (EN)	Headlines (NL)	Headlines (EN/NL)	Full text (NL)	Full text (EN/NL)
Information retrieval[e]	No	TB, FB	TB, FB	FB	TB, FB	TB, FB
Spatiotemporal outputs	No	No	Temporal series, map	Temporal series, map	Map	Temporal series, map
References	(Carrion and Madoff, 2017; Velasco et al., 2014)	(Blench, 2008; Keller et al., 2009; Mykhalovskiy and Weir, 2006)	(Grishman et al., 2002; Yangarber et al., 2007)	(Brownstein et al., 2008; Freifeld et al., 2008)	(Lyon et al., 2013a, 2013b)	(Arsevska et al., 2018)

[a] A: animal, H: human, P: plant, E: environment.
[b] Source types, O: official sources, U: unofficial sources.
[c] H: human, A: automatic.
[d] Data source language, NL: native language, EN: English-translated.
[e] Retrieval from database, TB: text-based (free-text queries), FB: feature-based (epidemiological attributes).

Figure 9. Comparative table of existing biosurveillance tools including animal health threats, according to their scope and data processing approaches (Valentin et al., 2020b).

These systems are not domain-specific and focus mainly on human health. Although some include animal-related news, none of them focuses specifically on animal health threats.

3.2.2 Platform for automated extraction of animal disease information from the web (PADI-web)

Although many biosurveillance tools exist and have proven their efficiency in detecting outbreak news on the web, they provide limited coverage of animal diseases (Valentin *et al.*, 2020b).

The Platform for Automated extraction of animal Disease Information from the web (PADI-web) is an automated text mining platform that detects, categorizes and extracts disease outbreak information from news articles published on the Internet (Figure 10) (Arsevska *et al.*, 2018). PADI-web was designed for the FEIS to facilitate the monitoring of animal disease outbreaks from unofficial sources of information such as online news articles. It incorporates intelligent systems based on text

Figure 10. The logo of PADI-web

mining which include natural language processing, machine learning and data mining techniques (Arsevska *et al.*, 2018).

A first module of the platform aims to identify and collect online news articles using a series of customized Really Simple Syndication (RSS) feeds on Google News. Google News was chosen as the main data source because it is freely accessible and allows users to tailor search parameters. The RSS feeds use a list of predefined keywords relating to hosts, symptoms and disease names (Arsevska *et al.*, 2016). They can be disease-specific (using disease names) or non-specific (using a combination of symptoms and hosts). This allows the tool to monitor nine specific diseases of interest (ASF, classical swine fever, avian influenza, FMD, bluetongue, Schmallenberg virus, lumpy skin disease, peste des petits ruminants and West Nile), as well as information on other diseases or syndromes (e.g. early stages of emergence, before official confirmation of etiology).

The tool identifies and collects news articles containing a predefined combination of keywords.

The majority of RSS feeds use English keywords, but we have also implemented feeds in other languages to increase local media coverage. These languages were selected to target areas with enzootic circulation of specific diseases or at high risk of disease emergence (e.g. adding Arabic to monitor FMD in endemic Arabic countries, or Chinese to monitor ASF). The integration of multilingual RSS feeds has significantly increased the number of relevant news articles detected (Valentin *et al.*, 2020b).

Once collected, news articles are processed to remove duplicates from the database. News articles that were retrieved using non-English RSS feeds are translated into English. News items are then classified to determine if they are pertinent, i.e. relating to an animal disease event (e.g. describing a current outbreak, prevention and control measures, or socioeconomic impact of a disease). This classification step is run by a supervised machine learning process. In this process, experts define two classification categories (pertinent/non pertinent) and manually annotate a small dataset in order to build a model (supervised classification). Based on labeled data, the machine-learning approach takes into account textual content of both classes in order to construct the classification model. This model is then able to establish definitions for the two classes based on the expert-annotated dataset, and annotate new data (machine learning). The model is continuously enriched as new data is added to the database and classified (daily update of the model). This underlines the importance of expert annotation and input at the beginning of the process to set the foundation for the model classification, and to continuously update the tool's keywords if new disease threats emerge. A more specific type of classification has been recently implemented, and consists of five topic categories to go beyond binary relevance classification (Valentin *et al.*, 2020c):

- confirmed outbreak: information about a new or ongoing confirmed outbreak,
- suspected outbreak: information about new or ongoing cases which have not yet been diagnosed but are associated with a suspected disease,
- unknown outbreak: information about new or current cases not yet diagnosed and not associated with a suspected disease,
- preparedness: information about prevention measures in a country not yet affected by the diseases but on alert to prevent the introduction of the disease, and

- impact: information on economic, societal or political impact of disease outbreaks in an affected country or region.

The last module relates to information extraction, which aims to extract from the content of the news article epidemiological information describing the event, such as disease, dates, geographic location, affected host, clinical signs and number of cases. The information extraction process is based on a combination of data mining techniques, expert validation and ruled-based systems using a series of dictionaries (Arsevska *et al.*, 2018). The experts first annotate epidemiological identities in news articles from a specific dataset, from which the model learns rules to identify these epidemiological features (rule-based). Then, the model applies these rules to identify pertinent entities in other news articles (machine learning).

Figure 11 illustrates the PADI-web process, from data collection to information extraction.
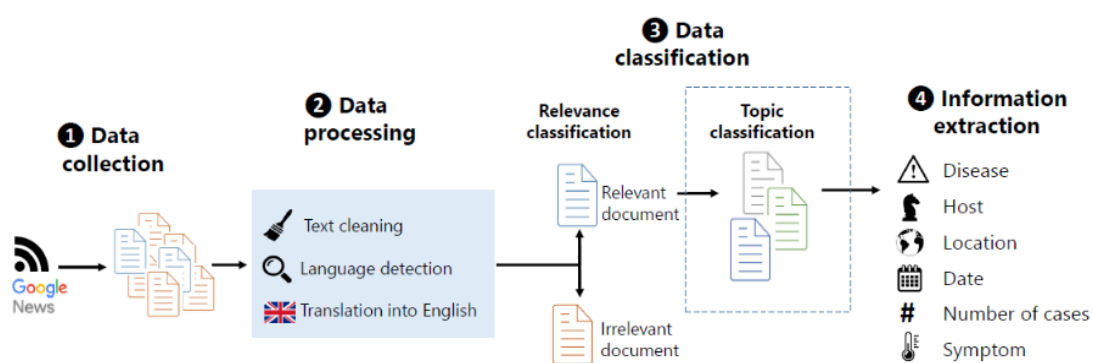
Figure 11. PADI-web process (Valentin et al., 2020c)

The PADI-web interface allows users to view the content of each news article and visually identify the key epidemiological information extracted (Figure 12). It also allows the user to view trends (e.g. monthly number of relevant articles for a specific disease), filter the view of selected news articles according to several parameters (e.g. disease, dates), and download the extracted epidemiological information for a selection of news articles. The query can also be exported through an RSS feed, allowing users to save its parameters and results.
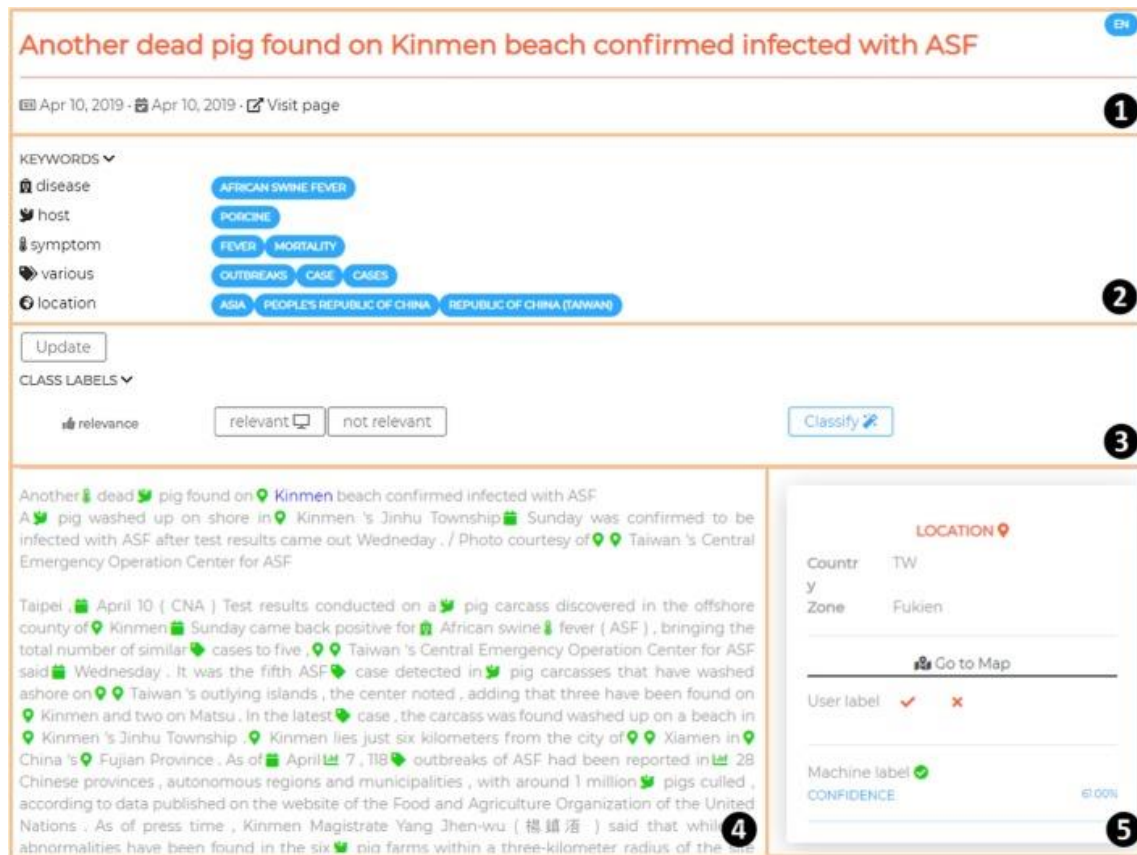
Figure 12. PADI-web interface viewing the news article content with identified extraction information and keywords; 1) basic information of the news article (title, publication date, link to the original content), 2) list of epidemiological entities, 3) class label predicted by the classifier, 4) tagged epidemiological entities and 5) details on the selected location (Valentin et al., 2020b)

PADI-web was developed to improve the EI activities of the FEIS. As team leader of the FEIS and member of the PADI-web team from 2016 to 2020, I contributed on two levels. The first level is a meta-level and includes the integration of expert knowledge to ensure the co-design of the tool. The second level focuses on the participation to technical developments. I actively contributed to finding solutions in terms of methodological developments to fit the needs of the FEIS in terms of disease and geographic scopes, languages, extracted information, visualization and user interface for the tool's development and testing. I contributed to the improvement of the classification process (selection of classes, defining pertinence), identifying pertinent epidemiological entities to better define information extraction, and providing feedback on the tool's use for EI activities.

I also contributed to the development and evaluation of additional modules of PADI-web which aimed to improve online diseases surveillance through the use of novel methods for data collection such as visual analytics and visualization of extracted information. My contributions focused on integrating expert knowledge to 1) implement innovative visualization methods and 2) collect and integrate annotated data in automated processes. One of these modules is EpidVis, a tool that uses visualization techniques to identify the most pertinent keyword associations and provide suggestions to improve data queries in PADI-web (Fadloun *et al.*, 2020). I contributed to the discussions on the design of the interface (Annex 1) and the link with PADI-web, and led a case study on the use of EpidVis for EI. Another example is EpidNews, a visual module that creates figures presenting the percentage of articles for each keyword and maps of the epidemiological

entities to facilitate the visual detection of anomalies (e.g. identifying a disease in a region where this disease is absent according to official sources) (Annex 2) (Goel *et al.*, 2020). I contributed throughout the development process by: 1) leading the identification of user needs, 2) co-constructing the method and 3) analyzing and interpreting results through different case studies.

A first version of PADI-web was developed in 2013 in collaboration with researchers from CIRAD (TETIS unit), INRAE, the Informatics, Robotics and Microelectronics Laboratory in Montpellier (LIRMM), and epidemiologists from CIRAD (ASTRE unit) involved in the FEIS. Developmental work was carried out since 2013 to continuously improve the tool, particularly the classification module in order to reduce the number of non-relevant articles collected (Valentin *et al.*, 2020b). A second version of PADI-web is available since January 2019, and continuous developments implemented in 2020 will provide an updated version at the end of the year. Further methodological developments will focus on improving the classification module by setting up more detailed classes to go beyond pertinence (e.g. first occurrence of a disease, control measures or economic and social impact) (Valentin *et al.*, 2020c). It will also build on a machine-learning process to construct a classification module. The tool has been integrated in the FEIS' activities on an *ad hoc* use depending on epidemiological news, for example to alert on circulation of avian influenza viruses in Southeast Asia or outbreaks of FMD in Africa several days before official OIE notification (Arsevska *et al.*, 2018; Valentin *et al.*, 2018).

3.2.3 Retrospective study of the novel coronavirus disease (COVID-19) in China using PADI-web

3.2.3.1 Context of the study

On 31st December 2019, the Municipal Health Commission in Wuhan, China (Hubei province) reported a cluster of pneumonia cases with an unknown etiology. A common link to Wuhan's Huanan Seafood Wholesale Market (a fish and live animal market selling different animal species) was reported by authorities. The market was closed to the public on 1st January 2020. Cases showed symptoms of influenza-like illness such as fever, dry cough and radiological findings of bilateral lung infiltrates. On 9th January 2020, a novel coronavirus was identified as the cause of the outbreak of respiratory illness (World Health Organization, 2020b). The virus was identified as SARS-CoV-2 (previously referred to as 2019-nCoV) and the disease it causes was named COVID-2019 (coronavirus disease 2019). As of 21st September 2020, the outbreak has resulted in a global pandemic with over 31 091 469 cases and 961 352 deaths reported worldwide (European Centre for Disease Prevention and Control, 2020).

CIRAD coordinates the H2020 MOOD project. The project started in January 2020 for a duration of four years, and I actively contributed to the design of the project proposal. In January 2020, following the rapid spread of COVID-19 to other countries, the European Commission asked the coordination team of the MOOD project to adapt the project's activities to support European national public health agencies in the response to the COVID-19 pandemic. Even though the MOOD project had just started, several tools were already made available by its members, including PADI-web. PADI-web was designed to be generic and applicable to other domains such as human health through its customizable keywords defined by users.

The objective of the study was to test the genericity of the tool in a One Health context, i.e. its ability to detect the emergence of a new virus in humans with lists of keywords designed for animal health surveillance. We designed a retrospective study to analyze PADI-web's capacity to identify online news articles relating to the COVID-19 emergence in China, in comparison with two other biosurveillance tools, ProMED and HealthMap. ProMED is a human-moderated system that relies on a large network of experts worldwide who produce and share verified reports on disease outbreaks through a common platform (Carrion *et al.*, 2017). HealthMap is a semi-automated system founded by the Boston Children's Hospital in 2006 to monitor both official and unofficial news sources on the web (Freifeld *et al.*, 2008). HealthMap and ProMED both monitor a broad range of human, animal and environmental known and unknown threats. They were selected because they are two main sources of unofficial information freely accessible online.

This retrospective study focused on three specific objectives. First, we aimed to evaluate the three EBS systems on their capacity to timely detect the COVID-19 emergence in China. Second, we focused on PADI-web to understand how an animal health EBS tool contributed to the detection of a human EID. We analyzed the RSS feeds from PADI-web that detected the COVID-19-related news articles. Third, we assessed the vocabulary in the news articles detected by PADI-web and its evolution in relation to the identification of the pathogen and the spread of the disease.

As part of the MOOD team and as second author of the paper, I actively contributed to the study design particularly in terms of integrating expert knowledge on EI for human health and early detection of unknown threats. I also contributed to the manual tagging of news articles, data analysis and interpretation of results to provide solutions to improve EI activities.

3.2.3.2   Material and methods

In this study, we defined "news articles" as online media reports, whereas scientific publications are referred to as "papers".

To assess the timeliness of the three EBS systems (PADI-web, ProMED and HealthMap), we searched for COVID-19-related news articles from 1st to 31st December 2019. We compared the first news article detected by each EBS system in terms of publication date, language and source.

To understand how PADI-web detected news articles relating to the COVID-19 emergence, we filtered a second corpus of news articles from 31st December 2019 to 6th January 2020, containing at least one of the following keywords: "pneumonia", "respiratory illness", "coronavirus", "nCoV" (the first temporary name of COVID-19) and "Wuhan" in the body or the title of the news article. Following manual verification, 58 news articles were excluded from the initial set of 333 news articles because they were either duplicates or unrelated to the novel coronavirus outbreak. The final dataset contained 275 news articles.

To analyze the link between PADI-web's animal health RSS feeds and the detected news articles, we screened each news article and assigned it to one of the following two categories depending on the type of RSS feed that detected the news article: 1) disease-specific RSS feeds (containing specific disease names) and 2) syndromic RSS feeds (containing combinations of symptoms and animal hosts).

We analyzed the evolution of the vocabulary from the initial discovery of the COVID-19 emergence to its spread outside China by extracting terms from the whole corpus referring either to the virus or the disease in the news content. We manually categorized the terms into the following categories: "mystery" (terms referring to an unknown threat), "pneumonia" (terms referring to the clinical signs), "coronavirus" (terms referring to the virus taxonomy) and "technical" (technical terms and acronyms referring to the virus) (Table 1). One news article can contain terms from several categories. We calculated the daily proportion of each category, expressed as the sum of the occurrences of the category divided by the total number of occurrences for that specific day. We merged daily counts for Saturday and Sunday to account for weekdays/week-end trends.

Table 1. Terms used to describe SARS-CoV-2 and COVID-19 in the corpus and their corresponding category after manual classification.

Category	Terms
coronavirus	coronavirus, betacoronavirus, "coronovirus"
mystery	mystery, mysterious, unidentified, undocumented, disease x, unknown, abnormal, unexplained
pneumonia	pneumonia, respiratory outbreak, lung disease, respiratory tract illness, respiratory illness, respiratory infection, pneumonia-like disease, upper-respiratory illness, respiratory condition, lung infection, pneumonia-like cases, pneumonia-like illness, respiratory virus, lung virus, pneumonia-like virus, pneumonia-causing virus, pneumonia-like virus
technical	2019-ncov, 2019 novel coronavirus, cov2019, cov19, covid-19, n-cov2019, ncov, ncov2019, novel coronavirus 2019

3.2.3.3   Main results

PADI-web detected COVID-2019-related information in Chinese and English news articles on 31st December 2019, the same day as the first official notification by Chinese health authorities of pneumonia-like cases. HealthMap also detected the first COVID-19-related news article on the 31st December 2019. However, ProMED detected news relating to the emergence on 30th December 2019, one day before official notification.

Out of 275 news articles relating to COVID-19 identified by PADI-web, 54.5% (n=150) were detected by syndromic RSS feeds and 45.5% (n=125) were detected by disease-specific RSS feeds.

When relating to a disease, news articles were detected because they compared COVID-19 to another disease (31.7%), because a disease was ruled out from the diagnosis (18.2%) or because they described ongoing disease outbreaks, including COVID-19 (7.7%). When relating to an animal, news articles were detected because they described animal species susceptible to coronaviruses (24.4%), because they referred to animal species present in the Chinese market, thus as a potential COVID-19 virus source (2.5%), or because they advised to avoid contact with animals (0.7%).

Before the official identification of the virus, keywords referring to clinical signs ("pneumonia") and the unknown cause of the outbreak ("mystery") were most often used to describe the emergence (Figure 13). Once the causative agent was identified, the category "coronavirus"

became most used, along with the appearance of technical terms and acronyms such as "2019-nCoV".
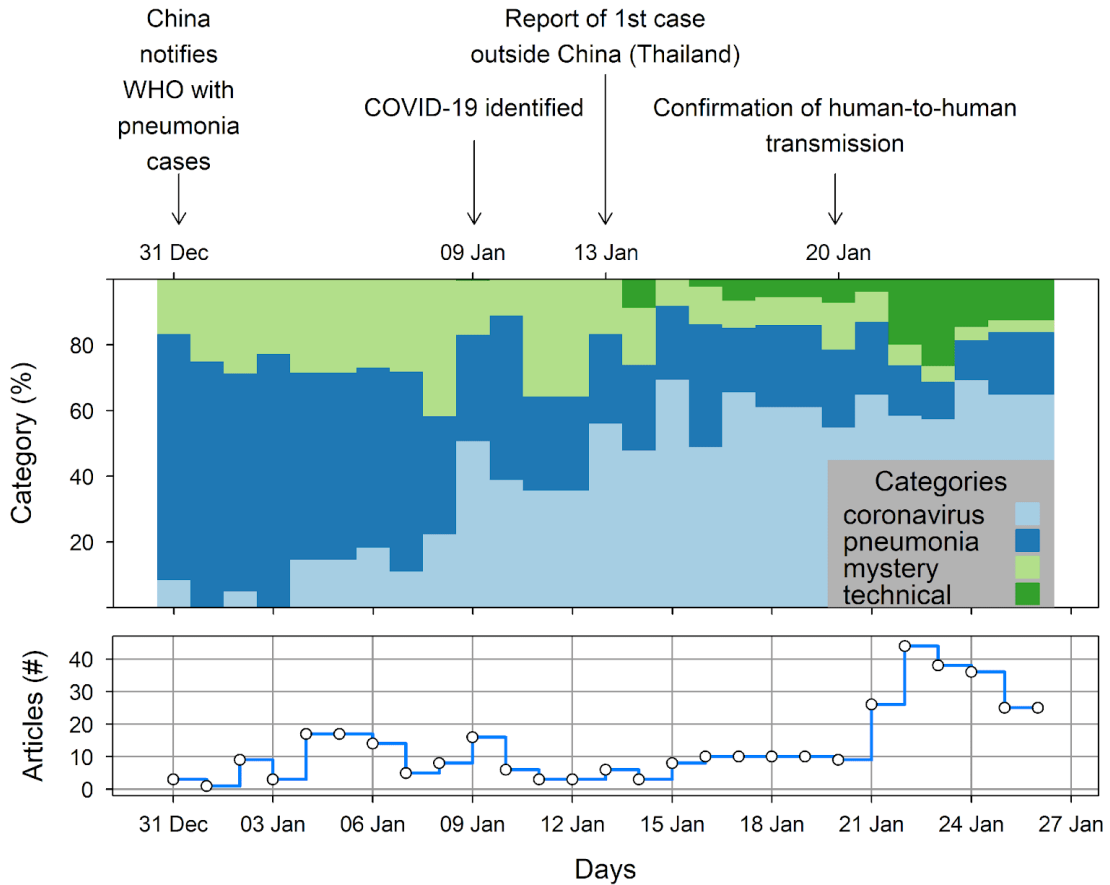

Figure 13. Frequency of the different categories used to describe the COVID-19 outbreak (above), and stepped curve of the daily number of COVID-19 news articles retrieved by PADI-web (below).

The paper entitled "Monitoring online media reports for the early detection of unknown diseases: insights from a retrospective study of COVID-19 emergence" was submitted to *Transboundary and Emerging Diseases* in April 2020 and accepted in July 2020. It is currently in press. The latest version of the paper is available in Annex 3.

3.2.3.4   Study discussion

This case study showcased an example of pluridisciplinary collaboration between epidemiologists, EI experts, computer scientists and text mining experts in the aim of facilitating and automatizing data collection to improve the early detection of health threats.

The results of our study showed that ProMED was the first to detect a news article relating to the COVID-19 emergence in China, just one day before the first detection by PADI-web and HealthMap and the official notification. Out of the three biosurveillance tools, ProMED is the only one to rely on a network of experts to collect and share first-hand information on health events at the local level to alert on potential health threats. This suggests that the network of local field experts is crucial for the rapid detection of EID events. PADI-web and Healthmap detected the first news article on the same day as the official notification by Chinese health authorities. This points out a

limitation of some biosurveillance tools, and the need to integrate and promote the inclusion of local experts in the sources of information of EBS systems.

PADI-web's disease-specific RSS feeds contributed as much as syndrome-related RSS feeds to the detection of COVID-19 news. This was unexpected but illustrates the importance of combining both specific and non-specific RSS feeds to increase the coverage of search queries. Indeed, I noticed in my experience that many media articles provide information on the epidemiological situation of more than one disease, usually a clinically-similar disease, another disease circulating in the same area or country, or a disease with an economic impact of the same magnitude (e.g. comparison of ASF and avian influenza). This "bulk" feature of media articles mentioning several outbreaks of different diseases allows EBS tools such as PADI-web to broaden the scope of their search with a limited number of RSS feeds. This key feature compared to IBS systems allows them to increase the probability and the timeliness of the detection of EID events, particularly when relating to zoonotic events.

Our results indicated that the vocabulary changed as the disease spread. The analysis of the evolution of the vocabulary during the early stages of emergence (e.g. suspicion, confirmation of etiology, international spread) illustrates the importance of specifically selecting keywords relating to "mystery" or "unknown" to detect suspicions of novel virus emergence, both in animals and humans. EBS tools used to monitor information from online media sources should, therefore, be adapted to the different stages of disease epidemiology.

PADI-web was able to detect news relating to an emergence event affecting humans through its animal-health related RSS feeds, thus demonstrating its value as a trans-sectoral tool for the timely detection of health events affecting both animals and humans, of both known and unknown origins. To promote this use in a One Health approach, PADI-web has been presented and shared in the framework of inter-sectoral collaborations with institutions involved in human health (e.g. WHO and the French network of epidemic intelligence) and in plant health (e.g. ESV Platform and INRAE). PADI-web is also part of the MOOD project which promotes the development and improvement of new and existing tools in a One Health context, in collaboration with over 40 European partners in both animal and human health.

The three EBS systems included in our study monitor information in multiple languages, which facilitates the detection of events in local media outlets. Increasing the number of languages monitored by the systems can enhance their sensitivity and improve timely detection (Barboza *et al.*, 2014). The three EBS systems are also complementary in terms of scope (animal and public health) and moderation (manual, semi-automated, automated).

In hindsight, I have identified a few ways to improve the study. Instead of manually extracting terms in our analysis of the vocabulary, we could have used text mining techniques to automate the process, such as the BioTex software which automatically extracts relevant terminology. We could, for instance, add a new category of keywords relating to unknown health events in PADI-web and analyze the news articles detected by the tool in a retrospective study of another emergence (e.g. Ebola, SARS). This would allow us to validate and refine our findings relating to the vocabulary linked to novel pathogen emergence (e.g. "unknown", "mystery").

PADI-web offers a strong coverage of the animal sector, a multilingual approach and an efficient and automated information extraction module compared to other biosurveillance tools. Multilingual approaches are uncommon (only 32% of reviewed biosurveillance tools are multilingual) and increase the amount of information collected, thus improving early detection of an event by including local media sources (O'Shea, 2017). Previous studies have also shown that PADI-web detects information on health events with a wider thematic scope, e.g. the detection of information relating to control measures such as vaccination (Arsevska, 2017).

Through this case study, PADI-web illustrated the key contribution of unstructured data extracted from news articles. However, several challenges of managing unstructured data have been discussed, such as user bias relating to human moderation, the need for an annotated training dataset for machine learning algorithms, determining suitable baselines to detect anomalies in disease trends, or selecting pertinent keyword associations for online queries (Yan *et al.*, 2017a). Although digital disease detection improves the timeliness and sensitivity of disease surveillance systems, the use of informal sources is likely to generate bias (Yan *et al.*, 2017b). The information extracted from these unofficial sources should be verified and validated by experts before analysis, hence the need for pluridisciplinary collaborations. Because biosurveillance tools collect information from many common sources (e.g. social media, Google News) and sometimes collect information from one another (e.g. ProMED and HealthMap mutually), data collection using internet-based biosurveillance tools can create duplicates and overlap in the collected information (O'Shea, 2017). This highlights the need to improve the detection of information duplicates when combining data collected from different tools and heterogeneous sources.

Although the first news article detected usually contains limited, preliminary and vague information, biosurveillance tools provide a first warning for the emergence of new and unknown pathogens. Biosurveillance tools rely on syndrome keywords to detect such threats and, although there might be some level of noise regarding the collected information due to the limited specificity of syndromes, these tools are the first line of detection of new disease emergences. This supports the need to integrate weak signals in biosurveillance tools to increase the sensitivity of EBS systems and better detect the early stages of disease emergence, even when available information is limited. For this reason, I have led the integration of PADI-web into the FEIS' EI activities on an *ad hoc* basis to increase the coverage of the information monitored. We plan to integrate PADI-web on a permanent basis to go beyond *ad hoc* use, but this will generate more information to validate and analyze on a daily basis and might require additional tool adaptation, planning and resources. The level of additional resources and time needed for the integration of EBS biosurveillance tools in existing EI systems depends on whether these tools complement the monitoring of official sources (e.g. FAO or European commission databases) or if the EI system solely relies on these biosurveillance tools, which may be the case if limited official notification data is available.

Existing biosurveillance tools display complementary features relating to data collection, languages, moderation, extraction and dissemination of information (Yan *et al.*, 2017a). Combining them can increase the sensitivity and timeliness of disease surveillance systems, from data collection to reporting (Barboza *et al.*, 2013). This was the idea behind the Epidemic Intelligence from Open Sources (EIOS) platform (Abdelmalik *et al.*, 2018). The EIOS initiative is a unique collaboration between WHO, the Global Outbreak, Alert and Response Network (GOARN),

FAO, OIE, the Global Health Security Initiative (GHSI), ECDC, Africa CDC and the Joint Research Centre of the European Commission. EIOS aims to create a common, all-hazards, One Health platform by using open source information for the early detection, analysis and reporting of health threats (Abdelmalik *et al.*, 2018). The initiative brings together end-users (health professionals working in EI), system developers, data providers and stakeholders to mutualize expertise, efforts and resources, in order to combine existing developments and improve systems' performance in terms of early detection and monitoring of threats.

The combination of complementary tools has also been implemented in PADI-web, with the integration of complementary modules such as EpidVis and EpidNews. PADI-web is the product of several years of pluridisciplinary collaborations between experts in computer sciences, visual analytics, animal health, EI and epidemiology. This co-conception of the tool ensured the developments met the end-user needs in terms of online media monitoring to complement unofficial sources of information monitored by the FEIS. As stated, expert input is essential for text-mining and machine learning algorithms, which make up PADI-web. For this reason, it was important for me to actively contribute to each work meeting and pluridisciplinary group discussions with experts in data science and text mining, as part of the PADI-web team, to provide my expertise in EI and my operational needs as a main end-user. During the early stages of development of PADI-web, a Delphi consensus method was used to facilitate discussions between experts in order to agree on class definitions and keyword selection, a potentially challenging task given the different experiences and perspectives of participants (Rayens *et al.*, 2000; Arsevska *et al.*, 2016).

It is important to integrate end-users in the early stages of development to ensure the tool meets their needs. The need for the tool itself should also be validated by end-users as a first step of the project, through an in-depth assessment of user needs prior to the launching of the project. End users involved in the development of the tool should be representative of all end-users. As the development advances, additional key stakeholders can be involved in the process through iterative feedback loops (as is planned in the H2020 MOOD project). These feedback loops can extend beyond the development phase and continue during the tool's implementation to ensure it can adapt to the evolution of the users' needs. This might be at the source of some issues we have faced with PADI-web's implementation beyond *ad hoc* use. Unfortunately, we noticed that the tool does not meet some specific needs of the FEIS end-users such as a concise and synthetized view of all collected news articles, allowing a rapid overview of all news articles. Such specific needs are operational and could have been identified during feedback and testing loops during and following the tool's development. Today, the implementation of the PADI-web in the FEIS' daily activities is delayed due to the need for technical adjustments to address these operational needs. Also, the development of the tool was conducted in parallel to the FEIS which was still in the process of being set up and implemented when the development of PADI-web was underway. Both were launched in 2013. Some operational needs might not have been identified during the tool's design simply because they had not yet been identified by the FEIS members at the time. The tool's development process, in collaboration with FEIS members, might have been different if the project had been launched once the FEIS was operational, mature and able to provide operational feedback on specific needs.

In retrospect and with the knowledge acquired during my experience, I have identified several ways to improve the development and facilitate the implementation of newly developed tools, such as PADI-web, in existing surveillance systems. Including a representative group of end users in the design of the tool can help identify key operational needs to make sure the tool fits the needs of the users. Identifying a facilitator, preferably an end-user, is also key to further facilitate and drive the process. I also suggest to organize feedback meetings with additional end users at different stages of the process. These meetings would allow the tool development team to identify addition operational needs by progressively including more and more end-users in an iterative process, to validate the tool's design and to organize testing loops with the future users. This approach requires more time at the development phase but will save time during the implementation phase. We have chosen such an approach for the H2020 MOOD project, with the help of sociologists to facilitate this co-conception with end-users.

3.3. Development of an online data collection tool for mass gathering surveillance

The second case study is another example of the pluridisciplinary co-development of an electronic tool to improve disease surveillance. The objective of this case study was to develop and implement an online tool for electronic data collection and analysis of health data to enhance disease surveillance in the context of mass gathering events in the Pacific region, in this case the 8th Micronesian Games hosted by the Federated States of Micronesia in 2014 (White *et al.*, 2018).

3.3.1 Context of mass gatherings

WHO defines mass gatherings as "events attended by a sufficient number of people to strain the planning and response resources of a community, state or nation" (World Health Organization, 2008a). Mass gatherings can be recurrent or sporadic. These events can be for example religious (e.g. the Hajj), athletic (e.g. the Olympics) or socio-cultural (e.g. the Festival of Pacific Arts) (Figure 14). They should be distinguished from humanitarian emergencies because mass gatherings are non-emergency events that allow sufficient time to prepare for the events (Kaiser *et al.*, 2006).

These events are characterized by a large attendance, although specific size is not linked to the definition because the capacity of local communities and health services to manage large crowds varies from one region to another (World Health Organization, 2015). Their size may vary from several thousand people to several million people such as the 3.2 million spectators of the "Fédération Internationale de Football" Association World Cup in Germany in 2006 (Josephsen *et al.*, 2006).

Figure 14. (left) Crowds of people at the London 2012 Olympic Games Park in Stratford in August 2012; (right) Muslim pilgrims at the Ka'aba during the Hajj in Makkah, Saudia Arabia in October 2013 (Memish et al., 2014 - © 2014 Corbis)

Through the favorable context they provide, mass gatherings can represent serious health risks (Lombardo *et al.*, 2008). Public health risks associated with mass gatherings are well documented and encompass a variety of focus areas, from environmental health hazards to infectious diseases (Milsten *et al.*, 2002; Arbon, 2007). Crowding favors the emergence of infectious diseases through increased contacts between participants. The temporarily increased population density at the location of the event can exacerbate an on-going outbreak in the host country and strain the planning and response resources of the country or community. In addition, by involving international participants, mass gatherings represent a threat of importation of new diseases into the host countries from participants' countries upon their arrival, or the exportation of a disease worldwide when infected participants return to their home country. An important lesson learnt from past epidemics like SARS in 2003 was that weaknesses in "surveillance and response capacity in a single country can endanger national populations and the public health security of the entire world" (Heymann *et al.*, 2004).

The hosting country's health agency must be prepared to enhance their surveillance capacity to detect, investigate and respond to an infectious disease outbreak that could damage the reputation of the event, spread to other regions or countries, and exert a substantial human or economic impact. Enhancing surveillance implies increasing the timeliness and accuracy of existing surveillance capacities and potentially implementing additional active surveillance systems (Fleischauer *et al.*, 2017).

Preparing public health systems for managing a mass gathering is a complex procedure. In accordance with IHR, WHO offers guidance for public health planning, surveillance and response during mass gatherings (World Health Organization, 2008b, 2015). To enhance existing surveillance systems, thorough risk assessments for participating countries and host country are essential prior to the event in order to identify potential public health risks and available resources (World Health Organization, 2015). As part of the medical service preparations, health authorities often implement an enhanced syndromic surveillance system (Kaiser *et al.*, 2006). The enhancement of the surveillance system focuses on capacity for diagnostics (e.g. available human and material resources), control (e.g. investigation, isolation, treatment) and prevention (e.g. awareness, vaccination).

The majority of outbreaks that occur at mass gatherings involve vaccine-preventable diseases, mainly influenza, measles, mumps and hepatitis A (Gautret *et al.*, 2016). Several outbreaks during mass gatherings led to international spread of communicable diseases, with secondary and sometimes tertiary cases reported in a participant's country. For example, a measles outbreak during two sport competitions in Italy in 2011 led to secondary cases in Germany and Slovenia (Santibanez *et al.*, 2014), and another measles outbreak during a mass gathering in Taizé, France in 2010 led to secondary and tertiary cases reported in Germany (Pfaff *et al.*, 2010). Another example is the introduction of dengue serotype 4 in American Samoa in 2008 during its hosting of the Festival of Pacific Arts (Institut de Veille Sanitaire, 2012).

3.3.2 Disease surveillance in the Pacific

The Pacific region covers about a third of the Earth's surface and counts more than 3 000 islands in 22 Pacific island countries and territories (PICTs), which include some of the world's smallest nations with under 25 000 residents (Kool *et al.*, 2012a). PICTs are culturally diverse and some can be very geographically isolated.

Rates of infectious diseases are high in the Pacific region (Gani, 2009). PICTs are characterized by insularity, relative remoteness, significant mobility both within islands and outside the region, which make them particularly vulnerable to disease outbreak and spread (Souarès, 2000; Nelesone *et al.*, 2006). In addition to a vulnerable context increasing the risk of disease outbreaks, outbreak detection and response in PICTs are constrained by several factors including limited health infrastructures and communication networks, limited availability of trained public health staff and many notifiable conditions for which overseas laboratory confirmation is required, which can result in poor reporting (Souarès, 2000; Kool *et al.*, 2012b). These factors can overwhelm health services (often only one person) and weaken their early warning and response capacities, resulting in poor timeliness, completeness and sustainability of surveillance systems.

Syndromic surveillance has been successfully implemented in developing countries in Africa and Asia (Durrheim *et al.*, 2001; John *et al.*, 2004). Case definitions are based on clinical signs and symptoms rather than laboratory confirmation, making it particularly useful in settings with limited access to laboratories, a common feature in most PICTs. The gain in timeliness provided by a syndromic system is substantial and can lead to rapid response and limited disease spread (Nelesone *et al.*, 2006).

The SPC (originally Secretariat of the Pacific Community) is an international development organization governed by its 26 members, which include 22 PICTs, Australia, France, New Zealand and the United States of America. SPC aims to facilitate the sharing of technical experience and knowledge, and provides support to its members to implement specific development projects and activities. SPC's expertise is structured into nine divisions, including the Public Health Division (PHD). The Research, Evidence and Information Program (REI), which is part of the PHD, aims to provide support to its PICT members in terms of infectious disease surveillance. The REI team coordinates regional EI activities to provide up-to-date information on the circulation of infectious diseases in the region. The team also coordinates the Pacific Public Health Surveillance Network (PPHSN), created in 1996 under the auspices of WHO and SPC. The PPHSN is a voluntary network of countries and organizations dedicated to the promotion of public health surveillance and appropriate response to the health challenges of 22 PICTs. To improve public health surveillance

and response in the Pacific in a sustainable way, the network aims to harmonize health data needs and surveillance, develop supportive computer applications, train national staff in epidemiology and public health surveillance, promote the sharing of information between PICTs, publish regular bulletins to disseminate health information, and improve laboratory capacity and connectivity. PPHSN services include an email list to promote timely exchange of information among over 680 health professionals (PacNet), and a diagnostic support network working on the identification and verification of pathogens (LabNet).

In 2010, the Pacific Syndromic Surveillance System (PSSS) was introduced in the PPHSN to simplify disease surveillance and improve early warning for the main outbreak-prone diseases in the Pacific. The PSSS focuses on four core syndromes defined according to standardized case definitions: acute fever and rash (AFR), diarrhea, influenza-like-illness (ILI) and prolonged fever (Table 2).

The PSSS complements existing surveillance systems in terms of early warning and builds on existing data collection, reporting and response procedures (Kool *et al.*, 2012b). It does not replace laboratory confirmation, still needed for major outbreak-prone diseases. The PSSS provides an efficient early warning system for many PICTs, enabling them to achieve several key capacities required by the 2005 IHR (World Health Organization, 2008b).

Table 2. Case definitions for the four identified syndromes of the Pacific Syndromic Surveillance System (fever: 38°C or higher) (Kool et al., 2012).

Syndrome	Case definition	Important diseases to consider
Acute fever and rash (AFR)	Sudden onset of fever, with acute non-blistering rash	Measles, dengue, rubella, meningitis, leptospirosis
Diarrhea	Three or more loose or watery stools in 24 hours	Viral and bacterial gastroenteritis including cholera, food poisoning, ciguatera fish poisoning
Influenza-like illness (ILI)	Sudden onset of fever, with cough and/or sore throat	Influenza, other viral or bacterial respiratory infections
Prolonged fever	Any fever lasting three or more days	Typhoid fever, dengue, leptospirosis, malaria, other communicable diseases

Since 2012, SPC has implemented a mass gathering program to support PICTs in enhancing their disease surveillance system. It aims to limit the risk of infectious disease outbreaks during mass gatherings. Enhanced syndromic surveillance (ESS) has three primary objectives: 1) to provide a simple disease surveillance system allowing timely detection and response of disease events, 2) to provide daily dissemination of situation reports to national and regional health authorities and stakeholders, and 3) to improve the existing disease surveillance system in a sustainable manner (White *et al.*, 2017). ESS involves increasing the number of syndromes and sentinel sites monitored, switching from weekly to daily reporting, and going from aggregated data to case-based reporting (Hoy *et al.*, 2016). ESS is increasingly implemented for mass gatherings, although it has generally been limited to high-income countries (Nelesone *et al.*, 2006; Lombardo *et al.*, 2008). In low to medium-income countries, establishing ESS for mass gatherings can provide a great opportunity to strengthen health system capacity in a sustainable way, building from and strengthening the existing surveillance system (Henning, 2004).

Since 2012, SPC has provided support to Pacific health authorities for the enhancement of disease surveillance during the following events:

- 11th Festival of Pacific Arts in the Solomon Islands (2012),
- 9th Pacific Mini-Games in Wallis and Futuna (2013),
- 8th Micronesian Games in Pohnpei State, Federated States of Micronesia (2014),
- 3rd International Conference on Small Island Developing States (SIDS) in Apia, Samoa (2014),
- Commonwealth Youth Games in Apia, Samoa (2015),
- 12th Festival of the Pacific Arts in Guam (2016),
- 10th Pacific Mini-Games in Vanuatu (2017), and
- 9th Micronesian Games in Yap State, Federated States of Micronesia (2018).

3.3.3   Electronic disease surveillance

Over the past 15 years, there have been great improvements in the collection, analysis, visualization, and reporting of health data, mainly driven by advances in information technology (Feighner *et al.*, 2014). Incorporating technological advances significantly increased the timeliness of data collection, analysis and reporting, and allowed more complex and automated analyses of disease data, thus facilitating early detection, preparedness and rapid control of disease outbreaks.

Electronic disease surveillance can improve health security by reducing delays in data availability and analysis, and improving early detection and reporting (Jajosky *et al.*, 2004; Chretien *et al.*, 2008; Soto *et al.*, 2008). Countries can, thereby, enhance their compliance with the WHO's 2005 IHRs which require strengthening disease detection and response capacities in order to report, within 24 hours of assessment, any public health event of international concern (World Health Organization, 2008b). An electronic disease surveillance system can address a number of pertinent objectives, including: 1) detection of disease outbreaks, 2) monitoring trends in disease rates or the effectiveness of an intervention, and 3) strengthening local capacity in outbreak detection and response (Henning, 2004).

Electronic disease surveillance, particularly electronic syndromic surveillance, holds promise to improve health security in resource-limited environments (Chretien *et al.*, 2008; Soto *et al.*, 2008). Resource-limited countries have lagged behind due to challenges with information infrastructures and available resources. In developing countries, epidemiological surveillance is usually led by the Ministry of Health, which often still relies on traditional pen and paper methods for disease reporting (Soto *et al.*, 2008). In developing countries where public health infrastructure can sometimes be suboptimum, efforts are in progress to implement robust data collection and analysis methods and improve local capacity for electronic disease surveillance (Chretien *et al.*, 2008). When considering available information and communication technologies, it is essential to select technologies that are both easy to incorporate into existing health systems and sustainable with little or no additional financial investment, thus ensuring proper implementation and sustained use (Feighner *et al.*, 2014).

3.3.4   SAGES tool

SAGES (Suite for Automated Global Electronic bioSurveillance), developed in 2008 by the Johns Hopkins University Applied Physics Laboratory (JHU-APL), provides an inexpensive, customized, and sustainable disease surveillance system that can complement and strengthen existing systems. SAGES is a collection of modular, flexible, freely-available software tools designed to enhance electronic disease surveillance capacity in resource-limited settings (Lewis *et al.*, 2011; Feighner *et al.*, 2014). SAGES tools are organized in four categories: 1) data collection, 2) analysis and visualization, 3) communications, and 4) modelling, simulation and evaluation. They are built in a modular nature, which allows each locality or country to select all or specific tools from SAGES on the basis of their needs, capabilities and existing systems to create a customized electronic disease surveillance system (Feighner *et al.*, 2014).

The SAGES analysis and visualization tools are built on the features and functionality of the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE) system. This system was previously developed by JUH-APL in collaboration with the United States Department of Defense (Lewis *et al.*, 2011). ESSENCE allows real-time collection, analysis and visualization of non-traditional data sources (e.g. poison control center calls, pharmaceutical sales) leading to the timely detection and reporting of anomalies in disease activity within a community (Lombardo *et al.*, 2003). The current SAGES initiative leverages the experience gained with ESSENCE and its analysis and visualization components are built with the same features.

One of the most successful tools of the SAGES toolbox is OpenESSENCE (OE), a multi-user web-based tool for data entry, analysis and visualization that enables epidemiologists to monitor the population's health (Feighner *et al.*, 2014). SAGES OE provides a web-based data collection and analysis platform that automatizes key steps of reporting such as generating time series or detecting threshold crossing, thus allowing timely data analysis and reporting, which are crucial for enhanced surveillance.

A collaboration was set up between SPC and JHU-APL to adapt OE to the context of disease surveillance enhancement for mass gatherings in the Pacific. SAGES' OE tool was successfully implemented for the 8th Micronesian Games which I will present as a case study in this next section (Hoy *et al.*, 2015; White *et al.*, 2018).

3.3.5   Application of SAGES to enhance disease surveillance during the Micronesian Games in the Federated States of Micronesia in 2014

3.3.5.1   Context of the study

The Federated States of Micronesia (FSM) is a Pacific Island country located north of Papua New Guinea. It is made up of four independent states: Yap, Chuuk, Kosrae and Pohnpei (Figure 15). The capital of FSM is Palikir, located in Pohnpei State. FSM covers 701 square kilometers and the population was estimated at 103 000 inhabitants in 2010 (the Pacific Community, 2017; World Health Organization, 2017a). Located in the Eastern part of FSM, Pohnpei is the second largest

state after Chuuk. It is made up of the main island of Pohnpei, the largest island in FSM with 129 square miles, and eight smaller outer islands (Ichiho *et al.*, 2004).
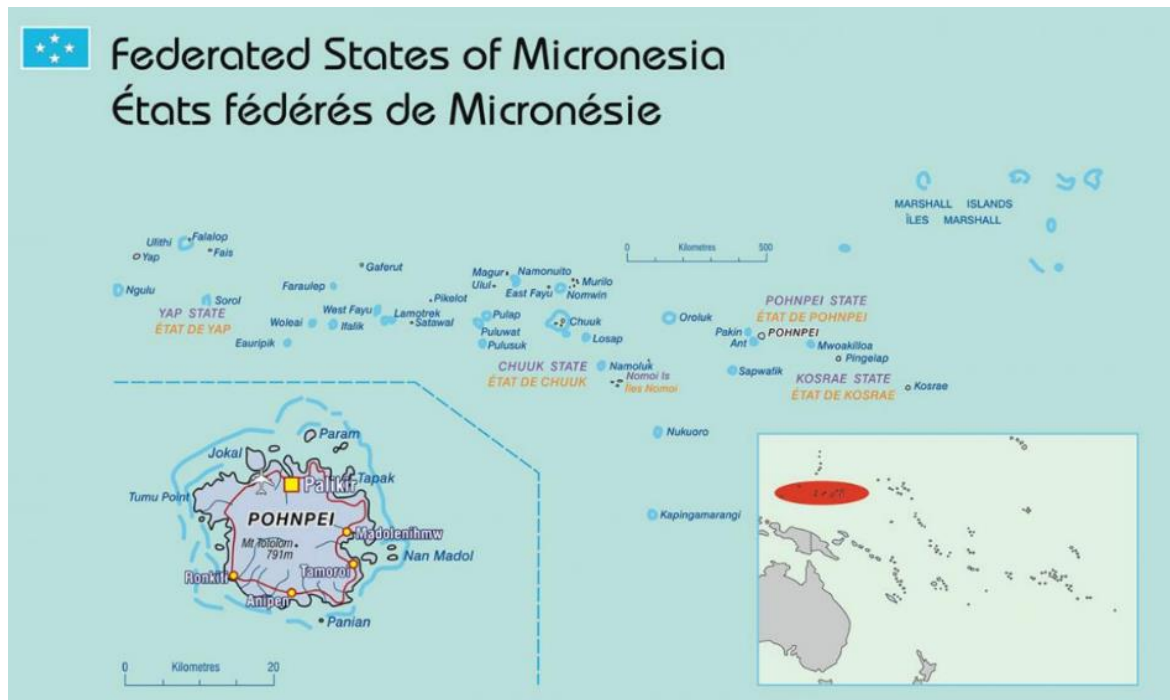

Figure 15. Map of the Federated States of Micronesia (SPC's Member Map - the Pacific Community 2017)

Figure 16. 8th Micronesian Games logo

From 19th to 29th July 2014, Pohnpei hosted the 8th Micronesian Games (or Micro Games) which gathered participants from seven Micronesian island countries and territories: Kiribati, Guam, Marshall Islands, Nauru, the Commonwealth of the Northern Mariana Islands, Palau and FSM (Figure 16) (White *et al.*, 2018).

The event took place in the area around the main town of Kolonia and attracted about 1 700 athletes and officials. The event was held two months after a widespread measles outbreak in Pohnpei, which presented a risk of spread across FSM and the Pacific region following the mass gathering.

During my experience as a public health surveillance officer at SPC from 2014 to 2016, I participated in the REI team's projects, which included the mass gathering enhancement program. Similar to the PADI-web case study, I contributed on two levels to the adaptation of OE to mass gathering surveillance: a meta level to integrate user knowledge, and a methodological level to contribute to the technical and methodological developments of the tool. As part of a pluridisciplinary team of experts in computer sciences, epidemiology, epidemic intelligence and public health, I contributed to the integration of expert knowledge on the EI process in the tool's design and implementation. I also participated in methodological developments of the tool to adapt it to the local context, thus ensuring it fits the needs of local health authorities. I contributed to the analysis and reporting of the data collected daily, provided back-office support when

technical issues arose, and provided training for health officials as well as a detailed user guide manual to facilitate the use of the tool.

In addition to my contribution to the surveillance enhancement for the Micro Games in FSM, I also participated in SPC's support for another mass gathering event that occurred in 2014, just two months after the Micro Games: the 3rd United Nations SIDS Conference hosted in Samoa. The SIDS conference took place at the same time as the Teuila festival also organized in Samoa, while a chikungunya outbreak was reported locally and the largest Ebola outbreak was ongoing in Western Africa. SPC implemented the same program for mass gathering enhanced surveillance. We had initially planned to use the SAGES OE tool. However, we were not able to use the tool due to technical challenges in hosting the tool server in Samoa and the country's worries about data confidentiality with cloud hosting. We had to adapt by creating an Excel spreadsheet system with programmed threshold alerts, data analysis and visualization, to which I contributed. I traveled to Apia, Samoa two weeks prior to the event to meet health authorities and health professionals at the different sentinel sites (existing and newly set-up for the mass gathering), to train the staff on the use of the spreadsheet tool, as well as the creation and publication of daily situation reports to inform stakeholders. I provided support for the enhancement of the surveillance system to all sentinel sites, then to a daily basis instead of weekly, with test runs implemented. Upon my return to SPC offices, I provided back-office support for the dissemination of the daily situation reports.

3.3.5.2 Material and methods

SPC's program to enhance disease surveillance during mass gatherings consists of three steps that focus on preparation, operational implementation and sustainability.

The first phase of the mass gathering surveillance process is preparation. Health authorities of the hosting country or territory contact SPC prior to the mass gathering to ask for support in strengthening the island's disease surveillance system. This step is formalized by a signed agreement between SPC and the hosting country or territory. This contact is ideally established at least a year before the event, though it is usually done a few months before in practice.

The next step of the protocol for disease surveillance enhancement is to assess the existing disease surveillance system in the hosting country or territory. Most of the existing surveillance systems are based on weekly reporting, but need to be enhanced to daily reporting for mass gathering surveillance in order to ensure timely detection of outbreaks, i.e. unusual increase in syndrome cases, and rapid response. The team also conducts a disease risk assessment by monitoring ongoing disease circulation in the hosting country to identify risks of disease exportation, and in the participant's country of origin to identify risks of disease introduction in the hosting country. A work plan is developed based on these findings.

A surveillance tool is then developed based on the needs of the national health authorities. We can start from an existing tool, if they are already using one, that can fit the need for enhanced surveillance with daily reporting. The REI team adapted the OE tool which can easily be applied to different mass gathering contexts.

Following the preparation phase, operational implementation is carried out, starting ideally at least six months prior to the event in order to allow time to test the tool and the enhanced system, to train the staff, and to plan for necessary resources (e.g. cars, phones, office supplies). The

training delivered to health authorities and sentinel site staff focused on the use of the OE tool, collection and referral of laboratory samples, completion of the surveillance registers, and comprehension of the case definitions.

The enhancement of the system is performed in two ways: by increasing the number of sentinel sites and syndromes, and by increasing the reporting frequency. First, the number of sentinel sites is increased to increase the geographic coverage of the island. Then, the frequency is increased from weekly to daily for the collection, analysis and reporting of the health data. The enhancement is done progressively to limit the strain on the existing system, with a first expansion to all sentinel sites, followed by an expansion to daily reports.

A surveillance form available at each sentinel site was filled in manually and captured the daily number of patient encounters (or visits) and syndrome cases (Annex 4). One encounter can be counted as one or more syndromes depending on the patient's symptoms. The paper surveillance form was collected and replaced with a new form daily. The data from these forms was manually entered into the SAGES OE tool (Figure 17). Unfortunately, data collection could not be directly entered at sentinel sites due to limited connectivity coverage across the area, although the SPC team had envisaged to use wireless tablets. This demonstrates the necessary flexibility of the system which needs to be adapted to each specific context for each mass gathering. The data was analyzed in SAGES OE, which provided time series to monitor the trends in syndrome cases and were used for the daily situation reports. These reports were disseminated daily to stakeholders in the Department of Health and Social Affairs at national level and to the Games organizing committee. They were also posted on PacNet.

Figure 17. Supporting local health authorities with manual data entry from surveillance forms into the online OE application.

The enhanced surveillance system usually starts a week before the event to better determine threshold baselines and pilot the new system and tool in real conditions. It continues one to two weeks after the event, to take into account incubation periods and delays due to detection or patients visiting a doctor.

The REI team also provided support to health authorities for investigation measures, once an unusual increase (above a predefined threshold) of syndrome cases was detected.

The third and final stage focuses on sustainability. Mass gatherings represent an opportunity to strengthen local health surveillance and response capacities in a sustainable manner, by training staff or setting up new sentinel sites for example. Following an evaluation of the enhanced surveillance phase to identify strong points and weaknesses of the system, the system can transition back to the existing system by returning to the usual number of sentinel sites and syndromes, and return to weekly reporting. The system can also be enhanced by, for instance, increasing the number of usual sentinel sites or syndromes, or promoting evidence-based decision-making to influence policy-making. Post-event surveillance plays a key role in this process as it accompanies the country in implementation of event-related efforts into routine surveillance and response activities.

Figure 18 illustrates all the steps of the surveillance enhancement process.
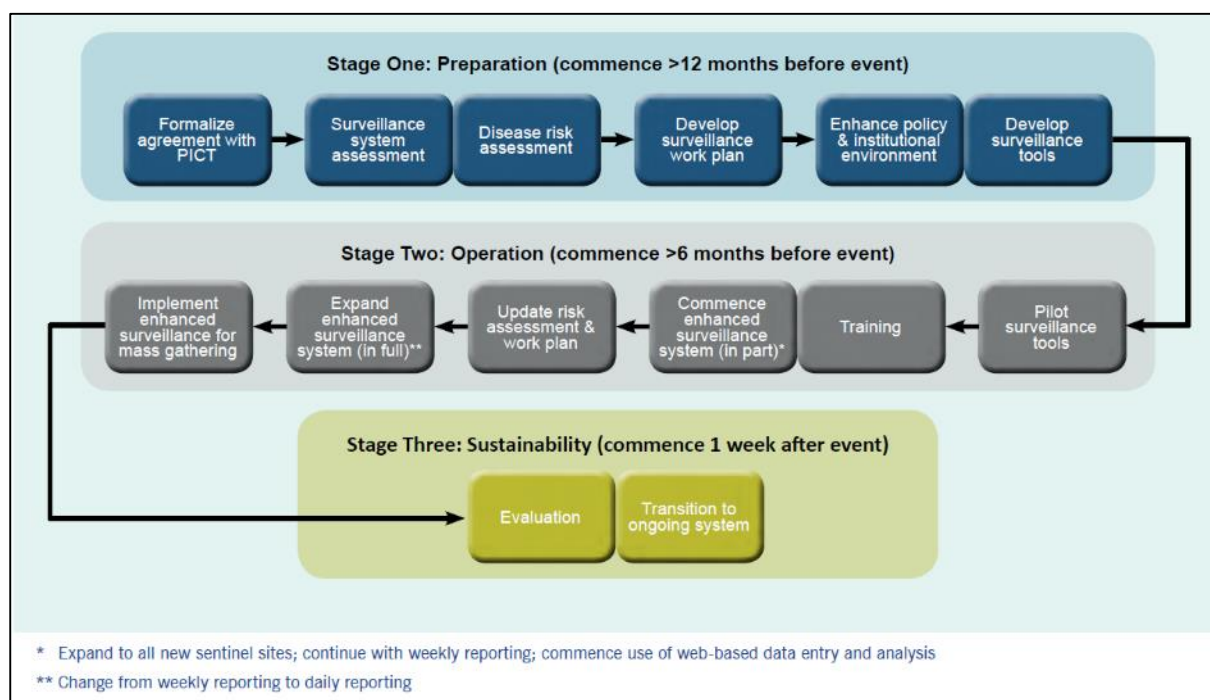

Figure 18. SPC's process map for the enhancement of disease surveillance in the framework of mass gatherings (White et al., 2017).

Several country visits are needed in order to better understand the local system and the stakeholders involved, train the staff and provide support during the mass gathering and after the event, if needed, in order to sustainably improve the national surveillance system.

For the 8th Micro Games in FSM, the number of sentinel sites was expanded to 11 to include two Game venues. The number of syndromes was increased from five to eight (Table 3). The enhanced surveillance system was implemented two days before the Games, due to short notice before the event, and continued for a week after the event.

Table 3. List of original and new syndromes and corresponding suspected diseases for the enhanced surveillance system of the 8th Micronesian Games.

Original syndromes	Addition syndromes for enhanced surveillance
• Acute fever and rash (AFR) (measles, dengue, rubella, meningitis, leptospirosis) • Influenza-like illness (ILI) (influenza and other viral of bacterial respiratory diseases) • Prolonged fever (typhoid fever, dengue, leptospirosis, malaria) • Watery diarrhea (cholera) • Non-watery diarrhea (viral or bacterial gastroenteritis including food poisoning and ciguatera)	• Foodborne disease outbreak (bacterial or viral gastro-enteritis) • Fever and jaundice (hepatitis A infection) • Heat-related illness (heat cramps, heat exhaustion and heat stroke)

3.3.5.3   Main results

During the 8th Micronesian Games, 408 syndrome cases were reported during the 21 days of enhanced surveillance, which represented on average 7% of encounters (patient visits). ILI was the most frequent syndrome recorded (55%) followed by watery diarrhea (24%), non-watery diarrhea (9%) and AFR (8%). Watery diarrhea and AFR are indicative of more severe diseases (Table 3), and a rapid investigation was set up by the response team.

The proportion of syndrome cases for rural and urban sentinel sites is shown in Figure 19. We can notice a variation in the distribution of syndrome cases between rural sites (with more diarrhea cases) and urban sites (with more ILI and AFR cases).

The measles outbreak that was ongoing in Pohnpei at the time of the event had no detrimental impact on the mass gathering.
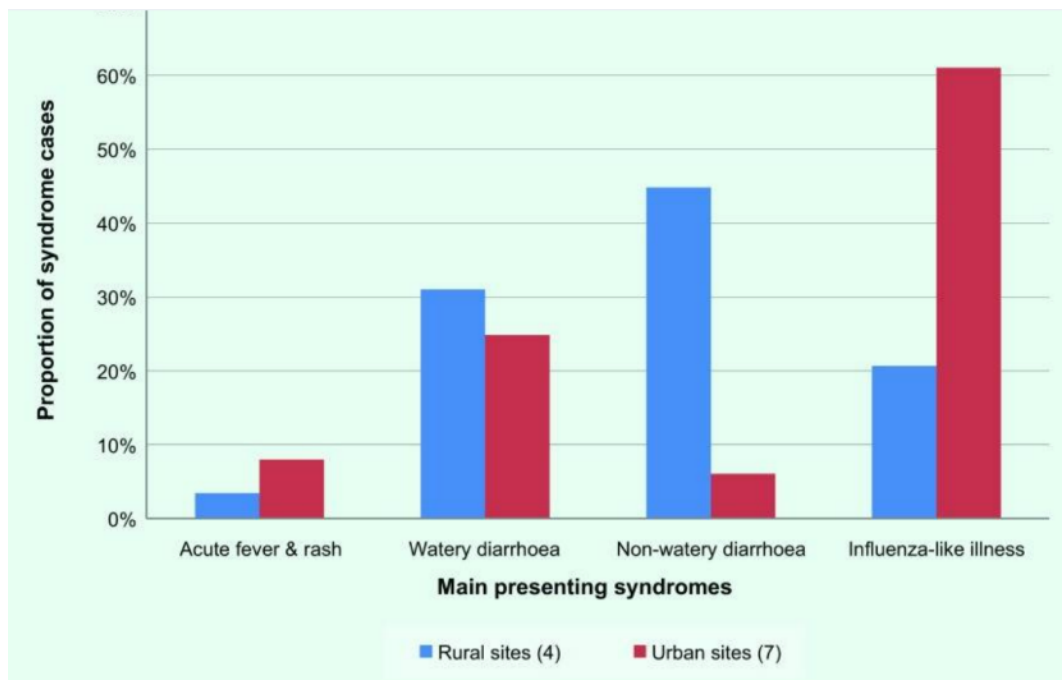
Figure 19. Distribution of syndrome cases reported in rural and urban sentinel sites, Pohnpei State, 17th July to 6th August 2014 (White et al., 2018).

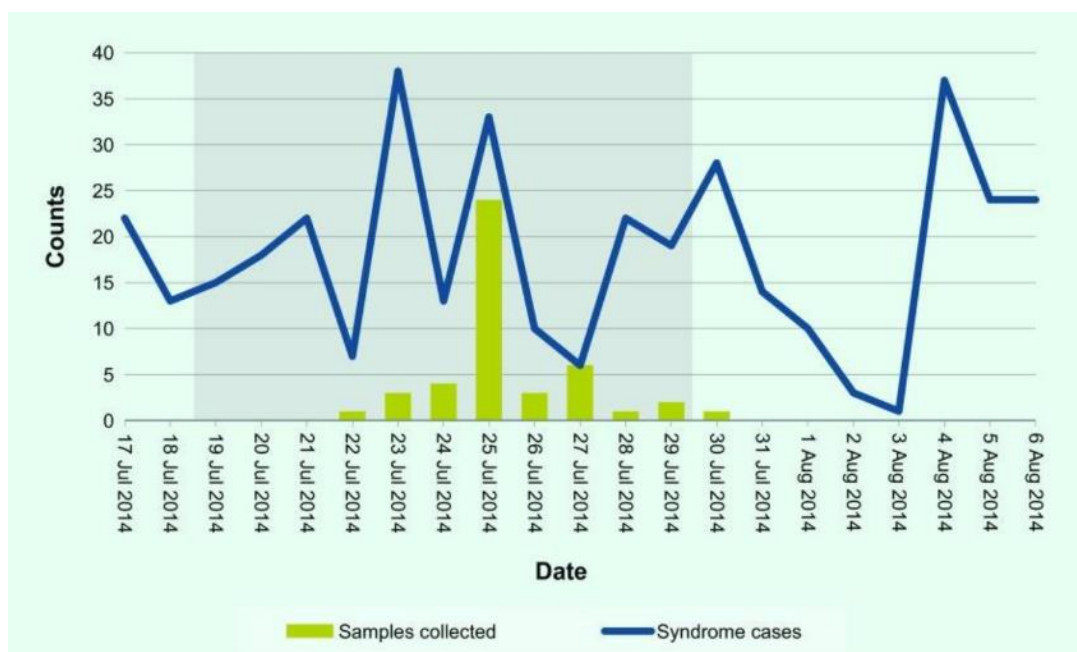Figure 20 presents the distribution of syndrome cases (in blue) and laboratory samples (in green).

Figure 20. Comparison of daily syndrome counts and laboratory sample distributions, Pohnpei State, 17th July to 6th August 2014 (the grey time period corresponds to the Games) (White et al., 2018).

A total of 18 daily situation reports were produced, and were well received by health professionals through PPHSN's PacNet network (White *et al.*, 2018). OE was rapidly adapted within a couple of weeks to fit the needs of the event and hosting country prior to the event. The tool was well received by local health authorities and provided a useful web application for data entry, storage, analysis and reporting, partly due to simultaneous multi-user access and cloud storage (Hoy *et al.*,

2015; White *et al.*, 2018). Enhancing surveillance systems and providing daily situation reports with close monitoring of syndrome trends provided reassurance to public health officials and event organizers.

The paper, entitled "Mass gathering enhanced syndromic surveillance for the 8th Micronesia Games in 2014, Pohnpei State, Federated States of Micronesia" was published in 2018 in the *Western Pacific surveillance and response* journal. The full paper of White *et al.,* 2018 is available in Annex 5.

3.3.5.4   Study discussion

The study revealed that the enhancement of the sentinel sites increased the coverage and the sensitivity of disease surveillance, allowing us to identify a disparity in the distribution of syndrome cases between rural and urban environments (Figure 19). Greater burden of ILI cases in urban sites might be linked to greater respiratory transmission in highly populated areas, whereas higher rates of diarrhea cases in rural areas might indicate issues with waste water treatment and access to clean water. Also, the Games-specific sentinel sites had the third highest rate of syndrome cases but only 3% of encounter cases (visits). This rate of syndromes was much higher than for Pohnpei State Hospital which had the largest number of encounters but fewer syndrome cases. These results illustrate the need to adapt surveillance strategies to the mass gathering event and ensure good coverage of both rural and urban sites. They can help identify gaps in public health surveillance and help local authorities design adapted, prioritized and targeted public health interventions.

The results of the study allowed us to identify issues with the distribution of laboratory samples which was unequal compared to syndromic activity (Figure 20). This strengthens the need for training prior to the event for all actors involved at local level, including clinicians, sentinel site personnel and laboratory personnel.

In our study, electronic surveillance technologies played a significant role in facilitating the enhancement of surveillance activities in-country. The use of OE greatly improved the timeliness of data collection, analysis and reporting, providing reassurance to the event organizers that infectious diseases would not impact the event's activities. The results of the study showed that, despite an ongoing measles outbreak in the hosting country, no infectious disease spread threatened the health of the event's participants.

The efficient implementation of an enhanced syndromic surveillance system can face some challenges. The case study of the Micro Games emphasized the need for good planning, preparation and testing prior to the event, which requires a sufficiently long pilot phase. Unfortunately, health authorities often ask for SPC's assistance only a few weeks before the mass gathering, which significantly reduces the time for the adaptation and the testing of the available tools. Perhaps SPC should proactively contact PICTs who have planned upcoming mass gatherings to propose an enhancement plan if they would like regional assistance. Also, organizing regional workshops with PICT health authorities to present the enhancement program and showcase examples and feedback of previous events might help increase awareness in terms of the time needed to efficiently implement such a program. Several challenges may arise from a limited pilot phase, such as system functions, availability of resources or organizational challenges during the

beginning of the event. Some examples from my experience include the lack of available computers, the roles of local public health agents not being clearly defined ahead of time, or the vehicle of the Ministry of Health not being available the morning we had to make our rounds to collect surveillance forms.

Training of staff ensures a clear understanding of the case definitions and procedures of the newly enhanced surveillance system. The high sensitivity needed for the system to detect anomalies in syndrome trends requires high quality, timely and representative data. This underlines the importance of clearly determining syndrome thresholds in close collaboration with local health authorities, as we had done for the Micronesian Games in the weeks prior to the event. Ensuring a sufficiently long pilot phase can help better define syndrome threshold baselines which may vary according to the time period and the location. Also, although similar methods are implemented and we can learn from past events, experiences of mass gatherings in routinely changing locations and seasons might not be transferable due to the significant variability linked to the context of each event (e.g. location, timing, global distribution of participants). As emphasized by the SIDS conference experience, data confidentiality and ownership issues (particularly relating to health data) should be discussed and addressed with local health authorities during the pilot phase in order to assess the possibility of cloud hosting. This stresses the need to adapt the tool and procedure to the new mass gathering event and its local context.

In hindsight, I have identified several potential improvements to facilitate the implementation of the tool in the local surveillance system. The study could have benefited from an entirely-electronic data collection process, without relying on paper forms to collect the data. This, however, would require improved internet and cellphone coverage at all sentinel sites. Perhaps, instead of implementing a direct data collection into the electronic system through computers at each sentinel sites, we could design an electronic data collection system using mobile phones, ideally through an application, or – if not possible – by sending a text message to a centralized unit. This would lead to a significant time gain because the rounds to collect paper forms would often take all morning. In addition to organizing regional workshops on mass gathering surveillance enhancement as mentioned above, I insist once again on the need for a sufficiently long pilot phase and a possible proactive approach to contact health authorities six months to a year before the event. This would allow a thorough assessment of the local context to adapt the tool to the needs of the local authorities, and an assessment of available resources sufficiently long in advance to allow for the funding and purchase of additional equipment if necessary. The SPC team in charge of providing support to local health authorities could also include public health personnel from another PICT health agency who were involved in their own country or territory's mass gathering event, in addition to SPC staff. Along with the suggestion of a regional workshop, this regional team roster promotes inter-PICT collaborations and strengthens regional enhanced surveillance capacity.

The enhanced surveillance of mass gatherings presents an opportunity to strengthen the disease surveillance system once the event is finished by implementing long-term enhancements through the sustainability plan elaborated with health authorities, as was the case in the framework of the Micronesian Games. The training of health professionals in governmental agencies, laboratories and sentinel points can sustainably improve awareness of circulating disease threats but also of

other potential emerging pathogens circulating at regional or global level. Mass gathering surveillance enhancements can also improve communication between different stakeholders, not only during the event but also after. Instead of progressively returning to the number of sentinel sites and syndromes used prior to the event, local health authorities can, for instance, decide to keep an increased number of sites or syndromes depending on results from the mass gathering enhanced surveillance to improve surveillance coverage. This transition from mass gathering surveillance improvements to routine surveillance requires adequate resources because, as mentioned, enhancing disease surveillance can further strain the system particularly in resource-limited settings. But this can be part of the local health authorities' strategy to sustainably improve disease surveillance at local and national level.

This case study showcased an example of pluridisciplinary collaboration between epidemiologists, EI experts, microbiologists, computer scientists as well as local health authorities and stakeholders, to facilitate data collection and reporting in the context of mass gatherings and improve local early detection and alerting capacities in a sustainable manner.

As mass gatherings occur over a short period of time but require intense activity, they can overburden public health systems, particularly in developing countries. Enhancing surveillance by building on existing systems can help minimize this strain on staff and resources. It can also facilitate the transition phase back to routine surveillance and enable sustainable improvements in terms of capacity (e.g. training of staff, improvements of surveillance system functions). This requires both the involvement of local health authorities to adapt the tool to the local context and ensure it fits the needs of users, and strengthened communication between all stakeholders including clinicians, surveillance officers and disease control authorities. Strengthening the link with local laboratories for sample testing and with clinicians for sampling of syndrome cases is also crucial to ensure rapid alerting of health authorities and timely investigation and response.

Given the large attendance of participants from many different countries, international collaborations and partnerships are increasingly necessary in order to prevent the introduction and international spread of infectious diseases between the host country and participating countries (Memish *et al.*, 2014). Indeed, mass gatherings can be seen as a global-to-local-to-global risk. Health threats can be imported in the hosting country from participants' countries, these health threats can spread during the event, and be exported to other countries worldwide upon the participants' return. Strengthening the links with health authorities in the participants' countries enables follow-up of the participants' health to detect if they contracted any disease while participating and, if so, to alert other participating nations.

3.4. Section discussion

The PADI-web case study presented an example of tool development to improve and automatize data collection from online media sources based on innovative text mining and machine learning techniques. This tool allows the collection and monitoring of unstructured data from online media sources, which represent an additional valuable source of information for EI activities.

The OE case study presented an example of tool development to improve data collection and analysis for reporting. Automatizing data analysis by automatically updating and exporting time series and maps of syndromes once the new data is entered in the system saves time for reporting. This is particularly valuable when data collection, analysis and reporting are done on a daily basis.

In these two cases studies, the automatization process focuses on different steps of the EI process. For PADI-web, the automatization process lies in the data identification, collection and extraction. For OE, the automatization process focuses on the analysis of the information through visualization (e.g. creating time series and graphs). For OE, the data collection process could also be improved through direct electronic data entry at each sentinel site if sufficient internet access or phone network coverage could allow the implementation of the tool on computers or the use of wireless tablets. This would help avoid the intermediary use of paper surveillance forms which duplicates data entry but is used as a back-up system in resource-limited settings. Although they are applied to two different contexts with different needs, these two automatization processes could be combined as modules in a common platform of automated enhanced disease surveillance, providing information from EBS (e.g. online media) and IBS (e.g. sentinels sites and clinicians).

Including multiple information sources has been shown to improve the detection of signals and, with increasing volumes of information available online, automatization facilitates the processing of this significant quantity of information. However, human moderation remains essential for validation, review and interpretation of health-related events (Yan *et al.*, 2017b; Wilburn *et al.*, 2019). The automatization of data collection and analysis should therefore complement and support health professionals instead of replacing their input in the EI process. This is particularly important when some might consider that a 'click-button' tool is enough to conduct EI activities, when it is clearly not the case. Tools help improve EI systems but these systems are run by experts who are able to transform gathered information into useable knowledge and intelligence. EI is a complex and time-consuming process, and significant resources need to be dedicated, even with the use of automated tools, in order to ensure the efficiency of the system and provide quality validated information in real-time (Barboza *et al.*, 2014).

Several challenges come with the use of biosurveillance tools to collect unstructured data or the use of enhanced syndromic surveillance to timely detect health events. These include the need for real-time high-quality data, duplicate detection and human moderation for validation and interpretation. Despite these challenges, the use of biosurveillance tools has demonstrated improved timeliness, sensitivity, accessibility and cost-effectiveness compared to traditional surveillance systems relying on official indicator-based sources, which prove to be more accurate and specific (Yan *et al.*, 2017a). The trade-off between timeliness and accuracy when choosing tools depends on the objective and scope of the EI system. EBS, internet-based digital disease detection and enhanced syndromic surveillance can complement traditional surveillance systems to help enhance the early detection and monitoring of disease threats, whether by targeting periods of increased risk (e.g. mass gatherings) or new information sources (e.g. online media).

The OE and PADI-web case studies provided examples of pluridisciplinary collaborations to facilitate the collection of health data in order to improve the early detection and alerting of health threats. The two case studies highlight the importance of integrating tool developments in a global, functional and pluridisciplinary approach involving stakeholders. This is in line with the

meta-level of my contributions, which focuses on integrating expert knowledge and promoting interactions with stakeholders. To better identify the needs in terms of output, interface, data storage and other important tool features, researchers should involve end-users, such as epidemiologists, in tool development from the early stages of conception and design. This collaboration throughout the project also allows end-users to have a global understanding of the process, the underlying principles and the algorithms used to develop the tool, otherwise perceived as a 'black box'. It ensures the tool fits the needs of the users and is adapted to the local context, thus ensuring appropriation by end-users and a sustainable implementation in the user community, i.e. high Technology Readiness Level (TRL). This approach has been implemented in SPC's mass gathering enhancement program, as well as the H2020 MOOD project coordinated by CIRAD. The MOOD project has a work package almost entirely dedicated to sociological research and the use of social sciences to facilitate co-conception. It is based on participatory methods aiming to identify the needs of the users and the challenges they encounter during their EI activities, thus ensuring a co-conception of the tool and its successful and sustainable implementation. This strong participatory sociological component has strongly contributed to the project's acceptance by the European Commission in August 2019.

Tool genericity, and particularly the use of user-customizable features, can facilitate the adaptation of the tools to different contexts, e.g. from animal and plant health to bioterrorism. The development of generic tools allows the sharing of knowledge, expertise and resources, and promotes pluridisciplinary collaborations between projects. This aspect is also central to the H2020 MOOD project, which aims to strengthen disease surveillance in a One Health context through multi-institution collaborations between data scientists and health professionals from the animal and human health sectors.

Pluridisciplinary collaborations can be challenging**.** During my different work experiences, I noticed that some experts take great pride in their work – with possible territoriality – and adopt a discipline-based vision. Specialized in a particular field, they have their own agenda and interests, and usually prefer to keep a certain degree of autonomy and independence in their work (D'Amour *et al.*, 2008). This can make them less prone to include other disciplines in their projects for a more global and integrative approach. In addition, the context of precariousness and unemployment can exacerbate a natural competition between experts and limit the willingness to share one's work and learn new principles and perspectives from other disciplines. This type of behavior can unfortunately hamper pluridisciplinary collaborations. Indeed, the recognition and value of the work of peers is crucial to establish mutual trust and respect within a project, and lead to successful pluridisciplinary partnerships (D'Amour *et al.*, 2005). In such cases, the output of the whole becomes greater than the sum of the outputs of its individual parts, which highlights the interdependency between disciplines in the context of complex health issues.

There is no right or wrong type of collaboration, whether multidisciplinary, interdisciplinary or transdisciplinary. It is important to choose a level of integration and collaboration adapted to the context and objective of the project. Transdisciplinary collaboration is not always necessary or adapted to the context of the project. Trying to impose a strong-level of collaboration in a project where conditions are not favorable (e.g. lack of willingness of the participants) can be counter-productive. Willingness to understand other disciplines and their underlying principles is the first step to pave the way for fruitful pluridisciplinary interactions.

Finally, beyond pluridisciplinary collaborations among scientific disciplines or with health professionals, research should also inform policy-makers. Their implication in tool developments – even just by including them in the final loops of co-conception or informing them of the final product depending on what they would prefer – ensures that they become aware of the usefulness of the tool's outputs, and facilitates their decision-making process. The next level would be to bring pluridisciplinary and participatory processes up to the decision-making level, to go beyond policy advising. This would mean involving, or at least informing, decision-makers in the surveillance process and in research efforts to translate scientific results into policies.

Chapter 4

A pluridisciplinary approach to data analysis in the context of risk characterization

4.1. Introduction

A pluridisciplinary approach can also be implemented in the framework of the analysis of EI data. These analyses, conducted by EI teams, aim to characterize a detected health event in order to improve disease knowledge, better inform risk analyses, and target EI systems if needed. Risk detection and characterization are closely linked to risk analysis.

First, it is important to provide definitions of terms that are sometimes used indistinctively: risk analysis, risk assessment, risk estimation and risk evaluation. I present two frameworks that define risk analysis:

-   the Codex Alimentarius Commission (CAC), which is a joint WHO/FAO Food Standards Program, and
-   the OIE Terrestrial Animal Code.

The Codex Alimentarius, or "Food Code", and the OIE Animal Health Code are both a collection of standards, guidelines and codes of practice. OIE provides information on risk analysis relating to the importation of live animals or animal products, while the CAC focuses on the context of microbiological food safety.

In both of these frameworks, the risk analysis process consists of several steps which include risk assessment, risk management and risk communication. In this section, I will focus on risk assessment and will not consider risk management and risk communication which, although they are essential, are not as closely linked with the detection and the characterization of a health event (EI).

The CAC framework (WHO/FAO)

According to the CAC, risk analysis is defined as "a process consisting of *risk assessment*, *risk management* and *risk communication*" (World Health Organization *et al.*, 2011). It emphasizes the

functional separation of the three components while recommending interaction and communication between each component.

Risk assessment provides a framework for the review of relevant information in order to evaluate the possible outcome of an exposure to a health threat. It generally includes both a statement of the nature of the health threat and an estimation of the probability assertion of the harm it may cause. The CAC defines risk assessment as the process including the following steps:

- <u>hazard identification</u>**:** the identification of pathogenic agents capable of causing adverse health effects
- <u>hazard characterization</u>: the evaluation of the nature of the health threat
- <u>exposure assessment</u>: the evaluation of the likely exposure to biological, chemical or physical agents
- <u>risk characterization</u>: the estimation of the uncertainty and the probability of occurrence and severity of adverse health effects based on hazard identification, hazard characterization and exposure assessment

The OIE framework

The OIE risk analysis framework consists of the following steps:

- <u>hazard identification</u>: the identification of the pathogenic agents that could potentially be introduced in the commodity considered for importation
- <u>risk assessment</u>:
  - <u>release assessment</u>: the evaluation of the likelihood of entry/introduction
  - <u>exposure assessment</u>: the evaluation of the likelihood exposure of the target population
  - <u>consequence assessment</u>: the description of consequences (adverse health effects) and the likelihood of their occurrence and magnitude
  - <u>risk estimation:</u> the integration of the results from the release, exposure and consequence assessments to determine appropriate risk management measures
- <u>risk management</u>
- <u>risk communication</u>

Both frameworks have similar components but vary in terms of definitions and order of implementation (Figure 21). Although they share similar definitions, OIE separates hazard identification from risk assessment, while the CAC includes hazard identification in risk assessment. This separation leads to four components of risk analysis for the OIE, compared to three components for the CAC.

According to the CAC, hazard characterization is the first step of risk assessment and aims to evaluate the nature of the possible adverse health effects associated with the health threat. In the OIE framework, the term hazard characterization is not used as such, but it is linked to the consequence assessment, which is also part of risk assessment.

The OIE's risk estimation corresponds to the CAC's risk characterization, and involves a description of the uncertainty and the estimation of the risk in the risk assessment process, linked to the hazard as well as the exposure and its potential impact.

Codex Alimentarius Commission (Codex)				World organisation for Animal Health (OIE , 2010; Codex Alimentarius Commission, 2007)			
Risk analysis	Risk Assessment	Risk communication	Hazard Identification	Risk analysis	Risk Assessment	Risk communication	Hazard identification
			Hazard characterisation				
			Exposure assessment				Entry Assessment
							Exposure assessment
			Risk characterisation				Consequence assessment
			Risk estimate				Risk estimation
	Risk management				Risk management		Risk evaluation
			Option assessment				Option evaluation
							Implementation
			Monitoring and review				Monitoring and review

Figure 21. Comparison of the CAC and OIE frameworks for risk analysis (Henwood, 2018)

Another term that is sometimes used as a substitute for risk analysis or risk assessment is risk evaluation. Although it is not used by the CAC, it is defined by OIE as "the process of comparing the risk estimated in the risk assessment with the reduction in risk expected from the proposed risk management measures," i.e. determine whether risk management measures are warranted. It is included as a step of risk analysis and more specifically risk management.

I helped mobilize EI data and spatio-temporal analyses and models to conduct risk characterization analyses in two case studies, one in human health and the other in animal health. The case studies, presented in this section, illustrate examples of the analysis of EI data led by EI teams in order to characterize health threats and improve knowledge on their spread dynamics. They illustrate the added-value of a pluridisciplinary approach and the knowledge that can be provided by the rapid and preliminary analyses of outbreak data conducted by EI teams, before more in-depth risk analyses. I participated in these case studies during my work experiences at SPC (Roth *et al.*, 2014a) and CIRAD (Mercier *et al.*, 2018).

4.2. The analysis of the circulation of arboviruses in the Pacific (2012-2014)

This first case study presents the added-value of analyzing EI data in a pluridisciplinary context to better understand disease spread patterns through the spatio-temporal analysis of the circulation of arboviruses in the Pacific, from 2012 to 2014.

4.2.1 Introduction to arboviruses in the Pacific

4.2.1.1 Dengue, chikungunya and Zika viruses

Arboviruses are viruses transmitted by arthropods, mainly mosquitoes. The three most important arthropod-borne viral (or arboviral) diseases affecting the Pacific region are dengue, chikungunya and Zika.

Dengue is a severe flu-like illness caused by a flavivirus belonging to the *Flaviviridae* family. Dengue viruses (DENV) are categorized into four serotypes (DENV-1 to 4) based on antigenic characteristics and the immune response they induce in the host. Infection with one of the four serotypes leads to immunity for the specific serotype only (although temporary crossed immunity can be observed between two to nine months after infection), but can increase the probability of potentially lethal complications (called severe dengue or dengue hemorrhagic fever, DHF). Dengue is transmitted by mosquitoes of the *Aedes* genus, mainly *Aedes aegypti* and *Aedes albopictus,* which can transmit any of the four dengue serotypes. Dengue has severe health, social and economic impacts worldwide (World Health Organization, 2017b). With about 2.5 billion people living in endemic areas, dengue is estimated to cause approximately 25 000 deaths and 100 million cases each year, although recent estimates suggest an increase to nearly 390 million annual infections when considering asymptomatic cases (World Health Organization, 2009, 2017b; Bhatt *et al.*, 2013). The global incidence of dengue has dramatically increased in recent decades (30-fold increase in the number of reported cases globally over the past 50 years), and the four serotypes have spread to over a hundred countries in tropical and subtropical regions of Africa, Asia, America and the Pacific (Descloux *et al.*, 2012; World Health Organization, 2017b). As vaccine development is ongoing, vector control, surveillance and education are crucial to mitigate dengue outbreaks.

Chikungunya is an arthropod-borne disease transmitted by *Aedes* mosquitoes, mainly *Aedes aegypti* and *Aedes albopictus.* It is characterized by acute febrile illness associated with severe polyarthralgias (Staples *et al.*, 2009). The clinical illness is often associated with prolonged morbidity and significant economic and social consequences (Enserink, 2007). The chikungunya virus (CHIKV) is an alphavirus belonging to the *Togaviridae* family. Phylogenetic analyses have identified three distinct lineages of CHIKV strains according to phylogenetic origin: West Africa, Asia and East/Central/South Africa (ECSA). In comparison to most other common arboviral infections such as dengue, the rate of asymptomatic cases is lower, and the percentage of infected patients requiring medical attention is higher. No licensed vaccine or specific treatment is currently available.

Zika virus (ZIKV) is a flavivirus belonging to the *Flaviviridae* family, just like the DENV. Zika is transmitted by *Aedes* mosquitoes and causes mild fever, joint pain, conjunctivitis and rash,

although the majority of cases are asymptomatic (Musso *et al.*, 2016). The virus was first isolated from a monkey in the Zika forest of Uganda in 1947 (Kirya *et al.*, 1977). Following this first report, rare sporadic human infections were reported in Africa and Asia (World Health Organization, 2018b). The disease then emerged causing large outbreaks in the Pacific and South America. In March 2015, Brazilian authorities reported a large outbreak of ZIKV infections which soon spread throughout South America and to other regions of the world (World Health Organization, 2018b). First thought to cause mild illness, these Zika outbreaks caused widespread concern due to newly observed neurological complications such as Guillain Barré syndrome and microcephaly (Dejnirattisai *et al.*, 2016). To date, a total of 86 countries and territories have reported ZIKV infections (World Health Organization, 2018b).

Although complications may vary, all three arboviruses share similar clinical symptoms, mosquito vectors, and epidemiology, particularly in urban settings.

4.2.1.2   The Pacific context: health services and mosquito vectors

The Pacific region hosts potential vectors for many arboviruses to which local populations are mostly naïve. This makes the region an ideal setting for the emergence and spread of arboviral diseases, and greatly contributes to the globalization of dengue, chikungunya and Zika viruses as public health threats (Cao-Lormeau and Musso, 2014). Dengue, chikungunya, Zika are all transmitted by mosquitoes of the *Aedes* genus. The two main mosquito vectors of these three arboviruses worldwide are *Aedes albopictus* and *Aedes aegypti*, which both bite during the daytime and have adapted to urban and peri-urban settings. In the Pacific, in addition to these two species, the mosquito species identified as vectors of dengue are *Aedes polynesiensis, Aedes scutellaris, Aedes marshallensis, Aedes cooki, Aedes hebrideus, Aedes hensilli, Aedes kesseli, Aedes pseudoscutellaris, Aedes rotumae* and *Aedes tabu* (Guillaumot, 2005). *Aedes polynesiensis* and other local *Aedes* mosquito species are considered potential vectors for chikungunya and Zika (Musso *et al.*, 2018).

Figure 22 presents the spatial distribution of *Aedes* mosquitoes (subgenus *Stegomyia*), dengue vectors and possible vectors of chikungunya and Zika, in the Pacific region as provided by the Pasteur Institute of New Caledonia in 2014.
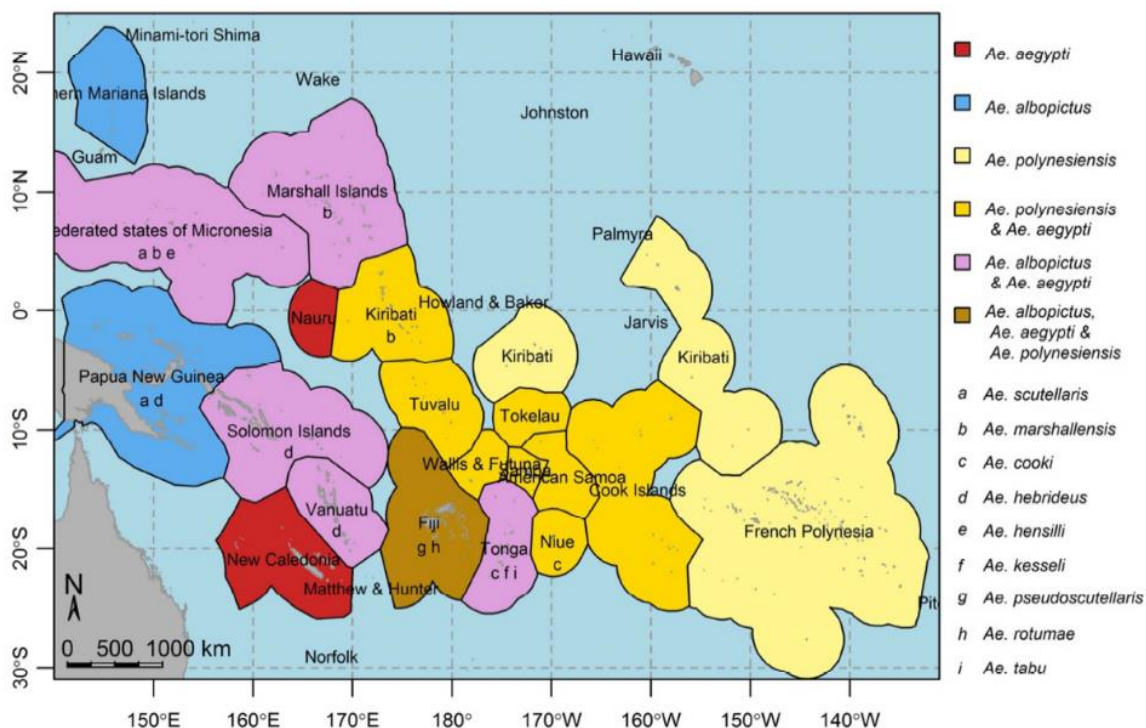
Figure 22. Distribution of dengue vectors in the Pacific (Ae: Aedes; colors correspond to the three main mosquito species Aedes aegypti, Aedes albopictus and Aedes polynesiensis; the presence of another species is noted with a letter) (Teurlai, 2014).

Aedes aegypti is present throughout most of the Pacific region including North Queensland. It is absent from the rest of Australia, New Zealand, Hawaii, Futuna and some other remote islands. It seems to be currently displaced by *Aedes albopictus* in some locations including Papua New Guinea and the Solomon Islands.

4.2.1.3   The evolution of arboviruses in the Pacific

Mosquito-borne viral diseases have a characteristic epidemiology in the Pacific due to a unique insular context. Small populations scattered over thousands of islands, in relative geographic isolation, and with significant mobility due to air travel, increase the risk of exposure to arboviruses (Roth *et al.*, 2014a).

The risk of importation of DENV, ZIKV or CHIKV in Pacific islands can be substantial, depending on travel patterns and the number of airline passengers between countries and territories where these arboviruses are circulating. The risk is especially high for PICTs with many air travelers to and from islands with ongoing circulation. However, in comparison to the large CHIKV epidemic that occurred in the Indian Ocean in 2005, population density in the Pacific is lower, which may decrease the risk of spread of arboviral diseases.

From 2007 to 2014, the epidemiology of arboviruses in the Pacific progressively evolved and the situation gradually worsened. The circulation of a single dominant DENV serotype (DENV-1) changed to the concurrent co-circulation of several serotypes as well as the emergence of new mosquito-borne viruses in the region (Figure 23). In 2014, concomitant outbreaks of dengue, chikungunya and Zika were reported for the first time in the Pacific region.
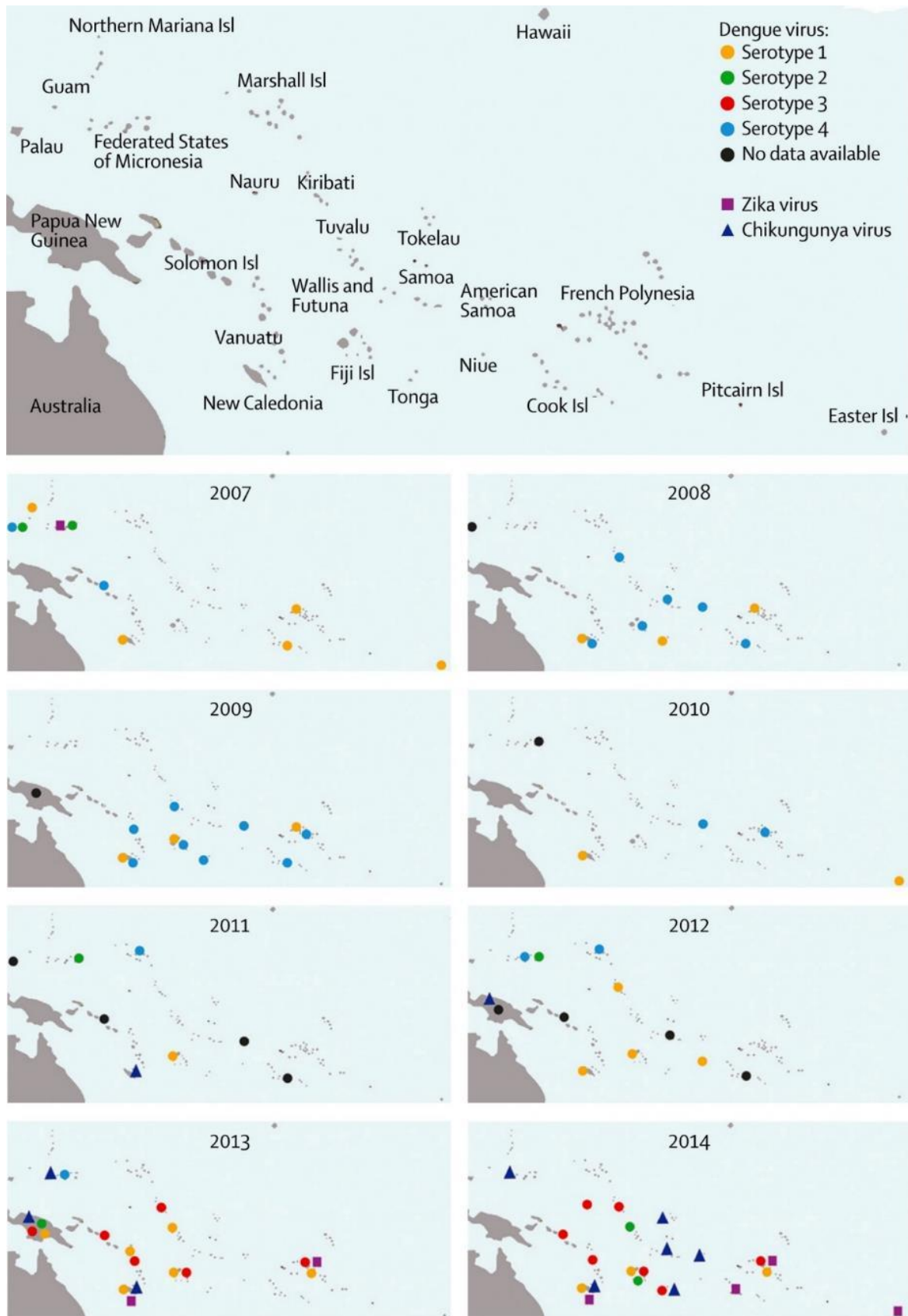
Figure 23. Spread of dengue, chikungunya and Zika viruses in PICTs from 2007 to 2014 (Isl = island; plot marks represent outbreak occurrences) (Cao-Lormeau et al., 2014).

Dengue outbreaks in the Pacific

In the Pacific region, the first dengue outbreaks were reported in Hawaii in 1844, in French Polynesia in 1852, and in Fiji and New Caledonia in 1883 (Perry, 1950; Descloux, 2011). Following World War II, the numerous movements of soldiers between PICTs led to several waves of dengue epidemics, and the dengue virus was isolated and serotyped as DENV-1 for the first time (Steel *et al.*, 2010). From 1950 to 1970, only two dengue epidemics were reported, both in French Polynesia, in 1964 and 1969. In 1971, dengue re-emerged in the Pacific region (not considering the two epidemics in French Polynesia) causing many outbreaks, and cases of DHF were reported for the first time (Singh *et al.*, 2005). Dengue viruses were once again introduced in the Pacific in the early 1970s following an absence of more than 25 years, and have caused many outbreaks since (Gubler *et al.*, 1995).

Today, dengue circulates in the form of epidemic waves. These epidemic waves are linked to the introduction and spread through the region of a new serotype (World Health Organization, 2017b). The spread of a new serotype through several PICTs usually lasts between three to six years, until a new serotype emerges and becomes the dominant serotype (Figure 24) (Teurlai, 2014). As illustrated in Figure 24, waves of dengue serotypes seem to alternate in a specific order: DENV-2, DENV-1, DENV-4 and DENV-3. However, this pattern was identified over the period 1971-2009 which is not long enough for this observation to be robust. An epidemic cycle of the same serotype occurs every 20 to 24 years (1975-1995 for DENV-2, 1978-2000 for DENV-1 and 1984-2008 for DENV-4).
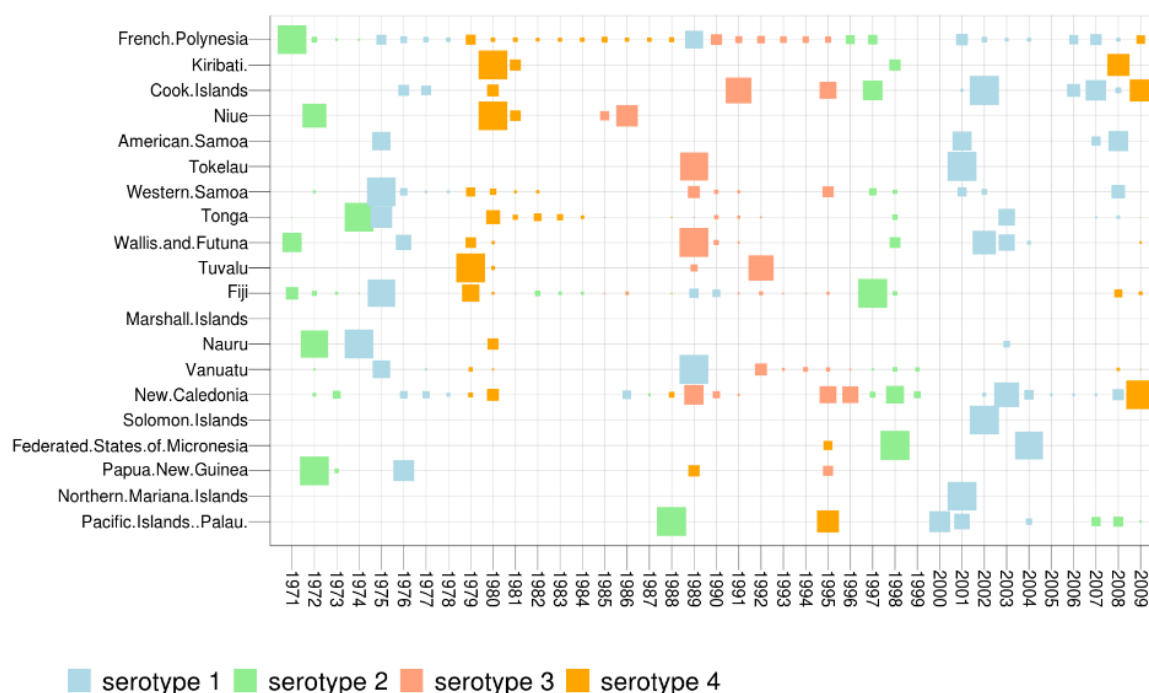

Figure 24. Distribution of dengue cases by country and serotype, from 1917 to 2009 (size of squares proportional to the number of reported cases) (Teurlai, 2014).

Dengue epidemiology is heterogeneous among PICTs. Smaller islands usually sustain dengue transmission for only several months, while larger islands (e.g. New Caledonia) may experience

active circulation of a serotype for several years until the emergence of a new serotype (A-Nuegoonpipat *et al.*, 2004; Li *et al.*, 2010).

The increasing co-circulation of more than one serotype of dengue in many countries of the Western Pacific Region, together with other factors, may be responsible for an increase in the number of DHF cases (World Health Organization, 2017b).

Chikungunya outbreaks in the Pacific

There is little documentation on previous CHIKV circulation in the Pacific, but studies from the 1970s in Papua New Guinea indicate a seroprevalence of CHIKV in the population of up to 30 % (Tesh *et al.*, 1975; Kanamitsu *et al.*, 1979). These findings indicate that CHIKV may have circulated in the region and that there could be immunity among some populations (Roth *et al.*, 2014b).

The first reports of autochthonous chikungunya infections in the Pacific were notified in 2011 in New Caledonia, with 33 confirmed cases (Dupont-Rouzeyrol *et al.*, 2012). Phylogenetic analysis showed that the CHIKV strain isolated in New Caledonia belonged to the Asian lineage, which is consistent with the Indonesian origin of the previously imported CHIKV cases. Subsequently, chikungunya outbreaks were reported in Papua New Guinea in 2012, in New Caledonia and Yap Island of the Federated States of Micronesia in 2013, and in Tonga, American Samoa, Samoa and Tokelau in 2014 (Horwood *et al.*, 2013; Cao-Lormeau and Musso, 2014; Roth *et al.*, 2014b). The CHIKV strain detected in Papua New Guinea has been shown to be of the ECSA genotype, therefore carrying the E1-A226V mutation which was detected in the large CHIKV outbreak in la Réunion in 2005. This mutation has been shown to increase vector competence and epidemic potential (Tsetsarkin *et al.*, 2007; Horwood *et al.*, 2013). Sporadic cases of CHIKV were reported in the region until 2015.

Zika outbreaks in the Pacific

In 2007, the Yap State of the Federated States of Micronesia reported the first outbreak of ZIKV outside of Africa and Asia (Duffy *et al.*, 2009). No subsequent outbreak of Zika was reported in the Pacific until 2013, when the virus re-emerged in French Polynesia causing a large outbreak with an estimated 28 000 human cases (approximately 11% of the population), before spreading throughout the Pacific region (Cao-Lormeau *et al.*, 2014; Musso *et al.*, 2014). Phylogenetic analyses demonstrated that the French Polynesia strain was closely related to the Cambodia 2010 and the Yap State 2007 strains, corroborating previous findings highlighting the expansion of the ZIKV Asian lineage (Cao-Lormeau *et al.*, 2014). Zika continued to spread in the Pacific from 2013 to 2017, with sporadic cases reported in 13 PICTs (Musso *et al.*, 2018).

4.2.2   Context of the study

As a public health surveillance officer at SPC from 2014 to 2016, I was in charge of updating the Pacific regional database of infectious disease outbreaks. This database contained detailed information on the circulation of arboviruses such as the date and location of occurrence, the

serotype and the number of cases reported. This database provided valuable information to monitor the evolution of arboviral circulation in the Pacific, and a historical logging of detailed outbreak data spanning several decades at regional level. With my colleagues of the REI team, we decided it would be useful to analyze such historical data to identify trends in the spatial and temporal circulation of dengue, chikungunya and Zika in the Pacific region. We noticed, through our EI activities, that the number of arbovirus outbreaks seemed to be increasing in the past years. We had also noticed an increasing co-circulation of different types and serotypes of arboviruses simultaneously in the region, sometimes even in the same country. In addition, arboviruses were a topic of interest in New Caledonia in 2014, when we decided to conduct the study. New Caledonia was hit by the largest ever recorded outbreak of dengue at the time with almost 11 000 cases of DENV-1 reported from September 2012 to September 2013. Dengue cases continued to be reported until September 2014, and DENV-3 emerged in February 2014, leading to the co-circulation of DENV-1 and DENV-3 in 2014. Cases of chikungunya and Zika were also recorded on the island in 2013 (for chikungunya) and 2014 (for chikungunya and Zika). This indicates significant and concomitant circulation of several arboviruses in New Caledonia at the time, which prompted concern of an increase in the risk of emergence of arboviruses in New Caledonia and the Pacific region.

We designed and implemented a descriptive study to confirm these hypotheses by analyzing the arbovirus outbreak data that had been gathered by EI over the past two years, 2012-2014. The aim of the study was to describe the circulation of arboviruses, namely dengue, chikungunya and Zika, in the Pacific from 2012 to 2014 in order to identify trends or changes in the epidemiology of these arboviral diseases. As second author, I co-lead the study's implementation. I contributed to the filtering, cleaning, standardization and verification of the collected data relating to outbreaks and vector distribution (e.g. detecting anomalies, filling missing information), as well as the analysis of the data to identify spatial and temporal trends. I also participated in the writing process.

4.2.3   Material and methods

An outbreak is defined by WHO as the occurrence of cases in excess compared to what is normally expected, whether the disease is endemic or not. If the disease is not endemic in a PICT, an outbreak can be just one or a few cases, excluding imported cases because the focus is on local transmission. The definition of an outbreak and its interpretation varies depending on the PICT. Therefore, in our study, we considered an outbreak when it was defined as such by the reporting health authorities in the data source, or when the first autochthonous cases were reported. When the term "outbreak" was not used by authorities, we used the term "circulation". When sporadic cases were continuously reported, we considered a new circulation (or a new outbreak) when no cases had been reported in at least one year.

Data relating to newly reported (not ongoing as of 1st January 2012) outbreaks or circulation of dengue, chikungunya and Zika reported in the Pacific region from 1st January 2012 to 17th September 2014 was extracted from SPC's regional database. This data included case numbers, dates, locations (country, region and village/town if available), information sources, serotypes and other available information. We considered outbreaks reported in the Pacific region, which includes the 22 PICT members of the PPHSN network.

The paper contains a brief description of the regional epidemiological situation of dengue, chikungunya and Zika, as well as a table summary of the collected information relating to outbreaks of these three arboviruses.

The data was aggregated by semester in order to plot the temporal evolution of the number of mosquito-borne outbreaks. Semester 1 corresponds to January-June and semester 2 corresponds to July-December.

The map of dengue, chikungunya and Zika outbreaks was taken from the weekly map of disease alerts in the Pacific, computed by SPC's EI team and sent to PICTs via the PacNet network of the PPHSN. I was in charge of updating this map.

Information relating to the spatial distribution of mosquito vectors was provided by the Pasteur Institute of New Caledonia. The information combined personal knowledge and expertise of entomologists, as well as information from the literature.

4.2.4   Main results

Between 1st January 2012 and 17th September 2014, 12 PICTs reported dengue outbreaks or circulation. Co-circulation of two serotypes was reported in at least five PICTs, including New Caledonia. Chikungunya outbreaks were reported in seven PICTs and Zika in three PICTs (Figure 25). A total of 28 outbreaks or circulation of dengue, chikungunya and Zika were reported in the Pacific region during the study period.

Figure 25. Map of newly reported dengue, chikungunya and Zika virus outbreaks or circulation in the Pacific region from 1st January 2012 to 17th September 2014 (Roth et al., 2014a).

The study identified an increase in the number of different arboviruses circulating in the Pacific from 2012 to 2014, and particularly during the first semester of 2014 (Figure 26). This is mainly due to the emergence of chikungunya in 2011, the re-emergence of Zika in 2013, and the increasing co-circulation of several arboviral diseases and/or serotypes in the same country, such as concurrent outbreaks of two distinct dengue viruses and Zika virus in New Caledonia in 2014.
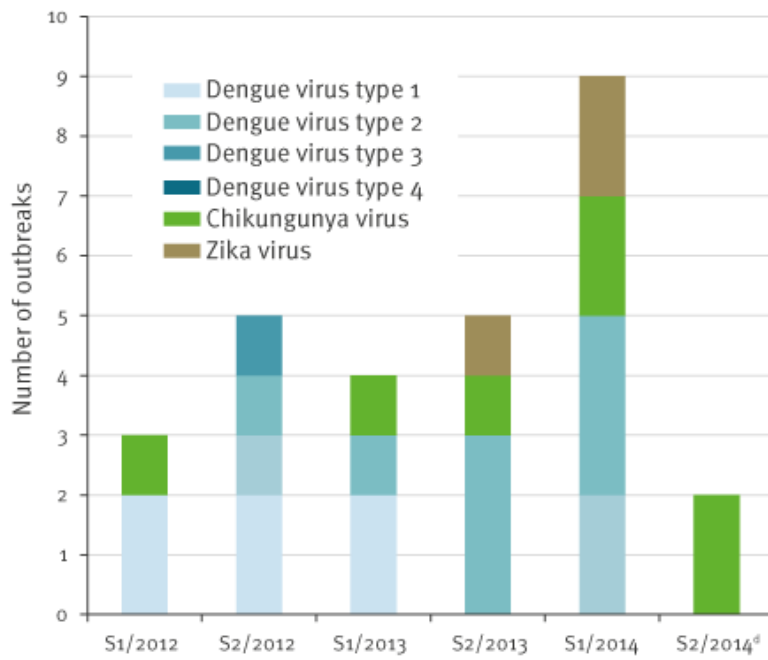
Figure 26. Incidence and etiology of newly reported mosquito-borne virus outbreaks and circulation by semester in the Pacific region from 1st January 2012 to 17th September 2014 (S: semester, semester 2 in 2014 is not complete and only includes reports for 2 out of 6 months) (Roth et al., 2014a).

The study also provides a map of the distribution of *Aedes* mosquito vectors in the Pacific region (Figure 27).
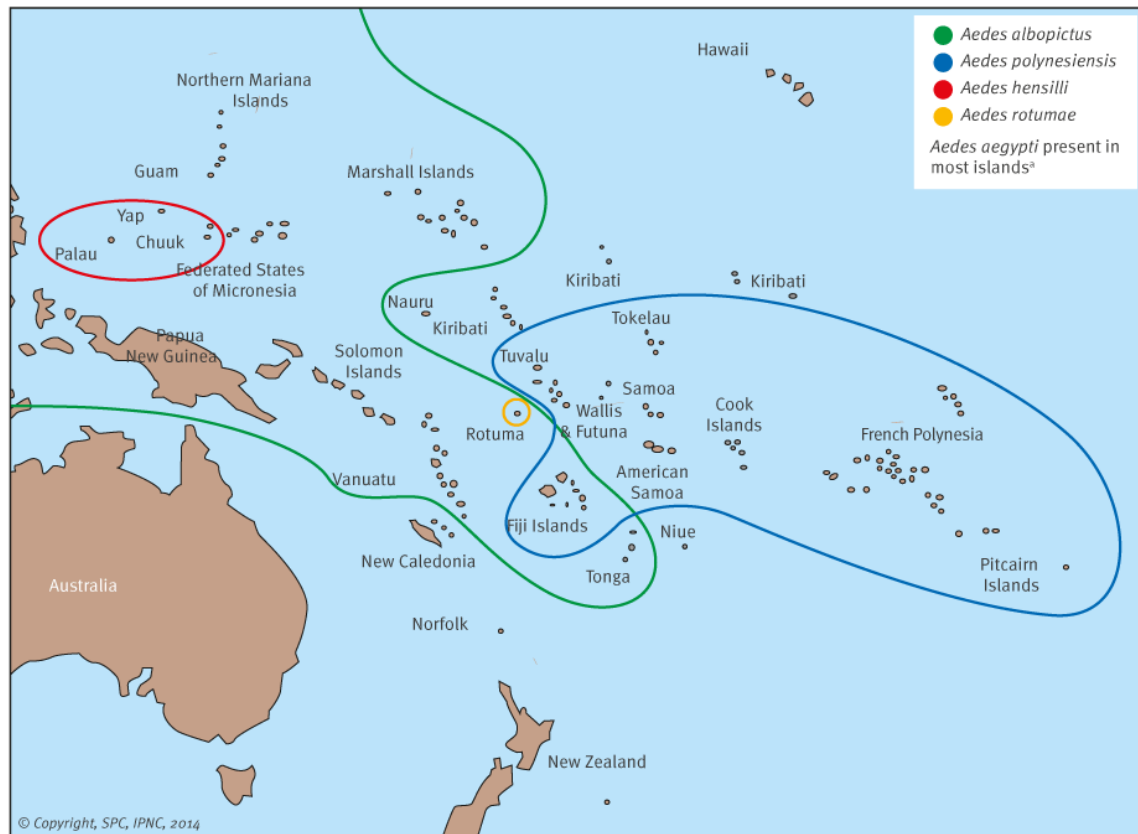
Figure 27. Map of the known distribution of Aedes (Stegomyia) mosquitoes, vectors of dengue and possible vectors of chikungunya and Zika viruses in the Pacific region as of early October 2014 (Roth et al., 2014a).

The paper, entitled "Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014" was published in 2014 in the journal *Eurosurveillance*. The full paper of Roth *et al.*, 2014a is available in Annex 6.

4.2.5   Study discussion

The study provides an example of a rapid, simple and descriptive analysis of EI data, conducted by EI teams, using time series and mapping of outbreaks and vector distributions. The study presented the surveillance and described the epidemiology of dengue, chikungunya and Zika viruses in the Pacific region from 2012 to 2014. The results revealed an increase in the number and diversity of arboviral disease outbreaks and circulation in the Pacific during the study period. Significant mobility within the region and with other parts of the world affected by arboviruses increases the risk of exposure and introduction through the airline network of the Asia-Pacific region. This stresses the need for improved disease surveillance and response to limit the risk of spread at regional and global level, and mitigate the already-heavy burden on PICT health systems.

The epidemiology of arboviruses is distinct in the Pacific due to the insular context with geographically scattered populations. The epidemic pattern of dengue in the Pacific is sporadic with epidemic waves, marked by the introduction of a new and dominant serotype which sweeps through the region every three to five years, with varying durations depending on the size of the naïve population. During my experience, we noticed that these epidemic waves sweeping through the Pacific were also observed for other infectious diseases such as measles. This pattern is linked to travel trends and ethnic groups, and is characteristic of island epidemiology.

However, the epidemiology of dengue seems to be changing with more frequent introductions due to increased mobility and co-circulation of several serotypes. Instead of having a dominant serotype replace the previous serotype, we can observe prolonged and uninterrupted circulation of DENV-1 in the region for over 10 years, as is the case in New Caledonia. The continued circulation of DENV-1 might be linked to a change in urbanization (leading to more cases in winter), more frequent introductions, and perhaps better diagnostic capacities as well. We can argue that dengue is becoming endemic in some regions of the Pacific and that the epidemiology is changing from sporadic epidemic waves to become more similar to the epidemiology of dengue in South-East Asia. This would mean that the epidemiology of dengue in the region is becoming less characteristic of insular epidemiology. Increased co-circulation of arboviruses could also mean increased risk of complications and severe forms including DHF, further increasing the burden on health systems.

In the paper, we consider all three arboviruses (dengue, chikungunya and Zika) because the regional diagnostic capacities for chikungunya and Zika are generally poor. This is the reason why regional surveillance focuses on a syndromic surveillance approach, and allows us to detect an increase in reports of high fever. This, however, means that we might have missed an emergence of chikungunya or Zika. Diagnostic capacities should therefore be improved at regional level through the PPHSN's LabNet service, with material support and training.

The study revealed the added value of analyzing historical data. In a broader sense, looking at 30 years of historical data on the circulation of arboviruses (available in SPC's regional database) is key to understanding the risk of large outbreaks in PICTs. For example, if the previous cases of a particular DENV serotype were reported more than a decade ago, a new introduction of this virus is more likely to cause a large outbreak due to low population immunity. If the previous cases were reported just a year or two beforehand, residual population immunity is likely to be greater (depending on the size of the previous outbreak), perhaps leading to less new cases. Therefore, historical data can be used as a tool to predict the potential size of outbreaks depending on the time of previous circulation in a PICT or at regional level. This is done by SPC and WHO which use data on past arboviral circulation in the Pacific to alert on the risk of large outbreaks following new introductions of arboviruses in the region.

The study also underlines the need for improved vector control capacity, which is often insufficient. The implementation and improvement of entomological surveillance targeting vectors of dengue and other arboviruses could help improve our knowledge on vector distributions and insecticide resistance. This could help improve the map of vector distributions provided in our study, which is mostly based on past entomological surveys dating back to the second half of the 20th century.

In hindsight, it would have been interesting to include more data in our study. Beyond the re-emergence of chikungunya (2011) and the emergence of Zika (2013), which greatly contributed to this unprecedented wave of arboviruses, I believe we should study the epidemiology of dengue in more detail. SPC's regional database contains 30 years of detailed data on the circulation of dengue serotypes in the Pacific, which could be analyzed to confirm the epidemic waves pattern and study more thoroughly this change in epidemiology with the continued circulation of DENV-1. Mathematical models including environmental and socio-economic drivers of dengue, as well

as phylogenetic studies, could help improve our knowledge of this continued circulation of DENV-1 and why other introduced serotypes do not take over and become dominant.

Since the publication of the paper in 2014, dengue has continued to circulate in the Pacific with increased co-circulation of several serotypes. Since 2015, DENV-1, 2 and 3 have circulated in the region with mainly DENV-1 reported in the South and DENV-3 reported in the North of the Pacific region. In 2017, all three serotypes were reported in the region. The change in epidemiology from the circulation of a single dominant serotype to the concurrent co-circulation of several serotypes continued to be observed. DENV-1 circulated uninterruptedly over a decade (2008-2018), with cases even reported in the cold season, in co-circulation with DENV-4 in 2009, DENV-3 in 2014, DENV-2 and 3 in 2017, and DENV-2 in 2018 (Inizan *et al.*, 2019). Chikungunya and Zika viruses continued to circulate in the Pacific with several outbreaks reported in 2014 and 2015, and a few sporadic cases of Zika reported in 2016 and 2017. SPC's REI team is still actively involved in EI and monitors infectious disease outbreaks in the Pacific, including arboviral diseases. Their weekly map of disease alerts is published online through the PacNet network along with an interactive version of the map available online[2]. SPC also continues to strengthen laboratory capacity, particularly relating to diagnostics, in Pacific islands through the LabNet service of the PPHSN, which improves the probability of detecting new arboviral emergence in the region.

The insular context of the Pacific has an impact on the epidemiology of arboviruses in the region, and several factors influence the risk of arbovirus emergence and spread. Isolated and scattered populations, high mobility and travel from dengue-affected regions (e.g. South-East Asia) and between Pacific islands, as well as limited population immunity, increase the risk of arbovirus introduction and spread in the Pacific region, with possible subsequent exportation to other unaffected regions like Europe. In addition, several competent vectors are present in the region, including *Aedes albopictus* and *Aedes polynesiensis*, which increase the risk of regional spread. Non-infectious diseases (e.g. diabetes, obesity) can also increase vulnerability to infectious diseases and should be considered when looking at the susceptibility of populations, particularly in the Pacific where non-communicable disease rates are among the highest in the world. A descriptive spatio-temporal study is the basis before conducting further detailed analyses to better understand the epidemiology of arboviruses. These include seroprevalence studies to clarify the level of population immunity in PICT populations, particularly for CHIKV and ZIKV, to evaluate the level of immunological susceptibility of these populations to new emergences of arboviruses.

Access to timely and reliable information is crucial to mitigate the risk and burden of arboviruses on Pacific health services, particularly given the limited-resources available in some islands. Networks such as the PPHSN are essential to facilitate the exchange of information between health professionals and the rapid implementation of prevention and control measures. Several different information sources are needed to have a more complete overview of the epidemiological circulation of diseases. These include official reports from national and international health authorities, unofficial communications between health professionals through PacNet, and media reports. The PPHSN also highlights the importance of cross-border surveillance. Surveillance by proxy is also used for EI in the Pacific region. It can provide

---

[2] https://www.spc.int/phd/epidemics/

information on the circulation of a disease in a specific country based on the number of imported cases from that country detected in other PICTs. Imported case data is often used as proxy for countries for which limited data is available, such as Papua New Guinea. Indeed, the level of exportation of a disease to other countries is an indicator of the level of disease incidence in the country: the higher the incidence rate, the higher the probability of infecting tourists who can import the disease into their home country upon their return.

Outbreaks of arboviruses in non-tropical regions such as Europe emphasize the need for preparedness and response to mitigate the risk of EIDs. This is particularly true in a context of globalization, with the expansion of air travel facilitating rapid spread of pathogens from endemic/epidemic areas to unaffected regions. Preparedness starts with being aware of ongoing disease circulation in affected regions. The information produced by SPC's EI team is accessible and disseminated at regional level but also beyond. In addition to the regular reports published on PacNet, SPC's online interactive map containing information on ongoing public health alerts is publicly available. It is used by European public health agencies, for example in the ArboFrance network which includes many different stakeholders (e.g. research centers, public health institutes, governmental agencies). This network uses SPC's regional map in their monthly meetings to summarize the epidemiological situation of infectious diseases in the Pacific region, as they do with other regions such as the Caribbean and the Indian Ocean. This allows public health authorities to launch preparedness measures if a risk is detected. Beyond Europe, it is of international interest to stay informed regarding the spread of arboviruses in the Pacific, as we have seen with the spread of Zika virus from French Polynesia to Brazil and its devastating consequences on public health in South America.

The study involved pluridisciplinary collaborations between epidemiologists, health authorities, EI experts, entomologists and microbiologists. It gathered pluridisciplinary and complementary perspectives to better understand the epidemiological dynamics relating both to the pathogen and the vector, and inform risk analyses. Through these data analyses, the EI team was able to confirm an increase in the number of outbreaks of arboviruses in the region, as well as a change in their epidemiology marked by increasing co-circulation. This new knowledge can trigger strengthened arboviral surveillance and inform health authorities on possible surveillance and control strategies, such as increasing serotyping during dengue outbreaks to monitor the possible emergence of a new serotype or increasing vector control measures.

4.3. The estimation of the spread rate of lumpy skin disease in the Balkans (2015-2016)

This second case study showcased another example of a rapid data analysis method, implemented by EI teams, to better characterize disease spread patterns by estimating the spread rate of lumpy skin disease through the Balkans in 2015-2016.

4.3.1 Lumpy skin disease

Lumpy skin disease (LSD) is caused by a poxvirus from the *Capripoxvirus* genus and the *Poxviridae* family. Capripoxviruses also include sheep and goat pox. It is transmitted by arthropod vectors,

but direct/indirect transmission may occur (Babiuk *et al.*, 2008). Although no specific vector has been identified, mosquitoes, biting flies and ticks are believed to play a role in the transmission of the disease. LSD is a species-specific virus infecting only cattle, buffalo and closely related wildlife. It causes fever, lymphadenopathy and very characteristic cutaneous nodules 2-5 cm in diameter, particularly on sparsely haired areas such as the head, neck, limbs, udder, genitalia and perineum (Beard, 2016). Clinical signs range from inapparent to deadly. The diagnosis of LSD is done by detecting viral DNA in blood or tissues of infected animals using polymerase chain reaction (PCR). LSD is included in the list of OIE diseases, and notification of outbreaks to the European Commission and its Member States is mandatory (Council Directive 82/894/EEC[3]).

The main prophylaxis measure is vaccination. In LSD-free countries, the importation of cattle, carcasses, leathers, skins and semen originating from infected areas is banned to avoid the introduction of the disease (World Organisation for Animal Health, 2019a). In infected countries, OIE recommends a strict quarantine to prevent the introduction of infected animals into disease-free herds. In case of an outbreak, animal isolation, animal movement ban, culling of infected animals, incineration of dead animals, disinfection of premises and materials, and vector control measures should be implemented. Prophylaxis measures other than vaccination remain inefficient.

LSD is a transboundary viral disease that has traditionally been found in Southern Africa (Beard, 2016). The disease was limited to Sub-Saharan Africa until 1986 when it spread to the Middle East, Jordan, Egypt and Iraq in 2012-2013. LSD reached Turkey for the first time in 2013 and spread to all parts of the country in 2014. LSD then followed two routes of transmission, North and West. The first route of transmission expanded North spreading to Dagestan, Russia in 2015 and Armenia in 2016. The second route spread West to the Eastern part of Greece in 2015 and to other Balkans countries.

Outbreak in the Balkans in 2015-2016

The LSD virus was first introduced in Greece in August 2015, with two outbreaks reported in cattle farms in the Thrace and Eastern Macedonia regions. In 2015, the disease spread to the Eastern part of Greece with 117 LSD outbreaks reported (Figure 28). The number of outbreaks decreased by December 2015 due to the implementation of control measures (stamping out and mass vaccination in the Northeastern provinces) and winter conditions limiting vector activity (European Food Safety Authority *et al.*, 2018).

In April 2016, LSD reappeared in Greece and spread to Bulgaria and North Macedonia. It then spread to Serbia, Kosovo and Albania in June 2016, and in Montenegro in July 2016. A total of 7 483 outbreaks of LSD were reported in 2016 in seven Eastern European countries (European Food Safety Authority *et al.*, 2019). The disease continued to circulate in North Macedonia, Montenegro and Albania in 2017 with 385 reported outbreaks. The last outbreak of LSD in Europe was reported in Montenegro in October 2017.

---

[3] https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:31982L0894&from=FR

Over 12 000 animals were reported affected by the disease, and most outbreaks were reported between May and August (European Food Safety Authority, 2017).
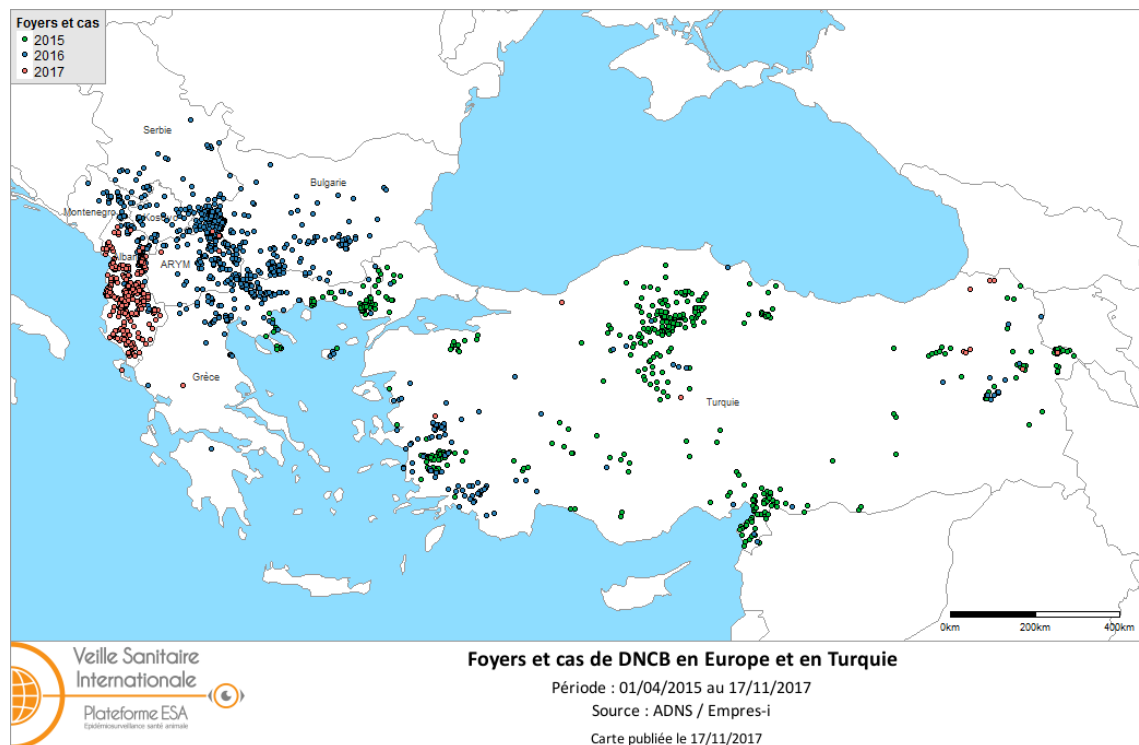

Figure 28. Map of LSD outbreaks reported in Europe and Turkey from April 2015 to November 2017 (data sources: European Commission ADNS & FAO Empres-I; figure source: ESA Platform)

In 2018-2019, sporadic cases were reported in Turkey, Georgia and Russia, but no outbreak of LSD was reported in the Balkans. This confirms the efficiency of the vaccination campaigns and the coordinated control measures implemented in the region (European Food Safety Authority *et al.*, 2019).

A regional vaccination campaign started in 2016 with a live attenuated vaccine based on a homologous strain (Neethling vaccine) in all affected European countries (Kitching, 2003; European Food Safety Authority *et al.*, 2019). In addition, two non-affected countries implemented LSD vaccination as a preventive measure, namely Croatia in 2016-2017 and Bosnia-Herzegovina in 2017. All of the Southeastern European countries (Albania, Bosnia-Herzegovina, Bulgaria, Greece, Kosovo, Montenegro, Serbia and North Macedonia) continued to vaccinate against LSD in 2018, except for Croatia which was recognized as free-from-LSD in 2018, following the implementation of a specific surveillance system as recommended by OIE. Over 2.5 million animals were vaccinated, reaching over 70% of vaccination coverage in the Balkans (European Food Safety Authority *et al.*, 2019). Mass vaccination of cattle against LSD using a live homologous vaccine has proven to be an effective control measure. However, persisting circulation of LSD in the region (Albania in 2017) proves that naïve cattle remain at risk of infection despite high vaccination coverage, and countries should remain vigilant.

4.3.2   Modelling the spread rate of infectious diseases

Pathogens rarely spread homogeneously through space and time, and the mechanisms behind disease spread are often uncertain and variable. Pathogens encounter different levels of resistance, which can be influenced by dispersal mode and other intrinsic factors, the presence of susceptible host or vector, and other environmental, socio-economic and ecological factors (Taylor *et al.*, 2001; Patz *et al.*, 2004; Jones *et al.*, 2008). Modelling the spread of pathogens provides valuable information for risk analysis, for example by estimating the duration of time before the disease affects a specific area depending on the distance to the current disease frontline and the spread velocity, which can in turn improve prevention and control measures.

Previous studies have analyzed and modelled the spread of diseases to identify spatial and temporal patterns. Few studies have looked at the spread rate of diseases, and they usually focused on the general mean estimate of the spread rate over a large area, instead of studying the variation of local spread rates in different areas within the infected perimeter (Gilbert *et al.*, 2010; Tisseuil *et al.*, 2016).

In epidemiology, mechanistic models are generally based on complex equations which require a detailed understanding of disease life-history parameters (e.g. spread rate, incubation period). An example of a mechanistic model often used in epidemiology is the susceptible-infected-recovered (SIR) model which is used to study the spread of a pathogen through a population. When many parameters are involved, the volume of parameter space to test increases and the search for optimal combinations of parameters becomes difficult. In contrast, statistical models characterize the spatio-temporal patterns of invasion to quantify some of their key features (e.g. rate of spread, correlation between date of first invasion and external predictor variables). Although the epidemiological interpretation of their outputs might be more challenging, they are easier to fit to observed spatio-temporal data describing the invasion because they do not require specific parameters. The merits of mechanistic vs statistical models have long been debated in ecology and epidemiology. The mix of both models often represents a programmatic approach: the use of a statistical model to quickly characterize a diseases spread pattern, followed by the application of a mechanistic model to test and validate more specific hypotheses (Dormann *et al.*, 2012). In this section, I will focus on statistical models.

Local spread rates can be estimated using two general types of spatio-temporal analysis approaches. First, boundary displacement (BD) methods are based on the division of the invasion into time steps corresponding to invasion front boundaries (Morin *et al.*, 2009). The local spread rate is estimated as the distance between two successive time steps or front boundaries. On the other hand, trend-surface analysis (TSA) calculates the date of first invasion at outbreak locations and uses a spatial interpolation model to predict this date across the study area. The slope of the surface corresponds to a friction index (units of time /space), and the spread rate is calculated as the inverse of the friction index (Farnsworth *et al.*, 2009). BD is more appropriate when the temporal resolution of the data is coarse (e.g. weekly). The displacement of the invasion front can be evaluated using aggregated data per week. However, it would be problematic to do so with daily data as the error in the estimation of the boundary would be too high compared to the relatively small daily displacements.

Estimating the spatio-temporal distribution of the invasion front to derive the date of first invasion can be done using different interpolation methods: a generalized linear model (GLM), kriging and thin plate spline regression (TPSR). A GLM is used to predict a binomial response (presence/absence) at each time step for the BD approach, and assumes a Gaussian distribution for the dependent variable for the TSA approach. Kriging aims to fit a variogram to outbreak location data within a 300 cell radius using a generalized least squares (GLS) regression (Firestone *et al.*, 2011). TPSR is used to estimate the surface of the date of first invasion (Wood, 2003). The slope of the surface corresponds to a friction index, and its inverse provides the magnitude of the spread rate while the gradient (angle or inclination) of the surface at each point provides to the direction of spread.

Three main methods exist to estimate spread rates (Figure 29) (Tisseuil *et al.*, 2016). With the neighboring method, the spread rate corresponds to the inverse of the local slope of the date of first invasion surface. With the nearest distance method, the distance of each pixel to the nearest previous and following invasion fronts is estimated as the length of the line that connects two sequential invasion front lines passing through a given pixel. With the Delaunay method, the space between two sequential invasion front lines is divided into geometric shapes using a Delaunay triangulation. The median of the triangles is used as the estimate of the displacement. The nearest distance and Delaunay methods both require invasion fronts and are, therefore, more appropriately used with a BD approach which provides a discrete output (presence/absence). As it requires a continuous variable, the neighboring method is more appropriately used with a TSA approach.
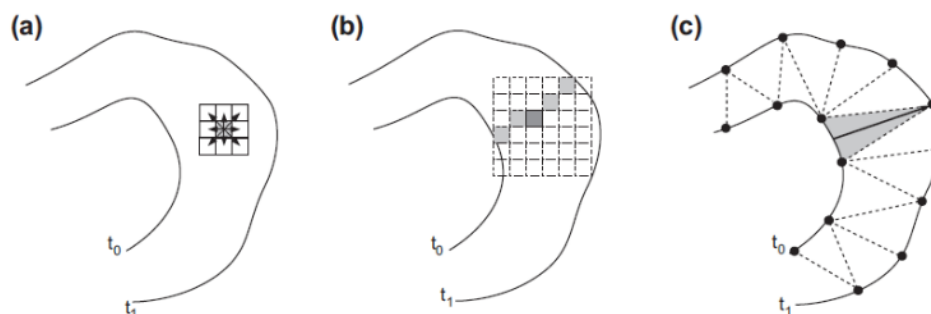

Figure 29. Neighboring (a), nearest distance (b) and Delaunay (c) methods for spread rate quantification (Tisseuil et al., 2016).

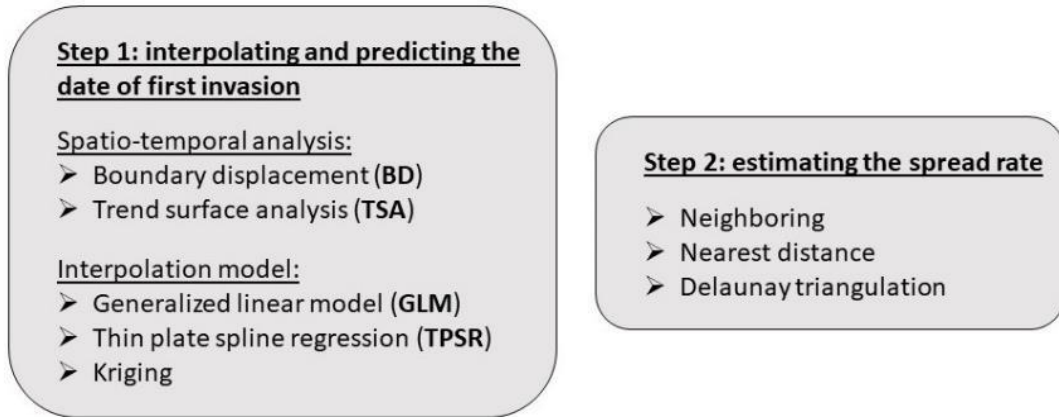Figure 30 summarizes the three processes along with the different methods.

Figure 30. Summary of the three main processes to interpolate and predict the date of first invasion, and to estimate the spread rate (Tisseuil et al., 2016).

4.3.3 Context of the study

The FEIS closely monitored the evolution of the epidemiological situation of LSD in the Balkans, particularly after its rapid spread through Turkey and its introduction into Eastern Greece. The FEIS published 22 reports on the LSD outbreak in the Balkans and Turkey, between August 2015 and December 2016. These reports were published on the ESA Platform website.

LSD is a category 1 health hazard for France according to the French decree of 29th July 2013, relating to the definition of category 1 and 2 health hazards for animal species. It causes significant economic loss in affected countries. Given its worrying introduction into Europe and its subsequent spread, the DGAL of the French Ministry of Agriculture, for whom the ESA Platform carries out EI activities, asked the FEIS to estimate how fast LSD was spreading through the Balkans in order to evaluate the risk of introduction of the disease into France.

CIRAD members of the FEIS team were involved in the previous development of a spread rate model, in collaboration with the University of Brussels (ULB) (Tisseuil *et al.*, 2016). We decided to apply this spread rate model to the outbreak of LSD in the Balkans. As first author, I led the design of the study (methodology, choice of study period and area), participated in the adaptation of the tool to the LSD outbreak, and conducted the analysis of the data in close collaboration with modelling experts, epidemiologists from CIRAD and FEIS members.

4.3.4 Material and methods

The aim of the study was to estimate and analyze the spread rate of LSD outbreaks reported in the Balkans in 2015 and 2016.

LSD outbreaks were described using the geographical coordinates (rounded to the second decimal degree to ensure confidentiality) and the confirmation date of reported outbreaks. The study included LSD outbreaks that occurred in the Balkans (countries cited above) and in the Western part of Turkey (Edirne, Kirklareli and Tekirdag provinces), from 13th May 2015 to 31st December 2016. Outbreak data was extracted from the European Commission's ADNS and the FAO's Empres-I databases.

To identify hotspots of disease occurrence, the density of LSD outbreaks was mapped using hexagonal binning (Carr *et al.*, 1992). The study area was divided into hexagons of 20 km, and outbreak data was spatially aggregated per hexagon.

Disease spread rates were calculated using a combination of TSA, TPSR and a neighboring spread rate estimator, which was identified by previous studies as providing the most robust estimates of local spread rates (Farnsworth *et al.*, 2009; Tisseuil *et al.*, 2016).

The week of first invasion was extracted from the date of occurrence at each outbreak location (Figure 31a), and interpolated across the study area using TPSR (Figure 31b). This generated a 1km resolution raster of the front wave of invasion across the study area.
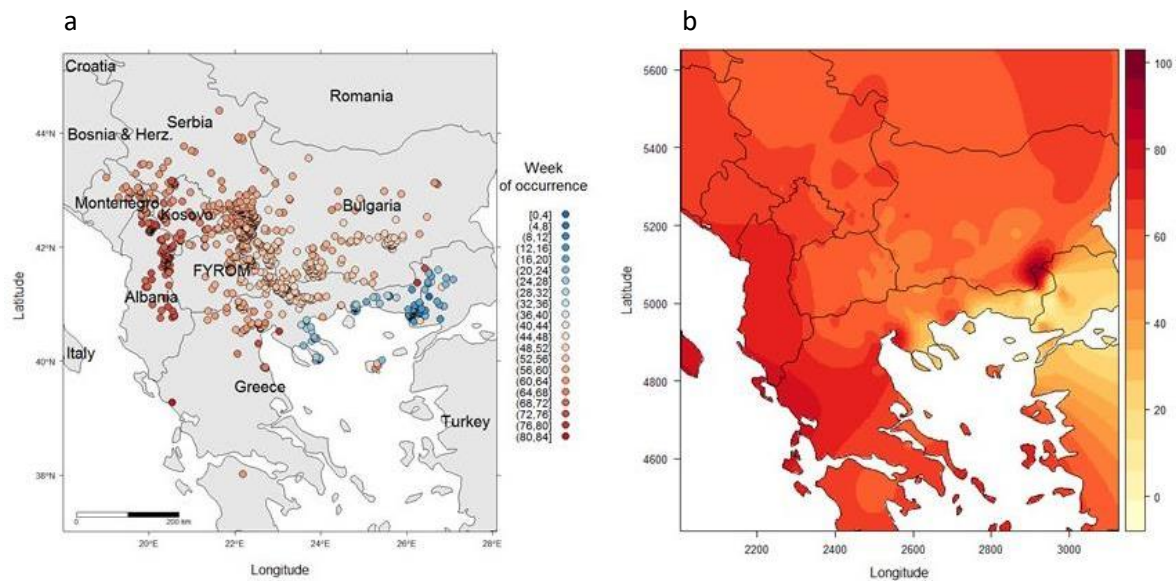
Figure 31. Map of LSD outbreaks according to the week of occurrence (a) and map of the interpolated week of first invasion (b) (Mercier et al., 2018).

A friction index, which represents the landscape resistance to the spread of the disease, was calculated as the difference of week number between each raster cell and its surrounding cells (neighboring method). The friction index (units of time per space) corresponds to the slope of the TPSR surface (Figure 32), and represents the mean duration of time (in weeks) for the virus to spread from a given raster cell to its neighboring cells, i.e. to cross 1 km.
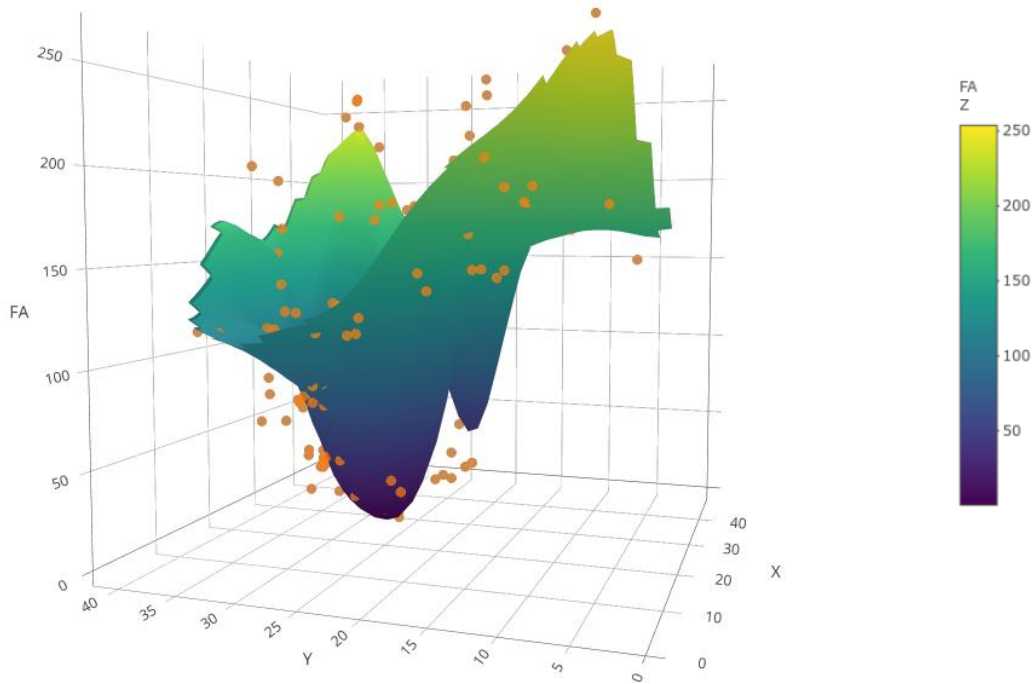
Figure 32. The estimated surface of the first date of invasion using TPSR. The X and Y axes represent space (km) and the z axis represents time (FA: first arrival or number of days since the first outbreak). Each point represents a reported outbreak.

The spread rate (week/km) was calculated as the inverse of the friction index (km/week). A steep slope means that the disease needed a lot of time to pass from one pixel to the next (high friction, low spread rate). Conversely, a flat surface on a pixel means that the disease passed through the pixel almost instantaneously (low friction, high spread rate). The error linked to the interpolation tends to increase as the distance from the observed outbreak location increases. Such errors tend to artificially inflate spread rate values. Therefore, the values of the spread rates were extracted at outbreak locations only, in order to minimize the bias caused by interpolation and limit edge effects.

Assuming that the spread of LSD is the outcome of multiple underlying processes (e.g. vector transmission, cattle movements), the estimated values of spread rates at outbreak locations should follow a mixture of Gaussian distributions (multi-modal distribution). A mixture model with a bootstrap procedure of 500 replications was used to estimate the number of Gaussian components.

Finally, the mean spread rate and its evolution since the first LSD introduction (year 1 and year 2) and according to seasons were estimated using a GLS model.

All the analyses were performed using the R software (R Core Team, 2019).

4.3.5   Main results

The median spread rate of LSD through the Balkans was estimated at 7.3 km/week (95% CI: 4.4 - 12.5 km/week). GLS estimates revealed an almost constant mean spread rate of 11 km/week across seasons, except during summer-fall 2015 when the spread rate estimate dropped to 6.5 km/week.

We identified hotspots of LSD transmission on the density map, which are mainly located along borders (e.g. Turkey-Greece, Greece-Bulgaria or Serbia-Bulgaria-FYROM) (Figure 33). We also highlighted the seasonality of LSD transmission, with an increased transmission from May to August.
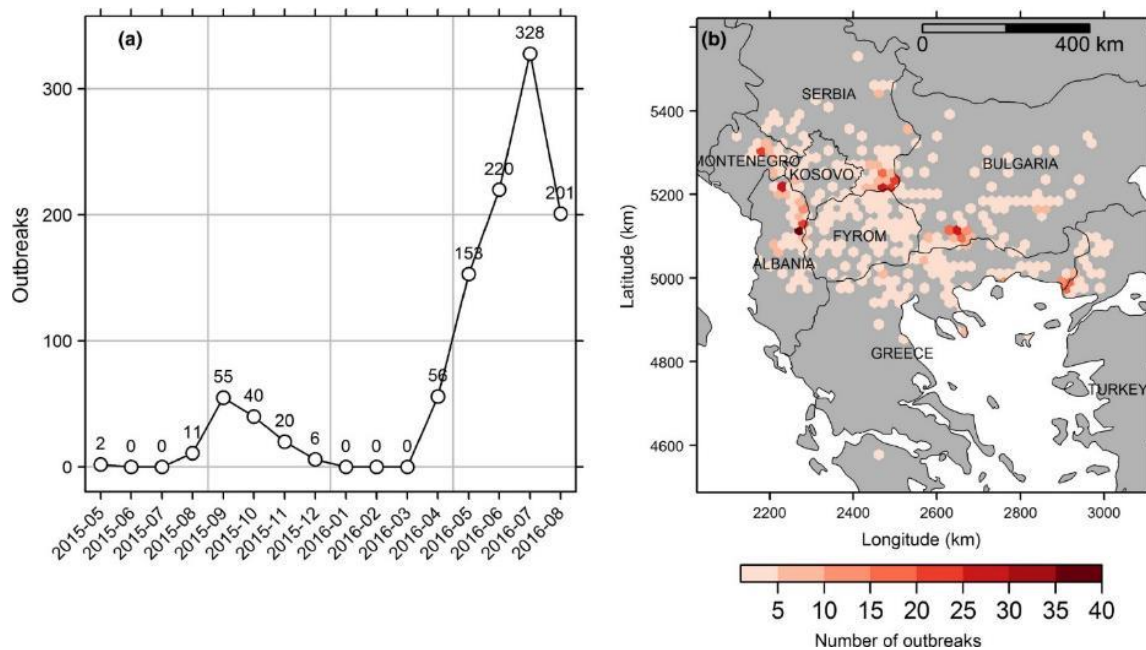
Figure 33. Time series of the number of reported outbreaks per month (a) and the density map of reported outbreaks (b) of LSD in the Balkans from May 2015 to August 2016 (FYROM = Former Yugoslav Republic of Macedonia) (Mercier et al., 2018).

Interpolated spread rate values across the study area were highly heterogeneous, but showed a well-structured pattern. The spread rate was higher in the latest frontline areas (with respect to the date of first occurrence), and lower and patchy in the center of the infected regions (Figure 34a).

We identified two modal distributions corresponding to two diffusion processes (Figure 34b). The first diffusion process corresponds to low spread rates (< 15 km/week), while the other diffusion process is linked to high spread rates (> 15 km/week, with a maximum value of 543.6 km/week).
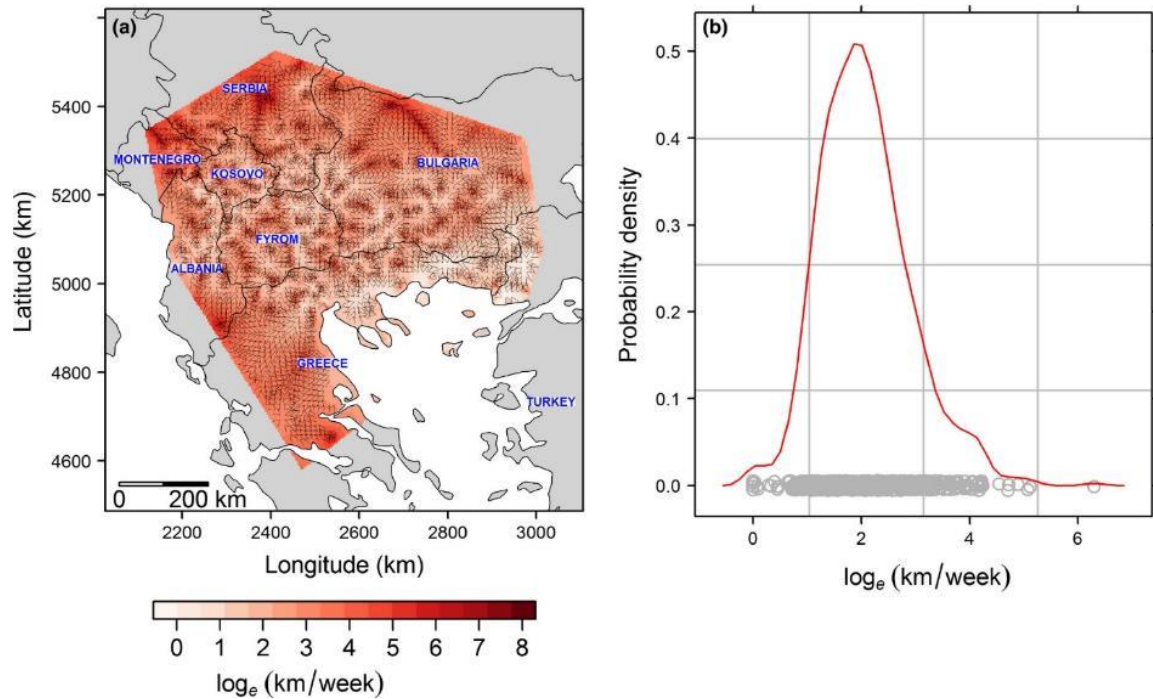
Figure 34. Lumpy skin disease spread rate in the Balkans from May 2015 to August 2016. (a) Map of estimated spread rates: the colored region represents the convex hull encompassing the data points, the small arrow heads represent the direction of spread; (b) probability distribution: the grey dots on the x axis represent the observed data (FYROM = Former Yugoslav Republic of Macedonia) (Mercier et al., 2018).

The paper, entitled "Spread rate of lumpy skin disease in the Balkans, 2015-2016", was published as a short communication in the journal *Transboundary and Emerging Diseases* in 2018. The full paper Mercier *et al.,* 2018 is available in Annex 7.

4.3.6   Study discussion

The median spread rate of 7.3 km/week is in line with similar results obtained by EFSA in a 2017 report on the LSD outbreak in the Balkans, with an estimated spread rate of 2 km/day (75% percentile) (European Food Safety Authority, 2017). The increased transmission of LSD from May to August is most likely linked to warmer temperatures and increased vector activity.

The hotspots of LSD transmission located at borders might be due to the European regulation at the time, which enabled vaccination only after a first detection in the country. This first detection often occurred along borders with infected countries, and the implementation of vaccine campaigns limited the spread of the disease to other parts of the country.

The results of the study identified two diffusion processes. The first diffusion process with low spread rates (< 15 km/week) corresponds to local-level transmission, linked to vector transmission or contact between infected and naïve animals. The other diffusion process corresponding to high spread rates (> 15 km/week, with a maximum value of 543.6 km/week) indicates "jumps" in the disease frontline, which might be linked to the transport of infected animals (e.g. cattle markets, trade, slaughterhouses). This jump leads to a new introduction of the disease in an unaffected area, followed by local-level diffusion unless effective control measures are implemented. These jumps correspond to hotspots on the density map.

The data needed as input for the model is limited (date and geographic location of outbreaks) and, therefore, easy and quick to collect. The data needs to be updated in real-time in order to accurately reflect the displacement of the disease frontline. Delayed or under-reporting can lead to bias by artificially creating jumps in the disease spread due to the absence of data. This can make the maximum estimated spread rate value unstable, and explains why we consider the median value. Spread rate estimates should, therefore, be regularly updated according to newly acquired data. The data sources used in the study were the European Commission's ADNS database and the FAO's Empres-I database. Combining several data sources is necessary to have a more complete dataset, but is a cumbersome task. To avoid multiple notifications by countries and improve inter-connection between notification systems, OIE and the European Commission are currently working on combining the WAHIS and ADNS systems into a single and common database of animal disease outbreaks. This should facilitate the reporting process for health authorities and the access to timely animal disease information online.

In hindsight, we could have improved our model by taking into account vaccination and other control measures that were set up in different Balkan countries as the disease progressed through the region. The implementation of vaccination campaigns increased host immunity and slowed disease spread to unaffected regions. Most countries implemented control measures following the first report of an outbreak in the country. This could explain why most of the observed hotspots are located along borders, which are areas at high risk of disease spread when the neighboring country is affected. Further spread in-land is usually mitigated through the timely implementation of control measures. Another important aspect is the fact that the Neethling vaccine used in the Balkans in 2015-2016 is not a 'Differentiating Infected animals versus Vaccinated Animals' (DIVA) vaccine. This means it is impossible to distinguish the immune response of a vaccinated animal and an infected animal. This incapacity to differentiate between vaccination and infection can impact the surveillance of the disease, the monitoring of its spread and proving disease-free status (Beard, 2016). This is the reason why CIRAD, which is a national reference laboratory for poxviruses in France, is currently working on developing a capripoxvirus DIVA vaccine strain.

The effective control of the spread of LSD remains difficult due to gaps in our knowledge of the disease, particularly relating to transmission modes, efficient serological testing and the lack of a suitable vaccine (Beard, 2016). We still need to understand the transmission dynamics between animals and between herds, and the impact of different environments on this transmission. This is particularly true regarding the role of vector transmission and which vectors are implicated. Better knowledge on vector transmission would help target vector control measures. The availability of simple, affordable and sensitive serological tests would improve the detection of historically or sub-clinically infected animals, thus improving our knowledge of past and present disease circulation and informing disease-free status. There is, therefore, a need to target future research efforts on these gaps and set up coordinated regional response to limit the risk of re-emergence of LSD in Europe, particularly in warmer months during increased vector activity.

The results of the spread rate model were used to inform risk analyses for France conducted by ANSES (ANSES, 2017). The estimate of the spread rate was used to determine the size of the area around a first potential outbreak to consider for vaccination, as well as the size of the vaccine bank necessary to ensure efficient vaccination around this first outbreak. The results of our study were

also cited by EFSA to highlight the seasonality of LSD spread (European Food Safety Authority *et al.*, 2019).

The spread rate model was designed to be generic and applicable to other infectious diseases that spread with a frontline of infection. It was applied to LSD in the Balkans as presented in the case study, but it was also used by the FEIS to analyze the spread of other diseases of concern such as ASF in Belgium from August 2018 to February 2019 (Muñoz *et al.*, 2020). I was second author of that study, which was led by an expert in modelling.

An R package named "spreadrate" was created by CIRAD modelling experts to facilitate the use of the spread rate model by the FEIS and other health professionals (R, 2019). CIRAD is continuing methodological developments to improve the model, which include the integration of covariates to analyze the effect of environmental and socio-economic drivers, the estimation of the uncertainty linked to the model, and the modelling of the spread rates to establish predictions beyond the study area. Another way to improve the model would be to incorporate simulated outbreak data, as was done by other studies, instead of observed data which might suffer from under or delayed reporting (Tisseuil *et al.*, 2016). Comparing the two methods (use of simulation data vs use of real data) would provide useful information for further disease spread modelling.

This case study presented an example of a pluridisciplinary collaboration between epidemiologists, EI experts and modelling experts in the aim of characterizing disease spread dynamics and improving prediction models. It illustrates the added-value of integrating end-users in the development and implementation of spatio-temporal models so they can better understand the underlying processes of the model, along with its advantages and limitations, which are useful to interpret the outputs. The FEIS used a tool that was already available through existing collaborations to better characterize the health hazard and improve the quality of the information on the LSD outbreak reported to French authorities and animal health professionals. Collaboration with modelling experts to create an R package with a user-friendly interface allows a better appropriation of the tool by health professionals for rapid analysis of outbreak data.

In hindsight, I would have strengthened the involvement of end-users, specifically EI experts in the implementation but also the design and development of the model. Epidemiologists were involved in its development, but not the leaders of the EI system, which are the main end-users. This implies that the EI leaders of the FEIS have to rely on the epidemiologist of the group that participated in the tool's design to run the model in order to obtain new knowledge and characterize health threats. Modelling is a complex process, but EI needs to ensure the continuity of activity and cannot depend on the availability of specific experts. Therefore, similarly to PADI-web improvement suggestions, a representative group of end-users, including EI team leaders, could have been more involved in the adaptation of the tool to LSD to understand the underlying processes of the modelling approach and be able to run the model using the user-friendly R package and interpret the outputs. However, EI team leaders might not always have available time to directly participate in the design and development process. In this case, the intermediary link between research developments and operational activities (i.e. the epidemiologist involved in the tool's development) should be more proactive in the transmission of knowledge about the tool's process and use. This can be done through training sessions that also include theoretical

explanations of the underlying processes to ensure clear and autonomous interpretation of the model's results.

4.4. Section discussion

This section is based on two case studies which both present examples of pluridisciplinary collaborations in the context of analysis of health data gathered by EI services to improve the characterization of health threats.

The case study on arboviruses in the Pacific aimed to characterize the change in the epidemiology of dengue, chikungunya and Zika relating to epidemic waves with alternating dominant serotypes, as well as the increase and diversification of outbreaks. Identifying spatial and temporal spread patterns allows a better understanding of the disease dynamics in an insular context like the Pacific region. It enables health authorities to better anticipate epidemic waves and target periods and countries at higher risk depending on the virus or the serotypes.

The case study on LSD in the Balkans provided an estimate of the spread rate of the disease to inform risk analyses of potential introduction into France. This modelling study provided insight about the different transmission modes of diseases linked to various external factors including mobility, and the impact of vaccination on the velocity of spread of the disease.

Both studies implemented a descriptive analysis with time series and maps of outbreaks, allowing the identification of hotspots of viral transmission and disease seasonality. The descriptive analysis of spread patterns of arboviruses in the Pacific was simple to conduct. It provided useful information on spread pattern in a limited amount of time, thus ensuring its compatibility with EI activities. The spread rate model is more complex but was developed ahead of time by researchers. They made sure the model was easy to use and created an R package to ensure rapid implementation and facilitate user appropriation. EI activities require a certain reactivity to minimize delays between the detection and the reporting of the health threats to allow the timely implementation of control measures. This short time span is not compatible with complex and long analyses that would require time and multiple expert inputs. The two case studies illustrate examples of analyses that are quick to implement. Providing timely knowledge on health threats (e.g. spread rate and pattern, seasonality, drivers) also allows experts to better understand the epidemiological phenomenon and target surveillance efforts depending on specific periods or areas at higher risk. This will, in turn, inform decision-makers who will be able to implement targeted control measures.

The arbovirus and LSD case studies provided examples of pluridisciplinary collaborations between epidemiologists, EI experts, entomologists, microbiologists and modelling experts in order to improve the characterization and prediction of health threats. These two case studies illustrate the added-value of integrating EI expertise in the analysis of health data to better inform risk analyses and disease control strategies. In the same sense that including disease experts in risk analyses for decision-making can improve knowledge of the disease system, the inclusion of EI experts can improve knowledge relating to the epidemiological situation of the disease and its context (e.g. past and ongoing circulation in the affected region to better describe seasonality or current immunity, or the epidemiological situation in surrounding regions or at global level to

analyze possible sources of introduction). EI experts also have access to the latest information and can update in near real-time the data used for risk analyses.

It is important to strengthen the links between the different domains of disease surveillance and control, from the detection of health threats and their characterization to the analysis of the risk they represent for specific populations and the recommendation of appropriate response measures. The different steps should be closely linked, either by involving the same teams or by promoting collaborations between dedicated experts. The involvement of EI teams in what is referred to as risk analysis varies depending on the country and the institution. Here are two examples of the scope of EI activities in human health at European level with ECDC, and in animal health at national level with the FEIS.

In France, before the ESA Platform and its centralized EI system, French authorities in charge of risk management (Ministry of Agriculture, DGAL) and risk analysis (ANSES) both conducted their own EI internally. This shows that risk detection and characterization are the common first steps to provide timely and complete information for further analysis and management purposes. The creation of the FEIS was meant to centralize EI activities, and strengthen, improve and formalize the system. By including members of DGAL and ANSES into the FEIS team, EI activities benefit from their expertise and perspectives as end-users of the validated and interpreted information generated by the FEIS. However, this collaboration is not bilateral as the FEIS is not involved in risk analyses or discussions relating to risk management.

At European level, the EI team at ECDC is in charge of risk detection and characterization. Contrary to the FEIS, they are also involved in risk analysis, notably the rapid risk assessments (RRA) regularly produced to provide epidemiological information and assess the risk for European Member States. During my EI training at ECDC, I participated in the RRA on dengue in Réunion Island (ECDC, 2018). With the EI team, I provided updated epidemiological information to characterize the outbreak, such as a description of the epidemiological evolution, an epicurve of the number of dengue cases over time and a map of cases worldwide. The RRA brings together complementary expertise, with disease experts from other units and the EI team, to compile a well-informed and rapid risk analysis of a public health situation. Providing real-time information on outbreak occurrence and spread is crucial to correctly reflect the current epidemiological situation and analyze its evolution.

In international organizations such as ECDC and WHO, EI teams take the lead for risk analyses and can request input from disease experts depending on the extent of the risk analysis. This is reflected in the name of the EI team in WHO: the "Detection, Verification and Risk Assessment" team. In contrast, disease experts at ANSES are in charge of risk analyses for animal health in France, with no interaction with the EI team.

Many agencies or institutions involved in human or veterinary health conduct their own targeted EI despite having a dedicated EI team or mandate. For example, disease experts monitor outbreak events of a disease at local, national or global scale to stay informed on the current epidemiological situation of their disease of expertise. By sharing specific expertise, tools and resources, **centralizing EI expertise** can improve the quality of the information produced, thus better informing decision-makers and authorities in charge of risk management and communication. It facilitates the work through mutualization of expertise, tools and resources,

and allows dedicated experts to conduct EI activities in a more efficient way (e.g. provide more detailed and timely information through the use of several information sources or use of automated tools). It does not, however, mean that it should be excluded from other processes such as risk analysis. Links should be established between the detection and characterization of a threat and the analysis of the risk it represents, for instance to ensure that up-to-date data on the epidemiological situation is used for risk analyses.

Pluridisciplinary collaborations with researchers to develop spatio-temporal models analyzing disease data (e.g. disease spread models) provides access of health professionals to innovative data analysis methods aiming at better understanding disease emergence and spread dynamics. This was the case for the spread rate model developed in collaboration with modelers and used in the FEIS' daily EI activities. Creating user-friendly applications, using the R and R Shiny software for example, can further facilitate the use of the tool by health professionals involved in EI on a daily basis. A few examples from my experience include the R package named "spreadrate" created by researchers to facilitate implementation of the spread rate model by health professionals, or the interactive map of disease outbreaks monitored by the FEIS. This interactive map, available on the ESA Platform website[4], allows health professionals to visualize the evolution of disease outbreaks in Europe using interactive features on a map and time series. This map was developed with researchers from CIRAD which are also involved in the FEIS and understand user needs in terms of visualization of disease data.

---

[4] https://www.plateforme-esa.fr/page/vsi-carte-interactive-multi-maladies

Chapter 5

Discussion

5.1. Summary of my contributions

In this manuscript, I have illustrated examples of pluridisciplinary collaborations at different steps of the EI process, from data collection to data analysis and reporting. I presented four case studies from my seven years of experience working in EI in research institutes and intergovernmental organizations, in human and animal health, in the Pacific and Europe. Two of these case studies (Chapter 3) involved the development of automated tools to facilitate EI activities in two different contexts: routine EI for animal health and enhanced surveillance for human mass gatherings. The two other case studies (Chapter 4) focused on the analysis of EI data to characterize the health threat, by providing information on spatio-temporal trends or estimated spread rates.

In these case studies, I contributed on two levels: a methodological level and a meta-level centered on the integration of expert knowledge.

First, I took part in the development of innovative methodologies, their translation into a user-friendly tool and the integration of this tool in existing systems. By representing end-users, I ensured the tool fit their needs and helped translate these needs into technical requirements. This contributed to the development of user-friendly and functional features for a sustainable use of the tool by end-users and an efficient implementation in existing surveillance systems.

Second, I promoted the integration of expert knowledge and the inclusion of end-users in the tool development process. I was also instrumental in the global consolidation of the different methodological innovations by sharing the developed tools and methods in a One Health context through networks, in the context of research projects, or at scientific meetings and conferences. This allows the tools and methods to be used by other stakeholders and adapted to other contexts such as human health or plant health. For instance, the PADI-web tool developments were shared with the French plant health surveillance platform so that they may benefit from developments in automated monitoring of information sources on the Internet. Another example is the H2020 MOOD project which provides a platform to share existing tools, including PADI-web and the spread rate model, and co-constructing new tools with health professionals from other disciplines.

These developments can also be integrated in existing EI systems. PADI-web provides timely information from unofficial sources, that require filtering and validation by experts to become

structured information. This unofficial information can complement official sources, such as syndromic surveillance (OE). This combination of sources can improve the quality of the health threat characterization (descriptive analysis with time series and mapping, as well as spread rate modelling) and the subsequent risk analyses. PADI-web has been integrated in the FEIS' activities on an *ad hoc* basis, while OE strengthened Pohnpei's syndromic surveillance system.

By illustrating a pluridisciplinary approach involving epidemiologists, microbiologists, entomologists and computer scientists, the case studies presented in Chapter 3 focused on the early detection and alerting of health threats, and the case studies from Chapter 4 analyzed these alerts to improve the characterization and prediction of health threats. Each case study mobilized different data, methods and stakeholders. The data collected and the alerts detected through the tools developed in Chapter 3 could feed into the analyses developed in Chapter 4. For instance, OE could go beyond syndromic surveillance and include a media monitoring component derived from PADI-web. The spatio-temporal analysis of arboviruses used EI data from SPC's regional database, which included a significant amount of information from online media sources. The outputs from the analyses presented in Chapter 4 can prompt EI experts to strengthen data collection or improve the sensitivity of the early alerting process depending on at-risk areas or periods for example.

5.2. Defining epidemic intelligence

Definition of EI

I agree with the definitions of EI provided by ECDC and WHO, and would define EI as the process of early identification, verification, assessment and reporting of potential health threats in order to timely alert and inform health authorities.

WHO often uses the term EBS instead of EI to refer to the rapid detection of outbreak events, as is the case for the COVID-19 surveillance strategy guidelines (World Health Organization, 2020a). EBS is an increasingly important component of EI given the recent developments in online communication outlets. Therefore, some organizations will use the term EBS instead of EI, referring to the same process. However, setting up an EBS component requires additional resources. The proportion of EBS and IBS in EI varies from one system to another, and depends largely on the scope of the system, the available resources and the local context (e.g. surveillance capacity, infrastructures).

According to ECDC, EI activities include risk monitoring and risk assessment, but not risk management (Paquet *et al.*, 2006). On the contrary, the CAC and the OIE include risk management in the risk analysis process. I believe that the management of the risk should remain separate from its detection and analysis to ensure objectivity and avoid conflict of interests in the recommendation vs the implementation of control measures (Figure 35). Such is the case, for instance, with ECDC and the French animal health authorities.

In the OIE framework, the identification of the health hazard is separate from the risk assessment. I believe this step of detecting, defining and characterizing the health threat is part of EI because the early detection of a health threat requires a specific expertise that I consider distinct from the

disease, environment or policy-specific expertise required for risk assessment and management (Figure 35). The characterization is essential because it allows the interpretation of the event through the collection of pertinent information on the context of the outbreak such as affected hosts, detected serotype or past and present circulation. Although EI might not be able to provide pathogen-related information such as host, vector or genetic features, it can provide useful information on the past/present circulation of the disease in/around the affected area and details on the epidemiological situation (e.g. reported cases, mortality, countries and hosts affected, observed spread, changes in the epidemiological situation).

The identification of the hazard is the first step in analyzing the risk it represents. Therefore, we can consider that EI provides information for the first step of risk analysis. In my experience and perspective (which provides the EI point of view as opposed to CAC and OIE frameworks), risk analysis corresponds to risk assessment and comes between risk detection and risk management (Figure 35). If risk assessment includes the release, exposure and consequence assessments leading to a quantified risk estimation, it requires specific disease expertise that differs from the EI expertise (i.e. how to timely detect, verify and characterize health events). It is challenging to set a clearly-defined boundary between EI and risk analysis – nor is it adapted to a global and integrated approach – because the **whole process of risk detection and analysis is continuous**. There needs to be at least a rapid and preliminary risk assessment to determine whether the detected health event represents a potential threat or not, without necessarily quantifying this risk. Therefore, the boundary is not clearly defined between EI and risk assessment. In France in the context of animal health, the two are separate and led by dedicated teams. At ECDC, however, the EI team leads the rapid risk assessments in close collaboration with disease-specific experts and teams. As different institutions have different mandates and provide different organizational structures, this does not exclude the possibility of integrating the EI expertise within a larger and pluridisciplinary team which can also include risk assessment and risk management experts. If both are not led by the same team, EI should be closely linked and collaborate with the risk assessment process, i.e. be involved and contribute with timely information on the epidemiological situation. Each step of the risk analysis process should be interlinked with strong interactions and collaborations between experts involved in each activity, as advised in the CAC by WHO and FAO.

CAC (WHO/FAO)			OIE			My framework	
Risk analysis	Risk assessment	Hazard identification	Risk analysis	Risk assessment	Hazard identification	EI	Hazard detection
		Hazard characterization					Hazard characterization
		Exposure assessment			Entry assessment	Risk analysis = risk assessment	
					Exposure assessment		
		Risk characterization			Consequence assessment		
		Risk estimate			Risk estimation		
	Risk management			Risk management	Risk evaluation	Risk management	
		Option assessment			Option evaluation		
					Implementation		
		Monitoring and review			Monitoring and review		

Figure 35. My proposed framework of epidemic intelligence and risk analysis, compared to the CAC and OIE frameworks

EI provides real-time information to inform risk analyses (Chapter 3), which in turn generate new knowledge on disease emergence and spread dynamics (Chapter 4) that can help target surveillance activities (Figure 36). For example, EI can enhance its activities during at-risk periods or for at-risk areas for specific diseases identified by mathematical models, which use EI data as input.
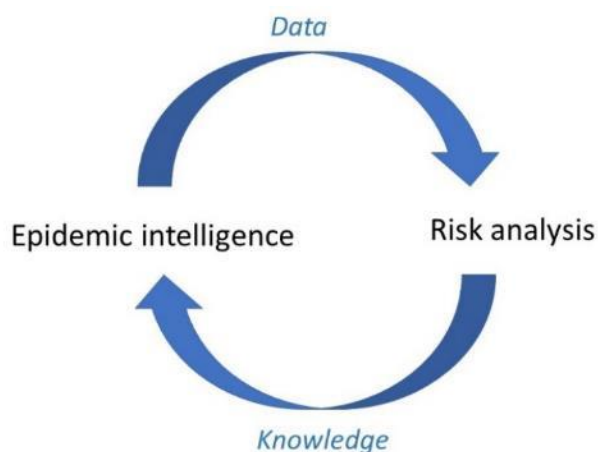
Figure 36. Information flow between epidemic intelligence and risk analysis

Epidemic intelligence at national vs international level

Regional or international agencies have set up EI systems that monitor health risks worldwide using different biosurveillance tools such as ProMED or GPHIN. Some countries have set up their own EI system to monitor and detect health threats at both national and international levels to anticipate the possible introduction of emerging pathogens from other regions. National-level EI systems, such as the FEIS for animal health in France, monitor the same signals at international level as supra-national systems, thus creating some overlap with the international agencies.

However, these nationally implemented systems also monitor other sources of information through their own networks. The FEIS, for example, aims to provide reports with interpreted and contextual information to better characterize the health threat and facilitate its interpretation by decision makers. The existence of the FEIS is justified by the extra layer of filter, which allows targeting animal health surveillance according to national context. Indeed, needs in terms of animal health surveillance may vary from one country to another depending on strategies and priorities (e.g. priority given to caterogy-1 health hazards or events with geographical proximity to France). In addition, the FEIS monitors several different types of information sources, from official sources to unofficial sources such as media reports, also gathering unofficial communications from its national and international pluridisciplinary network of experts. This allows the FEIS to contextualize the event when reporting and include contextual information (e.g. viral strain involved, previous occurrence and historical circulation of the virus in the area, vector and host distributions, animal mobility). Information from various fields, such as epidemiology, virology or entomology, is also useful to provide context information and a holistic approach considering several perspectives. This reinforces the need for a pluridisciplinary approach to EI, which is why the FEIS team and expert network include experts in epidemiology, veterinary health, informatics, entomology, virology, and many other specialties.

5.3. Identification of drivers

Understanding the causes of EID events has become part of a global strategy to address this health threat. When studying the underlying processes, key factors to take into account include human and animal mobility, climate change and vector biology for vector-borne diseases. Animal movements are essential to the economic health of livestock production, but also threaten it by facilitating disease spread. Animal movements are an important pathway of transmission from farm to farm, sometimes over great distances as seen with LSD in the Balkans (Mercier *et al.*, 2018).

After characterizing the spatial and temporal patterns of disease emergence and spread, the next step is use mathematical models to identify environmental and socio-economic drivers in order to better understand the underlying processes of disease emergence and spread, and how they are influenced by external factors. This helps improve expert knowledge of the disease dynamics in the aim of targeting efficient control measures and anticipating future outbreaks. The environmental and socio-economic **drivers** of disease emergence and transmission can become **proxies** to monitor as sentinels to facilitate disease surveillance. An example is the use of population movements, a key driver of disease spread, in the fight against the spread of the COVID-19 pandemic. Population mapping and modelling can help predict where the disease is more likely to spread and which control methods are more effective. These methods can help improve the timely detection of anomalies and disease emergence, and facilitate the monitoring of spatial and temporal trends.

Over the past several years, I have contributed to several projects aiming to identify drivers of disease emergence and spread. Future developments of the **spread rate model**, which was used by the FEIS to estimate the spread rate of LSD in the Balkans, include the identification of factors

that influence the spread rate. With my colleagues at CIRAD, we have started to develop a second complementary model that would use the estimated spread rates from the first model as input to analyze the impact of various environmental and socio-economic factors such as temperatures, rainfall, mobility and animal density.

Dengue drivers paper: The identification of drivers of dengue outbreaks was the subject of another study which aimed to identify socio-economic and environmental determinants of dengue outbreaks in Noumea, New Caledonia (Zellweger *et al.*, 2017). I contributed to this study as part of a 6-months professional internship at IRD in 2014. My work focused on the extraction of environmental drivers from remote sensing images (e.g. vegetation index) and contributing to the principal component analysis (PCA) to identify drivers of dengue outbreaks in the urban setting of Noumea, the capital of New Caledonia. The study demonstrated a correlation between dengue incidence and socio-economic status across the different neighborhoods of Noumea. Higher dengue incidence rates were linked higher unemployment, lower revenue, higher percentage of population born in the Pacific. Identifying key drivers of dengue allows experts to identify areas or time periods at higher risk, i.e. where or during which several risk determinants are present. With this knowledge, health authorities can better target prevention and control measures in at-risk areas and during dengue season.

Another study I'm currently leading is looking into the role of air travel in the risk of importation of dengue into Europe. Given the advent of commercial air travel, modelling of global movements of populations is essential to understand the potential implications of global outbreaks of infectious diseases. Indeed, with over two billion air travelers each year, a pathogen can travel to the other side of the world in just 24 hours so diseases are spreading faster (World Health Organization, 2007). Following my participation in ECDC's rapid risk assessment of the dengue outbreak in Réunion in 2019 and given my previous work on dengue in the Pacific, I designed with ECDC experts a study to analyze the risk of introduction of dengue into Europe through infected air-travelers returning from dengue endemic areas. Indeed, two important factors played a key role in the risk of dengue importation: dengue incidence in the visited country and the volume of passengers travelling from the dengue infected area to Europe. We set up a project in collaboration with French public health authorities (Santé publique France, in Paris and Réunion) to analyze the travel-associated risk of dengue introduction into Europe through a case study of dengue importation from Réunion to metropolitan France following the large outbreak in 2019. The aim of the study is to estimate the risk of introduction of dengue into France using data on air travelers and local dengue incidence in affected countries. This allows us to target surveillance and inform risk analyses by identifying countries or periods of higher risk of dengue importation depending on travel patterns and ongoing dengue circulation in destination countries. I am leading this study, which is currently ongoing, and will be first author of the upcoming manuscript. I co-led the study design, the collection and the analysis of travel and dengue data with the R software. The COVID-19 pandemic has generated delays in our study due to limited availability of the public health agencies involved, but we aim to publish the project results in 2021. Our project was presented at the 21st *Journées Nationales d'Infectiologie* conference in Poitiers, France on 9th September 2020.

The identification of key drivers of disease emergence and spread can improve prediction models and allows to better anticipate future outbreaks and global pandemics.

5.4. Integrating different disciplines and expertise

Society is increasingly calling for decompartmentalization of knowledge and expertise through pluridisciplinary collaborations. Human and animal health are based on **complex processes** that draw from many disciplines, including medicine, environmental sciences, biology, virology, epidemiology, ecology, farming, and more (Harris, 2010). Each field of expertise brings to the table a new perspective on cross-disciplinary issues such as disease surveillance. As increasing volumes of diverse health data are generated, disease surveillance needs technical support from data and computer sciences to implement new and innovative technologies aiming to improve health data analysis in the era of **big data and data sciences**.

To ensure an integrated approach, collaborations can be implemented at several levels:

- **the pooling of information and data sources:** collect data from diverse and complementary information sources, from both official and unofficial sources including personal communications through each stakeholder's contact network
- **the pooling of expertise:** improve the verification, the characterization and the interpretation of health-related events for risk assessment
- **the pooling of resources:** both human and financial to ensure common strategies, efficient capacity-building, continuous operation of EI activities, and to improve time and cost efficiency of disease surveillance systems

The centralization of pluridisciplinary data, expertise and resources can be done through a project, a platform or a network, to bring stakeholders together and facilitate discussions and data sharing.

Challenges of collaboration: Although the scientific expertise, innovative technologies and diverse information sources needed to generate real-time EI exist, their integration is suboptimal. Integration of different types of stakeholders and experts with a common goal of early detection and control of disease threats can be challenging. Gathering several institutions with varying, and sometimes contradictory, motivations and interests can be a potential source of discord within a network or project. The level of collaboration usually depends on the willingness of actors involved to share their opinions and open up to other disciplines and perspectives on the issue at hand. It may also vary depending on the type of collaboration, e.g. between different geographic levels or between scientific disciplines.

Despite these challenges, there is a strong need for collaboration between scientific disciplines within research, the involvement of various types of stakeholders (e.g. public/private, animal/human sectors, local/national) through participatory methods, and the integration of different expertise and domains of expertise from disease detection and characterization to risk analyses to better inform risk management. Issues in managing outbreaks of EIDs may stem from the lack of understanding of these pathogens, particularly in the case of unknown pathogens. Involving the research community, universities and reference laboratories can improve knowledge on the pathogen and its spread dynamics to help in the design and implementation of adequate surveillance and control strategies. The **integration of different types of stakeholders** can strengthen the surveillance and control process, as demonstrated by the French ESA Platform. For instance, including wildlife services can inform health professionals on diseases circulating in wild

animal populations thus accounting for the risk of spillover from wild animals to domestic animals, with the example of ASF in Europe.

Future efforts should focus on bridging the gap between complementary scientific disciplines and between the public and private sectors, embedding this collective knowledge in existing and new technologies, and integrating heterogeneous data while addressing legitimate concerns about data confidentiality (Khan 2012). These ethical considerations are essential in handling disease data, but will not be addressed in this manuscript.

5.5. Other levels of integration

Geographical integration

Infectious diseases can be detected and controlled at several geographical levels, as demonstrated with mass gathering surveillance. Mass gatherings can be seen as global-to-local-to-global events because they consist of a global-to-local convergence followed by a local-to-global divergence of populations from around the world. However, the implementation of disease surveillance systems at local, regional and global levels are **not always well integrated or linked** (Khan *et al.*, 2012). Successful disease surveillance requires the integration of stakeholders at all geographical scales in the process, and particularly efficient bilateral information flow between clinicians at the local level and health agencies in charge of disease control at regional, national and international levels.

Stakeholders can interact at different geographical levels, and they are different at each level. The local community, farmers and clinicians are key actors at the local level, while international health agencies and agricultural organizations decide on health guidelines and strategies to adopt at the international level. National health agencies and stakeholders are the intermediary link and interact with both the local and the international level. Integrating all these actors in the disease surveillance and control process requires the clear identification of each stakeholder's role and responsibility to enable rapid response. **Priorities** and the perception of risk can also vary depending on the geographical scale (Barnett *et al.*, 2020). For instance, emerging diseases such as avian influenza can be considered as a priority at international level by international stakeholders and health agencies, but national health agencies and local farmers may show more concern for the daily management of endemic diseases, which might not be considered as a priority but require the most efforts and resources to manage. Decision makers should aim to consider all perspectives, whether local or national, when establishing health priorities, strategies and guidelines.

One of the lessons learnt from the SARS epidemic in 2002 was that weaknesses in disease surveillance and control in one country can endanger countries all over the world, particularly in the current context of globalization and rapid air travel. Indeed, not all surveillance systems are mature enough to handle these large-scale pandemics of novel viruses. Also, recent outbreaks have shown that no country is able to ensure 100% security of its borders due for example to the illegal flow of animals and animal products, as well as migrant human populations (Jebara, 2004). **Cross-border collaborations** with health authorities from other countries is crucial to facilitate the timely exchange of validated information regarding outbreaks of EIDs and improve regional

surveillance and response capacities. In the Pacific region, SPC aims to strengthen the links between public health agencies from different PICTs across the region, for instance by organizing regional training courses and workshops to promote in-person interactions and feedback on the implementation of disease control measures in affected PICTs. Although the focus of SPC's initiatives have been at regional and national level, there is a growing realization that efforts at the **sub-national level** should be strengthened to include local actors, such as clinicians, to improve rapid detection and containment of disease outbreaks. In general, the majority of investments and efforts to improve surveillance and response capacity tend to focus on regional and national level. It is important to also consider sub-national level which is the source of the information where patients enter the healthcare system and the first line of action to contain outbreaks (Nelesone *et al.*, 2006).

The geographical level of implementation of EI activities depends on the **objective and scope of the system**. The level of specificity and sensitivity of these objectives will define the granularity of the geographical scale required for the implemented activities.

Some international EI systems can rely on **regional hubs** to monitor the epidemiological situation at regional level and relay the information at international level. This is the case for the FEIS which relies on regional networks such as the CaribVet and SEGA networks to monitor infectious diseases in French overseas territories in the Caribbean and the Indian Ocean (Gongora *et al.*, 2008; Halm *et al.*, 2017). Cross-border collaborations may also help attenuate the geographical disparity in different parts of the world relating to accessibility to real-time sensitive and specific information, most likely linked to technological infrastructures, level of communication and awareness, internet access and available resources.

Multi-sectoral integration (One Health)

Cross-border surveillance can relate to geographical borders but also to sectoral borders. Disease surveillance should also aim at being cross-sectoral, and pool information and expertise from different domains, with the example of the One Health approach. In a One Health approach, the animal-human health interface is based on the principle that humans and animals occupy a continuous health space and are interconnected (Barnett *et al.*, 2020). The threat of zoonotic diseases is exacerbated by several factors including climate change and deforestation, which lead to increased contact between human and animal populations. This growing global threat stresses the need for collaborations between human and animal health authorities. Ideally, in a One Health approach, collaborations should also be established with the environmental sector (e.g. plant health and food safety) but that is outside of the scope of my experience which focuses mainly on human and animal health.

As I discovered during my experience working in both human and veterinary health, EI activities in both sectors face similar challenges and share common objectives and methodologies. The process itself is identical, only the scope changes, as well as the implications in terms of impact and implementation of control measures. Collaborations between human and veterinary health agencies can open **access to data** relating to both human and animal cases, which can provide a sentinel system as well as a global picture of the disease's epidemiological situation (in the case of zoonoses). They can be implemented at different stages, from the early detection of unusual events to the collaborative design and implementation of control measures.

There are **different degrees of inter-sectoral collaborations** between human and veterinary health: sharing reports to sharing data, using common EI tools or databases, sharing resources for the detection, analysis and response to health threats, and defining common strategies for the control of zoonoses. **Cross-fertilization** and transfer-learning are terms used in informatics to describe the sharing of knowledge and methods between disciplines and sectors. The idea is to benefit from existing tools, knowledge and methods by adapting them to new systems, domains or scales.

Several **examples of cross-sectoral collaborations** can be cited. The **FEIS** has set up collaborations with ECDC to share EI methods, networks and information relating to zoonoses such as West Nile. Animal case counts are now included in ECDC's West Nile reports following their recent One Health approach, and vice versa the FEIS includes human case reports in their West Nile reports. The FEIS is also involved in cross-sectoral networks such as the **ArboFrance** network in France (focusing on arboviruses) and the French epidemic intelligence network involving stakeholders in both human and veterinary health. The H2020 **MOOD** project, coordinated by CIRAD which is a major stakeholder in animal health surveillance in France, stemmed from a call for tender in human health and is founded on a One Health approach. The global pandemic of **COVID-19** has also shined a light on several cross-sectoral initiatives such as the support of veterinary laboratories and the provision of testing material and protective equipment.

Other levels of integration to consider when optimizing an EI system include strengthening inter-organizational collaborations (e.g. between organizations such as WHO, ECDC, OIE or the European commission) as well as public-private partnerships, and improving inter-institutional communication and transparency through information flow between different hierarchical levels of an institution.

5.6. Strategies to facilitate integration

Co-creation of knowledge and shared decision-making are challenging processes which require time, role clarity, continuous attention to power imbalances and constant monitoring (Oliver *et al.*, 2019). Some determinants can facilitate integration initiatives in human and animal health: high motivation among stakeholders, involvement and support of local communities, and the set-up of a centralized system to oversee actions (Ingemann *et al.*, 2018). On the other hand, examples of constraining determinants are ambiguous program objectives, high turnovers, siloed budgets and work environments, as well as a lack of centralization of information and activities (Ingemann *et al.*, 2018).

When experts and researchers from multiple disciplines work together and share different opinions on priorities and methodologies, several **methods and tools** can be used to come to a holistic understanding of the disease system. Below are a few examples.

Organizing group discussions and workshops using consensus methods can lead to a common understanding, common objectives and a common strategy. Disagreements between researchers sharing a common objective can be overcome using **consensus** methods among experts like the Delphi method (Rayens *et al.*, 2000). This method is used by the ESA Platform when designing

surveillance protocols for example, and by the PADI-web team to help health professionals come to a common understanding in regards to methodology and definitions (Arsevska *et al.*, 2016).

D'Amour and his team developed a **model of collaboration**, which applies to interprofessional and interorganizational collaboration in healthcare organizations (D'Amour *et al.*, 2008). The model is based on four components (governance, shared goals and vision, formalization and internalization) and ten indicators (centrality, leadership, support for innovation, connectivity, goals, client-centered orientation, formalization tools, information exchange, mutual acquaintanceship and trust). It can be used to analyze the ways in which complex systems of actors collaborate, and is based on the concept of collective action in organizational sociology, a type of reasoning for the analysis of political, social and economic processes.

Once actors are willing to cooperate and co-construct a common strategy, the inclusion of **social scientists** can facilitate the integration process through the implementation of participatory methods (Duboz *et al.*, 2018). These methods can enable the appropriate contextualization of research practices and ensure a balanced representation of the roles and relationships of medical, biological, mathematical, and social disciplines. **Participatory methods** refer to the involvement of communities in defining and prioritizing problems, and in the development of solutions (Catley *et al.*, 2012). Participatory modelling is iterative and adaptive, and is necessary to deal with the complexity of issues and topics handled. Such methods are implemented in the H2020 MOOD project to ensure the co-conception of innovative tools based on user needs.

Participatory approaches can include the use of **modelling** techniques which encourage those involved to clarify which key variables affect the underlying system and the possible outcomes of different strategies. These integrated approaches consider the system as a whole, with interdependent and complex interactions between the human, animal and ecosystem components. The **Companion Modelling (ComMod)** approach promotes dialog among stakeholders and provides methodological support to integrate a plurality of viewpoints (Buchheit *et al.*, 2015). In the ComMod approach, participatory modelling tools such as role-playing games and agent-based models are used in an iterative and evolving process. Stakeholders are involved in the design of the simulation tools, which are then used to collectively design, simulate and discuss scenarios of change (e.g. implementation of control measures). This approach is implemented through several iterative cycles and is based on participatory and capacity-building workshops which bring together the different stakeholders.

Chapter 6

Perspectives

6.1. Perspectives relating to the case studies

My experience has allowed me to take a step back and have a more global approach and understanding of challenges in EI. In hindsight, I have identified several ways of improving the implementation of an integrated pluridisciplinary approach to the design of innovative methods for the collection and analysis of EI data.

The PADI-web case study of COVID-19 could have been improved by replacing manual extraction of relevant terms with an automated software such as BioTex specialized in terminology extraction. Also, a complementary study focusing on adding the new "unknown" category of keywords to PADI-web and conducting a retrospective study of another emergence such as Ebola or SARS would validate our results concerning the vocabulary related to novel pathogen emergence. To facilitate the implementation of newly developed tools such as PADI-web in existing surveillance systems, I would suggest to start with a needs assessment with a representative group of end users in the design of the tool to identify key operational needs and ensure that the tool meets the needs of the users. I would suggest to organize stakeholder meetings to clearly identify all users' needs, validate the tool's design and set up feedback testing loops with users.

Relating to the development and use of electronic tools for the enhancement of mass gathering surveillance, the study could have benefited from an entirely-electronic data collection without relying on paper forms to collect the data at sentinel sites. We could set up an electronic data collection system at sentinel sites using computers (if internet access is sufficient) or mobile phones. Organizing regional workshops on mass gathering surveillance enhancement would improve awareness and sharing of experience among PICT health authorities. SPC's mass gathering enhancement team could benefit from the additional support of public health professionals from other PICTs with previous experience in mass gathering surveillance. This would further strengthen inter-PICT collaborations. Given the need for a sufficiently long pilot phase, SPC could adopt a more proactive approach and directly contact health authorities long before the event to offer assistance and assess the local context and available resources.

In our study on the circulation of arboviruses in the Pacific, we could have included more data spanning over a longer period of time to analyze whether the epidemic wave process was recent or had been ongoing for several decades. I believe we should study the epidemiology of dengue more carefully. SPC's regional database contains 30 years of detailed data on the circulation of dengue serotypes in the Pacific, which could be analyzed to confirm the epidemiology in epidemic waves and study more carefully this change in epidemiology with the continued circulation of DENV-1. Mathematical models that would include environmental and socio-economic drivers, along with phylogenetic studies, could help improve our knowledge of the circulation of dengue and other arboviruses in the Pacific.

Further improvements of the spread rate model include taking into account vaccination and other control measures as well as integrating environmental and socio-economic drivers of LSD spread to improve knowledge of the disease spread dynamics and inform prediction models. The study would also have benefited from a collaboration with local veterinary health agencies who could have provided more precise outbreak data, local expertise and feedback on the response to LSD outbreaks.

The common challenge in my case studies is not only to include end-users in the early stages of tool and method development but to make sure that end-users involved are representative of all future users of the tool or method. This allows to anticipate any future needs in terms of operational use of the tool or implementation of the method. However, involving too many stakeholders from the start of the design and development of the tool can be counter-productive. Implementing an iterative process of feedback loops which would include an increasing number of stakeholders as the process advances would be more productive. And the support from social sciences can further facilitate the integration of user needs to ensure sustainable use of the tool or method.

Improvement of the FEIS: During my four years as team leader of the FEIS, I have identified several gaps which represent possible improvements of the EI system for animal health in France. The main challenge is the availability of sufficient and sustained resources. Assuring a permanent contract for the team leaders would allow them to invest fully into the system, benefit from the network of contacts that they have built over time and bring their full expertise to the system. Additional resources could allow the team leaders to implement the ideas of improvements they identified but have no spare time to set in motion due to the increasing amount of time needed to monitor daily signals and act when alerts are detected. These ideas, for my part, include more involvement in research projects such as the MOOD project which would allow the FEIS to benefit from tailored innovative methods and tools developed by the research community. The system needs to keep up with new technologies to facilitate the management of increasing amounts of heterogeneous data. I also believe the FEIS could benefit from the One Health collaborations I set up during my four years because, in my experience, EI in both human and animal health sectors have similar methods, tools and challenges. An example of collaboration is with the French national epidemic intelligence network with other agencies involved in EI (mainly human health) such as the Ministries of Health and Foreign Affairs, the Pasteur Institute, Santé publique France, and the epidemiology and public health center of the French armies (CESPA). The FEIS would also benefit from strengthening its network of national and international experts to improve access to

timely local information on new health threats and improve the bilateral flow of information and feedback with experts.

It is important to note that the potential implementation of such suggested improvements will be conditioned by available resources and time, which are both determined by the health agencies' strategy and priorities in terms of EI.

6.2. Exploring new data streams

The rapid and global expansion of the internet and mobile devices has provided opportunities to increase communication between public health stakeholders and the general public, including people attending mass gathering events for instance, through informal sources such as blogs, phone applications or social media platforms (Khan *et al.*, 2012). Electronic media, health expert forums and blogs, as well as internet search queries offer easily-accessible sources of unstructured information, which can provide local and near real-time information relating to suspected or confirmed disease outbreaks.

Citizen data has become an area of focus to broaden the extraction of health data to include participatory platforms and social media (e.g. FluNearYou, Twitter). An example is the DIZIE project developed in Japan which monitors syndromes through Twitter (Collier *et al.*, 2012). The implication of citizens in the collection of information through the use of social media or mobile phone applications will increase the amount of timely and accessible raw data for the monitoring of health threats, which is particularly important in high-risk contexts such as mass gatherings. However, the lack of health-related knowledge of the general public might lead to non-specific or non-accurate data, requiring expert verification. Broadening the scope of surveillance through citizen involvement can also enhance disease surveillance, for instance during mass gatherings, and create an opportunity for a bilateral exchange of information to collect data and inform participants of the event (Nsoesie *et al.*, 2015).

Through EBS, these data sources can help overcome some of the limitations of traditional surveillance systems, including delays in reporting, inconsistent population coverage or poor sensitivity for new and emerging diseases. These sources can complement traditional disease surveillance systems by allowing health professionals to detect weak signals across borders and thereby create awareness at an early stage of EID risks.

EI experts are also turning to metadata in addition to data relating directly to health events. These metadata include for instance social media trends or Google search queries. For instance, ECDC launched early October 2020 a new application called "epitweetr", an automated R-based tool for the early detection of public health threats from Twitter data. This indirect way of detecting unusual events can improve early alerting and trigger further investigation by switching from metadata to direct health data (e.g. syndromic surveillance, unofficial communication with local health authorities). The monitoring of metadata allows EI authorities to amplify weak signals and improve the coverage of EBS beyond unofficial sources such as electronic media. This paves the way for a shift in the EI paradigm and approach, proof that the EI process is evolving to adapt to the context of big data and new technologies (Figure 37).
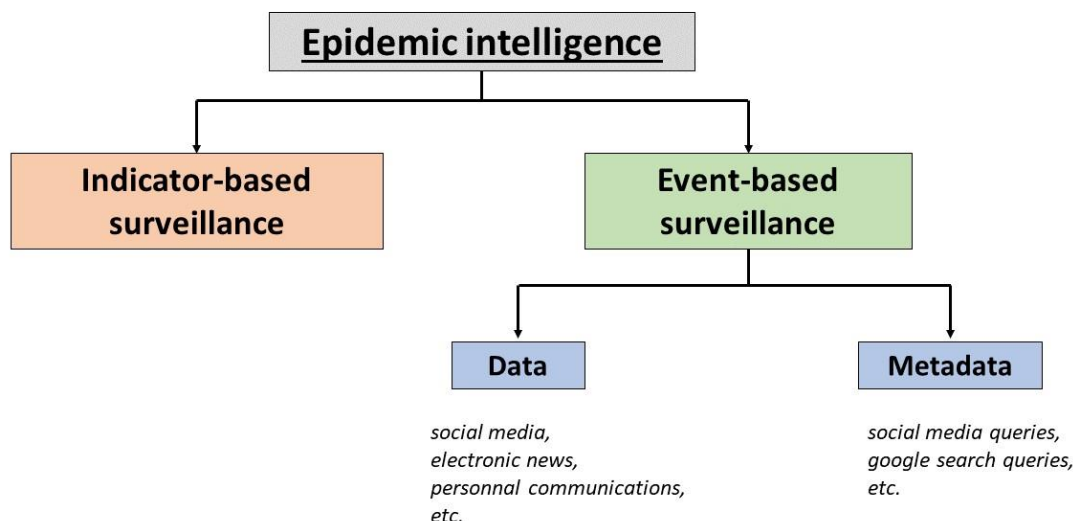
Figure 37. New paradigm of the epidemic intelligence process

The context of the COVID-19 pandemic has promoted **open sciences**, with open access to COVID-19 related data provided by numerous institutions and agencies, and at different geographic levels. This open access to data has provided a more complete dataset available for health professionals worldwide to analyze and interpret. However, it has also led to the possibility of information flows containing unverified and unvalidated data.

6.3. Integrating new technologies

Integrating **new and innovative technologies** can further improve EI activities, thus highlighting the added-value of the involvement of EI teams in research projects. **Automated tools** for data collection, analysis and reporting have been illustrated in this manuscript, with the example of OE and PADI-web. Automation of tools can considerably improve the timeliness of early detection and alerting, but human moderation remains essential to validate and interpret the signals to recommend efficient control or prevention measures. The use of **biosurveillance** tools can complement traditional disease surveillance by allowing health professionals to detect weak signals and create awareness at an early stage of EID risk. Recent efforts to centralize existing methods relating to biosurveillance tools in **platforms**, such as EIOS or the H2020 MOOD project, have further facilitated the process of integrating scientific results and innovations into EI processes. In the context of mass gatherings, easy to use point-of-care **diagnostic tests** will facilitate diagnosis of syndromic events. The use of **mobile phones** and portable wireless sensor networks to increase wireless coverage have been shown to be efficient by decreasing data entry time and reducing costs (Yu *et al.*, 2009).

As previously highlighted, EI is a complex and time-consuming process. Integrating additional data sources and new technologies will require additional resources to which the system should adapt to avoid increasing the burden on experts in charge of conducting daily EI activities. The integration of new sources and technologies should be adapted to the context and the available resources. For instance, it would be counterproductive to integrate an automated tool for the

monitoring of Google search queries in developing countries where internet coverage might be limited. In such contexts, efforts should focus more on improving the performance of the existing surveillance systems than on adding new components to the system.

6.4. Anticipating the emergence of unknown viruses

In 2016, WHO's Research and Development Blueprint was set up to reduce the time for the development, assessment and authorization of medical countermeasures for a list of **priority diseases** with epidemic potential for which there are no or limited medical countermeasures available (World Health Organization, 2018a). In 2018, to respond to the growing threat of new viral emergence, the WHO acknowledged the possibility that a serious international epidemic could be caused by a currently unknown pathogen by adding "disease x" to its list of priority diseases (World Health Organization, 2018a).

The monitoring of **weak signals**, such as increased syndromic activity or an unusual syndromic event with an unknown etiology, is crucial to timely detect emergences of new and unknown viruses. This can be done by increasing the scope and sensitivity of biosurveillance tools such as **PADI-web**. The PADI-web case study illustrated that future efforts should focus on clearly defining keywords for the detection of "unknown" or "mysterious events". Given the current risk of emergence of new diseases, we should aim to integrate weak signals in EI systems to improve the early detection and monitoring of emergence of unknown pathogens. **Human moderation** is crucial to interpret the increasing number of relevant signals detected, particularly if we include weak signals relating to syndromes. Adequate resources should, therefore, be made available to implement this new integration. The integration of weak signals in existing EI systems and the interpretation of the detected signals both require pluridisciplinary efforts to improve the system's performance.

Monitoring viral mutations: In addition to the early detection of emergence events, viral mutations should also be closely monitored as they can significantly worsen the impact of outbreaks by increasing the vector competence, the virulence of the virus or its resistance to treatments (Tsetsarkin *et al.*, 2007). An example of unexpected genetic mutations in circulating viral strains is the **E1-A226V mutation** that occurred in the ECSA CHIKV strain, which increased vector competence and was responsible for a large outbreak in La Réunion in 2005-2006. These genetic mutations are difficult to predict and highlight the need for strengthened pluridisciplinary collaborations in order to closely monitor the evolution of viral strains through phylogenetic studies.

6.5. From reactive to proactive

Public health care systems seem to focus more on treating the sick than on protecting public health by anticipating and setting up prevention measures. This is, in part, due to limited resources available. In contrast to human health, veterinary health seems to be much more focused on **preventive veterinary medicine**, with the health of the population being more important than the

health of the individual. It seems control measures such as travel bans are implemented much more rapidly than in human health. Another difference lies in the harmonization and standardization of control measures. In animal health, there is a common set of measures to be applied in case of an animal disease by each Member State of the EU, most of which are harmonized across the world by OIE. In the fight against COVID-19, different countries implemented different movement restrictions at different levels of in-country disease circulation resulting in undesired movements and further possible spread of the disease. Also, governments perceiving socio-economic risks might be reluctant to quickly and fully disclose information about risks of infectious diseases of international concern.

Pluridisciplinary collaborations between scientific disciplines is one thing. The next level is interdisciplinarity between researchers and **policy-makers** to better translate scientific results into adapted policies and implement rapid and efficient response measures. Another challenge is the difference in **timespan** between research, funding and policy-making. Research funding is often quite short compared to research agendas (Barnett *et al.*, 2020). In addition, policy makers often require rapid input from researchers to design adapted strategies and implement efficient control measures. The success of researchers is often judged by how fast they can deliver. Research projects rarely last longer than five years. However, interdisciplinarity and participatory research often require more time to be successfully implemented within research projects.

Integration of surveillance across geographical and sectoral borders in a One Health approach, involvement of stakeholders at both local, national and regional level, and modelling across scientific specialties could produce the first real-time risk detection and assessment platform that could strengthen awareness of global EID threats. This **integrated platform** could improve rapid detection, assessment and reporting of infectious disease threats of international concern, enable timely and coordinated implementation of response measures, provide mathematical modelling to predict the emergence and spread of infectious diseases and facilitate the surveillance through the use of proxies, simulate the impact of different scenarios of health interventions, serve as a foundation for scientific research and innovation, and strengthen engagement between the scientific community and decision-makers at local, national, and global levels (Khan *et al.*, 2012).

Given the increasing threat of EIDs illustrated by three coronavirus emergences in the past two decades, disease surveillance and control strategies should dedicate more efforts and investments into **anticipating** future emergence of both known and unknown disease threats. This requires a switch from **reactive to proactive,** and a strengthening of prevention and preparedness measures. Particularly in a time of global COVID-19 pandemic, it is important to draw lessons from the recent novel coronavirus emergence and the impact of response to better prepare for the next emergence. As mentioned, the timespan of research efforts to better understand and characterize the health threat is not compatible with the need for rapid response and the decision-makers' need for quick answers. To improve preparedness, an **arsenal of existing generic tools** can be consolidated and made available through regional or global platforms to provide timely knowledge and feedback to decision-makers. Future efforts should also focus on better anticipating the risks by identifying clear drivers of disease emergence, whether environmental, social or economic. Anticipating future risks, whether known or unknown, includes better

prediction through modelling and other tools, but also purchase and **stocking** of vaccines (if available), medications and protective gear in preparation of future emergences.

Pandemics are on the rise and we should **act at the root** of the issue, go from predicting to preventing. Health experts have been warning about disease x for some time now. Instead of focusing on the response to individual disease emergence, we should aim to understand and contain the underlying processes that drive the emergence and global spread of new emerging pathogens in a One Health context, for instance by focusing on the spillover from wildlife and the human-animal interface. Also, awareness of health issues at stake and the potential consequences of delayed implementation of countermeasures can be raised by **better informing decision-makers** and governments, and strengthening the link between them, researchers and EI experts.

References

A-Nuegoonpipat A., Berlioz-Arthaud A., Chow V., Endy T., Lowry K., Mai L. Q., Ninh T. U., Pyke A., Reid M., Reynes J.-M., *et al.* (2004) 'Sustained transmission of dengue virus type 1 in the Pacific due to repeated introductions of different Asian strains', *Virology*, 329(2), pp. 505–512. doi: 10.1016/J.VIROL.2004.08.029.

Abdelmalik P., Peron E., Schnitzler J., Fontaine J., Elfenkampera E. and Barboza P. (2018) 'The Epidemic Intelligence from Open Sources initiative: a collaboration to harmonize and standardize early detection and epidemic intelligence among public health organizations', *Weekly Epidemiological Record*, 93(20), pp. 238–244.

Animal and Plant Health Agency (2017) 'Disease surveillance in England and Wales', *Veterinary Record*, 181, pp. 135–138. doi: 10.1136/vr.j3660.

ANSES (2017) *Risque d'introduction de la dermatose nodulaire contagieuse en France*.

Arbon P. (2007) 'Mass-Gathering Medicine: A Review of the Evidence and Future Directions for Research', *Prehospital and Disaster Medicine*, 22(02), pp. 131–135. doi: 10.1017/S1049023X00004507.

Arsevska E., Roche M., Hendrikx P., Chavernac D., Falala S., Lancelot R. and Dufour B. (2016) 'Identification of terms for detecting early signals of emerging infectious disease outbreaks on the web', *Computers and Electronics in Agriculture*, 123, pp. 104–115. doi: 10.1016/j.compag.2016.02.010.

Arsevska E. (2017) *Élaboration d'une méthode semi-automatique pour l'identification et le traitement des signaux d'émergence pour la veille internationale sur les maladies animales infectieuses*. Université Paris-Sarclay.

Arsevska E., Valentin S., Rabatel J., de Goër de Hervé J., Falala S., Lancelot R. and Roche M. (2018) 'Web monitoring of emerging animal infectious diseases integrated in the French Animal Health Epidemic Intelligence System', *PLOS ONE*. Edited by F. C. Dórea, 13(8), p. e0199960. doi: 10.1371/journal.pone.0199960.

Aven T., Ben-Haim Y., Andersen H. B., Cox T., Droguett E. L., Greenberg M., Guikema S., Kröger W., Renn O., Thompson K. M., *et al.* (2018) *Society for Risk Analysis Glossary*. Available at: https://www.sra.org/sites/default/files/pdf/SRA Glossary - FINAL.pdf (Accessed: 22 April 2020).

Babiuk S., Bowden T. R., Boyle D. B., Wallace D. B. and Kitching R. P. (2008) 'Capripoxviruses: An Emerging Worldwide Threat to Sheep, Goats and Cattle', *Transboundary and Emerging Diseases*, 55(7), pp. 263–272. doi: 10.1111/j.1865-1682.2008.01043.x.

Barboza P., Vaillant L., Mawudeku A., Nelson N. P., Hartley D. M., Madoff L. C., Linge J. P., Collier N., Brownstein J. S., Yangarber R., *et al.* (2013) 'Evaluation of Epidemic Intelligence Systems Integrated in the Early Alerting and Reporting Project for the Detection of A/H5N1 Influenza Events', *PLoS ONE*, 8(3), pp. 1–9. doi: 10.1371/journal.pone.0057252.

Barboza P. (2014) *Evaluation des systèmes d'intelligence épidemiologique appliqués à la détection précoce des maladies infectieuses au niveau mondial*. Université Pierre et Marie Curie - Paris VI.

Barboza P., Vaillant L., Strat Y. Le, Hartley D. M., Nelson N. P., Mawudeku A., Madoff L. C., Linge J. P., Collier N., Brownstein J. S., *et al.* (2014) 'Factors influencing performance of internet-based biosurveillance systems used in epidemic intelligence for early detection of infectious diseases

outbreaks', *PLoS ONE*, 9(3), pp. 1–9. doi: 10.1371/journal.pone.0090536.

Barnett T., Pfeiffer D. U., Ahasanul Hoque M., Giasuddin M., Flora M. S., Biswas P. K., Debnath N. and Fournié G. (2020) 'Practising co-production and interdisciplinarity: Challenges and implications for one health research', *Preventive Veterinary Medicine*. Elsevier B.V., p. 104949. doi: 10.1016/j.prevetmed.2020.104949.

Beard P. M. (2016) 'Lumpy skin disease: a direct threat to Europe.', *The Veterinary record*, 178(22), pp. 557–8. doi: 10.1136/vr.i2800.

Bhatt S., Gething P. W., Brady O. J., Messina J. P., Farlow A. W., Moyes C. L., Drake J. M., Brownstein J. S., Hoen A. G., Sankoh O., *et al.* (2013) 'The global distribution and burden of dengue', *Nature*, 496(7446), pp. 504–507. doi: 10.1038/nature12060.

Bijkerk P., Monnier A. A., Fanoy E. B., Kardamanidis K., Friesema I. H. and Knol M. J. (2017) 'ECDC Round Table Report and ProMed-mail most useful international information sources for the Netherlands Early Warning Committee.', *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, 22(14). doi: 10.2807/1560-7917.ES.2017.22.14.30502.

Bitar D., Che D., Capek I., de Valk H. and Saura C. (2011) 'Veille sanitaire et appréciation du risque infectieux émergent: méthode et critères d'analyse du risque', *Medecine et Maladies Infectieuses*, pp. 53–62. doi: 10.1016/j.medmal.2010.12.006.

Brownstein J. S., Freifeld C. C. and Madoff L. C. (2009) 'Digital disease detection - Harnessing the web for public health surveillance', *New England Journal of Medicine*. Massachussetts Medical Society, pp. 2153–2157. doi: 10.1056/NEJMp0900702.

Buchheit P., Campo P., Dumrongrojwatthana P. and Promburom P. (2015) 'Companion Modelling for resilient water management: Stakeholders' perceptions of water dynamics and collective learning at catchment scale', in *21st International Congresson Modelling and Simulation*. Gold Coast, Australia. Available at: www.mssanz.org.au/modsim2015 (Accessed: 12 August 2020).

Cameron A. R., Meyer A., Faverjon C. and Mackenzie C. (2020) 'Quantification of the sensitivity of early detection surveillance', *Transboundary and Emerging Diseases*, n/a(n/a), p. tbed.13598. doi: 10.1111/tbed.13598.

Cao-Lormeau V.-M., Roche C., Teissier A., Robin E., Berry A.-L., Mallet H.-P., Sall A. A. and Musso D. (2014) 'Zika virus, French polynesia, South pacific, 2013', *Emerging infectious diseases*, 20(6), pp. 1085–6. doi: 10.3201/eid2006.140138.

Cao-Lormeau V.-M. and Musso D. (2014) 'Emerging arboviruses in the Pacific', *The Lancet*, 384(9954), pp. 1571–2. doi: 10.1016/S0140-6736(14)61977-2.

Carr D. B., Olsen A. R. and White D. (1992) 'Hexagon Mosaic Maps for Display of Univariate and Bivariate Geographical Data', *Cartography and Geographic Information Systems*, 19(4), pp. 228–236. doi: 10.1559/152304092783721231.

Carrion M. and Madoff L. C. (2017) 'ProMED-mail: 22 years of digital surveillance of emerging infectious diseases', *International Health*, 9(3), pp. 177–183. doi: 10.1093/inthealth/ihx014.

Catley A., Alders R. G. and Wood J. L. N. (2012) 'Participatory epidemiology: approaches, methods, experiences', *The Veterinary Journal*, 191(2), pp. 151–160. Available at: https://www.sciencedirect.com/science/article/pii/S1090023311001134 (Accessed: 23 March 2020).

Choi B. C. K. and Pak A. W. P. (2006) 'Multidisciplinarity, interdisciplinarity and transdisciplinarity in health research, services, education and policy: 1. Definitions, objectives, and evidence of effectiveness', *Clinical and Investigative Medicine*, 29(6), pp. 351–364.

Chretien J.-P., Burkom H. S., Sedyaningsih E. R., Larasati R. P., Lescano A. G., Mundaca C. C., Blazes D. L., Munayco C. V, Coberly J. S., Ashar R. J., *et al.* (2008) 'Syndromic Surveillance: Adapting Innovations to Developing Settings', *PLoS Medicine*, 5(3), p. e72. doi: 10.1371/journal.pmed.0050072.

Collier N. and Doan S. (2012) 'Syndromic classification of twitter messages', in *Lecture Notes of the Institute for Computer Sciences, Social-Informatics and Telecommunications Engineering*. Springer, Berlin, Heidelberg, pp. 186–195. doi: 10.1007/978-3-642-29262-0_27.

D'Amour D., Ferrada-Videla M., San Martin Rodriguez L. and Beaulieu M. D. (2005) 'The conceptual basis for interprofessional collaboration: Core concepts and theoretical frameworks', *Journal of Interprofessional Care*. Taylor & Francis, pp. 116–131. doi: 10.1080/13561820500082529.

D'Amour D., Goulet L., Labadie J. F., Martín-Rodriguez L. S. and Pineault R. (2008) 'A model and typology of collaboration between professionals in healthcare organizations', *BMC Health Services Research*, 8(1), p. 188. doi: 10.1186/1472-6963-8-188.

Darbellay F. (2008) *A vision of transdisciplinarity : laying foundations for a world knowledge dialogue*. EPFL Press.

Dejnirattisai W., Supasa P., Wongwiwat W., Rouvinski A., Barba-Spaeth G., Duangchinda T., Sakuntabhai A., Cao-Lormeau V. M., Malasit P., Rey F. A., *et al.* (2016) 'Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus', *Nature Immunology*, 17(9), pp. 1102–1108. doi: 10.1038/ni.3515.

Descloux E. (2011) *Dynamique moléculaire et épidémique du virus de la dengue dans différents écosystèmes*, *http://www.theses.fr*. Aix-Marseille 2. Available at: https://www.theses.fr/2011AIX20719 (Accessed: 26 February 2019).

Descloux E., Mangeas M., Menkes C. E., Lengaigne M., Leroy A., Tehei T., Guillaumot L., Teurlai M., Gourinat A.-C., Benzler J., *et al.* (2012) 'Climate-Based Models for Understanding and Forecasting Dengue Epidemics', *PLoS Neglected Tropical Diseases*. Edited by A. Anyamba, 6(2), p. e1470. doi: 10.1371/journal.pntd.0001470.

Desenclos J.-C., Vaillant V., Delarocque Astagneau E., Campèse C., Che D., Coignard B., Bonmarin I., Lévy Bruhl D. and de Valk H. (2007) 'Les principes de l'investigation d'une épidémie dans une finalité de santé publique', *Médecine et Maladies Infectieuses*, 37(2), pp. 77–94. doi: 10.1016/J.MEDMAL.2006.09.008.

Desenclos J.-C. and De Valk H. (2005) 'Les maladies infectieuses émergentes : importance en santé publique, aspects épidémiologiques, déterminants et prévention', *Médecine et Maladies Infectieuses*, 35(2), pp. 49–61. doi: 10.1016/J.MEDMAL.2004.09.005.

Dion M., AbdelMalik P. and Mawudeku A. (2015) 'Big Data and the Global Public Health Intelligence Network (GPHIN).', *Canada communicable disease report = Releve des maladies transmissibles au Canada*, 41(9), pp. 209–214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29769954 (Accessed: 27 March 2019).

Dominguez M., Gache K., Touratier A., Perrin J.-B., Fediaevsky A., Collin E., Bréard E., Sailleau C., Viarouge C., Zanella G., *et al.* (2014) 'Spread and impact of the Schmallenberg virus epidemic in France in 2012-2013', *BMC Veterinary Research*, 10(1), p. 248. doi: 10.1186/s12917-014-0248-x.

Dormann C. F., Schymanski S. J., Cabral J., Chuine I., Graham C., Hartig F., Kearney M., Morin X., Römermann C., Schröder B., *et al.* (2012) 'Correlation and process in species distribution models: bridging a dichotomy', *Journal of Biogeography*, 39(12), pp. 2119–2131. doi: 10.1111/j.1365-2699.2011.02659.x.

Duboz R., Echaubard P., Promburom P., Kilvington M., Ross H., Allen W., Ward J., Deffuant G., de Garine-Wichatitsky M. and Binot A. (2018) 'Systems Thinking in Practice: Participatory Modeling as a Foundation for Integrated Approaches to Health', *Frontiers in Veterinary Science*, 5(NOV), p. 303. doi: 10.3389/fvets.2018.00303.

Duffy M. R., Chen T.-H., Hancock W. T., Powers A. M., Kool J. L., Lanciotti R. S., Pretrick M., Marfel M., Holzbauer S., Dubray C., *et al.* (2009) 'Zika Virus Outbreak on Yap Island, Federated States of Micronesia', *New England Journal of Medicine*, 360(24), pp. 2536–2543. doi: 10.1056/NEJMoa0805715.

Dupont-Rouzeyrol M., Caro V., Guillaumot L., Vazeille M., D'Ortenzio E., Thiberge J.-M., Baroux N., Gourinat A.-C., Grandadam M. and Failloux A.-B. (2012) 'Chikungunya Virus and the Mosquito Vector Aedes aegypti in New Caledonia (South Pacific Region)', *Vector-Borne and Zoonotic Diseases*, 12(12), pp. 1036–1041. doi: 10.1089/vbz.2011.0937.

Durrheim D. N., Harris B. N., Speare R. and Billinghurst K. (2001) 'The use of hospital-based nurses for the surveillance of potential disease outbreaks', *Bulletin of the World Health Organization*, 79(1), pp. 22–27. doi: 10.1590/S0042-96862001000100006.

ECDC (2018) *Rapid risk assessment: Dengue outbreak in Réunion, France, and associated risk of autochthonous outbreak in the EU/EEA*. Available at: https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-dengue-outbreak-reunion-france-and-associated-risk (Accessed: 23 April 2020).

Enserink M. (2007) 'Chikungunya : No Longer a Third World Disease', *Science*, 318(5858), pp. 1860–1861. doi: 10.1126/science.318.5858.1860.

European Centre for Disease Prevention and Control (2020) *COVID-19 situation update worldwide, as of 21 September 2020*. Available at: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases (Accessed: 21 September 2020).

European Food Safety Authority (2017) 'Lumpy skin disease: I. Data collection and analysis', *EFSA Journal*, 15(4). doi: 10.2903/j.efsa.2017.4773.

European Food Safety Authority, Calistri P., DeClercq K., De Vleeschauwer A., Gubbins S., Klement E., Stegeman A., Cortiñas Abrahantes J., Antoniou S., Broglia A., *et al.* (2018) 'Lumpy skin disease: scientific and technical assistance on control and surveillance activities', *EFSA Journal*, 16(10). doi: 10.2903/j.efsa.2018.5452.

European Food Safety Authority, Calistri P., DeClercq K., Gubbins S., Klement E., Stegeman A., Cortiñas Abrahantes J., Antoniou S., Broglia A. and Gogin A. (2019) 'Lumpy skin disease III. Data collection and analysis', *EFSA Journal*, 17(3). doi: 10.2903/j.efsa.2019.5638.

European Food Safety Authority (2020) *Scientific topic: African swine fever*. Available at: https://www.efsa.europa.eu/en/topics/topic/african-swine-fever (Accessed: 8 May 2020).

Fadloun S., Sallaberry A., Mercier A., Arsevska E., Roche M. and Poncelet P. (2020) 'EpidVis: A visual web querying tool for animal epidemiology surveillance', *Information Visualization*, 19(1), pp. 48–64. doi: 10.1177/1473871619861786.

Farnsworth M. L. and Ward M. P. (2009) 'Identifying spatio-temporal patterns of transboundary

disease spread: examples using avian influenza H5N1 outbreaks', *Veterinary Research*, 40(3), p. 20. doi: 10.1051/vetres/2009003.

Feighner B. H., Campbell T. C., Katz A. T., Wojcik R. A., Coberly J. S., Patel S. V., Loschen W. A. and Lewis S. H. (2014) 'SAGES overview: Open-source software tools for electronic disease surveillance in resource-limited settings', *Johns Hopkins APL Technical Digest (Applied Physics Laboratory)*, 32(4), pp. 652–658.

Firestone S. M., Ward M. P., Christley R. M. and Dhand N. K. (2011) 'The importance of location in contact networks: Describing early epidemic spread using spatial social network analysis', *Preventive Veterinary Medicine*, 102(3), pp. 185–195. doi: 10.1016/j.prevetmed.2011.07.006.

Fleischauer A. T. and Gaines J. (2017) 'Enhancing Surveillance for Mass Gatherings: The Role of Syndromic Surveillance', *Public Health Reports*, 132(1_suppl), pp. 95S-98S. doi: 10.1177/0033354917706343.

Freifeld C. C., Mandl K. D., Reis B. Y. and Brownstein J. S. (2008) 'HealthMap: Global Infectious Disease Monitoring through Automated Classification and Visualization of Internet Media Reports', *Journal of the American Medical Informatics Association*, 15(2), pp. 150–157. doi: 10.1197/JAMIA.M2544.

Gani A. (2009) 'Some aspects of communicable and non-communicable diseases in pacific island countries', *Social Indicators Research*, 91(2), pp. 171–187. doi: 10.1007/s11205-008-9276-x.

Gautret P. and Steffen R. (2016) 'Communicable diseases as health risks at mass gatherings other than Hajj: what is the evidence?', *International Journal of Infectious Diseases*, 47, pp. 46–52. doi: 10.1016/J.IJID.2016.03.007.

Gilbert M. and Liebhold A. (2010) 'Comparing methods for measuring the rate of spread of invading populations', *Ecography*, 33(5), pp. 809–817. doi: 10.1111/j.1600-0587.2009.06018.x.

Goel R., Valentin S., Delaforge A., Fadloun S., Sallaberry A., Roche M. and Poncelet P. (2020) 'EpidNews: Extracting, exploring and annotating news for monitoring animal diseases', *Journal of Computer Languages*, 56, p. 100936. doi: 10.1016/j.cola.2019.100936.

Gongora V., Trotman M., Thomas R., Max M., Zamora P. A., Lepoureau M. T. F., Phanord S., Quirico J., Douglas K., Pegram R., *et al.* (2008) 'The Caribbean Animal Health Network: New Tools for Harmonization and Reinforcement of Animal Disease Surveillance', *Annals of the New York Academy of Sciences*, 1149(1), pp. 12–15. doi: 10.1196/annals.1428.055.

Gubler D. J. and Clark G. G. (1995) 'Dengue/dengue hemorrhagic fever: the emergence of a global health problem.', *Emerging infectious diseases*, 1(2), pp. 55–7. doi: 10.3201/eid0102.952004.

Guillaumot L. (2005) 'Arboviruses and their vectors in the Pacific - status report', *Pacific Health Surveillance and Response*, 12(2), pp. 45–52.

Guinat C., Nicolas G., Vergne T., Bronner A., Durand B., Courcoul A., Gilbert M., Guérin J.-L. and Paul M. C. (2018) 'Spatio-temporal patterns of highly pathogenic avian influenza virus subtype H5N8 spread, France, 2016 to 2017.', *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*, 23(26). doi: 10.2807/1560-7917.ES.2018.23.26.1700791.

Halm A., Seyler T., Mohamed S., Ali Mbaé S. Ben, Randrianarivo-Solofoniaina A. E., Ratsitorahina M., Nundlall R., Aboobakar S., Bibi J., Filleul L., *et al.* (2017) 'Four years into the Indian ocean field epidemiology training programme.', *The Pan African medical journal*, 26, p. 195. doi: 10.11604/pamj.2017.26.195.10358.

Harris K. M. (2010) 'An integrative approach to health', *Demography*, 47(1), pp. 1–22. doi: 10.1353/dem.0.0091.

Hartley D. M., Nelson N. P., Arthur R., Barboza P., Collier N., Lightfoot N., Linge J. P. and Goot E. Van Der (2013) 'An overview of Internet biosurveillance', *Clinical Microbiology and Infection*, 19, pp. 1003–1013. doi: 10.1111/1469-0691.12273.

Henning K. J. (2004) 'What is Syndromic Surveillance?', *Morbidity and Mortality Weekly Report*, 53, pp. 7–11. doi: 10.2307/23315680.

Henwood V. (2018) *A qualitative risk assessment of Salmonella enteritidis in the broiler production chain in the Western Cape, South Africa*.

Heymann D. L. and Rodier G. (2004) 'Global surveillance, national surveillance, and SARS.', *Emerging infectious diseases*, 10(2), pp. 173–5. doi: 10.3201/eid1002.031038.

Horwood P. F., Reimer L. J., Dagina R., Susapu M., Bande G., Katusele M., Koimbu G., Jimmy S., Ropa B., Siba P. M., *et al.* (2013) 'Outbreak of chikungunya virus infection, Vanimo, Papua New Guinea.', *Emerging infectious diseases*, 19(9), pp. 1535–8. doi: 10.3201/eid1909.130130.

Hoy D., Mercier A., White P., Saketa S. T., Roth A., Souares Y., Lepers C., Wojcik R., Katz A., Campbell T., *et al.* (2015) 'Using SAGES OpenESSENCE for Mass Gathering Events', *Online Journal of Public Health Informatics*, 7(1). doi: 10.5210/ojphi.v7i1.5800.

Hoy D., Saketa S. T., Maraka R. R., Sio A., Wanyeki I., Frison P., Ogaoga D., Iniakawala D., Joshua C., Duituturaga S., *et al.* (2016) 'Enhanced syndromic surveillance for mass gatherings in the Pacific: a case study of the 11th Festival of Pacific Arts in Solomon Islands, 2012.', *Western Pacific surveillance and response journal : WPSAR*, 7(3), pp. 15–20. doi: 10.5365/WPSAR.2016.7.1.004.

Huber C., Finelli L. and Stevens W. (2018) 'The Economic and Social Burden of the 2014 Ebola Outbreak in West Africa', *The Journal of Infectious Diseases*, 218(suppl_5), pp. S698–S704. Available at: https://europepmc.org/article/med/30321368 (Accessed: 27 May 2020).

Ichiho H. M., Wong V., Hedson J. and David W. J. (2004) 'Cancer in Pohnpei State, Federated States of Micronesia.', *Pacific health dialog*, 11(2), pp. 44–49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16281677 (Accessed: 7 May 2019).

Ingemann C., Regeer B. J. and Larsen C. V. L. (2018) 'Determinants of an integrated public health approach: the implementation process of Greenland's second public health program', *BMC Public Health*, 18(1), p. 1353. doi: 10.1186/s12889-018-6253-4.

Inizan C., Tarantola A., O'Connor O., Mangeas M., Pocquet N., Forfait C., Descloux E., Gourinat A.-C., Pfannstiel A., Klement-Frutos E., *et al.* (2019) 'Dengue in New Caledonia: Knowledge and Gaps', *Tropical Medicine and Infectious Disease*, 4(2), p. 95. doi: 10.3390/tropicalmed4020095.

Institut de Veille Sanitaire (2012) *Bilan épidémiologique Dengue Pacifique Sud (Bilan à fin 2011- Mise à jour Avril 2012)*.

Jajosky R. A. and Groseclose S. L. (2004) 'Evaluation of reporting timeliness of public health surveillance systems for infectious diseases', *BMC Public Health*, 4(1), p. 29. doi: 10.1186/1471-2458-4-29.

Jebara K. Ben (2004) 'Surveillance, detection and response: managing emerging diseases at national and international levels', *Revue scientifique et technique (International Office of Epizootics)*, 23(2), pp. 709–715.

John T. J., Rajappan K. and Arjunan K. K. (2004) 'Communicable diseases monitored by disease

surveillance in Kottayam district, Kerala state, India.', *Indian J Med Res*, pp. 86–93.

Jones K. E., Patel N. G., Levy M. A., Storeygard A., Balk D., Gittleman J. L. and Daszak P. (2008) 'Global trends in emerging infectious diseases', *Nature*, 451(7181), pp. 990–993. doi: 10.1038/nature06536.

Josephsen J., Schenkel K., Benzler J. and Krause G. (2006) 'Preparations for infectious disease surveillance during the football World Cup tournament, Germany 2006', *Weekly releases (1997–2007)*, 11(17), p. 2949. doi: 10.2807/esw.11.17.02949-en.

Kaiser R. and Coulombier D. (2006) 'Epidemic intelligence during mass gatherings', *Weekly releases (1997–2007)*, 11(51), p. 3100. doi: 10.2807/esw.11.51.03100-en.

Kanamitsu M., Taniguchi K., Urasawa S., Ogata T., Wada Yoshito, Wada Yoshitake and Saroso J. S. (1979) 'Geographic Distribution of Arbovirus Antibodies in Indigenous Human Populations in the Indo-Australian Archipelago *', *The American Journal of Tropical Medicine and Hygiene*, 28(2), pp. 351–363. doi: 10.4269/ajtmh.1979.28.351.

Khan K., McNabb S. J. N., Memish Z. A., Eckhardt R., Hu W., Kossowsky D., Sears J., Arino J., Johansson A., Barbeschi M., *et al.* (2012) 'Infectious disease surveillance and modelling across geographic frontiers and scientific specialties', *The Lancet Infectious Diseases*. Elsevier, pp. 222–230. doi: 10.1016/S1473-3099(11)70313-9.

Kirya B. G., Mukwaya L. G. and Sempala S. D. K. (1977) 'A yellow fever epizootic in Zika Forest, Uganda, during 1972: Part 1: Virus isolation and sentinel monkeys', *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 71(3), pp. 254–260. doi: 10.1016/0035-9203(77)90020-7.

Kitching R. P. (2003) 'Vaccines for lumpy skin disease, sheep pox and goat pox.', *Developments in biologicals*, 114, pp. 161–7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14677686 (Accessed: 16 April 2020).

Kool J. L., Paterson B., Pavlin B. I., Durrheim D., Musto J. and Kolbe A. (2012a) 'Pacific-wide simplified syndromic surveillance for early warning of outbreaks', *Global Public Health*, 7(7), pp. 670–681. doi: 10.1080/17441692.2012.699536.

Kool J. L., Paterson B., Pavlin B. I., Durrheim D., Musto J. and Kolbe A. (2012b) 'Pacific-wide simplified syndromic surveillance for early warning of outbreaks', *Global Public Health*, 7(7), pp. 670–681. doi: 10.1080/17441692.2012.699536.

Lewis S. L., Feighner B. H., Loschen W. A., Wojcik R. A., Skora J. F., Coberly J. S. and Blazes D. L. (2011) 'SAGES: A Suite of Freely-Available Software Tools for Electronic Disease Surveillance in Resource-Limited Settings', *PLoS ONE*. Edited by A. M. Noor, 6(5), p. e19750. doi: 10.1371/journal.pone.0019750.

Li D., Liu W., Guigon A., Mostyn C., Grant R. and Aaskov J. (2010) 'Rapid displacement of dengue virus type 1 by type 4, Pacific region, 2007-2009.', *Emerging infectious diseases*, 16(1), pp. 123–5. doi: 10.3201/eid1601.091275.

Lombardo J., Burkom H., Elbert E., Magruder S., Lewis S. H., Loschen W., Sari J., Sniegoski C., Wojcik R. and Pavlin J. (2003) 'A systems overview of the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE II)', *Journal of Urban Health*, 80(1), pp. i32–i42. doi: 10.1007/pl00022313.

Lombardo J., Sniegoski C., Loschen W., Westercamp M., Wade M., Dearth S. and Zhang G. (2008) 'Public health surveillance for mass gatherings', *Johns Hopkins APL Technical Digest (Applied Physics Laboratory)*, 27(4), pp. 347–355.

Memish Z. A., Zumla A., McCloskey B., Heymann D., Al Rabeeah A. A., Barbeschi M. and Horton R. (2014) 'Mass gatherings medicine: international cooperation and progress.', *The Lancet*, 383(9934), pp. 2030–2032. doi: 10.1016/S0140-6736(14)60225-7.

Mercier A., Arsevska E., Bournez L., Bronner A., Calavas D., Cauchard J., Falala S., Caufour P., Tisseuil C., Lefrançois T., *et al.* (2018) 'Spread rate of lumpy skin disease in the Balkans, 2015-2016', *Transboundary and Emerging Diseases*, 65(1), pp. 240–243. doi: 10.1111/tbed.12624.

Mercier A., Lancelot R., Hendrikx P., MacKinnon L., Madoff L., Lambert Y., Calavas D. and Cauchard J. (2020) 'The French Epidemic Intelligence System: comparing disease surveillance at national and international level using data from the Program for Monitoring Emerging Diseases', *OIE Scientific and Technical Review*, 39(3), p. in press. Available at: https://www.oie.int/fileadmin/Home/eng/Publications_%26_Documentation/docs/pdf/revue_plurithematique/2020/01042020-00162-EN_Mercier_ANG.pdf.

Milsten A. M., Maguire B. J., Bissell R. A. and Seaman K. G. (2002) 'Mass-Gathering Medical Care: A Review of the Literature', *Prehospital and Disaster Medicine*, 17(03), pp. 151–162. doi: 10.1017/S1049023X00000388.

Le Ministère de l'Agriculture de l'Agroalimentaire et de la F. (2013) *Arrêté du 29 juillet 2013 relatif à la définition des dangers sanitaires de première et deuxième catégorie pour les espèces animales*. Available at: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000027831750&categorieLien=id (Accessed: 25 January 2019).

Morens D., Folkers G. and Fauci A. (2004) 'The challenge of emerging and re-emerging infectious diseases.', *Nature*, 430, pp. 242–249. doi: 10.1038/nature02759.

Morin R. S., Liebhold A. M. and Gottschalk K. W. (2009) 'Anisotropic spread of hemlock woolly adelgid in the eastern United States', *Biological Invasions*, 11(10), pp. 2341–2350. doi: 10.1007/s10530-008-9420-1.

Morse S. S. (2001) 'Factors in the Emergence of Infectious Diseases', in *Plagues and Politics*. London: Palgrave Macmillan UK, pp. 8–26. doi: 10.1057/9780230524248_2.

Muñoz F., Mercier A., Cauchard J. and Lancelot R. (2020) 'Estimation de la vitesse de propagation de la PPA en Belgique', *Bulletin épidémiologique, santé animale et alimentation*. doi: 10.5281/ZENODO.4036288.

Musso D., Rodriguez-Morales A. J., Levi J. E., Cao-Lormeau V. M. and Gubler D. J. (2018) 'Unexpected outbreaks of arbovirus infections: lessons learned from the Pacific and tropical America', *The Lancet Infectious Diseases*. Lancet Publishing Group, pp. e355–e361. doi: 10.1016/S1473-3099(18)30269-X.

Musso D. and Gubler D. J. (2016) 'Zika virus', *Clinical Microbiology Reviews*, 29(3), pp. 487–524. doi: 10.1128/CMR.00072-15.

Musso D., Nilles E. J. and Cao-Lormeau V.-M. (2014) 'Rapid spread of emerging Zika virus in the Pacific area', *Clinical Microbiology and Infection*, 20(10), pp. O595–O596. doi: 10.1111/1469-0691.12707.

Nelesone T., Durrheim D. N., Speare R., Kiedrzynski T. and Melrose W. D. (2006) 'Strengthening sub-national communicable disease surveillance in a remote Pacific Island country by adapting a successful African outbreak surveillance model', *Tropical Medicine and International Health*, 11(1), pp. 17–21. doi: 10.1111/j.1365-3156.2005.01534.x.

Nsoesie E. O., Kluberg S. A., Mekaru S. R., Majumder M. S., Khan K., Hay S. I. and Brownstein J. S.

(2015) 'New digital technologies for the surveillance of infectious diseases at mass gathering events', *Clinical Microbiology and Infection*, 21(2), pp. 134–140. doi: 10.1016/J.CMI.2014.12.017.

O'Shea J. (2017) 'Digital disease detection: A systematic review of event-based internet biosurveillance systems', *International Journal of Medical Informatics*, 101, pp. 15–22. doi: 10.1016/j.ijmedinf.2017.01.019.

Oliver K., Kothari A. and Mays N. (2019) 'The dark side of coproduction: Do the costs outweigh the benefits for health research?', *Health Research Policy and Systems*. BioMed Central Ltd., pp. 1–10. doi: 10.1186/s12961-019-0432-3.

Paquet C., Coulombier D., Kaiser R. and Ciotti M. (2006) 'Epidemic intelligence: a new framework for strengthening disease surveillance in Europe', *Eurosurveillance*, 11(12), pp. 212–214.

Patz J. A., Daszak P., Tabor G. M., Aguirre A. A., Pearl M., Epstein J., Wolfe N. D., Kilpatrick A. M., Foufopoulos J., Molyneux D., *et al.* (2004) 'Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence', *Environmental Health Perspectives*, 112(10), pp. 1092–1098. doi: 10.1289/ehp.6877.

Perry W. J. (1950) 'The Mosquitoes and Mosquito-Borne Diseases on New Caledonia, an Historic Account: 1885–1946 1,2', *The American Journal of Tropical Medicine and Hygiene*, s1-30(1), pp. 103–114. doi: 10.4269/ajtmh.1950.s1-30.103.

Pfaff G., Lohr D., Santibanez S., Mankertz A., van Treeck U., Schönberger K. and Hautmann W. (2010) 'Spotlight on measles 2010: Measles outbreak among travellers returning from a mass gathering, Germany, September to October 2010', *Eurosurveillance*, 15(50), p. 19750. doi: 10.2807/ese.15.50.19750-en.

R (2019) 'R: A language and environment for statistical computing. R Foundation for Statistical Computing'. Vienna, Austria: R Core Team. Available at: https://www.r-project.org/.

Rayens M. K. and Hahn E. J. (2000) 'Building Consensus Using the Policy Delphi Method', *Policy, Politics, & Nursing Practice*, 1(4), pp. 308–315. doi: 10.1177/152715440000100409.

Rodríguez-Prieto V., Vicente-Rubiano M., Sánchez-Matamoros A., Rubio-Guerri C., Melero M., Martínez-López B., Martínez-Avilés M., Hoinville L., Vergne T., Comin A., *et al.* (2015) 'Systematic review of surveillance systems and methods for early detection of exotic, new and re-emerging diseases in animal populations', *Epidemiol. Infect.*, 143(2015), pp. 2018–2042. doi: 10.1017/S095026881400212X.

Rortais A., Belyaeva J., Gemo M., van der Goot E. and Linge J. P. (2010) 'MedISys: An early-warning system for the detection of (re-)emerging food- and feed-borne hazards', *Food Research International*, 43(5), pp. 1553–1556. doi: 10.1016/J.FOODRES.2010.04.009.

Roth A., Mercier A., Lepers C., Hoy D., Duituturaga S., Benyon E. K., Guillaumot L. and Souarès Y. (2014) 'Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012–2014', *Eurosurveillance*, 19(41), p. 20929. doi: 10.2807/1560-7917.ES2014.19.41.20929.

Roth A., Hoy D., Horwood P. F., Ropa B., Hancock T., Guillaumot L., Rickart K., Frison P., Pavlin B. and Souares Y. (2014) 'Preparedness for threat of chikungunya in the pacific', *Emerging infectious diseases*, 20(8). doi: 10.3201/eid2008.130696.

Rotureau B., Barboza P., Tarantola A. and Paquet C. (2007) 'International Epidemic Intelligence at the Institut de Veille Sanitaire, France', *Emerging Infectious Diseases*, 13(10), pp. 1590–1592. doi: 10.3201/eid1310.070522.

Sailleau C., Bréard E., Viarouge C., Vitour D., Romey A., Garnier A., Fablet A., Lowenski S., Gorna K., Caignard G., *et al.* (2017) 'Re-Emergence of Bluetongue Virus Serotype 8 in France, 2015', *Transboundary and Emerging Diseases*, 64(3), pp. 998–1000. doi: 10.1111/tbed.12453.

Santibanez S., Prosenc K., Lohr D., Pfaff G., Markocic O. J. and Mankertz A. (2014) 'Measles virus spread initiated at international mass gatherings in Europe, 2011', *Eurosurveillance*, 19(35), pp. 1–10. doi: 10.2807/1560-7917.es2014.19.35.20891.

Singh N., Kiedrzynski T., Lepers C., Benyon E. K., Rqfh G., Surshu W. K. H., Sh V. and Lqwurgxfhg L. V (2005) 'Dengue in the Pacific - an update of the current situation', *Pacific Health Surveillance and Response*, pp. 111–119.

Sobrino F. and Domingo E. (2001) 'Foot-and-mouth disease in Europe', *EMBO reports*, 2, pp. 459–461. doi: 10.1093/embo-reports/kve122.

Soto G., Araujo-Castillo R. V, Neyra J., Fernandez M., Leturia C., Mundaca C. C. and Blazes D. L. (2008) 'Challenges in the implementation of an electronic surveillance system in a resource-limited setting: Alerta, in Peru', *BMC Proceedings*, 2(S3), p. S4. doi: 10.1186/1753-6561-2-s3-s4.

Souarès Y. (2000) 'Telehealth and outbreak prevention and control: the foundations and advances of the Pacific Public Health Surveillance Network', *Pacific Health Dialog*, 7(2), pp. 11–28. Available at: http://www.pphsn.net/ENGLISH/Publications/PHD/PHDpages11-28.pdf (Accessed: 5 February 2019).

Staples J. E., Breiman R. F. and Powers A. M. (2009) 'Chikungunya Fever: An Epidemiological Review of a Re-Emerging Infectious Disease', *Clinical Infectious Diseases*, 49(6), pp. 942–948. doi: 10.1086/605496.

Steel A., Gubler D. J. and Bennett S. N. (2010) 'Natural attenuation of dengue virus type-2 after a series of island outbreaks: A retrospective phylogenetic study of events in the South Pacific three decades ago', *Virology*, 405(2), pp. 505–512. doi: 10.1016/J.VIROL.2010.05.033.

Taylor L. H., Latham S. M. and woolhouse M. E. J. (2001) 'Risk factors for human disease emergence', *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*. Edited by M. E. J. Woolhouse and C. Dye, 356(1411), pp. 983–989. doi: 10.1098/rstb.2001.0888.

Tesh R. B., Gajdusek D. C., Garruto R. M., Cross J. H. and Rosen L. (1975) 'The Distribution and Prevalence of Group a Arbovirus Neutralizing Antibodies Among Human Populations in Southeast Asia and the Pacific Islands', *The American Journal of Tropical Medicine and Hygiene*, 24(4), pp. 664–675. doi: 10.4269/ajtmh.1975.24.664.

Teurlai M. (2014) *Modélisation multi-échelle de la dynamique spatiale de la Dengue : application à la Nouvelle-Calédonie et à la région Pacifique*. Montpellier 2. Available at: http://www.theses.fr/2014MON20167 (Accessed: 7 February 2019).

the Pacific Community (2017) *SPC Member Map*. Available at: https://www.spc.int/our-members/ (Accessed: 18 April 2019).

Thompson D. K., Muriel P., Russell D., Osborne P., Bromley A., Rowland M., Creigh-Tyte S. and Brown C. (2002) 'Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001', *Revue Scientifique et Technique de l'OIE*, 21(3), pp. 675–687. doi: 10.20506/rst.21.3.1353.

Tisseuil C., Gryspeirt A., Lancelot R., Pioz M., Liebhold A. and Gilbert M. (2016) 'Evaluating methods to quantify spatial variation in the velocity of biological invasions', *Ecography*, 39(5), pp. 409–418. doi: 10.1111/ecog.01393.

Tsetsarkin K. A., Vanlandingham D. L., McGee C. E. and Higgs S. (2007) 'A Single Mutation in Chikungunya Virus Affects Vector Specificity and Epidemic Potential', *PLoS Pathogens*, 3(12), p. e201. doi: 10.1371/journal.ppat.0030201.

Valentin S., Mercier A., Lancelot R., Roche M. and Arsevska E. (2020) 'Monitoring online media reports for early detection of unknown diseases: Insight from a retrospective study of COVID-19 emergence', *Transboundary and Emerging Diseases*, p. tbed.13738. doi: 10.1111/tbed.13738.

Valentin S., Arsevska E., Falala S., de Goër J., Lancelot R., Mercier A., Rabatel J. and Roche M. (2020) 'PADI-web: A multilingual event-based surveillance system for monitoring animal infectious diseases', *Computers and Electronics in Agriculture*, 169. doi: 10.1016/j.compag.2019.105163.

Valentin S., Arsevska E., Mercier A., Falala S., Rabatel J., Lancelot R. and Roche M. (2020) 'PADI-web: an event-based surveillance system for detecting, classifying and processing online news', in *Post-Proceedings of 8th Language & Technology Conference, LTC 2017*.

Valentin S., Lancelot R. and Roche M. (2018) 'Surveillance automatisée de sources non-officielles pour la veille sanitaire internationale', in *Workshop « Agriculture Numérique en Afrique »*. Montpellier, France.

White P., Saketa S., Durand A., Vaai-Nielsen S., Leong-Lui T. A., Naseri T., Matalima A., Amosa F., Mercier A., Lepers C., *et al.* (2017) 'Enhanced surveillance for the Third United Nations Conference on Small Island Developing States, Apia, Samoa, September 2014.', *Western Pacific surveillance and response journal : WPSAR*, 8(1), pp. 15–21. doi: 10.5365/WPSAR.2016.7.4.002.

White P., Saketa S., Johnson E., Gopalani S. V, Edward E., Loney C., Mercier A., Toatu T., Wojcik R., Lewis S., *et al.* (2018) 'Mass gathering enhanced syndromic surveillance for the 8th Micronesian Games in 2014, Pohnpei State, Federated States of Micronesia.', *Western Pacific surveillance and response journal : WPSAR*, 9(1), pp. 1–7. doi: 10.5365/wpsar.2016.7.4.001.

Wilburn J., O'Connor C., Walsh A. L. and Morgan D. (2019) 'Identifying potential emerging threats through epidemic intelligence activities—looking for the needle in the haystack?', *International Journal of Infectious Diseases*, 89, pp. 146–153. doi: 10.1016/j.ijid.2019.10.011.

Wood S. N. (2003) 'Thin plate regression splines', *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 65(1), pp. 95–114. doi: 10.1111/1467-9868.00374.

Woolhouse M. and Gowtage-Sequeria S. (2005) 'Host range and emerging and reemerging pathogens.', *Emerging infectious diseases*, 11(12), pp. 1842–7. doi: 10.3201/eid1112.050997.

World Health Organization (2003) *Update 74 - Global decline in cases and deaths continues*, *WHO Press release*. Available at: https://www.who.int/csr/don/2003_06_05/en/ (Accessed: 17 February 2020).

World Health Organization (2007) *The world health report 2007 - A safer future: global public health security in the 21st century*, *WHO*. World Health Organization. Available at: https://www.who.int/whr/2007/en/ (Accessed: 5 March 2019).

World Health Organization (2008a) *Communicable disease alert and response for mass gatherings*. World Health Organization. Available at: https://www.who.int/csr/mass_gathering/en/ (Accessed: 5 February 2019).

World Health Organization (2008b) *International health regulations (2005).* World Health Organization.

World Health Organization (2009) *Dengue Guidelines for Diagnosis Treatment Prevention and*

Control (New Edition 2009). World Health Organization.

World Health Organization (2014) *Early detection, assessment and response to acute public health events: implementation of early warning and response with a focus on event-based surveillance*, *WHO*. Available at: https://apps.who.int/iris/handle/10665/112667.

World Health Organization (2015) *Public Health for Mass Gatherings: Key Considerations*. World Health Organization. Available at: https://www.who.int/ihr/publications/WHO_HSE_GCR_2015.5/en/ (Accessed: 14 January 2019).

World Health Organization (2016) *Epidemic intelligence - systematic event detection*, *WHO*. World Health Organization. Available at: https://www.who.int/csr/alertresponse/epidemicintelligence/en/ (Accessed: 4 April 2019).

World Health Organization (2017a) 'Federated States of Micronesia – WHO Country Cooperation Strategy 2018 – 2022', *WHO*, pp. 1–6.

World Health Organization (2017b) *Western Pacific Regional Action Plan for Dengue Prevention and Control (2016)*. Available at: http://iris.wpro.who.int/handle/10665.1/13599.

World Health Organization (2018a) *2018 Annual review of diseases prioritized under the Research and Development Blueprint*. Geneva, Switzerland. Available at: https://www.who.int/docs/default-source/blue-print/2018-annual-review-of-diseases-prioritized-under-the-research-and-development-blueprint.pdf?sfvrsn=4c22e36_2.

World Health Organization (2018b) *Zika virus*. Available at: https://www.who.int/en/news-room/fact-sheets/detail/zika-virus (Accessed: 18 February 2020).

World Health Organization (2019) *MERS situation update December 2019*. Available at: http://www.emro.who.int/health-topics/mers-cov/mers-outbreaks.html (Accessed: 17 February 2020).

World Health Organization (2020a) *Surveillance strategies for COVID-19 human infection: interim guidance, 10 May 2020*. Available at: https://apps.who.int/iris/handle/10665/332051.

World Health Organization (2020b) *WHO Statement regarding cluster of pneumonia cases in Wuhan, China*. Available at: https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china (Accessed: 21 September 2020).

World Health Organization and Food and Agriculture Organization (2011) *Principles and Methods for the Risk Assessment of Chemicals in Food - Chapter 2: Risk assessment and its role in risk analysis*, *International Journal of Environmental Studies*. World Health Organization. Available at: http://www.tandfonline.com/doi/full/10.1080/00207233.2010.549617 (Accessed: 12 May 2020).

World Organisation for Animal Health (2019a) *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*. Available at: https://www.oie.int/en/standard-setting/terrestrial-manual/access-online/ (Accessed: 10 April 2020).

World Organisation for Animal Health (2019b) *OIE Terrestrial Code*. Available at: https://www.oie.int/en/standard-setting/terrestrial-code/ (Accessed: 22 April 2020).

Yan S. J., Chughtai A. A. and Macintyre C. R. (2017a) 'Utility and potential of rapid epidemic intelligence from internet-based sources', *International Journal of Infectious Diseases*, 63, pp. 77–87. doi: 10.1016/J.IJID.2017.07.020.

Yan S. J., Chughtai A. A. and Macintyre C. R. (2017b) 'Utility and potential of rapid epidemic

intelligence from internet-based sources', *International Journal of Infectious Diseases*. Elsevier B.V., pp. 77–87. doi: 10.1016/j.ijid.2017.07.020.

Yu P., de Courten M., Pan E., Galea G. and Pryor J. (2009) 'The development and evaluation of a PDA-based method for public health surveillance data collection in developing countries', *International Journal of Medical Informatics*, 78(8), pp. 532–542. doi: 10.1016/j.ijmedinf.2009.03.002.

Zellweger R. M., Cano J., Mangeas M., Taglioni F., Mercier A., Despinoy M., Menkès C. E., Dupont-Rouzeyrol M., Nikolay B. and Teurlai M. (2017) 'Socioeconomic and environmental determinants of dengue transmission in an urban setting: An ecological study in Nouméa, New Caledonia', *PLOS Neglected Tropical Diseases*. Edited by W. B. Messer, 11(4), p. e0005471. doi: 10.1371/journal.pntd.0005471.

Annexes

Annex 1. The interface of the EpidVis tool (Fadloun *et al.*, 2020)

Figure 38 presents the web interface of the EpidVis tool: a) a KEYWORD MANAGER allows domain experts to express their knowledge, b) a QUERY BUILDER helps domain experts to build and launch queries, c) results are shown in the QUERY RESULT VIEW, d) a SUGGESTION VIEW helps to integrate external knowledge to the KEYWORD MANAGER (e). A toolbar enables interaction with the KEYWORD MANAGER. Buttons are available to launch the QUERY BUILDER (f) and the SUGGESTION VIEW (g). Files are created, saved, and loaded with specific buttons (h).
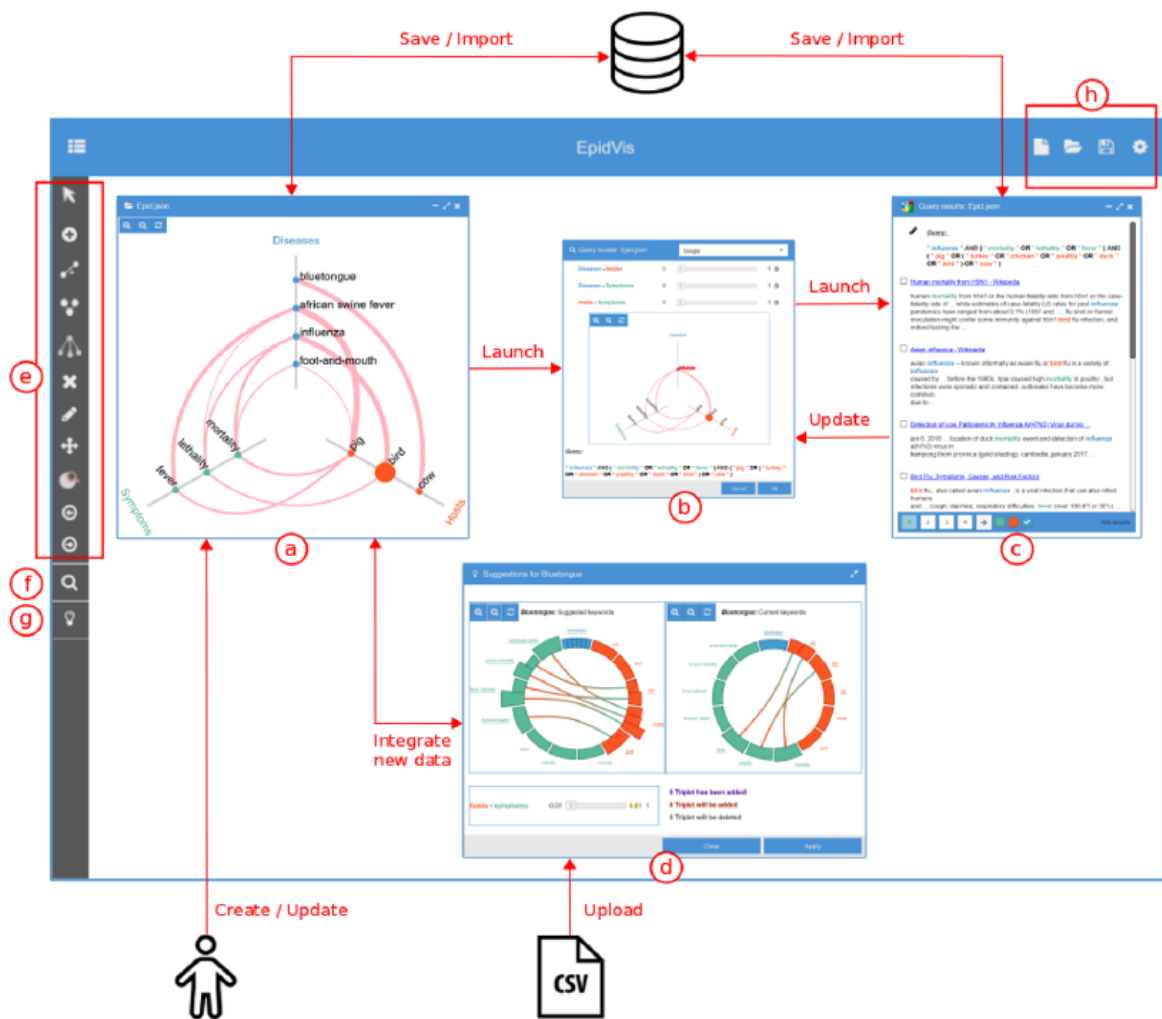
Figure 38. The interface of the EpidVis tool (Fadloun et al., 2019)

Annex 2. The interface of the EpidNews tool (Goer *et al.*, 2020)

Figure 39 presents an overview of the web interface of the EpidNews tool: a) a map shows disease outbreaks and signals locations using a circle or diamond depending on source type, b) streamgraphs compare the temporal evolution of official and unofficial sources, c) a sunburst presents relationships between diseases, hosts and symptoms in a hierarchical view, d) a data manager allows manipulation of the data represented in the other views (sources, entities types and entities values), and e) a toolbar provides other interactive functionalities.

Figure 39. The interface of the EpiNews tool (Goer et al., 2018)

Annex 3. Article for case study n°1 – Valentin *et al.,* 2020

RAPID COMMUNICATION

Transboundary and Emerging Diseases **WILEY**

Monitoring online media reports for early detection of unknown diseases: Insight from a retrospective study of COVID-19 emergence

Sarah Valentin[1,2,3,4] | Alizé Mercier[3,4] | Renaud Lancelot[3,4] | Mathieu Roche[1,2] | Elena Arsevska[3,4]

[1]UMR TETIS, CIRAD, Montpellier, France

[2]TETIS, AgroParisTech, CIRAD, CNRS, INRAE, Univ Montpellier, Montpellier, France

[3]UMR ASTRE, CIRAD, Montpellier, France

[4]ASTRE, CIRAD, INRAE, Univ Montpellier, Montpellier, France

Correspondence
Elena Arsevska, UMR ASTRE, CIRAD, F-34398 Montpellier, France.
Email: elena.arsevska@cirad.fr

Abstract

Event-based surveillance (EBS) systems monitor a broad range of information sources to detect early signals of disease emergence, including new and unknown diseases. In December 2019, a newly identified coronavirus emerged in Wuhan (China), causing a global coronavirus disease (COVID-19) pandemic. A retrospective study was conducted to evaluate the capacity of three event-based surveillance (EBS) systems (ProMED, HealthMap and PADI-web) to detect early COVID-19 emergence signals. We focused on changes in online news vocabulary over the period before/after the identification of COVID-19, while also assessing its contagiousness and pandemic potential. ProMED was the timeliest EBS, detecting signals one day before the official notification. At this early stage, the specific vocabulary used was related to 'pneumonia symptoms' and 'mystery illness'. Once COVID-19 was identified, the vocabulary changed to virus family and specific COVID-19 acronyms. Our results suggest that the three EBS systems are complementary regarding data sources, and all require timeliness improvements. EBS methods should be adapted to the different stages of disease emergence to enhance early detection of future unknown disease outbreaks.

KEYWORDS

COVID-19, emerging disease, epidemic intelligence, one Health, online news, PADI-web

1 | INTRODUCTION

Epidemic intelligence (EI) aims to detect, monitor and assess potential health threats for early warning and rapid response (Paquet, Coulombier, Kaiser, & Ciotti, 2006). In addition to indicator-based surveillance of official sources, public and animal health agencies increasingly incorporate an event-based surveillance (EBS) component into their EI system. EBS uses unstructured data from unofficial sources such as online news to improve early detection of emerging infectious diseases (EIDs). Several free-access EBS systems have been supporting epidemic intelligence since the late 1990s, such as the Program for Monitoring Emerging Diseases (ProMED; Woodall, 2001), HealthMap (Brownstein, Freifeld, Reis, & Mandl, 2008) and the recently developed PADI-web (Valentin, Arsevska, et al., 2020).

Program for Monitoring Emerging Diseases is a human-curated system that was launched by the International Society for Infectious Diseases (ISID) in 1994. The system relies on a

135

large network of experts worldwide who produce and share verified reports on disease outbreaks in a common platform (Carrion & Madoff, 2017). HealthMap is a semi-automated system launched by the Boston Children's Hospital in 2006. The tool monitors both official and non-official web news sources (Freifeld, Mandl, Reis, & Brownstein, 2008). Both HealthMap and ProMED monitor a list of human and animal diseases and syndromes thereof. The Platform for Automated extraction of animal Disease Information from the web (PADI-web) was created in 2016 to monitor online animal health-related news for the French Epidemic Intelligence System (FEIS) (Arsevska et al., 2018; Valentin, Arsevska, et al., 2020). Both HealthMap and PADI-web automatically retrieve health-related news from Google News using customized Really Simple Syndication (RSS) feeds. For news detection, the two systems mine terms for known diseases, as well as for clinical signs and syndromes (Arsevska et al., 2016). All three EBS systems monitor news in multiple languages, including Chinese.

On 31 December 2019, local health officials of the Chinese city of Wuhan reported a cluster of 27 cases of 'pneumonia of unknown cause'. These cases were linked to a wholesale live animal and seafood market in the city. The first death was reported in January 2020, and the causative agent was identified as a new coronavirus, that is SARS-CoV-2, and the disease was named COVID-19. The first epidemiological study on patients with laboratory-confirmed COVID-19 infection reported the onset of illness as early as 1 December 2019 (Huang et al., 2020).

This retrospective study aimed first to evaluate three EBS systems (ProMED, HealthMap and PADI-web) and their capacity for timely detection of the COVID-19 emergence in China. Secondly, we focused on PADI-web to understand how an animal health EBS system contributed to the detection of a human EID. We analysed the RSS feeds from PADI-web that detected COVID-19-related news articles (hereafter referred to as 'news'). Thirdly, we assessed the vocabulary in the news detected by PADI-web and its change in relation to identification of the pathogen and the EID spread.

2 | MATERIAL AND METHODS

2.1 | COVID-19-related news detection

News from 1 to 31 December 2019 was mined to assess the timeliness of the three EBS. We compared the first news regarding the publication date, language and source.

To gain insight into how PADI-web detected the COVID-19 emergence, we further filtered a second corpus of news published from 31 December 2019 to 26 January 2020 containing at least one of the following words in the title and body of the news: 'pneumonia', 'respiratory illness', 'coronavirus', 'nCoV' (an early name for COVID-19), and 'Wuhan'. After manual verification of their relevance, we retained 275 out of 333 news items for analysis (Valentin, Mercier, Mercier, Lancelot, Roche, & Arsevska, 2020).

We assessed the link between the detected news items and the animal health RSS feeds from PADI-web that served to retrieve those news items. To this end, we read each news item and categorized it into (i) disease-specific RSS feeds (containing specific disease names) and (ii) syndromic RSS feeds (containing combinations of symptoms and animal hosts).

2.2 | News vocabulary

We analysed the vocabulary change spanning the period from the initial discovery of the COVID-19 outbreak to its spread outside China by extracting terms from the whole corpus. A word frequency-based method was first implemented to highlight important keywords according periods (Figure 1). Secondly, we used a ranking function based on the frequency and discriminance[1] of terms (i.e. words and multi-word terms) extracted with BioTex, a text-mining tool tailored for biomedical terminology (Lossio-Ventura, Jonquet, Roche, & Teisseire, 2016). BioTex is based on the use of (i) a relevant combination of information retrieval techniques and statistical methods and (ii) a list of syntactic structures of terms that have been learnt

FIGURE 1 Wordclouds generated from COVID-19-related news articles during three consecutive periods: (a) 31 December 2019 – 08 January 2020, (b) 09–19 January 2020, (c) 20–26 January 2020

via relevant sources (e.g. UMLS, MeSH). BioTex-extracted terms can be lowercase words (e.g. influenza), or phrases (e.g. avian influenza).

We further identified terms referring to COVID-19, such as 'new virus' and 'mystery pneumonia'. We manually categorized the terms as 'mystery' (referring to the unknown threat), 'pneumonia' (referring to the clinical signs), 'coronavirus' (referring to the virus taxonomy) and 'technical' (technical acronyms specifically pertaining to the virus). One news item could contain terms from different categories. We calculated the daily proportion of each category, expressed as the sum of occurrences of the category divided by the total number of occurrences.

3 | RESULTS AND DISCUSSION

3.1 | News detection

Program for Monitoring Emerging Diseases was the first EBS system to detect and report a news item from a Chinese online source.[2] The ProMED report dated back to 30 December 2019—a day before the first official notification of pneumonia-like cases in Wuhan (Wuhan Municipal Health Commission, 2020). PADI-web and HealthMap respectively detected three and one COVID-19-related news items on 31 December 2019—the same day as the first official notification of pneumonia-like cases in Wuhan (one HealthMap news item from an English source, three PADI-web news items from two English sources and one Chinese source). The news detected by the three EBS originated from five different media outlets.

Among the three EBS systems compared, only ProMED relies on local expert information to alert on health threats. This result suggests that the network of local field experts is crucial for the detection of EID events and their reporting. Otherwise, HealthMap and PADI-web detected news on the same day as the official reporting. It is therefore essential to understand their current limitations and promote the key role of experts in EBS systems. Further studies

should also focus on assessing whether the timeliness of automated systems depends on the communication strategies of online media, as well as on determining their health event reporting threshold, and how these features impact the sensitivity of EBS systems.

The three EBS systems included in this study monitor media in multiple languages, thus facilitating detection of local media news. A further increase in the number of available languages should enhance the sensitivity of EBS systems (Barboza et al., 2014). Our study also showed that the three EBS systems were complementary regarding scope (animal and public health), moderation (manual, semi-automated, automated) and number of covered languages.

PADI-web could retrieve COVID-19-related news through animal health-related RSS feeds, thus proving its usefulness for the detection of information of relevance for public health risk assessors. From 275 COVID-19-related-news items retrieved by PADI-web, 54.5% ($n = 150$) were retrieved via syndromic RSS feeds, while the remaining 45.5% ($n = 125$) were retrieved via disease-specific RSS (Table 1).

Content-wise, 31.7% ($n = 87$) of the news items compared COVID-19 to five animal diseases (avian influenza, African swine fever, classical swine fever, West Nile virus and Rift Valley fever), 24.4% ($n = 67$) of the news items described the broad range of animal species sensible to coronaviruses, 18.2% ($n = 50$) reported that avian influenza was ruled out from possible causes of the outbreak, 7.7% ($n = 21$) described other ongoing outbreaks in addition to COVID-19 (avian influenza, African swine fever, classical swine fever and foot-and-mouth disease), 2.5% ($n = 7$) referred to animal species present in Chinese markets as potential COVID-19 sources, and 0.7% ($n = 2$) advised people to avoid contact with animals. Irrelevant keyword matches were found in 12 news items (e.g. finding a host keyword in the name of a source), and no link could be established between the RSS feed and the article for 29 other news items (10.5%).

The fact that disease-specific RSS feeds contributed as much as syndromic RSS feeds to the detection of COVID-19 news by PADI-web was unexpected, thus highlighting the importance of combining

TABLE 1 Percentage (%) and number (n) of COVID-19-related news items retrieved by PADI-web from 31 December 2019 to 26 January 2020

	Type of RSS feed		
Link with COVID-2019	Disease-specific	Syndromic	Total
Comparison with another disease	20.4% ($n = 56$)	11.3% ($n = 31$)	31.7% ($n = 87$)
Disease ruled out	17.8% ($n = 49$)	0.4% ($n = 1$)	18.2% ($n = 50$)
Aggregation with other disease outbreaks	6.2% ($n = 17$)	1.5% ($n = 4$)	7.7% ($n = 21$)
Coronaviruses in animals	-	24.4% ($n = 67$)	24.4% ($n = 67$)
Market animals	-	2.5% ($n = 7$)	2.5% ($n = 7$)
Avoid contact with animals	-	0.7% ($n = 2$)	0.7% ($n = 2$)
Irrelevant keyword matches	0.4% ($n = 1$)	4.0% ($n = 11$)	4.4% ($n = 12$)
Unknown	0.7% ($n = 2$)	9.8% ($n = 27$)	10.5% ($n = 29$)
Total	45.5% ($n = 125$)	54.5% ($n = 150$)	100% (275)

Note: Each article is categorized by type of feed (disease-related or syndromic) according to the link between the feed and COVID-19.

Category	Terms
Pneumonia	pneumonia, respiratory outbreak, lung disease, respiratory tract illness, respiratory illness, respiratory infection, pneumonia-like disease, upper-respiratory illness, respiratory condition, lung infection, pneumonia-like cases, pneumonia-like illness, respiratory virus, lung virus, pneumonia-like virus, pneumonia-causing virus, pneumonia-like virus.
Mystery	mystery, mysterious, unidentified, undocumented, disease x, unknown, abnormal, unexplained.
Technical	2019-ncov, ncov, 2019 novel coronavirus, n-cov2019, novel coronavirus 2019, ncov2019, cov2019.
Coronavirus	coronavirus, betacoronavirus, coronovirus

TABLE 2 Terms used to describe SARS-CoV-2 and COVID-19 in the corpus and their corresponding category after manual classification
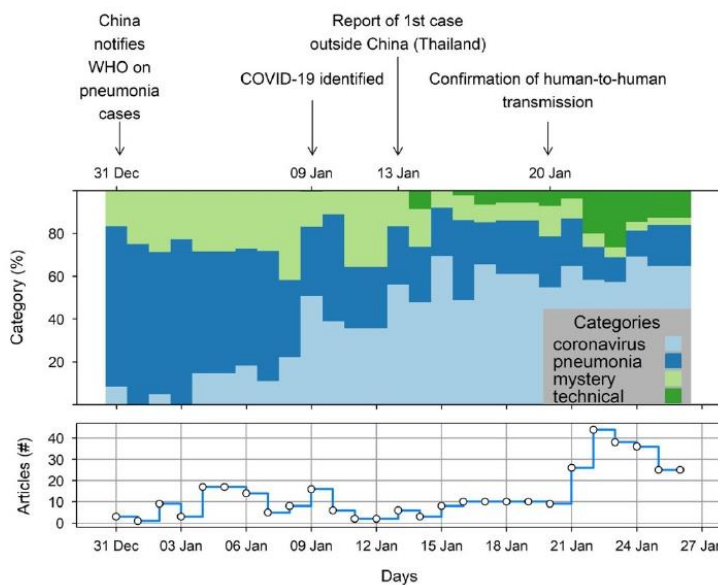
FIGURE 2 Frequency of the different categories used to describe COVID-19 outbreaks (above) and stepped curve of the daily number of COVID-19 news articles retrieved by PADI-web (below), from 31 December 2019 to 26 January 2020. Daily counts for Saturday and Sunday are merged to account for weekday/weekend trends

both disease-specific and syndromic feeds. Many of the news items detected by PADI-web compared the magnitude and economic impact of COVID-19 with regard to avian influenza and African swine fever outbreaks in China. Indeed, prior to COVID-19 identification, the reported pneumonia-like illness was compared to avian influenza zoonotic infections. Some news also presented a summary of several recent disease outbreaks in China, including African swine fever (which is not a zoonotic disease), thus explaining why they were detected by PADI-web.

The ability of EBS tools to encompass a broad scope of health-related topics through a limited number of queries (RSS feeds) is a major asset compared to formal sources. This capacity largely depends on the intrinsic features of online news in which outbreak-related content is often bulked up with additional information, such as comparisons with previous disease outbreaks, thus increasing the probability of being detected by EBS tools. However, the probability

of detection of an EID event might be higher for (actual or assumed) zoonotic diseases and countries with ongoing animal disease outbreaks. This is not a major shortcoming in practice.

3.2 | News vocabulary

From the terms referring to either the virus or the disease, 18 terms were in the 'pneumonia' category, eight terms in the 'mystery' category, three terms in the 'coronavirus' category (one of them, 'coronovirus' being a misspelt form of 'coronavirus'), and seven terms in the 'technical' category (Table 2).

The wordclouds generated from the overall news contents mined over three consecutive periods are shown in Figure 1.

Before identification of the virus (31 December 2019 – 8 January 2020), 58.1% (n = 317) of the COVID-19 terms were in the

'pneumonia' category, 29.1% ($n = 159$) in the 'mystery' category and 12.8% ($n = 70$) in the 'coronavirus' category. From the official identification of the virus to the first report of a case outside China (09 – 12 January 2020), 48.5% ($n = 127$) of the terms were in the 'coronavirus' category, 34.7% ($n = 91$) in the 'pneumonia' category, and 16.8% ($n = 44$) in the 'mystery' category. From this first report to the confirmation of human-to-human transmission (13–19 January 2020), 58.3% ($n = 196$) of the terms were in the 'coronavirus' category, 27.4% ($n = 92$) in the 'pneumonia' category, 11.3% ($n = 38$) in the 'mystery', category and 3.0% ($n = 10$) were in the 'technical' category. From the confirmation of human-to-human transmission to the end of the studied period 62.9% ($n = 906$) of the terms were in the 'coronavirus' category, 17.4% ($n = 250$) in the 'technical' category, 14.1% ($n = 203$) in the 'pneumonia' category, and 5.6% ($n = 81$) in the 'mystery' category (Figure 2).

The incorporation of terms semantically related to 'unknown' and 'mysterious' events into existing RSS feeds could enhance the detection and retrieval of relevant news. We suggest that this category of terms could boost the identification of classic epidemiological entities (e.g. disease, hosts, locations, dates) in news feeds.

Our results revealed that the vocabulary changed as the disease spread. EBS methods used to mine and analyse news from the web should thus be tailored to the different disease epidemiology stages.

With MERS-CoV in 2014 and SARS in 2003, COVID-19 is the third coronavirus outbreak emergence that has occurred over the past two decades, thereby highlighting the need to closely monitor the emergence of pneumonia-like illnesses using existing EBS systems. Our results revealed the complementarity of the existing systems and underlined the need for collaborative development. Pooling veterinary and public health information resources seems crucial to improve early detection of unknown diseases in a One Health context. Our future work will focus on identifying the most relevant keywords for rapid detection of unknown threats, in collaboration with experts of other EBS systems. Moreover, EBS tools may be used in a broader setting, such as monitoring the implementation of protective and control measures.

Efforts invested in improving the timeliness and sensitivity of EBS systems make sense if their outputs (EID event alerts) are formatted, supervised and interpreted by epidemiologists in collaboration with disease experts and reference laboratories. Most importantly, EID event alerts should feed the risk assessment process to ensure early mitigation of EID events by the health managers and decision-makers.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

The authors confirm compliance with the ethical policies of the journal, as noted on the journal's author guidelines page. No ethical approval was required because this study did not involve any experimental protocol on humans or animals, and only open source online data were used.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available for free download in the CIRAD Dataverse at https://doi.org/10.18167/DVN1/MSLEFC.

ORCID

Sarah Valentin [ID] https://orcid.org/0000-0002-9028-681X
Renaud Lancelot [ID] https://orcid.org/0000-0002-5826-5242
Mathieu Roche [ID] https://orcid.org/0000-0003-3272-8568
Elena Arsevska [ID] https://orcid.org/0000-0002-6693-2316

ENDNOTES

[1] Using the F-TFIDF-C measure (Lossio-Ventura et al., 2014).

[2] https://promedmail.org/promed-post/?id=6864153

REFERENCES

Arsevska, E., Roche, M., Hendrikx, P., Chavernac, D., Falala, S., Lancelot, R., & Dufour, B. (2016). Identification of terms for detecting early signals of emerging infectious disease outbreaks on the web. *Computers and Electronics in Agriculture, 123*, 104–115. https://doi.org/10.1016/j.compag.2016.02.010

Arsevska, E., Valentin, S., Rabatel, J., de Goër de Hervé, J., Falala, S., Lancelot, R., & Roche, M. (2018). Web monitoring of emerging animal infectious diseases integrated in the French Animal Health Epidemic Intelligence System. *PLoS One, 13*(8), e0199960. https://doi.org/10.1371/journal.pone.0199960

Barboza, P., Vaillant, L., Le Strat, Y., Hartley, D. M., Nelson, N. P., Mawudeku, A., ... Astagneau, P. (2014). Factors influencing performance of internet-based biosurveillance systems used in epidemic intelligence for early detection of infectious diseases outbreaks. *PLoS One, 9*(3), e90536. https://doi.org/10.1371/journal.pone.0090536

Brownstein, J. S., Freifeld, C. C., Reis, B. Y., & Mandl, K. D. (2008). Surveillance Sans Frontieres: Internet-based emerging infectious disease intelligence and the HealthMap project. *PLoS Med, 5*(7), e151.

Carrion, M., & Madoff, L. C. (2017). ProMED-mail: 22 years of digital surveillance of emerging infectious diseases. *International Health, 9*(3), 177–183. https://doi.org/10.1093/inthealth/ihx014

Freifeld, C. C., Mandl, K. D., Reis, B. Y., & Brownstein, J. S. (2008). HealthMap: Global infectious disease monitoring through automated classification and visualization of internet media reports. *Journal of the American Medical Informatics Association, 15*(2), 150–157. https://doi.org/10.1197/jamia.M2544

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Lossio-Ventura, J. A., Jonquet, C., Roche, M., & Teisseire, M. (2014). Towards a mixed approach to extract biomedical terms from text Corpus. *International Journal of Knowledge Discovery in Bioinformatics*, *4*(1), 1–15. https://doi.org/10.4018/ijkdb.2014010101

Lossio-Ventura, J. A., Jonquet, C., Roche, M., & Teisseire, M. (2016). Biomedical term extraction: Overview and a new methodology. *Information Retrieval Journal*, *19*(1), 59–99. https://doi.org/10.1007/s10791-015-9262-2

Paquet, C., Coulombier, D., Kaiser, R., & Ciotti, M. (2006). Epidemic intelligence: A new framework for strengthening disease surveillance in Europe. *Eurosurveillance*, *11*(12), 5–6. https://doi.org/10.2807/esm.11.12.00665-en

Valentin, S., Arsevska, E., Falala, S., de Goër, J., Lancelot, R., Mercier, A., ... Roche, M. (2020). PADI-web: A multilingual event-based surveillance system for monitoring animal infectious diseases. *Computers and Electronics in Agriculture*, *169*, 105163. https://doi.org/10.1016/j.compag.2019.105163

Valentin, S., Mercier, A., Lancelot, R., Roche, M., & Arsevska, E. (2020). *PADI-web COVID-2019 corpus: News articles manually labelled*. CIRAD Dataverse. https://doi.org/10.18167/DVN1/MSLEFC

Woodall, J. P. (2001). Global surveillance of emerging diseases: The ProMED-mail perspective. *Cadernos De Saúde Pública*, *17*, S147–S154. https://doi.org/10.1590/S0102-311X2001000700024

Wuhan Municipal Health Commision (2020). *Information session of the Wuhan Municipal Health and Health Commission on the current situation of the pneumonia epidemic in our city.* http://wjw.wuhan.gov.cn/front/web/showDetail/2019123108989 [in Chinese].

How to cite this article: Valentin S, Mercier A, Lancelot R, Roche M, Arsevska E. Monitoring online media reports for early detection of unknown diseases: Insight from a retrospective study of COVID-19 emergence. *Transbound Emerg Dis.* 2020;00:1–6. https://doi.org/10.1111/tbed.13738

Annex 4. Surveillance form for mass gathering enhanced surveillance at the 8th Micronesian Games in Pohnpei, Federated States of Micronesia (White *et al.*, 2018)

8TH MICRO GAMES 2014 — POHNPEI FSM

STATE OF POHNPEI Department of Health Services
Public Health Surveillance Form

SPC Secretariat of the Pacific Community

Point of Care (name of dispensary/community health centre/private clinic/hospital/games village/venue): _____

Note: Please enter information into the rows below for each patient who has one or more of the eight syndromes listed.

VISIT DATE: ____ /____ / 2014
mm / dd

First Name	Last Name	Date of birth	Age (Years)	Sex (M, F)	Country of residence	Village & Municipality of residence (for Pohnpei only)	Telephone/ Cell number	Current accommodation site (for visitors to Pohnpei)	Acute Fever and Rash (AFR)	Watery Diarrhea	Non-watery Diarrhea	Influenza-like-illness (ILI)	Prolonged Fever	Fever and Jaundice	Food-borne disease outbreak syndrome	Heat-related Illness	Onset date	Hospitalized?	Sample taken (and to be sent to lab)
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No
				☐M ☐F	☐ Pohnpei ☐ Other (specify)													☐ Yes ☐ No	☐ Yes ☐ No

Page __ / __   *On the last page of each working day, please report on the following fields*   Total number of encounters (all causes) for the day [.]   Total number of visits (syndromes only) for the day [.]

Annex 5. Article for case study n°2 – White *et al.*, 2018

Mass gathering enhanced syndromic surveillance for the 8th Micronesian Games in 2014, Pohnpei State, Federated States of Micronesia

Paul White,[a] Salanieta Saketa,[b] Eliaser Johnson,[c] Sameer V. Gopalani,[b] Eliashib Edward,[d] Charles Loney,[e] Alize Mercier,[a] Tebuka Toatu,[a] Richard Wojcik,[f] Sheri Lewis[f] and Damian Hoy[b]

Correspondence to Paul White (email: paul.white@dph.gov.mp)

Pohnpei State's Division of Primary Health Care implemented enhanced surveillance for early warning and detection of disease to support the 8th Micronesian Games (the Games) in July 2014.

The surveillance comprised 11 point-of-care sentinel sites around Pohnpei, Federated States of Micronesia, collecting data daily for eight syndromes using standard case definitions. Each sentinel site reported total acute care encounters, total syndrome cases and the total for each syndrome. A public health response, including epidemiological investigation and laboratory testing, followed when syndrome counts reached predetermined threshold levels.

The surveillance was implemented using the web-based Suite for Automated Global Electronic bioSurveillance Open-ESSENCE (SAGES-OE) application that was customized for the Games. Data were summarized in daily situation reports (SitReps) issued to key stakeholders and posted on PacNet, a Pacific public health e-mail network.

Influenza-like illness (ILI) was the most common syndrome reported (55%, n = 225). Most syndrome cases (75%) were among people from Pohnpei. Only 30 cases out of a total of 408 syndrome cases (7%) presented with acute fever and rash, despite the large and ongoing measles outbreak at the time. No new infectious disease outbreak was recorded during the Games. Peaks in diarrhoeal and ILI cases were followed up and did not result in widespread transmission.

The technology was a key feature of the enhanced surveillance. The introduction of the web-based tool greatly improved the timeliness of data entry, analysis and SitRep dissemination, providing assurance to the Games organizers that communicable diseases would not adversely impact the Games.

The 8th Micronesian Games took place in Pohnpei, Federated States of Micronesia, from 19 to 29 July 2014. Participants came from the six Micronesian island countries and territories: Guam, Kiribati, the Marshall Islands, the Federated States of Micronesia, Nauru, the Commonwealth of the Northern Mariana Islands and Palau.

Pohnpei is a small island state of 35 981 people (2010 census). The 8th Micronesian Games held in the area around Kolonia, the main town of Pohnpei, attracted approximately 1700 athletes and officials (Saketa S, Public Health Division, Pacific Community, unpublished report, 2014). This population influx posed public health risks for the introduction of communicable diseases,[1] as illustrated by a widespread measles outbreak in Pohnpei two months before the Games. This had the potential to overwhelm health services, disrupt the Games and trigger the spread of measles across the Federated States of Micronesia and the wider region.

To mitigate disease risks and aid identification of adverse health events, an enhanced syndromic surveillance system for mass gatherings was implemented by Pohnpei's Division of Primary Health Care (DPHC) in partnership with the country's Department of Health and

a   ELC Programme, PHEP Office, Commonwealth Health Care Corporation, Saipan, Commonwealth of the Northern Mariana Islands.
b   Research Evidence and Information Programme, Public Health Division, the Pacific Community.
c   Division of Primary Health Care, Pohnpei State, Federated States of Micronesia.
d   Department of Health and Social Affairs, Government of the Federated States of Micronesia.
e   Medical Records Unit, Pohnpei State Hospital, Federated States of Micronesia.
f   Applied Physics Laboratory, Johns Hopkins University.

Social Affairs (DHSA), the Pacific Community (SPC) and Johns Hopkins University (JHU). Enhanced surveillance for mass gatherings is increasingly used in large developed nations.[2] In the Pacific, mass gathering surveillance was used for the 2012 11th Festival of Pacific Arts, Solomon Islands and the 2013 Pacific Mini Games, Wallis and Futuna.[3,4] Here we describe the enhanced surveillance system implemented by Pohnpei State and discuss some of the sustainable benefits arising from the mass gathering surveillance experience.

METHODS

SPC has developed a three-stage strategy for preparing for and implementing enhanced surveillance for mass gatherings. This approach is summarized in a process map (available online).[4] The preparation stage includes a disease risk assessment and an assessment of the existing surveillance system to meet the mass gathering surveillance needs. Pohnpei implemented an early warning syndromic surveillance system in 2010 as part of the World Health Organization (WHO)/Pacific Public Health Surveillance Network Pacific Syndromic Surveillance System.[5] Data are collected daily from the central public hospital (Pohnpei State Hospital) and weekly from the private hospital (Genesis Hospital) for acute fever and rash, prolonged fever, influenza-like illness and diarrhoea syndromes covering important outbreak-prone diseases in Pohnpei State. A weekly surveillance report is disseminated to DHSA and WHO. As an early warning system, the syndromic surveillance system allows the Federated States of Micronesia to meet indicator-based surveillance requirements under the International Health Regulations (2005).[6] This system was the foundation for the mass gathering surveillance implemented for the Games.

For the Games, the number of sentinel sites was expanded to 11, comprising Games venues, hospitals and community clinics distributed around Pohnpei, the number of syndromes was increased to eight (diseases recorded in parentheses):

- acute fever and rash (AFR) (measles, dengue, rubella, meningitis, leptospirosis);
- influenza-like illness (ILI) (influenza and other viral or bacterial respiratory diseases);
- prolonged fever (typhoid fever, dengue, leptospirosis, malaria);

- fever and jaundice (hepatitis A infection);
- watery diarrhoea (cholera);
- non-watery diarrhoea (viral or bacterial gastroenteritis, including food poisoning and ciguatera fish poisoning);
- foodborne disease outbreak (salmonella, *Staphylococcus*, *Clostridium*, *Campylobacter* and rotavirus infections); and
- heat-related illness (heat cramps, heat exhaustion and heat stroke).

All sentinel sites except the two Games venues were community medical providers operating within their normal hours. Of the two Games sites, the Pohnpei Island Central School (PICS) High School provided a temporary clinic at the Games village for primary care services to athletes and officials, operating seven days a week. The second Games site, the College of Micronesia-FSM dispensary, provided acute, preventive health care and counselling staffed by a full-time nurse and was open Monday to Friday during normal working hours. All sentinel site staff underwent a two-day surveillance training that focused on understanding the syndrome case definitions, accurate completion of the surveillance register and laboratory specimen collection and referral processes.

Each sentinel site manually completed a daily surveillance form that recorded the number of acute care encounters and syndrome cases; the completed forms were collected daily from each sentinel site. The data were entered into the Suite for Automated Global Electronic bioSurveillance OpenESSENCE (SAGES-OE) open-source, web-based application. Developed by JHU, SAGES-OE was designed for surveillance and epidemiological analysis particularly in resource-constrained settings.[7] It was adapted for the Micronesian Games by JHU in partnership with SPC. Drop-down lists for key variables facilitated efficient data entry and helped to ensure the completeness and consistency of data. When incomplete data were discovered, the relevant sentinel site was contacted. It took approximately five hours each day to collect and enter data.

SAGES-OE analysis and visualization tools were used to summarize the epidemiological situation that was reported in daily situation reports (SitReps). These included totals for encounters and syndromes together

with epidemic curves used to track syndrome trends. SitReps were distributed to stakeholders in the DHSA and the Games organizing committee, and were posted to the Pacific health e-mail network, PacNet. The surveillance was operational from 17 July – two days before the Games – until 6 August, one week after the Games. Eighteen daily SitReps were produced.

Ethics

Ethics committee approval was not required.

RESULTS

There were 5640 encounter cases and 408 syndrome cases from the 11 sentinel sites during the 21 day surveillance period. Sentinel site encounters ranged from 52 to 2040 with a median of 165 and mean of 496. The variance in encounters reflects the highly variable catchments of hospital outpatient departments and smaller community clinics. The Games-specific sentinel site (PICS High School) recorded 3% of all encounters ($n = 165$) and 3% of all syndromic cases ($n = 13$). One site (Wone dispensary) reported no syndromes. **Table 1** summarizes acute care encounters and syndrome presentations by sentinel site from 17 July to 6 August 2014. There was a high degree of variation in daily syndrome presentations (**Fig. 1**). Overall, syndrome cases represented 7% of encounters (ranging from 2% to 18%). Residents of Pohnpei reported more syndromes (75% of all syndromes, $n = 305$) than those from outside Pohnpei.

The three larger Kolonia town sentinel sites, Pohnpei State Hospital, Genesis Hospital and Pohnpei/Kolonia Community Health Center, accounted for over three quarters of all encounters (77%, $n = 4336$) and a larger proportion (88%, $n = 359$) of all syndrome cases. Pohnpei State Hospital had a third of encounters (36%, $n = 2040$, 61.8 per 1000 encounters) and syndromes (31%, $n = 126$). Pohnpei Community Health Center had the second greatest number of encounters (21%, $n = 1157$), 15% lower than the State Hospital, but it had a greater catchment of cases accounting for half of all syndromes (50%, $n = 202$) and by far the highest rate of syndromes (174.6 per 1000 encounters). The private Genesis Hospital accounted for the third greatest number of encounters (20%, $n = 1139$), but it had a far lower surveillance sensitivity with 8% ($n = 31$) of syndrome

cases (27.2 per 1000 encounters).

ILI was the most prominent syndrome accounting for half of all cases (55%, $n = 225$) followed by watery diarrhoea (24%, $n = 99$), non-watery diarrhoea (9%, $n = 36$) and AFR (8%, $n = 31$). There were two prolonged fever cases. Both fever and jaundice and heat-related illness had one case. No foodborne disease outbreak was reported. Watery diarrhoea (24%) and AFR (8%) accounted for almost one third (32%) of all reported syndromes and are indicative of more severe diseases requiring urgent attention. These cases were prioritized and followed up by the response team.

A marked difference in the sex distribution of syndrome cases was noted in the four sentinel sites in the rural areas with nearly three quarters of cases being female (72%). Whereas the seven sentinel sites in the more populated or urban areas (see **Table 1**) had roughly an equal male (52%) and female (48%) representation.

The urban–rural difference was also evident in the distribution of syndromes. **Fig. 2** describes the distribution of the four main syndromes, AFR, watery and non-watery diarrhoea, and ILI, in the seven urban area sentinel sites and in the remaining four rural sites. In the urban areas, ILI was the largest syndrome burden (61% of urban syndromes); in the rural areas, non-watery and watery diarrhoea were the two main presenting syndromes (75% of rural syndromes), while ILI was the third highest represented syndrome (21%).

Between 22 and 30 July, 45 clinical samples were collected, comprising 23 nasopharyngeal swabs/aspirate samples for ILI testing and 22 stool samples for watery and non-watery diarrhoea testing. **Fig. 1** illustrates the large sample collection peak on 25 July, while the remaining days produced fewer samples.

DISCUSSION

The enhanced surveillance implemented at the 8th Micronesian Games provided important data for public health security reassurance for the Games organizers. The SitReps were well received by the Pacific public health community who posted positive comments on PacNet (personal communication with Dr Eliaser Johnson, DPHC, Pohnpei State). The 31 cases of AFR were followed up, and the ongoing measles outbreak had no detrimental

Table 1. Summary total encounters and syndromes by reporting sentinel site, Pohnpei State, 17 July to 6 August 2014

Sentinel site (shaded green: the urban area around Kolonia)	Number encounter cases*	Number syndrome cases# (% of encounters)	Syndrome cases per 1000 encounters	Acute fever and rash	Watery diarrhoea	Non-watery diarrhoea	Influenza-like illness	Prolonged fever	Fever and jaundice	Heat-related illness	Food-borne disease syndrome
Berysin CHC	66	3 (5%)	45.5	0	1	0	2	0	0	0	0
Genesis Hospital	1139	31 (3%)	27.2	2	10	1	18	0	0	0	0
Medpharm CHC	145	7 (5)	48.3	0	0	4	3	0	0	0	0
PICS High School	165	13 (8%)	78.8	0	5	0	5	2	0	1	0
Pohnpei CHC	1157	202 (18%)	174.6	1	24	11	159	6	0	1	0
Pohnpei State Hospital	2040	126 (7%)	61.8	26	49	9	35	6	1	0	0
Sokehs Dispensary	52	4 (8%)	76.9	1	1	2	0	0	0	0	0
COM Dispensary	63	4 (6%)	63.5	0	2	2	0	0	0	0	0
Lukop Dispensary	95	8 (8%)	84.2	0	4	2	2	0	0	0	0
Pohnlangas Dispensary	512	10 (2%)	19.5	1	3	5	1	0	0	0	0
Wone Dispensary	206	0 (0%)	0	0	0	0	0	0	0	0	0
TOTAL	5640	408 (7%)		31	99	36	225	2	1	1	0

* Encounter cases represent all acute care cases visiting a clinic regardless of whether they have one or more of the eight syndromes; e.g. a sprained ankle would be included in the encounter case count.

\# Syndrome cases represent all acute care cases visiting a clinic who have one or more of the eight syndromes; e.g. a sprained ankle would NOT be included in the syndrome case count.

CHC = Community Health Center

COM = College of Federated States of Micronesia

Fig. 1. Comparison of daily syndrome counts and laboratory sample submissions, Pohnpei State, 17 July to 6 August 2014 (dates of Games shaded)
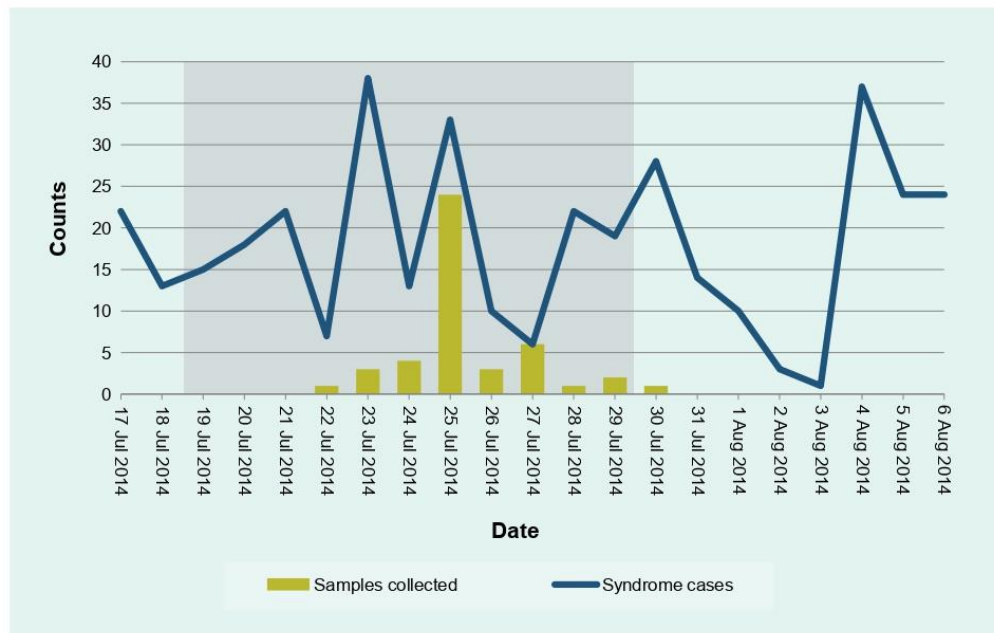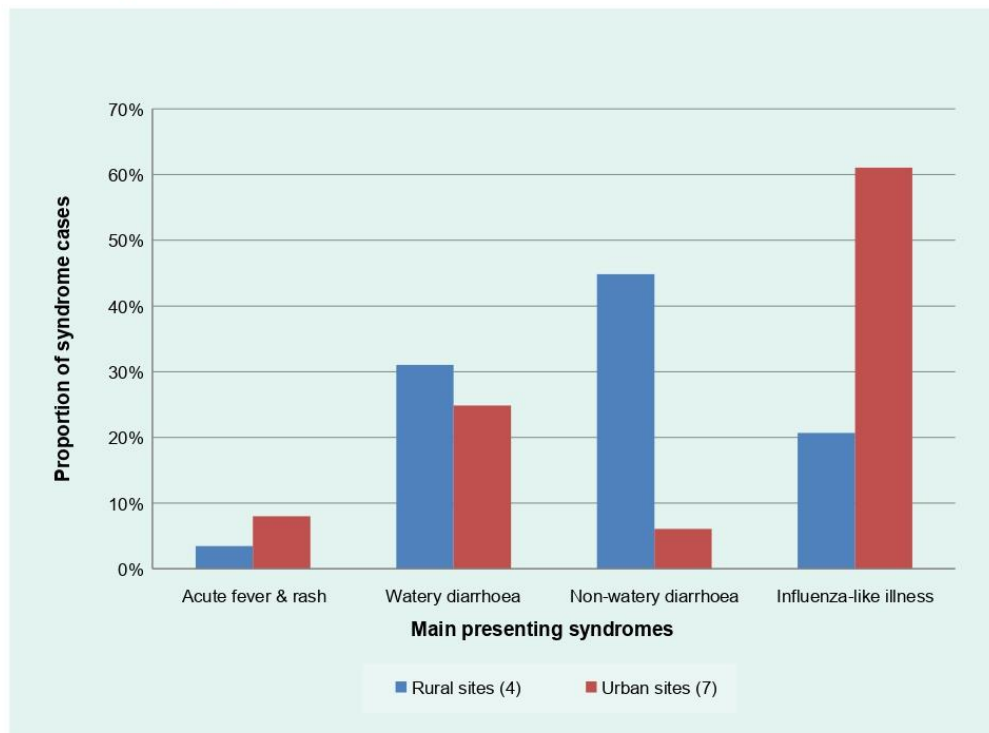
Fig. 2.   **Distribution of syndrome cases reported in rural and urban point-of-care sentinel sites, Pohnpei State, 17 July to 6 August 2014**

impact on the Games. The sentinel sites demonstrated good surveillance coverage and sensitivity; the Games-specific site had the third highest rate of syndrome cases (78.8 per 1000 encounters) but with only 3% (2.9%) of all encounters. This was greater than Pohnpei State Hospital, which had the largest number of encounters (36%) but fewer syndrome cases (61.8 syndrome cases per 1000 encounters).

The web-based SAGES-OE system enabled easy data entry, data storing, data collation and analysis and accelerated SitRep production as multiple users could access data simultaneously. The cloud storage feature helped to reduce local storage server costs as well as increase efficiency and off-site security. However, while SAGES-OE was used in the Pohnpei public health office and regional SPC office, it could not be implemented as a fully networked sentinel site data entry system due to a lack of computers and computer-trained staff. More challenging was the lack of connectivity to all health-care facilities, especially in the rural areas where

wireless connectivity is hampered by low or no coverage. Nevertheless, as a public health tool, SAGES-OE is one of the key success factors of the surveillance and features in the post-Games surveillance sustainability plan of DPHC, where the goal is achieving an integrated surveillance system that allows daily data entry at sentinel sites.

Beyond outbreak detection there are additional benefits to population-representative surveillance data. Surveillance data have intrinsic value as indicators of health service performance.[8] The regular collection of syndromic surveillance data serves as a powerful evidence base that can be exploited for better-informed health planning and decision-making.[9] This includes understanding demands on laboratory services during peak times and understanding differences in disease burdens across the population.

The laboratory sample submissions data identified the unequal distribution of samples sent to the laboratory compared to daily syndrome activity (**Fig. 1**). The single

peak in clinical sample collection contrasts with the greater variation of daily syndrome counts. Identifying the mismatched laboratory sample collection to syndrome case activity can be used to demonstrate to sentinel sites the importance of more regular sample collection as an effective tool to support public health surveillance (i.e. matching sample collection to syndrome activity).

The urban–rural syndrome differences can help identify important public health gaps for better prioritized and more efficient interventions and use of resources. For example, diarrhoea from polluted water sources might be more prevalent in rural areas. Whereas a greater ILI burden in urban areas indicates greater respiratory disease transmission in more densely populated areas while also indicating clean water access and waste water treatment that reduce diarrhoea episodes. This assists prioritization as watery diarrhoea can be indicative of severe diseases requiring urgent attention, particularly in children, indicating the need for different health promotion messaging and interventions. Finally, this information assists in identifying the appropriate type of public health interventions, for example joint public and environmental health responses to watery diarrhoea outbreaks, whereas a joint response is not necessary for ILI.

Challenges and lessons learnt

The enhanced surveillance system implemented for the 8th Micronesian Games demonstrated the need for good planning and preparation including a substantial lead time of at least 12 months to establish and test the web-based surveillance tools; and for areas with low connectivity, to test methods for timely manual data collection. The enhanced surveillance also indicated the importance of adequate staff resourcing to address staff fatigue caused by the intense daily operation of the surveillance for multiple weeks. This point demonstrates the value of a joint implementation in small-island states where resources are limited. The joint implementation with SPC leveraged capability (expertise) and capacity (extra people). Based on the existing syndromic surveillance, the Pohnpei DPHC had the necessary skills and experience to undertake the enhanced surveillance; however, the small team benefited from the support provided by SPC in running the surveillance. Additionally, the use of SAGES-OE was made easier through the partnership between SPC and JHU. Finally, there is a need to ensure effective connection with laboratory services to ensure that clinical sample collection more closely matches syndrome patterns.

Conclusions and recommendations

The enhanced surveillance system used at the 8th Micronesian Games demonstrated: (1) the value of enhanced surveillance to provide public health security assurance during mass gatherings particularly in the face of significant, existing disease threats; (2) the benefit of web-based tools in improving the efficiency of the surveillance; (3) the potential for sustainable improvements to routine surveillance through leveraging the surveillance experience; (4) and improved health planning and informed decision-making that arise from the evidence base that is generated from the enhanced surveillance. Pohnpei was one of the first places in the Pacific region to implement the web-based SAGES-OE tool for mass gathering surveillance, and the enhanced surveillance implemented for the 8th Micronesian Games in Pohnpei provides a constructive model for future mass gathering surveillance across the Pacific and elsewhere.

Conflicts of interest

None.

References

1. Abubakar I, Gautret P, Brunette GW, Blumberg L, Johnson D, Poumerol G, et al. Global perspectives for prevention of infectious diseases associated with mass gatherings. Lancet Infect Dis. 2012 Jan;12(1):66–74. doi:10.1016/S1473-3099(11)70246-8 pmid:22192131

2. Communicable disease alert and response for mass gatherings: key considerations June 2008. Geneva: World Health Organization; 2008 (http://www.who.int/csr/Mass_gatherings2.pdf).

3. Hoy D, Saketa ST, Maraka RR, Sio A, Wanyeki I, Frison P, et al. Enhanced syndromic surveillance for mass gatherings in the Pacific: a case study of the 11th Festival of Pacific Arts in Solomon Islands, 2012. West Pac Surveill Response. 2016 09 27;7(3):15–20. doi:10.5365/wpsar.2016.7.1.004 pmid:27766181

4. White P, Saketa S, Durand A, Vaai-Nielsen S, Leong-Lui TA, Naseri T, et al. Enhanced surveillance for the Third United Nations Conference on Small Island Developing States, Apia, Samoa, September 2014. West Pac Surveill Response. 2017 02 6;8(1):15–21. doi:10.5365/wpsar.2016.7.4.002 pmid:28409055

5. Kool JL, Paterson B, Pavlin BI, Durrheim D, Musto J, Kolbe A. Pacific-wide simplified syndromic surveillance for early warning of outbreaks. Glob Public Health. 2012;7(7):670–81. doi:10.1080/17441692.2012.699536 pmid:22823595

6. International Health Regulations (2005). Geneva: World Health Organization; 2008 (http://www.who.int/ihr/publications/9789241580496/en/).

7. Feighner BH, Campbell TC, Katz AT, Wojcik RA, Coberly JS, Patel SV, et al. SAGES Overview: Open-source software tools for electronic disease surveillance in resource limited settings. Johns Hopkins APL Tech Dig. 2014;32(4):652–8.

8. Babin S, Magruder S, Hakre S, Coberly J, Lombardo JS. Understanding the data: Health indicators in disease surveillance. In: Lombardo JS, Buckeridge DL, editors. Disease surveillance: a public health informatics approach. New Jersey: John Wiley & Sons, Ltd; 2007:41–90.

9. M'ikanatha NM, Lynfield R, Julian KG, Van Beneden CA, de Valk H. Infectious disease surveillance: a cornerstone for prevention and control. In: M'ikanatha NM, Lynfield R, Van Beneden CA, de Valk H, editors. Infectious disease surveillance. 2nd ed. New Jersey: John Wiley & Sons, Ltd; 2013:1–20. doi:10.1002/9781118543504.ch1

148

Annex 6. Article for case study n°3 – Roth *et al., 2014a*

Concurrent outbreaks of dengue, chikungunya and Zika virus infections – an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012–2014

A Roth (adamr@spc.int)[1], A Mercier[1], C Lepers[1], D Hoy[1], S Duituturaga[1], E Benyon[1], L Guillaumot[2], Y Souarès[1]
1. Secretariat of the Pacific Community, New Caledonia
2. Institut Pasteur de Nouvelle-Caledonie, Noumea, New Caledonia

Since January 2012, the Pacific Region has experienced 28 new documented outbreaks and circulation of dengue, chikungunya and Zika virus. These mosquito-borne disease epidemics seem to become more frequent and diverse, and it is likely that this is only the early stages of a wave that will continue for several years. Improved surveillance and response measures are needed to mitigate the already heavy burden on island health systems and limit further spread to other parts of the world.

Since January 2012, the Pacific is experiencing a high burden of mosquito-borne disease due to concurrent epidemics of dengue, chikungunya and Zika virus infections. So far over 120,000 people have been reported to be affected, a figure that is likely to substantially underestimate the real numbers due to underreporting. For as long as there has been data available from the Region (i.e. 40 years), this epidemic wave of mosquito-borne viruses with 28 new mosquito-borne viral outbreaks (n=25) and circulation (n=3) documented since January 2012 (18 Dengue virus (DENV) serotype 1–4, 7 chikungunya virus and 3 Zika virus infection outbreaks, respectively) is unprecedented (Table) [1-3]. We here present an overview of the surveillance and epidemiology of these mosquito-borne disease epidemics in the Pacific Region, to help facilitate response measures that are needed to mitigate the already heavy burden on island health systems and to limit further spread to other parts of the world.

Surveillance of mosquito-borne viruses in the Pacific Region

The Pacific Public Health Surveillance Network (PPHSN) is a voluntary network of countries, territories and organisations created in 1996. It is dedicated to the promotion of public health surveillance and response to health emergencies in the Pacific Region. It covers 22 Pacific Island countries and territories (hereafter referred to as the Pacific Region) with a population of 10.6 million inhabitants [4]. The network services include the timely exchange of information on outbreak-prone disease through PacNet, an email list with around 680 health professionals, and diagnostic support through a network of laboratories for identification and verification of pathogens.

In 2010, the Pacific Syndromic Surveillance System was introduced in the PPHSN. It monitors four syndromes and aims at improved early warning to complement routine notifiable disease notification systems that generally are not timely and seldom used for regional surveillance purposes in the Pacific Region. The Syndromic Surveillance system is under development and currently includes sentinel reporting from primary healthcare or hospital sites in all countries [5]. Manifest dengue, chikungunya and Zika virus infections have a similar initial clinical presentation and may be reported as any of the first three of the following four monitored syndromes: (i) acute fever and rash, (ii) prolonged fever, (iii) influenza-like illness and (iv) diarrhoea. Due to similar initial clinical features to the three mosquito-borne diseases, concurrent measles epidemics and leptospirosis pose diagnostic challenges in the Region.

There is a need for timely, reliable and detailed data on mosquito-borne virus outbreaks and circulation of the viruses in the Pacific Region. To obtain a comprehensible overview of the present epidemiological picture, several sources of information are used. Further to PacNet, syndromic and laboratory-based surveillance, event-based surveillance (mainly media and personal communications with health professionals) and surveillance by-proxy (reports of exported cases to neighbouring countries) [6] are also important. To facilitate better risk assessments and efficiency of data dissemination, this data is visualized in a recently launched interactive map available from: www.spc.int/phd/epidemics. The map, updated weekly, provides the region for the first time with a dynamic real-time picture of the current epidemic situation.

TABLE

Characteristics of new dengue, chikungunya and Zika virus infection outbreaks and circulation[a,b], Pacific Region, January 2012–17 September 2014[c] (n=28)

	Country	Month of onset	Latest information	Implicated mosquito borne virus	Summary	Sources
Dengue						
●	Tuvalu	Mar-14	10/07/2014	DENV-2	408 suspected cases with 195 cases positive in rapid tests (NS1/IgM).	[32]
●	Nauru	Mar-14	7/08/2014	DENV-3	251 suspected cases with 91 confirmed using IgM ELISA and/or rapid test. Samples sent for confirmatory serotyping.	[32, 33]
●	Tonga	Feb-14	21/08/2014	DENV-3	Outbreak ongoing; 2 cases of dengue imported into New Zealand since 12 July 2014.	[32–34]
●	New Caledonia	Feb-14	17/09/2014	DENV-3	In 2014, 338 cases of dengue recorded of which 55% were DENV-3. Virus circulation ongoing, with latest reported dengue case on 12 September 2014.	[35]
●	Fiji	15/01/2014[c]	23/06/2014	DENV-2	Circulation of virus, no outbreak declared; 6 confirmed cases of DENV-2 imported into Queensland Australia from January to June 2014.	[33]
●	Vanuatu	Dec-13	20/04/2014	DENV-3	1,561 dengue cases reported; 5 imported cases in Queensland Australia since January 2014 and 10 imported cases in New Caledonia from January to March 2014; 4 cases of DENV with serotype unknown imported into New Zealand since April 2014, of which 1 in July 2014.	[32–35]
○	Kiribati	Nov-13	24/01/2014	DENV-3	As of 16 Jan 2014, 198 suspected dengue cases of which 85 were laboratory-confirmed. Outbreak over, only sporadic cases of fever.	[32], media: Radio New Zealand International
●	Vanuatu	27/10/2012[c]	20/04/2014	DENV-1	Circulation of virus, no outbreak declared; 2 confirmed cases imported into Queensland Australia (1 case in 2013 and 1 case in 2014) and 6 cases into New Caledonia (5 cases in 2013 and 1 case in 2014); 4 cases of dengue serotype unknown imported into New Zealand since April 2014, of which 1 in July 2014.	[33, 35]
●	Fiji	Oct-13	5/06/2014	DENV-3	25,300 suspected cases, 15 deaths. Outbreak is ongoing; 15 confirmed cases imported into Queensland Australia from December 2013 to May 2014.	[33], media: Radio Australia, Fiji Broadcasting Corporation
● ○	French Polynesia	Feb-13	6/09/2014	DENV-1 DENV-3	As of 23 May 2014, 2188 positive cases since February 2013, and between 16 400 and 34 000 clinical visits estimated. 11 severe cases in March 2014 and 5 severe cases requiring hospitalisation in July 2014. DENV1 outbreak is still ongoing, but there are no cases of DENV3 reported since April 2014.	[36]
○	Wallis & Futuna	Jan-13	28/03/2013	DENV-1	88 suspected cases and 16 confirmed of which 11 imported cases from New Caledonia.	[37]
●	Solomon Islands	Dec-12	15/08/2014	DENV-3	7,697 reported cases as of 31 December 2013. As of June 2014, 1,762 suspected cases since January 2014, and 282 out of 1,500 samples tested positive in rapid tests. In March 2014 DENV-3 confirmed. Outbreak still ongoing.	[32, 33], media: Solomon Star
○	Kosrae, Federated States of Micronesia	Sep-12	19/07/2013	DENV-4	729 reported clinical cases; 206 cases laboratory confirmed by rapid diagnostic tests. No deaths reported.	[9, 37]
●	New Caledonia	Sep-12	17/09/2014	DENV-1	Largest ever recorded outbreak of dengue in New Caledonia with 10,978 cases and 5 deaths from September 2012 to September 2013; 338 cases of dengue recorded in 2014 of which 45% were DENV-1. Virus circulation ongoing, with latest reported dengue case on 128 September 2014.	[35]
○	Fiji	15/07/2012[c]	31/12/2012	DENV-2	Circulation of virus, no outbreak declared. 2 imported cases in Queensland Australia;	[33]
○	Kiribati	Mar-12	4/05/2012	DENV-1	243 clinical cases.	[32]
○	Niue	Feb-12	20/07/2012	DENV-1	More than 100 cases.	Media: Radio New Zealand International

	Country	Month of onset	Latest information	Implicated mosquito borne virus	Summary	Sources
Chikungunya						
●	Tokelau	Jul-14	11/09/2014	CHIKV	164 suspected cases reported. CHIKV confirmed.	[32]
●	Samoa	Jul-14	1/09/2014	CHIKV	433 cases reported over 4 weeks. 21 RT-PCR positives out of 59 samples (as of 28 Aug 2014).	[37], media: Samoa Observer
●	American Samoa	Jun-14	17/09/2014	CHIKV	823 probable cases reported, with 15 hospitalisations. CHIKV confirmed.	[37], media Radio New Zealand International
●	Tonga	Feb-14	11/09/2014	CHIKV	Over 10,000 suspected cases reported. Ongoing circulation of CHIKV confirmed.	[32–34]
●	Yap, Federated States of Micronesia	Aug-13	10/09/2014	CHIKV	A total of 1,711 suspected cases identified in Yap State. Circulation of CHIKV reconfirmed.	[37]
●	New Caledonia	Jan-13	2/06/2014	CHIKV	A total of 32 confirmed cases from January to May 2013.	[35]
●	Papua New Guinea	Jun-12	25/11/2013	CHIKV	A major outbreak spread over Papua New Guinea in 2013. Number of cases not reported, but estimated in media to be tens of thousands of cases.	[2], media: Australia Network News, Pacnews
Zika virus infections[d]						
●	Cook Islands	Feb-14	29/05/2014	ZIKV	Outbreak is over. 932 suspected and 50 confirmed cases.	[32], media: Radio New Zealand International
●	New Caledonia	Jan-14	17/09/2014	ZIKV	Imported cases reported in November 2013, first autochtonous case reported in January 2014; 1,400 confirmed cases of which 35 imported cases. Outbreak peaked in April 2014. Last case reported on 2nd August 2014.	[35]
●	French Polynesia	Oct-13	4/05/2014	ZIKV	8,723 suspected cases reported and more than 30,000 estimated clinical visits due to Zika. Outbreak declared over but virus circulation may be ongoing.	[36]

● Cases reported are increasing or peaking

● Cases reported are decreasing or viral circulation is ongoing

● Outbreak is reported to be over and/or no cases have been reported for one year.

CHIKV: chikungunya virus; DENV: dengue virus serotype 1-4; RT-PCR: reverse-transcriptase polymerase chain reaction; ZIKV: Zika virus.

a Only incident outbreaks and circulation notified during the reported period. Outbreaks first reported in 2011 (DENV-4 in Marshal Islands, DENV-2 in Yap and circulation of DENV in Papua New Guinea and Fiji) and still ongoing in 2012 are not presented.

b An outbreak is considered an outbreak when reported as such or when the first autochtonous cases are reported, and new circulation if there have been no events reported during one year.

c Month of start equals the month of first report, as this reflects circulation of virus.

d Easter Island experienced a Zika virus infection outbreak starting February 2014, but is not presented in the table as it is not part of the 22 countries and territories of the Pacific Public Health Surveillance Network. .

The epidemiology of mosquito-borne viruses in the Pacific Region

Mosquito-borne virus diseases in the Pacific Region have a distinct epidemiology due to small populations scattered over thousands of tropical and sub-tropical islands on both sides of the equator in relative geographic isolation, together with (nowadays) significant people's mobility and thereby exposure to circulating arboviruses through the airline networks of the Asia-Pacific region (Figure 1).

Between January 2012 and 17 September 2014, a total of 28 new mosquito-borne viral outbreaks (n=25) and circulation (n=3) were documented: 18 DENV 1–4 outbreaks (2012: 7; 2013: 6; 2014: 5), 7 chikungunya virus (CHIKV) (2012: 1; 2013: 2; 2014: 4) and 3 Zika virus infection outbreaks (2012: 0; 2013: 1; 2014: 2), respectively.

Looking at the first semester of 2014, the number of outbreaks and circulating mosquito-borne viruses seem to be increasing (Figure 2). During the same period, DENV-3 became the dominating dengue virus, and since Zika virus started to spread in the end of 2013, there was concurrent circulation of DENV-1,-2 and -3, CHIKV and Zika virus (Table, Figure 2)

Dengue

The epidemic pattern of dengue in the Pacific Region has typically presented in form of sporadic or rare epidemics rather than a hyperepidemic/endemic pattern, with one dominating serotype sweeping across the islands every 3 to 5 years, and with varying duration of circulation in different islands largely depending on population size [1,7- 8]. During 2012, there were outbreaks of all four serotypes of DENV documented for the first time during one year (Figure 2) [1]. DENV-1 was the dominating serotype in 2012 and beginning 2013, causing the largest documented dengue outbreak ever in New Caledonia, with 10,978 confirmed cases and 5 deaths from September 2012 to September 2013. Since 2012 there have only been reports of one outbreak with DENV-2 and -4 respectively: DENV- 2 recently caused an outbreak in Tuvalu with 408 suspected cases (4% of the population) and DENV-4 caused a large outbreak in Kosrae in September 2012 to March 2013 with 729 clinical cases (11% of the population) (Table) [9]. Furthermore there have been reports of new circulation of DENV-2 in Fiji. (Table) After having been absent in the region for 18 years, DENV- 3 has after the reintroduction in 2012, become the dominating DENV in the region with five ongoing outbreaks, one of them in Fiji, with 25,300 suspected cases and 15 deaths (Table, Figure 1) [1,10].

Map of newly reported dengue, chikungunya and Zika virus infection outbreaks or new virus circulation[a], Pacific Region[b], January 2012–17 September 2014[c] (n=28)

CHIKV: chikungunya virus; DENV: dengue virus serotype 1-4; ZIKV: Zika virus.

[a] Only incident outbreaks and virus circulation reported during the period. Outbreaks first reported in 2011 (DENV-4 in Marshal Islands, DENV-2 in Yap and circulation of DENV in Papua New Guinea and Fiji) and still ongoing in 2012 are not presented.

[b] The 22 Pacific Island countries and territories that are core members of the Pacific Public Health Surveillance Network and referred to as the Pacific Region.

[c] Real-time interactive map with current epidemiological situation and alerts is available from: www.spc.int?phd/epidemics

Chikungunya

After being reported in the Pacific for the first time in a small tightly controlled outbreak in New Caledonia in 2011 [11], CHIKV is currently becoming established in the Region (Figure 1, Table) [2]. In Papua New-Guinea in 2012-13, the largest epidemic in the Region so far with estimated (though poorly documented) tens of thousands of cases, was caused by the East Central South African (ECSA) lineage of the virus [2]. The Asian lineage of the virus was responsible for the outbreak in Yap State (2013-14) [12] and also in New Caledonia (2013) where CHIKV re-emerged in the middle of a large DENV-1 epidemic and caused a small outbreak, similar to the 2011 outbreak (Table) [13]. Phylogenetic analyses of the CHIKV involved in the outbreaks in Tonga, Samoa and American Samoa are not yet available. Due to the on-going geographic expansion of *Aedes albopictus* in the Pacific region (Figure 3), virus genotype monitoring is a crucial aspect of surveillance.

Zika virus infections

After the first documented Pacific Zika outbreak in Yap in 2007 [14], the Asian lineage of the virus reappeared in French Polynesia in October 2013, and has since caused large outbreaks in New Caledonia (1,400 confirmed cases), Cook Islands (over 900 cases) and Easter Island that is not part of the PPHSN (Figure 1, Table) [3]. In French Polynesia, extrapolation of the 8,746 suspect cases reported by the sentinel surveillance network allows to infer that over 30,000 medical consultations were due to the spread of Zika virus throughout the archipelago. Between November 2013 and February 2014, increased incidence of neurological complications, including 42 cases of Guillain-Barré syndrome, was a unique and worrying feature of the French Polynesia outbreak that warrants further studies [3].

Discussion and Conclusions

Burden on the Pacific countries and territories

Mosquito-borne outbreaks are greatly exacerbating the pre-existing burden that Pacific Island primary healthcare systems face. If not managed well, the epidemic wave may threaten societies broadly, affecting trade, tourism and work force beyond the direct morbidity and mortality toll [2]. During the chikungunya outbreak in Reunion Island, one third of the around 800,000 inhabitants were infected, peaking at more than 47,000 estimated cases in one week, with estimated productivity loss of €17.4 million (range €6 to €28.9 million) and medical costs of €43.9 million that were met by the French state [15-17]. Much of the burden on the Pacific Region of the concurrent epidemics of all three diseases covered here is unknown and further studies are warranted, especially on co-infection and the effect of sequential infection with different viruses.

Zika virus disease, generally reported to have a mild clinical presentation, was associated with neurological complications during concurrent Zika virus disease and dengue epidemics in French Polynesia [3,18]. The Pacific Region may be particularly vulnerable to communicable diseases due to isolation and immunologically naive populations, but also due to rates of non-communicable disease, such as obesity, diabetes and cardiovascular disease, that are among the world's highest on some islands [19].

The risk for further spread

While there have been efforts to improve surveillance in the Pacific over the past two decades, it is not likely that the extent of the current increase in diversity and frequency of mosquito-borne virus outbreaks in the Pacific can be explained solely by improved surveillance systems. In the island setting of the Indian Ocean, the largest documented CHIKV outbreak lasted four years (2004–2007) [15]. Therefore, considering also the previous dengue outbreaks in the Pacific Region [1-2] and the diversity of the current outbreaks, it seems likely that the Pacific Region is in the early stages of an epidemic wave for the three mosquito-borne viruses that started in 2012 and is likely to continue for several years.

The risk for further spread in the Pacific Region is high for several reasons. Firstly, it is likely that there is little immunity to these diseases, as DENV-3 had not been

FIGURE 2

Incidence and aetiology of newly reported mosquito-borne virus outbreaks and circulation[a] by semester[b], Pacific Region, January 2012–17 September 2014[c] (n=28)
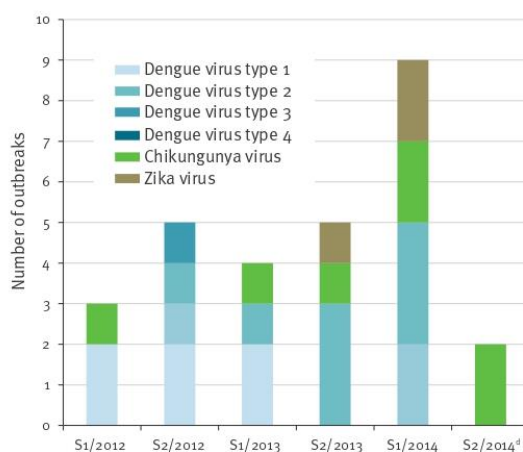
S: semester.
[a] An outbreak is considered an outbreak when reported as such, and new circulation of virus if there has been no event with the same virus reported during one year previously.
[b] S1 includes the months from January to June and S2 the months from July to December.
[c] Outbreaks or circulation that started before January 2012 or after 17 September 2014 are not presented in this graph to allow observation of a possible trend over time.
[d] Semester 2 in 2014 is not complete, and only includes reports from two full months of six.

153

circulating in the Region since 1995 [1] and prior to the current wave, CHIKV and Zika virus occurrence in the Pacific was limited to two documented outbreaks [11, 14]. Secondly, competent vectors present in the Region, mainly *Ae. aegypti* and *Ae. albopictus*, but also other local mosquitoes such as *Ae. polynesiensis* or *Ae. hensilli* are known to transmit these viruses (Figure 3) [20]. These species have been incriminated in DENV transmission on epidemiological and/or experimental (laboratory infections) grounds. Several of them are confirmed or strongly suspected vectors of CHIKV and Zika viruses [21]. Thirdly, large population mobility and airline travel facilitate the spread [22].

Vector control capacity in the Pacific Region is often limited or insufficient [11]. At present, there is no ongoing entomological surveillance system targeting vectors of dengue and other arboviruses established in the Region except in New Caledonia, Fiji and French Polynesia. The current knowledge about mosquito distribution in the other countries and territories is based on data collected during entomological investigations in surveys from the second half of the 20th century and from some more recent surveys [20]. Interestingly, the three viruses involved in this epidemic wave are not broadly mosquito-borne, but specifically *Aedes (Stegomyia)*-borne.

The cause of the recent increase in mosquito-borne disease in the Pacific Region is largely unknown, but is in line with a global increase of emerging diseases, and likely driven by a combination of socio-economic, environmental and ecological factors [23].

The continuous challenges of dengue and chikungunya [24] and more recently Zika virus infections [25]

FIGURE 3

Map of the known distribution of *Aedes (Stegomyia)* mosquitoes, vectors of dengue and possible vectors of chikungunya and Zika viruses, Pacific Region as of beginning October 2014

© Copyright, SPC, IPNC, 2014
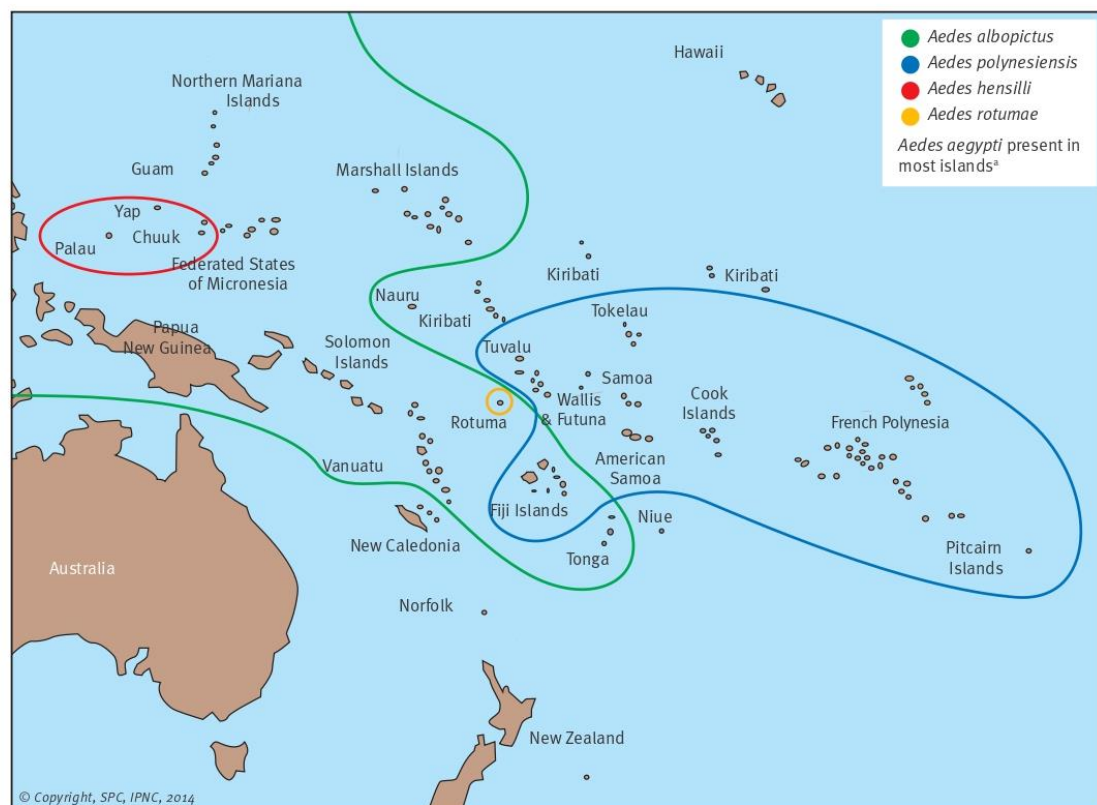
a *Aedes aegypti* (not represented on the map) is present throughout most of the region including North Queensland. It is absent from the rest of Australia, New Zealand, Hawaii, Futuna and some other remote islands, and it seems to be currently displaced by *Ae. albopictus* in many locations (e.g. Papua New Guinea and Solomon Islands).
The known or strongly suspected distributions of other vectors are as follows (not exhaustive): *Ae. scutellaris* (Indonesia; Northern Australia, Papua New Guinea); *Ae. marshallensis* (Marshall Islands; Western Kiribati; Kosrae; Pohnpei); *Ae. hebrideus* (Papua New Guinea; Solomon Islands; Vanuatu); *Ae. cooki* (Niue, Vava'u Group, Tonga); *Ae. tongae* (Ha'apai Group, Tonga); *Ae. tabu* (Tongatapu group, Tonga); *Ae. kesseli* (Niua group, Tonga); *Ae. pseudoscutellaris* (Fiji). [25]

154

for Europe, the re-emergence of dengue in Japan [26], and the first-time chikungunya transmission in the Americas [27], show that these viruses pose a threat to any country with competent vectors. The epidemiology of mosquito-borne viruses in the Pacific may be changing. There are close links between the several European overseas countries and territories in the Pacific Region and Europe and the United States [28]. Considering the extensive airline travel between the Pacific Region and other parts of the world where the viruses have not yet been established e.g. Europe and the United States, it should be of international interest to stay informed of the spread of the current Pacific Region wave of mosquito-borne viruses and to support surveillance and control efforts [2,23,29].

Examples of response from PPHSN partners to the epidemic situation include the provision of support and capacity building to Pacific Islands in surveillance, outbreak investigation and response, and mass-gathering surveillance. The Pacific Outbreak Manual is also being updated to include specific response guidelines for the three viruses [30].

To further enhance surveillance and response measures, Pacific Directors and Ministers of Health have shared the current risk assessment, and the upcoming Pacific International Health Regulations meeting will focus on mosquito-borne diseases. Island primary healthcare-based systems have difficulties to cope with high caseloads and there is a need for early multidisciplinary preparedness and response to face larger outbreaks adequately [2].

Conflict of interest

None declared.

Authors' contributions

AR, YS, CL, DH conceived the idea of the paper. AR, AM, CL, SD and EB contributed to data gathering and cleaning. AR, CL and AM conducted the analysis. LG gathered and compiled all vector data and analysis. AR and AM drafted the first draft, and all
authors commented and agreed upon the final manuscript.

References

1. Singh N, Kiedrzynski T, Lepers C, Benyon EK. Dengue in the Pacific--an update of the current situation. Pacific Health Dialog. 2005;12(2):111-9.

2. Roth A, Hoy D, Horwood PF, Ropa B, Hancock T, Guillaumot L, et al. Preparedness for threat of chikungunya in the pacific. Emerging Infect Dis. 2014;20(8). http://dx.doi.org/10.3201/eid2008.130696

3. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. Clin Microbiol Infect. 2014. http://dx.doi.org/10.1111/1469-0691.12707

4. Les populations du Pacifique 2013. [Pacific Island Populations 2013]. French. Nouméa, 2013. Statistics for Development Division, Secretariat of the Pacific Community. Available from: http://www.spc.int/sdd/index.php/en/downloads/doc_download/738-2013-pacific-population-poster

5. Kool JL, Paterson B, Pavlin BI, Durrheim D, Musto J, Kolbe A. Pacific-wide simplified syndromic surveillance for early warning of outbreaks. Global Public Health. 2012;7(7):670-81. http://dx.doi.org/10.1080/17441692.2012.699536

6. Lau CL, Weinstein P, Slaney D. Dengue surveillance by proxy: travellers as sentinels for outbreaks in the Pacific Islands. Epidemiol Infect. 2013;141(11):2328-34. http://dx.doi.org/10.1017/S0950268813000058

7. Dupont-Rouzeyrol M, Aubry M, O'Connor O, Roche C, Gourinat AC, Guigon A, et al. Epidemiological and molecular features of dengue virus type-1 in New Caledonia, South Pacific, 2001-2013. Virol J. 2014;11:61. http://dx.doi.org/10.1186/1743-422X-11-61

8. Morens DM. Dengue fever: a prevention summary for Pacific health workers. Pacific Health Dialog. 1996;3(1):240-52.

9. Centers for Disease Control and Prevention (CDC). Dengue outbreak--Federated States of Micronesia, 2012-2013. MMWR. Morbidity and mortality weekly report. 2013;62(28):570-3.

10. Cao-Lormeau VM, Roche C, Musso D, Mallet HP, Dalipanda T, Dofai A, et al. Dengue virus type 3, South Pacific Islands, 2013. Emerg Infect Dis. 2014;20(6):1034-6. http://dx.doi.org/10.3201/eid2006.131413

11. Dupont-Rouzeyrol M, Caro V, Guillaumot L, Vazeille M, D'Ortenzio E, Thiberge JM, et al. Chikungunya virus and the mosquito vector Aedes aegypti in New Caledonia (South Pacific Region). Vector Borne Zoonotic Dis. 2012;12(12):1036-41. http://dx.doi.org/10.1089/vbz.2011.0937

12. Nhan TX, Claverie A, Roche C, Teissier A, Colleuil M, Baudet JM, et al. Chikungunya virus imported into French polynesia, 2014. Emerg Infect Dis. 2014;20(10):1773-4. http://dx.doi.org/10.3201/eid2010.141060

13. Dupont-Rouzeyrol M, O'Connor O. Phylogénie moléculaire des Arbobirus en Nouvelle-Calédonie. Institut Pasteur de Nouvelle-Calédonie: La Recherche: Rapport d'activité 2013. [Molecular Phylogeny of Arboviruses in New Caledonia. Pasteur Institute of New Caledonia; Annual report 2013. p 24. Doc. n° 156/2014-IPNC/DG of 25 June 2014. Noumea, 2013.] p 24. Doc.n° 156/2014-IPNC/DG du 25 juin 2014. Nouméa, 2013. Available from: http://www.institutpasteur.nc/wp-content/uploads/2013/07/Rapport-2013-IPNC-RECHERCHE-n%C2%B0-156-26-juin-2014.pdf

14. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360(24):2536-43. http://dx.doi.org/10.1056/NEJMoa0805715

15. Renault P, Balleydier E, D'Ortenzio E, Baville M, Filleul L. Epidemiology of Chikungunya infection on Reunion Island, Mayotte, and neighboring countries. Med Mal Infect. 2012;42(3):93-101. http://dx.doi.org/10.1016/j.medmal.2011.12.002

16. Lagacherie P. [Coverage of the chikungunya epidemic on Reunion Island in 2006 by the French healthcare system]. Med Trop (Mars). 2012;72 Spec No:97-8.

17. Soumahoro MK, Boelle PY, Gauzere BA, Atsou K, Pelat C, Lambert B, et al. The Chikungunya epidemic on La Reunion Island in 2005-2006: a cost-of-illness study. PLoS Negl

Trop Dis. 2011;5(6):e1197. http://dx.doi.org/10.1371/journal.pntd.0001197

18. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome - case report, French Polynesia, December 2013. Eurosurveill. 2014;19(9). pii: 20720.

19. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81. http://dx.doi.org/10.1016/S0140-6736(14)60460-8

20. Guillaumot L, Ofanoa R, Swillen L, Singh N, Bossin HC, Schaffner F. Distribution of Aedes albopictus (Diptera, Culicidae) in southwestern Pacific countries, with a first report from the Kingdom of Tonga. Parasit Vectors. 2012;5:247. http://dx.doi.org/10.1186/1756-3305-5-247

21. Ledermann JP, Guillaumot L, Yug L, Saweyog SC, Tided M, Machieng P, et al. Aedes hensilli as a Potential Vector of Chikungunya and Zika Viruses. PLoS Negl Trop Dis 2014 8(10): e3188. http://dx.doi.org/10.1371/journal.pntd.0003188

22. Tatem AJ, Huang Z, Das A, Qi Q, Roth J, Qiu Y. Air travel and vector-borne disease movement. Parasitology. 2012;139(14):1816-30. http://dx.doi.org/10.1017/S0031182012000352

23. Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, et al. Global trends in emerging infectious diseases. Nature. 2008;451(7181):990-3. http://dx.doi.org/10.1038/nature06536

24. Chretien JP, Linthicum KJ. Chikungunya in Europe: what's next? Lancet. 2007;370(9602):1805-6. http://dx.doi.org/10.1016/S0140-6736(07)61752-8

25. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Zika virus infection outbreak, French Polynesia. 14 Feb 2014. Stockholm:,ECDC; 2014.

26. DENGUE - JAPAN: (SAITAMA) [Internet]. International Society for Infectious Diseases. 2014 [cited 2014-09-08]. Available with archive number: 20140828.2731079 from: http://www.promedmail.org/.

27. Staples JE, Fischer M. Chikungunya virus in the Americas--what a vectorborne pathogen can do. N Engl J Med. 2014;371(10):887-9. http://dx.doi.org/10.1056/NEJMp1407698

28. Jones J, Gastellu-Etchegorry M, Stenz FK, Baudon C, Bloem SJ, Bondonneau M, et al. Epidemiology, surveillance and control of infectious diseases in the European overseas countries and territories, 2011. Eurosurveill. 2011;16(29). pii: 19923.

29. Kuehn BM. World leaders push to prepare for global threats. JAMA. 2014;311(12):1189-90. http://dx.doi.org/10.1001/jama.2014.2272

30. The Pacific Outbreak Manual. Pacific Public Health Surveillance Network (PPHSN). February 2014. Available from: http://www.spc.int/phs/PPHSN/Publications/Pacific_Outbreak_Manual_wersion1-2.pdf

31. Guillaumot L. Arboviruses and their vectors in the Pacific--status report. Pac Health Dialog. 2005;12(2):45-52.

32. World Health Organization, West Pacific Region (WPRO). Emerging disease surveillance and response. Division of Pacific Technical Support. Weekly Pacific Syndromic Surveillance Report. Fiji: WPRO; 2014. Available from: http://www.wpro.who.int/southpacific/programmes/communicable_diseases/disease_surveillance_response/page/en/index2.html

33. Queensland Government. Queensland Health. Queensland notifiable conditions data. Last updated: 14 Oct 2014. Brisbane: Queensland Health; 2014.Available from: http://www.health.qld.gov.au/ph/cdb/sru_data.asp

34. Institute of Environmental Science and Research Ltd (ESR). Dengue weekly updates. Porirua, New Zealand. For details, contact ESR (Institute of Environmental Science and Research Ltd) (ange.bissielo@esr.cri.nz)

35. La direction des affaires sanitaires et sociales de Nouvelle-Calédonie (DASS). [Department of Health and Social Affairs] Veille sanitaire. French. Nouméa, 2014. [Accessed 17 Sep 2014]. Available from : http://www.dass.gouv.nc/portal/page/portal/dass/observatoire_sante/veille_sanitaire/

36. Bulletin de surveillance et veille sanitaire en Polynésie français - Bureau de veille sanitaire. [Public Health Surveillance and Monitoring in French Polynesia – Public Health Surveillance Office]. French. Accessed 17 Sep 2014. Available from: http://www.spc.int/phs/PPHSN/Surveillance/Routine_reports.htm

37. PacNet country reports. For details in PacNet report archives, contact the Focal Point of the Pacific Public Health Surveillance Coordinating Body (FocalPointPPHSNCB@spc.int<mailto:FocalPointPPHSNCB@spc.int>)

156

Annex 7. Article for case study n°4 – Mercier *et al.* 2018

SHORT COMMUNICATION

WILEY Transboundary and Emerging Diseases

Spread rate of lumpy skin disease in the Balkans, 2015–2016

A. Mercier[1] | E. Arsevska[1] | L. Bournez[2] | A. Bronner[3] | D. Calavas[4] | J. Cauchard[4] |
S. Falala[1] | P. Caufour[1] | C. Tisseuil[5] | T. Lefrançois[1] | R. Lancelot[1] (iD)

[1]French Agricultural Research for Development (CIRAD), Campus International de Baillarguet, Montpellier, France

[2] Unité de coordination et d'appui à la surveillance, Direction des laboratoires, Agency for Food, Environmental and Occupational Health & Safety (ANSES), Maisons-Alfort, France

[3]General Directorate for Food, Ministry of Agriculture and Food, Paris, France

[4]Agency for Food, Environmental and Occupational Health & Safety (ANSES), Lyon, France

[5]Biological Control and Spatial Ecology, Université Libre de Bruxelles, Brussels, Belgium

Correspondence
R. Lancelot, French Agricultural Research for Development (CIRAD), Campus International de Baillarguet, Montpellier, France.
Email: renaud.lancelot@cirad.fr

Summary

After its introduction in Turkey in November 2013 and subsequent spread in this country, lumpy skin disease (LSD) was first reported in the western Turkey in May 2015. It was observed in cattle in Greece and reported to the World Organization for Animal Health (OIE) in August 2015. From May 2015 to August 2016, 1,092 outbreaks of lumpy skin disease were reported in cattle from western Turkey and eight Balkan countries: Greece, Bulgaria, The Former Yugoslav Republic of Macedonia, Serbia, Kosovo, and Albania. During this period, the median LSD spread rate was 7.3 km/week. The frequency of outbreaks was highly seasonal, with little or no transmission reported during the winter. Also, the skewed distribution of spread rates suggested two distinct underlying epidemiological processes, associating local and distant spread possibly related to vectors and cattle trade movements, respectively.

KEYWORDS
epidemic intelligence, lumpy skin disease, spread rate

1 | INTRODUCTION

Lumpy skin disease (LSD) is an infectious disease of cattle caused by a virus (LSDV) belonging to the genus *Capripoxvirus* and family *Poxviridae*. It is mostly transmitted by arthropods, although direct and indirect transmission may also occur (Babiuk, Bowden, Boyle, Wallace, & Kitching, 2008). The distribution of LSD was limited to sub-Saharan Africa until 1986 when it spread to the Middle East (Rweyemamu et al., 2000; Tuppurainen & Oura, 2012). It reached Turkey in November 2013, Greece in August 2015, then Bulgaria and the Former Yugoslav Republic of Macedonia (FYROM) in April 2016, Serbia, Kosovo, and Albania in June 2016 and Montenegro in July 2016. European regulation at that time enabled vaccination in a given country only after disease occurrence in this country. The goal

of this study was to estimate the LSDV spread rate for further use in risk analysis for LSDV introduction in other European countries.

2 | MATERIAL AND METHODS

Epidemiological data on LSD outbreaks were combined from the Animal Disease Notification System (ADNS) developed and maintained by the European Commission, and the EMPRES Global Animal Disease Information System (EMPRES-i) developed and maintained by the Food and Agriculture Organization of the United Nations (FAO). We cross-checked these data with the information available in the World Animal Health Information System (WAHIS) of the World Animal Health Organization (OIE), in particular for the date

and place of first occurrence in a given country. The LSD outbreaks were described with their geographical coordinates (decimal degrees trimmed to the second decimal place for confidentiality), and their occurrence date. The infected area encompassed western Turkey (Edirne, Kirklareli, and Tekirdag provinces), and the above cited Balkan countries. The studied time period ranged from the date of first occurrence in western Turkey (13 May 2015) to 31 August 2016.

Lumpy skin disease outbreaks were firstly mapped using hexagonal binning (Carr, Olsen, & White, 1992). Secondly, to estimate the LSD spread rate, the week number of first occurrence at each location was derived from the outbreak date and interpolated over the study area using thin-plate spline regression (Tisseuil et al., 2015). The landscape resistance to LSD spread, i.e., the inverse of the spread rate, was then computed using a transition matrix with each cell connected to its four orthogonal neighbours. For further steps, we only kept spread rates corresponding to observations (i.e., discarding interpolated values), thus limiting possible edge effects, as well as biases in variance estimate. Assuming the observed spread rates was generated by several underlying processes (e.g., LSDV transmission by arthropod vectors or by cattle movements, such as trade), the most likely number n of Gaussian components in the observed distribution was estimated with a bootstrap procedure simulating the likelihood ratio statistic for n versus $n + 1$ components. Their mean, variance, and proportion were estimated using an expectation-maximization algorithm. At last, the mean spread rate, and its variations with the time lag from LSDV introduction, as well as the season, were estimated with a generalized least squares (GLS) model with an exponential spatial correlation structure. All the analyses were done with the R software (R Core Team, 2016).

3 | RESULTS

From May 2015 to August 2016, 1,092 outbreaks of LSD were reported in eight countries. The epidemic curve (Figure 1a) shows a marked seasonal pattern, with a summer peak and a winter stop, in line with a vector transmission process. The 2016 peak was earlier and higher than in 2015, in relation with the quick spread of LSDV. Figure 1b reveals the geographical aggregation of LSD outbreaks (red areas). The main hot spots were located in border areas: Turkey-Greece, Bulgaria-Greece, Serbia-Bulgaria-FYROM, Albania-FYROM and Albania-Kosovo, and Montenegro-Serbia. A dynamic representation of LSD incidence (Supporting information) reveals that these hot spots corresponded to long-distance LSD spread events, followed by local diffusion.

The map of interpolated LSD spread rates (Figure 2a: natural log scale) shows a highly heterogeneous—although well-structured, pattern. Indeed, the spread rate was higher in the latest front line areas (with respect to the date of first occurrence), and lower and patchy in the centre of the infected region. The lowest spread rates were encountered on the northern Greek coast, where LSD was first observed in this country.

The observed median spread rate was 7.3 km/week, with an inter-quartile interval of 4.4–12.5 km/week. However, the distribution on the original scale (km/week) was highly skewed to the right, with a maximum value reaching 543.6 km/week. Moreover, the spread rate distribution on a log scale (Figure 2b) showed a mode close to 2 (7.4 km/week) and a much lower peak close to 4 (54.6 km/week).
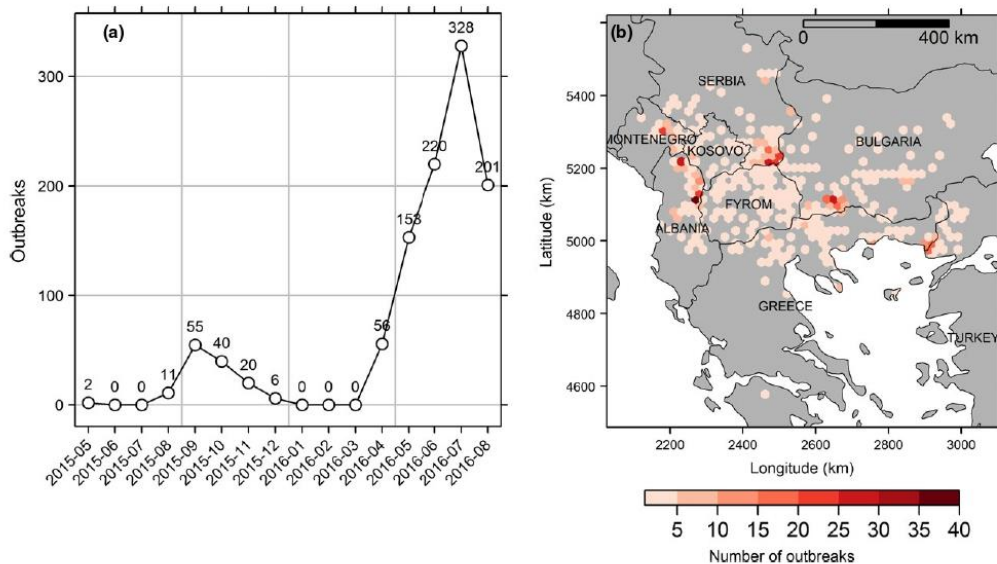

FIGURE 1 Temporal and spatial pattern of lumpy skin disease in the Balkans from May 2015 to August 2016: (a) epidemic curve and (b) cumulative incidence map. FYROM, Former Yugoslav Republic of Macedonia. Data sources: ADNS, EMPRES-i, and WAHIS
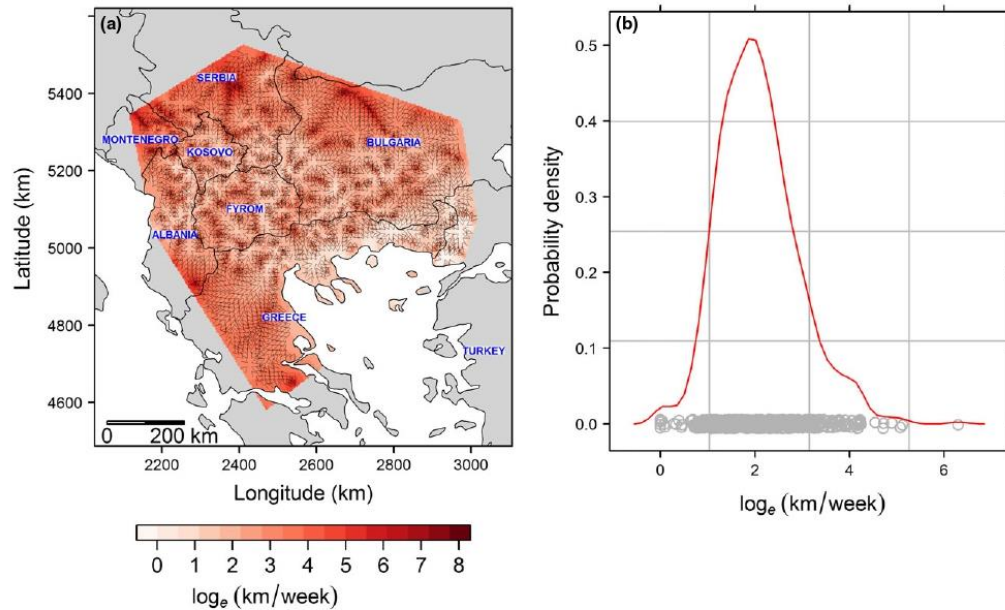
FIGURE 2 Lumpy skin disease spread rate in the Balkans from May 2015 to August 2016. (a) Map: The coloured region represents the convex hull encompassing the data points; FYROM: Former Yugoslav Republic of Macedonia; the small arrow heads represent the spread direction. (b) Probability distribution; the grey dots on the x axis represent the observed data. Data sources: ADNS, EMPRES-i, and WAHIS

TABLE 1 Estimated spread rate of lumpy skin disease in the Balkans from May 2015 to August 2015

Years after introduction	Season	Spread rate (km/week)	95% CI
1	Spring	11.2	[9.0; 13.8]
	Summer-fall	6.5	[4.5; 9.5]
2	Spring	11.2	[9.2; 13.6]
	Summer-fall	11.3	[9.3; 13.7]

The bootstrap procedure (500 replications) allowed identifying three Gaussian components in the spread rate distribution, on a log scale ($p = .006$) with a relative frequency of 65%, 34%, and 1%. Their respective mean and 95% CI were 6.2 [2.0; 19.8], 12.1 [1.7; 84.7], and 67.1 [64.3; 70.0] km/week. At last, GLS estimates (Table 1) revealed a quasi-constant spread rate of 11.2–11.3 km/week except during summer-fall 2015 when it dropped to 6.5 km/week ($\chi^2 = 8.5$, $df = 1$, $p = .004$).

4 | DISCUSSION

In this study, we had to combine several data sources (EMPRES-I, ADNS, and WAHIS) to obtain a complete as possible dataset allowing an overview of the epidemiological situation. This step was cumbersome: It would be useful to improve the inter-connection of these information systems. In addition, the availability of animal health data depends on the willingness and capacity of the national competent bodies to collect and share these data. The situation has much improved over the years, thus enabling this analysis. However, there is still a need for improvements, notably in the systematic detection and rapid reporting of notifiable diseases.

Because of the possible under- or delayed-reporting, the maximum spread rate found in this study is probably unstable. However, this is a parameter of interest for risk analysis. For this purpose, estimates are regularly updated, and results are made available on the website of the French Platform for Animal Health Surveillance (http://plateforme-esa.fr/).

After the disease was first detected by the national disease surveillance systems, mass vaccination was performed using the Neethling vaccine which was shown to be effective for controlling LSD (Kitching, 2003). These vaccination campaigns must have strongly influenced the spread of the disease. One finding of this study that may support this assumption is the fact that LSD transmission hot spots were mainly located in the border areas. Because the European regulation at that time enabled vaccination only after disease occurrence in a given country, it might be that vaccination after introduction of the disease into the country could have reduced the rate of spread of the outbreak as it was shown for other diseases (Pioz et al., 2014). Therefore, for a full analysis of LSD spread rate, it will be important to incorporate vaccination data in the model.

The assumption of several underlying process generating the LSDV incidence and spread pattern is supported by this analysis. Low spread rates (<10–15 km/week) were probably related to local

LSDV transmission by infected arthropods and contacts between infected and naive cattle, covering small daily distances (Magori-Cohen et al., 2012). Similar estimates were reported for other vector-borne diseases such as bluetongue. Conversely, high spread rates (>15 km/week) might be related to the movement of infected animals: between-farm trade, cattle markets, or slaughterhouses (EFSA, 2015). Dispersion of infected vectors by wind might also have played a limited role.

5 | CONCLUSION

A limited amount of data was required for this study (outbreak date and coordinates), thus illustrating the value of such data. In case of disease emergence and spread, up-to-date outbreak data are crucial for real-time monitoring of its spread (Khan et al., 2012). Our results are compatible with the assumption of two joint LSDV spread processes: (i) A local vector-borne transmission—by far the most frequent, and a long-distance anthropogenic transmission (cattle trade, farming activities)—much less frequent, but important from an epidemiological viewpoint. Future works will try to confirm these assumptions and to assess the importance of factors influencing variations of spread rates in space and time (Pioz et al., 2011, 2012, 2014; Tisseuil et al., 2015). Also, bio-ecological studies are needed to better understand the mechanisms of LSDV transmission by arthropod vectors (Tuppurainen et al., 2013). In addition, it is essential to improve early detection and reporting of diseases to facilitate the implementation of control measures such as restrictions in animal movements, and vaccination which proved their efficiency in the case of other vector-borne diseases, such as bluetongue (Pioz et al., 2014).

RESEARCH LOCATION

- French agricultural research and international cooperation organization (CIRAD), French National Institute for Agricultural Research (INRA), mixed research unit "Animals, health, territories, risks and ecosystems" (UMR ASTRE), Campus International de Baillarguet, Montpellier, France.
- French Agency for Food, Environmental and Occupational Health & Safety (ANSES),

  Coordination and surveillance support unit, Laboratories Directorate, Maisons-Alfort.
  Lyon Laboratory, Epidemiology unit, Lyon, France.
- French Ministry of Agriculture and Food, General Directorate for Food.

REFERENCES

Babiuk, S., Bowden, T., Boyle, D., Wallace, D. B., & Kitching, R. (2008). Capripoxviruses: An emerging worldwide threat to sheep, goats and cattle. *Transboundary and Emerging Diseases*, *55*(7), 263–272.

Carr, D. B., Olsen, A. R., & White, D. (1992). Hexagon mosaic maps for display of univariate and bivariate geographical data. *Cartography and Geographic Information Systems*, *19*(4), 228–236.

EFSA (2015). Scientific opinion on lumpy skin disease. *EFSA Journal, 13*(1), 27–37.

Khan, K., McNabb, S. J., Memish, Z. A., Eckhardt, R., Hu, W., Kossowsky, D., ... Brownstein, J. S. (2012). Infectious disease surveillance and modelling across geographic frontiers and scientific specialties. *Lancet Infectious Diseases*, *12*(3), 222–230.

Kitching, R. P. (2003). Vaccines for lumpy skin disease, sheep pox and goat pox. *Developments in Biologicals*, *114*, 161–167.

Magori-Cohen, R., Louzoun, Y., Herziger, Y., Oron, E., Arazi, A., Tuppurainen, E., ... Klement, E. (2012). Mathematical modelling and evaluation of the different routes of transmission of lumpy skin disease virus. *Veterinary Research*, *43*(1), 1. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3268087/

Pioz, M., Guis, H., Calavas, D., Durand, B., Abrial, D., & Ducrot, C. (2011). Estimating front-wave velocity of infectious diseases: A simple, efficient method applied to bluetongue. *Veterinary Research*, *42*(1), 60.

Pioz, M., Guis, H., Crespin, L., Gay, E., Calavas, D., Durand, B., ... Ducrot, C. (2012). Why did bluetongue spread the way it did? Environmental factors influencing the velocity of bluetongue virus serotype 8 epizootic wave in france. *PLoS One*, *7*(8), e43360.

Pioz, M., Guis, H., Pleydell, D., Gay, E., Calavas, D., Durand, B., ... Lancelot, R. (2014). Did vaccination slow the spread of bluetongue in France? *PLoS One*, *9*(1), e85444.

R Core Team. (2016). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from https://www.R-project.org/

Rweyemamu, M., Paskin, R., Benkirane, A., Martin, V., Roeder, P., & Wojciechowski, K. (2000). Emerging diseases of Africa and the Middle East. *Annals of the New York Academy of Sciences*, *916*, 61–70.

Tisseuil, C., Gryspeirt, A., Lancelot, R., Pioz, M., Liebhold, A., & Gilbert, M. (2015). Evaluating methods to quantify spatial variation in the velocity of biological invasions. *Ecography*, *38*, 001–010.

Tuppurainen, E., Lubinga, J. C., Stoltsz, W. H., Troskie, M., Carpenter, S., Coetzer, J. A., ... Oura, C. (2013). Mechanical transmission of lumpy skin disease virus by *Rhipicephalus appendiculatus* male ticks. *Epidemiology and Infection*, *141*(02), 425–430.

Tuppurainen, E., & Oura, C. (2012). Review: Lumpy skin disease: An emerging threat to Europe, the Middle East and Asia. *Transboundary and Emerging Diseases*, *59*(1), 40–48.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Mercier A, Arsevska E, Bournez L, et al. Spread rate of lumpy skin disease in the Balkans, 2015–2016. *Transbound Emerg Dis.* 2018;65:240–243. https://doi.org/10.1111/tbed.12624