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Development of an optimal antimicrobial resistance surveillance system in Viet Nam

Present by VU Tien Viet Dung
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Under the supervision of Marisa Peyre, Marc Choisy and H. Rogier van Doorn

Defended in front of the following doctoral committee:

Katharina Staerk, Adjunct Professor, City University, Hong Kong	Reviewer
Lulla Opatowski, Professor, University of Versailles Saint Quentin	Reviewer
Nicolas Antoine-Moussiaux, Professor, Université de Liège, Belgique	Examiner
Sylvain Godreuil, Professor, IRD Montpellier/CHU Arnaud de Villeneuve	Examiner
Christian Ducrot, Research Director, UMR ASTRE CIRAD INRA, Centre CIRAD de Baillarguet	Jury President
Marisa Peyre, Researcher, UMR ASTRE CIRAD INRA, Centre CIRAD de Baillarguet	Thesis director

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THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

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Unité de recherches CIRAD and OUCRU

Développement d'un système de surveillance de l'antibiorésistance au Viet Nam

Présentée par VU Tien Viet Dung
Le 24 Juin 2020

Sous la direction de Marisa Peyre,
Marc Choisy et H. Rogier van Doorn

Devant le jury composé de :

Katharina Staerk, Professeur adjoint, City University, Hong Kong	Rapporteur
Lulla Opatowski, Professeur, Université de Versailles Saint Quentin	Rapporteur
Nicolas Antoine-Moussiaux, Professeur, Université de Liège, Belgique	Examinateur
Sylvain Godreuil, Professeur, IRD Montpellier/CHU Arnaud de Villeneuve	Examinateur
Christian Ducrot, Directeur de recherche, UMR ASTRE CIRAD INRA, Centre CIRAD de Baillarguet	Président du Jury
Marisa Peyre, Chercheur, UMR ASTRE CIRAD INRA, Centre CIRAD de Baillarguet	Directrice de thèse

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Abstract

Antimicrobial resistance (AMR) is a major global public health concern. The Viet Nam National Action Plan on AMR recognised surveillance as one of critical components for control. However, the current AMR surveillance system (AMRSS) in Viet Nam is likely to be over-representing severe and hospital acquired infections (HAI), potentially resulting in an overestimation of resistance among community acquired infection (CAI). This thesis aims to evaluate the AMRSS in Viet Nam and to make suggestions to optimize the AMRSS effectiveness in providing accurate and representative AMR data for CAI patients in this setting.

A systematic litterature review was conducted to generate an overview of the AMRSSs that have been implemented globally and any evaluations of such systems. There is no standardized framework or guidelines for conducting evaluation of AMRSS. Less than 10% of the systems reported some system evaluation, focusing on few attributes such as representativeness, timeliness, bias, cost, coverage, and sensitivity. This review highlighted the need for systematic evaluation to assess AMRSS performance and for developing specific methods, building on current evaluation guidelines, with additional attributes specific for AMR surveillance.

An evaluation of the hospital-based VINARES (Viet Nam Resistance) AMRSS in Viet Nam in two time periods, 2012-2013 and 2016-2017, was carried out. The sensitivity of the AMRSS was in the 2-5% range and remained similar between the two periods. There was a delay in data submission from the hospitals, which affected surveillance timeliness. No evaluation of the surveillance system was carried out to identify problems and implement prompt resolutions. Data from these two periods showed increasing trends of resistance among key pathogen – antimicrobial combinations, and a lack of discrimination in resistance results between CAI and HAI patients.

Optimization through modelling of the hospital based AMRSS was then carried out focusing on carbapenem resistant *Klebsiella pneumoniae* using baseline data from VINARES and employing model-based methodologies examining key attributes including accuracy, sensitivity, coverage, and representativeness with two assumptions: (1) hospitals of a same type (national, specialized and provincial) were similar; (2) resistant proportions were similar by type of hospitals for CAI while they varied for HAI. Overall, the results showed that the accuracy of AMR data is enhanced when the number of hospitals increases (0.6% decrease in mean squared error for one additional hospital (CI 0.6% - 0.7%)). For a given amount of budget,

the optimal numbers of hospitals by type can be determined using this modelling approach to identify a system with the best values for each performance attribute.

The results indicate that the current AMRSS can increase the proportions of specialized and provincial hospitals to increase accuracy of data and system representativeness. The models were based on VINARES data, therefore the results are likely to be valid for an AMRSS with similar organizational structures and data collection protocols. The amount of budget that the government and foreign development partners are willing to spend on AMR surveillance is also an important factor in identifying the optimal hospital combination for the AMRSS.

Résumé en français

Introduction

La résistance aux antimicrobiens (AMR) est une préoccupation majeure de santé publique mondiale car elle peut restreindre les choix et augmenter les échecs de traitement, les coûts médicaux et les décès. Le fardeau de l'AMR est probablement plus élevé dans les pays à revenu faible ou intermédiaire (PRFI), tel le Viet Nam.

Il existe un consensus général parmi les décideurs politiques et sanitaires sur les problèmes graves et croissants causés par l'AMR au Viet Nam. Un plan d'action national de lutte contre l'AMR a été approuvé pour la période 2013-2020, qui souligne l'importance des systèmes de surveillance systématique pour évaluer l'utilisation et la résistance aux antibiotiques. Cela est également conforme au plan de lutte mondial contre l'AMR lancé par l'Organisation mondiale de la santé (OMS) en 2015.

Plusieurs programmes de surveillance de l'AMR ont été mis en œuvre au Viet Nam depuis la fin des années 80 avec un nombre variable d'hôpitaux participants, certains de ces programmes ont été soutenus par des organisations internationales. Le projet VINARES a été lancé en 2012 dans le cadre d'une collaboration entre le Ministère de la Santé, l'Hôpital National pour les Maladies Tropicales, la Société Vietnamienne des Maladies Infectieuses, l'Unité de Recherche Clinique de l'Université d'Oxford - Viet Nam (OUCRU) et l'université de Linköping, Suède, ainsi que 16 hôpitaux à travers le pays. VINARES visait à soutenir le développement d'une gestion efficace des antimicrobiens et à renforcer le contrôle national de l'utilisation des antibiotiques dans le pays. En 2016, la deuxième génération de VINARES a été lancée et le réseau est désormais officiellement reconnu par le Ministère de la Santé comme le réseau national de surveillance de l'AMR. Cependant aucune évaluation du système de surveillance d'AMR n'a été réalisé au Viet Nam.

Une des préoccupations en ce qui concerne l'évaluation de l'efficacité du système de surveillance de l'AMR est la surreprésentation probable des infections graves, y compris des infections nosocomiales (HAI), ce qui se traduit par une surestimation de la résistance aux infections nosocomiales (CAI). Ce problème limite l'utilité des données de surveillance de l'AMR pour informer le développement et la mise à jour des lignes directrices nationales et

locales sur l'utilisation des traitements antibiotiques. Avec notamment la possibilité d'observer une prescription excessive s'il n'est pas interprété et utilisé de manière appropriée par les médecins dans leur traitement. Par conséquent, mes recherches portent sur les questions d'évaluation des systèmes de surveillance de l'AMR et explorent les solutions pour améliorer leur efficacité et leur intérêt dans le contexte du Viet Nam, un PRFI.

Buts et objectifs du travail de recherche

Cette étude de doctorat vise à évaluer de manière systématique le système de surveillance de l'AMR (AMRSS) au Viet Nam et à développer un modèle d'AMRSS efficace et efficient en fournissant une estimation précise et représentative de la proportion de résistance chez les patients CAI. Plus précisément, les objectifs sont les suivants: 1) faire un état des lieux des système de surveillance de la résistance aux antimicrobiens dans le monde par une analyse systématique de la littérature et identifier les différentes caractéristiques opérationnelles pertinentes ainsi que les attributs d'efficacité affectant les performances du système; 2) évaluer de façon systématique le système de surveillance de l'AMR au Viet Nam au cours des deux périodes VINARES 2012-2013 et 2016-2017 afin d'identifier les attributs importants qui impactent les performances de surveillance dans le pays; 3) analyser les résultats des tests de sensibilité aux antibiotiques (AST) qui ont été soumis au système VINARES en 2012-2013 et 2016-2017 pour fournir des données de référence et analyser l'évolution de la résistance aux antibiotiques au Viet Nam; 4) développer un modèle de classification pour estimer la proportion de patients par source d'infection (CAI et HAI) et les proportions de résistance spécifiques à chaque groupe pour les données VINARES; et 5) optimiser l'efficacité du système de surveillance de l'AMR au Viet Nam en ce qui concerne la précision et la représentativité des données d'AMR pour les patients CAI et ce en faisant varier les attributs clefs du système de surveillance identifiés précédemment.

Je vise à répondre à deux hypothèses clés et questions de recherche :

Hypothèse 1 : La proportion de résistance aux antibiotiques utilisée pour informer les directives locales de traitement est surestimée dans le système actuel de surveillance passive au laboratoire, car les diagnostics microbiologiques sont souvent réservés aux cas les plus graves et aucune métadonnée n'est collectée pour faire la distinction entre les infections communautaires (CAI) et nosocomiales (HAI) où la proportion de résistance aux antibiotiques est beaucoup plus élevée les derniers.

Question de recherche 1 : Comment estimer la proportion de résistance pour informer les directives locales de traitement pour les patients CAI?

Hypothèse 2 : Les ressources humaines et économiques pour la surveillance de l'AMR au Viet Nam ne sont pas allouées de manière adéquate. Le résultat (proportion de la résistance aux antibiotiques) pourrait être affecté par le nombre d'hôpitaux et le type d'hôpital (national, spécifique et provincial) participant au système de surveillance.

Question de recherche 2 : Comment pouvons-nous optimiser l'efficacité et le coût du système de surveillance de l'AMR au Viet Nam ?

Résultats

Revue littérature des systèmes de surveillance de l'AMR dans le monde

Le nombre de systèmes de surveillance de l'AMR dans le monde a considérablement augmenté à la fin des années 90 ; la plupart des systèmes mis en place après 2010 sont des systèmes internationaux passifs (qui reçoivent les données des systèmes de surveillance nationaux). Ces systèmes peuvent être très différent, notamment en ce qui concerne les objectifs de surveillance, les agents pathogènes ciblés, le nombre d'hôpitaux participants, l'inclusion de laboratoires centraux / de référence, les normes d'interprétation des résultats de l'AST, les mesures de contrôle de la qualité, les informations sur la déduplication et l'intégration des informations cliniques. Ces variations entraînent des difficultés lors de l'agrégation des données et de la comparaison entre les régions.

Il n'y a pas non plus de cadre et de lignes directrices normalisés pour mener une évaluation des systèmes de surveillance de l'AMR. Une évaluation des systèmes a été rapportée dans moins de 10% des cas, se concentrant sur quelques attributs tels que la représentativité, la rapidité, le biais, le coût, la couverture et la sensibilité. Les informations sur l'évaluation de ces attributs sont peu explicitées dans ces études. À l'exception de l'évaluation systématique du programme australien de surveillance du gonocoque (Australian Gonococcal Surveillance Programme), l'évaluation est présentée comme une analyse complémentaire plutôt qu'une évaluation systématique de l'ensemble du système de surveillance de l'AMR. Dans toutes les études, le contexte dans lequel s'inscrit la surveillance était également peu explicité.

Cette revue a mis en évidence la nécessité d'une évaluation systématique pour évaluer les performances de l'AMRSS et peut-être la nécessité de développer des méthodes spécifiques

s'appuyant sur les directives d'évaluation existantes avec la prise en compte d'attributs complémentaires spécifiques à la surveillance de l'AMR.

Évaluation du système de surveillance de l'AMR au Viet Nam – basé sur VINARES

Le réseau VINARES était opérationnel en tant qu'AMRSS en 2012-13 et 2016-17. Il est ensuite devenu le Système National de Surveillance de l'AMR et la collecte de données a repris en 2018. 16 hôpitaux faisait partie du réseau VINARES en 2012 : 4 hôpitaux nationaux, 5 hôpitaux spécialisés et 7 hôpitaux provinciaux. En 2016, le nombre d'hôpitaux ayant soumis des données a été réduit à 13 avec 3 hôpitaux nationaux, 3 hôpitaux spécialisés et 7 hôpitaux provinciaux. Alors que la contribution des isolats des hôpitaux provinciaux est demeurée la même entre les 2 périodes (44%) et des hôpitaux nationaux a augmenté de 10% en 2016-2017 par rapport à 2012-2013. La représentativité géographique a également changé en raison des fluctuations du nombre d'hôpitaux, avec une sensibilité faible pour les deux périodes. Ces variations pourraient affecter les proportions globales de résistance estimées entre les deux périodes.

Dans le cadre d'un protocole de surveillance passive, les laboratoires des hôpitaux inclus dans VINARES ont été invités à envoyer des données à l'unité centrale dans un délai spécifié (mensuel pour la première période et trimestriel pour la deuxième). La qualité et la cohérence des données ont été assurées par la formation, l'utilisation des directives Clinical & Laboratory Standards Institute (CLSI) traduites, l'inscription au UK-NEQAS et la soumission des données standardisées à l'aide de WHONET. Malgré cela, un délai dans la soumission des données des hôpitaux (10% de soumission dans un délai de 1 à 3 mois) a été observé, ce qui a affecté la rapidité du système de surveillance. Ce problème et de nombreux autres problèmes opérationnels peuvent être améliorés grâce à une évaluation régulière en temps réel du système de surveillance pour identifier les problèmes et mettre en œuvre des actions correctives rapides.

Résultats de l'analyse des données AST du réseau de surveillance VINARES

Au cours de la période 2012-2013, les données d'un total de 24 732 isolats cliniques dédoublés ont été signalés. Les bactéries les plus courantes : *Escherichia coli* (4437 isolats, 18%), *Klebsiella spp.* (3290 isolats, 13%) et *Acinetobacter spp.* (2895 isolats, 12%). La consommation moyenne d'antibiotiques à l'hôpital était de 918 doses quotidiennes définies (DDD) / 1000 jours-patients. Les céphalosporines de troisième génération étaient la classe d'antibiotiques la plus utilisée (223 DDD / 1000 jours-patients, 24%), suivies des

fluoroquinolones (151 DDD / 1000 jours-patients, 16%) et des céphalosporines de deuxième génération (112 DDD / 1000 patients -jours, 12%). Les proportions de résistance aux antibiotiques étaient élevées : 1098/1580 (69%) des isolats de *Staphylococcus aureus* étaient résistants à la méthicilline (MRSA); 115/344 isolats (33%) et 90/358 (25%). *Streptococcus pneumoniae* avait une sensibilité réduite à la pénicilline et à la ceftriaxone, respectivement. Un total de 180/2977 (6%) *E. coli* et 242/1526 (16%) *K. pneumoniae* étaient résistants à l'imipénème, respectivement ; 602/1826 (33%) *Pseudomonas aeruginosa* étaient résistants à la ceftazidime et 578/1765 (33%) à l'imipénème. 1495/2138 (70%) d'*Acinetobacter spp.* étaient résistants aux carbapénèmes et 2/333 (1%) à la colistine.

Au cours de la période 2016-2017, 42553 isolats ont été inclus pour l'analyse ; dont 30222 (71%) bactéries Gram-négatives et 12331 (29%) Gram-positives. 8793 (21%) provenaient d'USI et 7439 (18%) d'isolats provenaient d'infections invasives.

E. coli et *S. aureus* étaient les espèces les plus fréquemment détectées avec respectivement 9092 (21%) et 4833 isolats (11%) ; suivie de *K. pneumoniae* (3858 isolats - 9%) et *Acinetobacter baumannii* (3870 isolats - 9%). Les bactéries étaient principalement isolées des expectorations (8798 isolats - 21%), du sang (7118 isolats - 17%) et de l'urine (5202 isolats - 12%).

1824/2510 (73%) des isolats de S. aureus étaient MRSA. 99/290 (34%) d'*Enterococcus faecium* étaient résistants à la vancomycine. La proportion de *S. pneumoniae* résistant à la pénicilline était de 83% (657/794). La proportion d'*E. coli* portant de béta-lactamases à spectre élargi (ESBL) était de 59% (4085/6953) et de 40% (1186/2958) chez *K. pneumoniae*. La proportion de *A. baumannii* et *P. aeruginosa* résistants aux carbapénèmes était de 79% (2855/3622) et 45% (1514/3376), respectivement. La proportion de *Haemophilus influenzae* résistant à l'ampicilline était de 88% (804/911) parmi tous les isolats. 18/253 (7%) de *Salmonella spp.* et 7/46 (15%) de *Shigella spp.* étaient résistants aux fluoroquinolones.

Une variation importante des profils de résistance a été observée entre les différents hôpitaux. Le nombre d'isolats soumis au cours de la période 2016-2017 était deux fois plus élevé qu'en 2012-2013. Les proportions d'AMR détéctées étaient plus élevées en 2016-2017 pour la plupart des combinaisons pathogènes-antimicrobiens d'intérêt, y compris les entérobactéries résistantes aux imipénèmes, *A. baumannii* et *P. aeruginosa*.

Optimisation du système de surveillance de la RAM au Viet Nam

L'optimisation de l'AMRSS au Viet Nam se base sur 3 hypothèses : (1) il existe trois types d'hôpitaux (national, spécialisé et provincial) similaires en termes taille de (admissions de patients, capacité en lits), proportion de CAI : HAI chez les patients présentant une infection et des proportions résistantes chez les patients CAI / HAI ; (2) la proportion de résistantes dans les CAI est similaire dans tous les types d'hôpitaux, tandis que celle dans les HAI varie selon le type d'hôpitaux.

Sur la base d'un modèle de classification d'ensemble, 1216 (76%) des patients VINARES ont été classés comme ayant un CAI et 385 (24%) ayant un HAI. La proportion estimée de *K. pneumoniae* résistante aux carbapénèmes était de 9% pour le CAI et de 9% à 15% pour le HAI selon le type d'hôpitaux. L'erreur quadratique moyenne (MSE) de la proportion de résistants pour le CAI de VINARES 2012-2013, qui comprenait 4 hôpitaux nationaux, 5 hôpitaux spécialisés et 7 hôpitaux provinciaux, est de $2,27 \times 10^{-4}$.

Dans l'ensemble, le MSE diminue tandis que le nombre d'hôpitaux augmente (diminution de 0,6% pour un hôpital supplémentaire en moyenne (IC 0,6% - 0,7%)), ce qui montre qu'un nombre plus élevé d'hôpitaux peut améliorer la précision des données sur l'AMR. Cependant, cela n'est correct que pour les hôpitaux spécialisés ou provinciaux : le MSE réduit de 1,8% (IC 1,8% - 1,8%) et 2,2% (IC 2,2% - 2,2%) pour l'ajout d'un hôpital spécialisé et d'un hôpital provincial, respectivement ; mais le MSE augmente de 3,5% (IC 3,4% - 3,5%) pour l'ajout d'un hôpital national. En particulier, les combinaisons comprenant une proportion d'hôpitaux nationaux et spécialisés variant entre 0 et 33% ainsi qu'une proportion d'hôpitaux provinciaux> 67% obtiennent le MSE le plus faible. La valeur la plus fable de MSE dans ces combinaisons est obtenue pour un nombre total d'hôpitaux de 43.

La sensibilité et la couverture augmentent avec l'ajout d'un hôpital de plus, mais la vitesse d'augmentation ralenti avec l'augmentation de nombre d'hôpitaux. Par exemple, on observe une augmentation de 1,09 si on ajoute un hôpital dans un AMRSS ayant 11 hôpitaux, cette valeur est réduite à 1,05 fois dans un AMRSS ayant 20 hôpitaux. En ce qui concerne la représentativité, pour un nombre total fixe d'hôpitaux, la meilleure combinaison par type d'hôpital peut être identifiée en terme du plus haut niveau de représentativité. Par exemple, pour les combinaisons de 25 hôpitaux, la combinaison de 1 hôpital national, 7 hôpitaux spécialisés et 17 hôpitaux provinciaux (n = 25) était la plus représentative, et cela semblait

également être la plus représentative de toutes les combinaisons avec la plus petite valeur de Chi - statistique carrée.

Le coût total de la surveillance pour VINARES 2012-2013 a été estimé à 386 milliers USD pour 24 mois. Le coût de l'unité centrale, d'un hôpital de référence et d'un hôpital participant était de 38 000, 21 300 et 7 300 USD par an, respectivement (avec une période de 5 ans présumée pour les coûts fixes initiaux). Le coût annuel augmente de 7300 USD avec l'ajout d'un hôpital supplémentaire, quel que soit le type d'hôpital. Le MSE diminue rapidement au début, mais le changement dans la courbe du MSE diminue plus lentement lorsque le coût supplémentaire dépasse 1 million USD. La sensibilité et le taux de couverture diminuent progressivement. Avec 830 000 USD rajoutés dans de budget de l'AMRSS, la MSE diminuerait de 50%.

Pour une combinaison bactérie-antibiotique prioritaire donnée (*K. pneumoniae* – carbapénèmes dans cette thèse), avec un budget donné, le nombre optimal d'hôpitaux peut être déterminé en utilisant les attributs d'efficacité décrits ci-dessus. Pour un nombre donné d'hôpitaux, nous pouvons identifier la combinaison d'hôpitaux nationaux-provinciaux-spécialisés qui affiche la MSE la plus faible, la sensibilité la plus élevée et la représentativité la plus élevée (tableau 1).

Tableau 1 : Liste des AMRSS optimales par nombre d'hôpitaux après sélection basée sur MSE, sensibilité et représentativité

Nombre total d'hôpitaux	AMRSS optimal (a)	Coût de l'AMRSS ($)	Augmentation de la sensibilité (%)	Augmentation de la couverture (%)	Diminution de MSE (%)	Augmentation des coûts (%)
12	1 : 6 : 5	153 600	107	111	90	84
13	1 : 5 : 7	160 900	109	106	87	88
14	1 : 4 : 9	168 200	103	103	80	92
15	1 : 4 : 10	175 500	104	109	72	96
16	1 : 5 : 10	182 800	118	119	64	100
16(*)	**04:05:07**	**182 800**	**100**	**100**	**100**	**100**
17	1 : 5 : 11	190 100	123	126	71	104
18	1 : 11 : 6	197 400	166	175	70	108
19	1 : 7 : 11	204 700	152	153	69	112
20	1 : 7 : 12	212 000	154	155	61	116
25	1 : 12 : 12	248 500	214	220	58	136
30	1 : 7 : 22	285 000	191	204	43	156
40	2 : 11 : 27	358 000	277	292	42	196
50	1 : 13 : 36	431 000	342	352	38	236

60	1 : 19 : 40	504 000	435	448	36	276
70	1 : 29 : 40	577 000	546	574	37	316

(a) Ratio des hôpitaux National : Spécialisé : Provincial. (*) Combinaison de référence, qui était la combinaison des hôpitaux créés à VINARES en 2012 et reste la même dans l'actuel réseau national de surveillance de la résistance aux antimicrobiens. Le pourcentage d'augmentation / diminution des attributs d'efficacité a été comparé à cette combinaison de référence.

Discussion et conclusion

Dans cette recherche, j'ai utilisé diverses méthodes pour évaluer l'efficacité d'un système de surveillance de la résistance aux antimicrobiens dans le contexte vietnamien avec les données de référence du projet VINARES. VINARES et le système national de surveillance actuel utilisent une approche de surveillance passive, qui a été efficace pour obtenir des données d'un grand nombre d'hôpitaux à faible coût en utilisant les infrastructures de santé existantes. La surveillance passive est considérée comme une stratégie relativement peu coûteuse pour obtenir des informations sur la santé auprès de populations ayant une large couverture géographique, cependant, cette approche pose également des problèmes dans le contrôle de la qualité des données et dans la rapidité du système, car le système dépend fortement du personnel des hôpitaux participants pour effectuer l'activité de surveillance requise. Des évaluations systématiques périodiques du système de surveillance peuvent aider à garantir que le système fonctionne efficacement, que les informations fournies par le système sont utiles pour la pratique de la santé publique et que les ressources de santé sont dépensées de manière appropriée pour la surveillance.

Malgré les limites intrinsèques à l'approche de surveillance passive et l'absence de métadonnées cliniques, les données collectées dans VINARES au cours des deux périodes 2012-2013 et 2016-2017 ont fourni une description des proportions résistantes de bactéries importantes - combinaisons d'antibiotiques pour chacun des hôpitaux participants du réseau et pour tous les hôpitaux combinés, avec stratification par échantillon (le sang et la liquide cérébrospinal vs. autre) et par salle (Unités de Soins Intensifs (USI) vs. non USI). Ces données sont importantes pour comprendre la distribution et l'ampleur du problème de l'AMR dans les hôpitaux du Viet Nam.

Comme souligné tout au long de cette thèse, un objectif important de la surveillance de la résistance aux antimicrobiens au Viet Nam est d'obtenir des informations précises sur les profils

de résistance pour éclairer les actions de contrôle et le traitement. Par conséquent, il est important d'identifier la combinaison d'hôpitaux qui fournissent des données avec moins de biais et une plus grande précision tout en économisant les ressources investies dans le système de surveillance. À l'aide de méthodes de simulation, j'ai identifié les solutions d'optimisation en fonction des principaux attributs et coûts d'efficacité et en faisant varier le nombre d'hôpitaux selon leur type. Les résultats ont montré qu'afin d'augmenter la précision et la représentativité du système, les proportions des hôpitaux spécialisés et provinciaux inclus dans le système devraient être augmentée

Ces estimations sont basées sur les données VINARES, par conséquent, les résultats sont susceptibles d'être valables pour des systèmes de surveillance qui ont des structures organisationnelles et des protocoles de collecte de données similaires comme VINARES. Avec un cadre à ressources limitées comme le Viet Nam et de nombreux autres PRFI, cette méthodologie pourrait être appliquée pour optimiser les systèmes de surveillance avec un budget restreint. En substituant les données de référence correspondantes (nombre de types d'hôpitaux, nombre de patients avec CAI / HAI, nombre de patients porteurs d'isolats résistants), les attributs d'efficacité de ces systèmes de surveillance peuvent être évalués pour déterminer la structure la plus souhaitable.

Il n'y a pas de solution unique pour la combinaison optimale d'hôpitaux. Cela dépend du budget que le gouvernement est prêt à dépenser pour la surveillance de l'AMR. L'approche que j'ai utilisée pour déterminer le rapport coût-efficacité des systèmes peut apporter une réponse à l'option qui conduirait aux meilleurs résultats pour atteindre les objectifs de la surveillance en prenant en compte la contrainte budgétaire. Bien que l'approche de surveillance passive présente des limites inhérentes, il s'agit d'une solution à long terme et à faible coût adaptée aux paramètres des PRFI comme le Viet Nam.

Des initiatives continues sont mises en œuvre pour améliorer la surveillance de l'AMR au Viet Nam. Le Ministère de la Santé a reconnu VINARES comme réseau national de surveillance de la résistance aux antimicrobiens et la surveillance s'est poursuivie dans le cadre du projet pilote du Fonds Fleming (OUCRU) et de la subvention nationale (FHI360, PATH, NIHE, OUCRU) et du programme de sécurité sanitaire mondiale. Un protocole de surveillance des agents pathogènes de l'OMS GLASS avec ajout d'agents pathogènes spécifiques et la collecte simultanée de métadonnées cliniques limitées est également en cours d'élaboration. Grâce à ces

développements et à une mise en œuvre en continue, l'efficacité du système national de surveillance peut être encore améliorée et les données de surveillance de l'AMR peuvent être utilisées pour soutenir les actions de lutte contre l'AMR au Viet Nam.

Depuis 2019, OUCRU et l'Hôpital national pour les maladies tropicales pilotent ACORN (A Clinically - Oriented Antimicrobial Resistance Surveillance Network), avec des sites d'inscription supplémentaires au Laos et au Cambodge. ACORN combine la collecte de données cliniques et de laboratoire avec un feedback direct aux médecins locaux. Les données de ce projet pilote seront également utilisées dans notre modèle afin de trouver le réglage optimal pour un AMRSS étendu à l'avenir.

En conclusion, les performances du système de surveillance de l'AMR au Viet Nam et son optimisation sont étroitement dépendantes de la structure du réseau des hôpitaux, l'approche de surveillance mise en œuvre, y compris la conception de protocoles de collecte de données pour inclure les métadonnées nécessaires, la surveillance simultanée et le feedback rapide des données aux participants. La mise en place d'une évaluation en continue pour identifier en temps opportun les problèmes et mettre en œuvre des résolutions d'amélioration dans les hôpitaux est primordiale. La structure actuelle comprenant 4 hôpitaux nationaux, 5 hôpitaux spécialisés et 7 hôpitaux provinciaux devrait être réexaminée avec une augmentation des proportions d'hôpitaux spécialisés et provinciaux pour améliorer la précision et la représentativité des données sur l'AMR.

Sur la base des résultats de cette recherche et de la situation actuelle au Viet Nam, les recommandations suivantes sont avancées pour les prochaines étapes de l'amélioration du rapport coût-efficacité de la surveillance de la résistance aux antimicrobiens au Viet Nam et dans d'autres pays à faible revenu ou à faible revenu :

- Élaborer un plan d'évaluation réaliste et pertinent à intégrer au réseau national de surveillance de la résistance aux antimicrobiens en place pour surveiller et améliorer régulièrement les performances techniques et l'efficacité du système. Il est également tout aussi important d'assurer que les données recueillies auprès du système de surveillance soient utilisées de manière appropriée et efficace pour améliorer le traitement antibiotique et contrôler les problèmes de l'AMR – et ainsi assurer l'impact de cette surveillance.

- La surveillance de l’AMR est l'une des stratégies importantes du plan d'action national de lutte contre l’AMR. Les données du système de surveillance de l’AMR devraient être utilisées pour la conception et l'évaluation des actions et des interventions nationales et locales pour s'attaquer aux problèmes de l’AMR, y compris l'élaboration de lignes directrices et d'outils de traitement pour les médecins des hôpitaux locaux. Ces données devraient donc être dans un format en libre accès, qui devrait être accessible pour la recherche et la mise en œuvre du programme ainsi que pour les praticiens locaux.
- La conception du protocole national actuel de surveillance de la résistance aux antimicrobiens devrait être étendue pour inclure les informations cliniques clés de chaque patient, en particulier les informations sur l'origine de l'infection afin d'améliorer l'utilité des données de surveillance de la résistance aux antimicrobiens pour guider le traitement et élaborer des directives de traitement spécifiques. La faisabilité de cette extension doit être soigneusement évaluée sur la base des données d'ACORN et des preuves de la mise en œuvre de GLASS provenant d'autres pays.
- Envisager d'autres composants ou alternatives de surveillance de l’AMR, y compris une approche de surveillance active et une approche intégrée de surveillance de la santé-prenant en compte les problématiques de l’AMR en santé animale. Une évaluation économique plus approfondie de ces composantes serait intéressante, y compris une analyse de l'impact budgétaire pour fournir plus d’évidences aux décideurs politiques dans leur prise de décision en termes d’optimisation de la surveillance de l’AMR.

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ACER	Average Cost-Effectiveness Ratio
ACORN	A Clinically-Oriented Antimicrobial Resistance Surveillance Network
AMC	Antimicrobial Consumption
AMC	Amoxicillin/Clavulanic Acid
AMR	Antimicrobial Resistance
AMRSS	Antimicrobial Resistance Surveillance System
ANSES	French Agency For Food, Environmental And Occupational Health Safety
ANSORP	Asian Network For Surveillance Of Resistant Pathogens
AST	Antimicrobial Susceptibility Testing
ASTS	Antimicrobial Sensitivity Testing Study
ATCC	American Type Culture Collection
ATLASS	Assessment Tool For Laboratories And Antimicrobial Resistance Surveillance Systems
CAI	Community-Acquired Infection
CI	Confidence Interval
CLSI	Clinical & Laboratory Standards Institute
COMPACT	Comparative Activity Of Carbapenem Testing
CRO	Ceftriaxone
CSF	Cerebrospinal Fluid
DD	Disk Diffusion
DDD	Defined Daily Dose
DoH	Departments Of Health
DOT	Days Of Antimicrobial Therapy
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre For Disease Prevention And Control
EQA	External Quality Assessment
ESBL	Extended-Spectrum Beta-Lactamase
EUCAST	European Committee On Antimicrobial Susceptibility Testing
FAO	Food And Agriculture Organization Of The United Nations
FHI360	Family Health International
GARP	Global Antibiotic Resistance Partnership
GDP	Gross Domestic Product
GLASS	Global Antimicrobial Resistance Surveillance System
GLM	Generalized Linear Model
HAI	Hospital-Acquired Infection
HIC	High Income Country
ICU	Intensive Care Unit
IPM	Imipenem
LMIC	Low And Middle Income Country
MDR	Multiple Drug Resistance
MIC	Minimum Inhibitory Concentration
MoH	Ministry Of Health
MORU	Mahidol Oxford Tropical Medicine Research Unit
MRSA	Methicillin-Resistant Staphylococcus Aureus

MSE	Mean Squared Error
NHTD	National Hospital For Tropical Diseases
NPSAR	National Program For Surveillance Of Antibiotic Resistance
OASIS	Outil d'Analyse De Systèmes d'Information En Santé (French) – Analysis Tool For Surveillance Systems In Human And Animal Health
OIE	World Organisation For Animal Health
OUCRU	Oxford University Clinical Research Unit, Viet Nam
PATH	Program For Appropriate Technology In Health
PCA	Principal Component Analysis
PEN	Penicillin
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
SMART	Study For Monitoring Antimicrobial Resistance Trends
SOAR	Surveillance Of Antibiotic Resistance
SXT	Trimethoprim/Sulfamethoxazole
TCC	Ticarcillin/Clavulanic Acid
UK-NEQAS	Uk National External Quality Assessment Service
UMIC	Upper Middle Income Country
US CDC	United States Centers For Disease Control And Prevention
VAN	Vancomycin
VINARES	Viet Nam Resistance
VRE	Vancomycin-Resistant Enterococci
WHO	World Health Organization

List of publications

- Paper: Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam- the VINARES project, 2012-2013 (the Journal of Global Antimicrobial Resistance).
- Presentation: Antimicrobial susceptibility testing results from hospitals in Viet Nam – the VINARES project, 2012-2013 and 2016-2017. Short talk in Oxford Tropical Network (Oxford, UK 2019)
- Presentation: Vu Tien Viet Dung, Anne-lise Tran, Marc Choisy, Rogier Van Doorn, Marisa Peyre. Antimicrobial resistance surveillance system: a systematic review. Poster and presentation at Congress "Printemps de Baillarguet" (Montpellier, April 2017).
- Presentation: Vu Tien Viet Dung, Anne-lise Tran, Marc Choisy, Rogier Van Doorn, Marisa Peyre. Economic evaluation of antimicrobial resistance surveillance system in Viet Nam. Oral presentation and poster in the International Society for Economics and Social Sciences of Animal Health Conference (Montpellier, May 2018).

General introduction

The development of antimicrobial resistance

What we classify today as antibiotics and antimicrobial substances are chemical compounds that bacteria and fungi have been producing for billions of years, before and during the evolution of humans. In addition, synthetically produced compound with antimicrobial activity are also included in this definition. Since the discovery of antibiotics, innumerable human lives have been saved from various infections, from common conditions such as urinary tract, skin and soft tissue infections, and pneumonia through to life-threatening conditions such as endocarditis, meningitis and sepsis [1]. Without antibiotics, routine and advanced medical procedures such as cancer treatment, organ transplants and open-heart surgery can be complicated with high risk of infection [2].

As predicted by Alexander Fleming, who discovered penicillin, antimicrobial resistance (AMR) evolved alongside antibiotics, a phenomenon that was also discovered soon after the discovery of antibiotics: clinical penicillin resistance was described within 10 years after its wide-scale introduction [3]. AMR is a naturally occurring evolutionary phenomenon in response to exposure to antimicrobials. Resistance conferring genes have been described in ancient DNA from far before the use of antimicrobials by humans [4]. All microorganisms, including bacteria, viruses, parasites and fungi have evolved resistance against the antimicrobial agents humans are using to treat their infections, and this hinders successful treatment of the most important human infections such as malaria, HIV/AIDS and tuberculosis. Throughout this thesis I will focus on bacteria and antimicrobial resistance among bacteria only, excluding mycobacteria.

The spread of AMR over the world

The widespread use of antibiotics in humans and animals can potentially lead to a form of ecological imbalance whereby resistant strains survive and spread globally and across populations more efficiently than sensitive strains [5]. In addition to the antibiotic consumption in human and animals, a number of other factors also contribute to the world-wide increase of antimicrobial resistance among bacteria, including inadequate healthcare diagnostics capacity and infection control practices, lack of clean water and effective sewage systems and high population densities [6]. The spread and persistence of resistant bacterial species in the agricultural industrial complex also present a great challenge for the control of AMR attributed by complex and interconnected factors including antimicrobial usage and biosecurity and disease control practices on farms [7]. AMR has become a worldwide problem that was further enhanced by increasing transmission through movement of people, animals and food across international boundaries [8]. Resistance has made infections more difficult or impossible to treat, has resulted in increased mortality, prolonged illness in people and animals, increased healthcare costs, and production losses in agriculture, livestock and aquaculture [9,10]. Therefore, an integrated and multi-sectoral one-health approach to combat AMR has been proposed in the literature [11].

The health and economic impact of AMR

The problems caused by AMR through reducing treatment options are the main source of global concern for population health, healthcare systems, and national income [12]. The increases in number and global distribution of resistant pathogens pose a huge threat to global health; resistant infections frequently result in longer hospital stays, higher medical costs, and increased mortality. The Review on Antimicrobial Resistance reports that by 2050, there will be ten million deaths a year attributable to AMR [1]. Despite criticism on the assumptions and methodologies used for estimating the burden of AMR [13], these estimates continue to be quoted to show the size of the burden that can be caused by AMR. However, there is still a large gap in our understanding of the burden of AMR due to the limited and unreliable data available, particularly from low- and middle-income countries (LMICs) [14]. The contribution of use of antimicrobials in livestock production on the burden of resistance for public health is also not quantified yet [15,16].

With a higher incidence of infectious diseases, often poorly functioning public health infrastructure, unrestricted and poorly regulated antibiotic sales and use, and lack of reliable

AMR surveillance data, the burden of AMR is likely to be higher in LMICs [17–19], including Viet Nam. This can also have consequences to other parts of the world because globalization increases the vulnerability of any country to diseases occurring in other countries [20] and international travel is a risk factor for the acquisition of infections with multidrug-resistant bacteria [21,22].

Compared to the 23,000 deaths (7 per 100 000 inhabitants) estimated to be attributable to drug resistant bacterial infections in the USA [23] and the 25,000 deaths (5 per 100 000 inhabitants) in the European Union [24], much more attributable deaths were estimated in Asia, despite the limited data available from Southeast Asia [25]. In Thailand (population of 66 million), based on retrospective data from hospitals, a total of 38,481 deaths (58 per 100 000 inhabitants) were estimated to be caused by hospital acquired resistant infections alone in 2010 [26].

The World Bank estimated a cost of US$ 1–3.4 trillion each year by 2030 to the global economy if the AMR problem is not contained, and the cost will be the highest for LMICs with significant drops in their economic growth [27]. Based on the framework of the Review on Antimicrobial Resistance' [12], two modelling studies also provided estimated costs of over $14 billion to over $3 trillion in loss attributed to AMR to the global GDP by 2050 [28,29].

AMR in Viet Nam

Located in Southeast Asia, a hot spot for emerging infectious diseases and AMR [19], Viet Nam faces alarming increases in AMR among many organisms with rates among the highest in the region and the world [30].

An analysis of the situation from 2010 and 2013 showed the first overall picture of antibiotic use with unregulated and unrestricted access and increasing burden in Viet Nam [31]. At that time, oral second and third generation cephalosporins were the most commonly sold and prescribed antibiotics, followed by oral broad-spectrum penicillins, macrolides/azalides and fluoroquinolones. Furthermore, with the increasing usage of injectable cephalosporins and carbapenems in hospitals, antibiotics continue to account for a large share in hospital treatment expenditures [31].

Resistance rates have increased among many organisms in the past two decades. For example, an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study, carried out in Asian countries, reported penicillin-resistance to increase from 8% to over 70% between 1995 and 2000 among community-acquired invasive pneumococci [32]. Between 2004-2006,

methicillin resistance was found among 30% of community acquired and 74% of hospital acquired *Staphylococcus aureus* infections, according to an another ANSORP study [33]. Among *S. aureus* bloodstream infections, 19% were found to be methicillin resistant in 2008-2009 (n=80) [2].

The Comparative Activity of Carbapenem Testing (COMPACT) II study found that high rates of resistance were also reported among 1,260 Gram-negative pathogens isolated from hospitalized patients at 20 centres in five Asia-Pacific countries including 3 in Viet Nam [34]. Data from Viet Nam showed the proportion of Enterobacteriaceae producing extended-spectrum beta-lactamase (ESBL) was 44% among isolates from non-critical care and 81% from critical care patients (n = 71) [34]. Carbapenem resistance in *Pseudomonas aeruginosa* and *Acinetobacter baumannii* was also detected in particularly high proportions in this study, (47%, 42/90) and (89%, 17/19), respectively. There was a dramatic increase in nalidixic acid resistance from 4% to 97% among 1,393 isolates of *Salmonella enterica* serovar Typhi isolated in 4 hospitals in southern Viet Nam between 1993 and 2005 [35].

There is an overall consensus among the political and medical leadership on the serious and growing problem caused by AMR in Viet Nam. A National Action Plan to combat AMR has been approved for the 2013-2020 time period, which outlines the importance of systematic surveillance systems to monitor antibiotic use and resistance [31]. This is also in accordance with the Global Action Plan on Antimicrobial Resistance launched by the World Health Organization (WHO) in the year 2015 [36].

AMR surveillance: a critical element for efficient AMR control

Widely acknowledged as one of critical components in the global and national response to control AMR, there have been a number of international and national efforts to implement AMR surveillance systems / activities. Strengthening evidence-based decision-making through enhanced surveillance and research is one of the five strategic objectives of the Viet Nam National Action Plan and the Global Action Plan on Antimicrobial Resistance [36]. WHO recommended that a national AMR surveillance system should be developed in every member state to systematically collect and analyse AMR data for defined key organisms in healthcare and community settings, and to detect and report emerging resistance of public health concern.

The United States Centers for Disease Control and Prevention (US CDC) have defined public health surveillance as “the ongoing, systematic collection, analysis, interpretation, and

dissemination of data regarding a health-related event for use in public health action to reduce morbidity and mortality and to improve health" [37]. An effective surveillance system therefore must provide chronological data that are consistent and comparable across sites and regions and accurately describe and monitor a health event to inform timely control actions [38].

The strategic objective of surveillance in the Global Action Plan was consolidated through the WHO's establishment of the Global Antimicrobial Resistance Surveillance System (GLASS) to enable the collection of standardized, comparable and validated data on AMR to support the global and national action plans to combat AMR [39]. Strengthening global AMR surveillance is critical to inform global strategies, monitor the effectiveness of public health interventions, and detect new trends and threats [8]. According to US CDC recommendations, an AMR surveillance system should tracks changes in microbial populations, permits the early detection of resistant strains of public health importance, and support the prompt notification and investigation of outbreaks [37]. Data from surveillance can help countries to detect the emergence of AMR and provide necessary information to guide clinical decision-making and inform treatment guidelines, identify target populations, trends over time and informs the development and implementation of policy and interventions and serve as a benchmark for measuring their impact [27].

AMR surveillance worldwide

Soon after the recognition of the emergence of resistance, surveillance has been set up to monitor resistance as part of disease-specific programs such as for tuberculosis, malaria, HIV/AIDS and influenza. Surveillance programs targeting resistance among important bacterial pathogens are more recent. The first report from WHO in 2014 shows a diverse picture of the status of AMR surveillance worldwide [8]. By 2014, accross the WHO regions, longstanding regional surveillance and collaboration had only been established in the European Region and the Region of the Americas. In other countries, there were only individual surveillance sites or programs with small numbers of tested isolates per bacterium. AMR surveillance in most countries is based on routine samples often taken from hospitalized patients and as microbiological investigations are often underused and reserved for patients with more severe or unresponsive illness, has an over-representation of severe infections and includes both community- and hospital acquired infections [8].

Following the WHO report on surveillance, GLASS was lauched and, as of December 2018, had 71 countries enrolled as shown in a report on the early implementation of GLASS [40].

Data on selected priority bacteria causing human infections including *Acinetobacter spp., Escherichia coli, Klebsiella pneumoniae, Neisseria gonorrhoeae, Salmonella spp., Shigella spp., S. aureus*, and *Streptococcus pneumoniae* were collected through a case-finding surveillance system. This system focuses on priority specimens including blood, urine, stool, and cervical and urethral specimens sent to laboratories for clinical purposes and accompanied by population data such as the overall number of patients tested per specific specimen, age, gender and infection origin which can be used to define whether the infection has been contracted in hospital or from the community. The increasing number of countries enrolled in this system has shown a collective understanding and active participation of countries in the global effort to control AMR [40].

Since AMR has now become a worldwide problem not only for human but also animal health, international recommendations have been made by The Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (OIE) and WHO on integrated surveillance systems in humans, food-producing animals and food –commonly referred to as One Health surveillance [41–44]. In 2014, this integrated surveillance has only been initiated in 9 high income countries [8], e.g. DANMAP of Denmark [45] or NORM/NORMVET of Norway [46].

Challenges in AMR surveillance

The WHO report from 2014 also pointed out the gaps in current AMR surveillance [8]. Although there have been successful surveillance programs on specific bacterial pathogens, many gaps and challenges remain, including the lack of surveillance for a number of important common pathogens, the lack of common standards for methods, data sharing, and coordination between the programs. Other reports also pointed out limitations inherent in most surveillance systems, including the conventional laboratory-based ones, such as the undetermined nature of the isolate (causative, colonizing or contaminant), the lack of information on the source and type of infection (community or hospital acquired), or duplication of microbiological reports [47,48]. Additionally, current AMR surveillance programs are limited, as clinical and demographic metadata, which are important for better understanding of relevance and representativeness, are often lacking [38]. Most AMR surveillance reports are from Europe. A recent review showed many variations in the surveillance protocols including the types of microbiological samples monitored and the criteria for susceptibility intepretation in 42

regional and national systems in 20 countries. Importantly, none of these systems collected outcome data; and most were using the proportion of resistant isolates as one and often the only indicator (in 43% of systems) [49].

GLASS does not recommend the use of laboratory-based surveillance only, which has nonetheless been very commonly used to monitor AMR, as this approach does not provide information of the population. GLASS recommends 2 main types of surveillance approaches, which should include data on AMR combined with patient and microbiological information: case finding based on priority specimens sent routinely to laboratories (passive surveillance) and case-based surveillance of clinical syndromes (active surveillance) [39]. The former approach allows clinical data to be combined with microbiological data, which provides critical elements to ensure meaningful recommendations to take actions (e.g. monitoring, evaluation and de-duplication of data). 40 national reports were sent to GLASS in the first data call in 2017, which included 5 (12.5%) sample-based (provide both basic insight into patterns and the extent of AMR in the tested populations) and 35 (87.5%) isolate-based (provides data on resistance patterns within the bacterial population) systems [50]. However, this additional collection of data also requires additional investment of time and resources compared to the passive laboratory-based systems. In a recent study using GLASS recommendations, the collected data were shown to be informative for developing antimicrobial treatment guidelines for patients suspected of having bacteremia [47]. Since additional clinical and antimicrobial consumption data were also collected, this program could provide useful information on the attributable burden of AMR including mortality and costs.

AMR surveillance evaluation

There is limited literature on the evaluation of different aspects of AMR surveillance systems. The WHO, FAO and OIE have recently released a framework and recommended indicators for monitoring and evaluation of the Global Action Plan on AMR, which also contains indicators for the surveillance component. Surveillance related output indicators mainly include countries that report to GLASS and the percentage of hospitals where AMR data are collected on a regular basis to local prescribing hospital-based physicians, at the regional or local level [51]. There are a small number of individual studies that evaluated the performance and effectiveness of local AMR surveillance systems using various and inconsistent evaluation approaches [52–55].

Evaluation is "*the systematic and objective assessment of the relevance, adequacy, progress, efficiency, effectiveness and impact of a course of action, in relation to objectives and taking into account the resources and facilities that have been deployed*" [56]. Evaluation of surveillance systems is critically important because it can assess if the systems have been effective in achieving the predefined surveillance objectives and if they have performed in an efficient manner [57]. The costs of setting up and maintaining a surveillance system need to be justified against the benefits that data generated from the system can provide. Evaluation can help identify areas for improvement in surveillance methods and result in cost savings for the surveillance system [58]. Evaluation of human health surveillance systems typically includes an assessment of a range of attributes as seen in several existing generic guidelines [59–61]. For example, the guidelines developed by the US CDC suggest ten attributes for evaluation: simplicity, flexibility, data quality, acceptability, sensitivity, positive predictive value, representativeness, timeliness, stability and usefulness [59]. Studies evaluating surveillance systems often focused on a subset of attributes deemed relevant for the context under evaluation [57]. A description of the structure of a surveillance system has to be derived in order to understand the surveillance process, select relevant attributes and provide relevant recommendations [62].

Problem statement for the research included in my thesis

In Viet Nam, there have been several AMR surveillance programs since the late 1980s with varying numbers of participating hospitals, some of these programs were supported by international organizations. These include the National Program for Surveillance of Antibiotic Resistance (NPSAR), the Global Antibiotic Resistance Partnership (GARP), Surveillance of Antibiotic Resistance (SOAR), Viet Nam Resistance (VINARES) I and II, and the current National AMR Surveillance Network (supported through the Fleming Fund pilot and country grant and the Global Health Security Agenda).

VINARES was initiated in 2012 as a collaboration between the Ministry of Health, the National Hospital for Tropical Diseases, the Vietnamese Infectious Diseases Society, the Oxford University Clinical Research Unit, Viet Nam (OUCRU) and Linköping University, Sweden, together with 16 hospitals across the country. VINARES aimed to support the development of effective antimicrobial stewardship and strengthen national evidence-based control of antibiotic use in the country. In 2016, the second generation of VINARES was started and the

network is now formally recognized by the Ministry of Health as the National AMR Surveillance Network. Despite the successful continuation and upgrading of the VINARES network to the national network, there has not been any evaluation of past AMR surveillance systems in the country.

Surveillance is among the key strategies in the National Action Plan to combat AMR. Despite initial achievements in AMR data collected from the hospital networks, these data have been discontinuous and mostly dependent on external funding for data submission and quality control. Given the already tightened healthcare budget allocation in a LMIC setting like Viet Nam, identifying conditions under which the national surveillance system would perform efficiently and effectively in achieving the surveillance objectives will be critical for the implementation and evaluation of the National Action Plan. Evaluation of AMR surveillance systems in Viet Nam will provide practical data for the government and foreign development partners to justify their resource allocation and make appropriate decisions on further investments on the surveillance system in the country. The results of evaluation will also be useful for improving the design of the system to make it more efficient and effective.

In addition, through the viewing and analysis of the data collected from the AMR surveillance programs, it can be seen that these data currently do not contain population metadata and patient clinical information required to identify the origin of infection. Therefore, AMR data cannot be separated into hospital-acquired infections (HAI) and community-acquired infections (CAI). This issue, together with likely over-representation of severe infections leads to a problem of overestimation of resistant proportions for use in informing the development and updating of national and local antibiotic treatment guidelines. If this is not interpreted and used appropriately, data generated from existing AMR surveillance systems can contribute to over-prescription of broad-spectrum and reserved antibiotics in response to the reported higher resistance rates.

Research aim and objectives

The research presented in this thesis aims to systematically evaluate the AMR surveillance system (AMRSS) in Viet Nam and develop an AMRSS model that is effective and cost-effective in providing an accurate and representative estimate of resistant proportions among patients with CAI.

Specific objectives are to:

- Systematically review the literature to obtain an overview of the current status of AMR surveillance and identify relevant technical and operational aspects and effectiveness attributes affecting system performance in the studies reporting the implementation and evaluation of AMR surveillance systems in the world
- Systematically evaluate the AMR surveillance system in Viet Nam in two periods 2012-2013 and 2016-2017 to identify the important attributes affecting surveillance performance in the country, using data collected from VINARES and applying two evaluation tools that have been considered as providing a flexible and detailed framework for evaluation of surveillance systems.
- Analyse the antimicrobial susceptibility testing results that have been submitted to VINARES in 2012-2013 and 2016-2017 to provide baseline data and describe trends in the resistant proportions in Viet Nam.
- Develop a classification model to estimate the proportion of patients by origin of infection (CAI or HAI) and resistant proportions specific to each group for the VINARES data to be used in optimizing the effectiveness of AMR surveillance system in Viet Nam.
- Optimize the effectiveness of AMR surveillance in Viet Nam in providing accurate and representative AMR data for CAI patients by varying the key system parameters representing the important surveillance attributes.

Research hypotheses and questions

Hypothesis 1: The proportion of antibiotic resistance for informing local treatment guidelines is overestimated in the current passive laboratory-based surveillance system since microbiology diagnostics are under-used and often reserved for more severe and unresponsive cases and no metadata are collected to distinguish between community- and hospital-acquired infections (HAI), while the proportion of antibiotic resistance in HAI is much higher than in CAI.

Research question 1: How to estimate the proportion of resistance to inform local treatment guidelines for patients with CAI?

Hypothesis 2: Human and economic resources for AMR surveillance in Viet Nam are not adequately allocated. The result (resistant proportion) could be affected by the number of

hospitals and the types of hospitals (national, specific and provincial) participating in the surveillance system.

Research question 2: How can we optimize the effectiveness and cost and effectiveness of AMR surveillance system in Viet Nam?

Thesis outline

This thesis consists of four chapters, each of these was written in a manuscript format.

In Chapter 1, I present the results of a systematic literature review of the AMR surveillance systems in public health that have been implemented globally. I summarize the information on all identified AMR surveillance systems, identify the gaps in the current literature on AMR surveillance overall and highlight the lack of systematic evaluation of such systems to help improve their performance and effectiveness.

Following the findings from Chapter 1, in Chapter 2 I focus on evaluation of an AMR surveillance system in Viet Nam (VINARES) during two time periods, 2012-2013 and 2016-2017. Despite the existence of several surveillance projects in the past, VINARES was selected for evaluation in this chapter because of available information on the organization, functioning, costs and performance of system in the two time periods. In this chapter I point out the strengths and weaknesses of this surveillance network and identify the areas for improvement that can be considered for the National AMR Surveillance Network.

In Chapter 3 I describe the findings from the analysis of antimicrobial susceptibility testing data collected in VINARES in the two time periods. I present the resistant proportions of nine priority pathogen-antimicrobial combinations and a comparison of data between the two time periods. These data can be used as a baseline for monitoring the AMR trends and evaluation of interventions to control AMR in Viet Nam.

In Chapter 4 I assess the effectiveness and cost of an AMR surveillance system in Viet Nam by varying the key system parameters. A number of potential AMR surveillance models were generated using baseline data from VINARES. Modelling results show how the effectiveness of an AMR surveillance system changes when the numbers of the different types of participating hospitals change and under what conditions a balance between effectiveness and costs is reached to give the best outcome in the most cost-effective manner.

In each chapter, I have included a discussion on the significant findings and study strengths and limitations. In the concluding chapter, key research findings throughout the PhD program are recapped and linked back to the research hypotheses and questions stated at the beginning of the study. I conclude with a number of recommendations for future research and implementation of AMR surveillance in Viet Nam and beyond.

Chapter 1

A systematic review of antimicrobial resistance surveillance systems

1.1. Introduction

The development of antimicrobials have put an environmental pressure on bacteria selecting mutations allowing them to survive. This evolution results in antimicrobial resistance that hinders the treatment of infectious diseases. The use of antimicrobials, whether appropriate or inappropriate, is considered the main driving force speeding up the development of resistance among bacteria against antimicrobials [2]. Examples of inappropriate use include using antimicrobials for growth promotion in agriculture, using antimicrobials for viral infections or naturally resistant bacterial species, using too broad spectrum antimicrobials, using an incorrect dose or using antimicrobials for an insufficient or excessive duration [63]. Resistance among bacteria causing infections difficult or impossible to treat, results in increased mortality, prolonged illnesses in people and animals, increased healthcare costs, and production losses in agriculture, livestock and aquaculture [10,64].

Surveillance has long been recognised as one of the important tools to understand the problem and support the fight against AMR [65]. The US CDC have defined public health surveillance as "the ongoing, systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event for use in public health action to

reduce morbidity and mortality and to improve health" [37]. An effective surveillance system therefore must provide chronological data that are consistent and comparable across sites and regions and accurately describe and monitor a health event to inform timely control actions [38]. As stated by US CDC, surveillance of antimicrobial resistance (AMR) tracks changes in microbial populations, permits the early detection of resistance, and supports the prompt notification and investigation of outbreaks [37]. Surveillance provides information for clinical decision-making, guides policy recommendations and to assess the impact of resistance containment interventions [37].

Surveillance systems usually employ a passive and/or active approach [66]. Passive surveillance is a widely used approach, defined as "the ongoing monitoring of infections, based on diagnostic isolates submitted from clinically diseased individuals or groups". This approach is usually less costly, however, many biases can arise including lack of representativeness (collected data may not reflect the characteristics of the target populations), variation in reporting practices, outbreak occurrence, the issue of multiple isolates per individual being submitted, different laboratory methods, and lack of data on useful denominator information (e.g. number of samples tested but found negative). On the other hand, active surveillance, defined as "the planned collection of targeted and representative samples" is usually more costly but can provide more representative estimates of the target populations [66].

Under WHO classifications of surveillance systems [67], passive surveillance involves regular reporting of disease data by all institutions that see patients (or test specimens) and are part of a reporting network, while active surveillance is defined as the planned collection of targeted and representative samples. A third type of surveillance was also considered, called sentinel surveillance. This is used when high-quality data are needed but cannot be obtained from the passive surveillance system; it is set up by deliberately selecting the reporting sites that have high probability of seeing cases of the disease under question.

In general, objectives of AMRSS at the national level can be grouped into the following categories [68]:

- to monitor trends in infection and resistance,
- to develop standard treatment guidelines,
- to assess resistance containment interventions,

- to provide an early alert for novel resistant strains,
- to promptly identify and control outbreaks.

Moreover, an AMRSS can be established to link information on AMR from different sectors, such as human, animal, food, agriculture, environment, and data on antimicrobial consumption in human and animal populations and environmental antimicrobial usage [69]. Another objective of AMRSS was to study susceptibility patterns of bacteria to targeted antimicrobials.

In response to the alarming increase of AMR, WHO has launched the Global Action Plan on Antimicrobial Resistance in the year 2015 with five strategic objectives; one of which is to strengthen evidence-based decisions through enhanced surveillance and research [36]. Following this, the Global Antimicrobial Resistance Surveillance System (GLASS) was launched by WHO in the same year to enable the collection of standardized, comparable and validated data on AMR to support the global and national action plans to combat AMR [39]. As emphasized by WHO, there is still a big gap in our understanding of the spread, evolution and impact of AMR; and strengthening global AMR surveillance is critical to inform global strategies, monitor the effectiveness of public health interventions, and detect new trends and threats [8].

Characteristics of a relevant AMR surveillance system were the topic of a discussion panel in 2000, consisting of experts in clinical microbiology, infectious diseases, epidemiology, statistics, antimicrobial development. These systems *"should be able to detect significant differences and shifts in susceptibility to various antibacterial agents, and the information derived from them should reach as many interested parties as possible in a timely manner"*, whether focusing especially on few organisms or covering many diseases or organisms [65]. Thus, AMR surveillance systems need to be sufficiently sensitive to identify changes in susceptibility to inform treatment decisions and interventions to control resistance. The information obtained from such surveillance systems can help identify any new trends and emergence of resistance in targeted pathogens and agents and inform alternative therapies for treatment and strategies to control and prevent resistance from further development and spread [65].

The requirements for an effective AMR surveillance system have been identified for nearly two decades, consisting of components related to the program design, methodology, clinical aspects, and dissemination [38]. More precisely, an effective

program should (1) be longitudinal, comprehensive, independent and incorporating a quality assurance system for program management; (2) have standardized specimen and testing protocols, centralized laboratory testing, quantitative determination for wide range of antimicrobials, determination of resistance mechanisms, assessment of antimicrobial usage and resistance, and quality control for testing and data analysis; (3) have guidelines for inclusion of patients and specimens, collection and integration of clinical and demographical data and guidelines for intepretation of surveillance data; (4) have easy access to up-to-date data and ability to perform custom analyses. AMR surveillance also should include appropriate denominator data and clinical metadata in order to estimate the proportion of AMR among different pathogens and clinical diagnoses [70].

There have been few reviews on AMR surveillance systems around the world. The most commonly cited review is the one reported by WHO in 2014 which pointed out many gaps and challenges such as a lack of common standards for methods, data sharing, and coordination between the program [8]. There was a more recent systematic review focusing on the methodology of surveillance on AMR and healthcare associated infections; however it focused on European countries only. This review showed that the European systems varied widely in the types of microbiological samples and susceptibility intepretation as well as outcome indicators [49]. In 2018, a review of Ashley E.A. et al. about supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000 highlighted that the biggest challenges faced by these networks has been achieving high coverage, complying with the recommended frequency of reporting and obtaining high quality, representative surveillance data [71].

Therefore we conducted this systematic review of the AMR surveillance systems that have been implemented globally, looking at their organisation, performance and evaluation protocols and outputs. We aimed to identify relevant technical and operational aspects and effectiveness attributes that could affect the performance of AMR surveillance systems around the world, and review the evaluation processes that have been used for these systems.

1.2. Methods

1.2.1. Literature sources and search strategy

A systematic literature search was performed following key principles of PRISMA requirements (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [72] using PubMed, Web of Science and Google Scholar to identify articles. Supplementary table S1.1 listed requirements which were applied and explained those that were not applicable in this systematic review. Searched items were restricted to articles published in English and French (two foreign languages known by the reviewer) until December 31st of 2017.

Four domains were included in the search, with several keywords for each: surveillance ("surveillance or report or monitor"), system ("system or network or program or programme"), antimicrobial ("antibiotic or antimicrobial") and resistance ("resistance or resistant").

Articles from references of selected papers were identified and were subsequently added to the review.

1.2.2. Article selection

Two screening phases were carried out to select articles. In the first phase, articles were screened by titles and abstracts which included AMR surveillance systems information. In the second phase the articles were screened based on the full-text and excluded according to the following exclusion criteria:

1) does not mention any of these terms: antimicrobial, antibiotic, resistance, surveillance;
2) only describes the trend/pattern/distribution of resistant bacteria;
3) only presents results of an AMR surveillance system- not describing the system itself;
4) only describes the techniques/methods for AMR diagnostic;
5) only emphasizes the importance of AMR surveillance system in general, without describing any specific system;
6) only describes the association between the antimicrobial consumption (AMC) and AMR;
7) only describes the treatment of infections caused by resistant bacteria;
8) only presents microbiological information; and

9) a systematic review which did not cover AMR surveillance system organisation and evaluation.

1.2.3. Data selection and analysis

The following data were retrieved from the articles included in the review: surveillance level (international or national), country(ies) included, surveillance type (sentinel, active or passive), surveillance field (human or animal health), collection of antimicrobial consumption data, target of investigation (pathogens, antimicrobial agents and types of microbiological samples), denominator information, laboratory quality control method, performance standard for AST interpretation (Clinical & Laboratory Standards Institute (CLSI) [73], European Committee on Antimicrobial Susceptibility Testing (EUCAST) [74] or local standard) and outcome parameters. For the articles that provided information on the evaluation of the surveillance systems, additional data were retrieved including the type of evaluation (performance, functional or economic), the attributes assessed (representativeness, timeliness, acceptability, flexibility, sensitivity, simplicity, bias, completeness of reporting, level of coverage, protocol quality, quality of data, utility of surveillance data and cost), the evaluation standards, the evaluation methods, and the main evaluation results.

The AMRSS were classified by human versus animal, national versus international, or community versus hospital-based. For each system, the objectives, surveillance methods, strengths and weaknesses were identified based on the information reported in the included articles. The main analysis focused on hospital-based AMRSS and forms the baseline of my PhD project.

1.3. Results

1.3.1. Article selection

1810 articles were identified by the literature search and 197 were retrieved for full text screening. After full-text screening, 127 articles were excluded. Among the excluded articles, 45 articles only present results of an AMR surveillance system, 21 describe the techniques/methods for determining AMR and 17 emphasize the importance of surveillance system.

A total of 79 articles were included in the final review and analysis, including nine 9 citations (Figure 1.1). Among this, 70 systems focused on human health, four on animal

health, and five on both human and animal health. Evaluation of surveillance system was reported for 7 AMRSS.

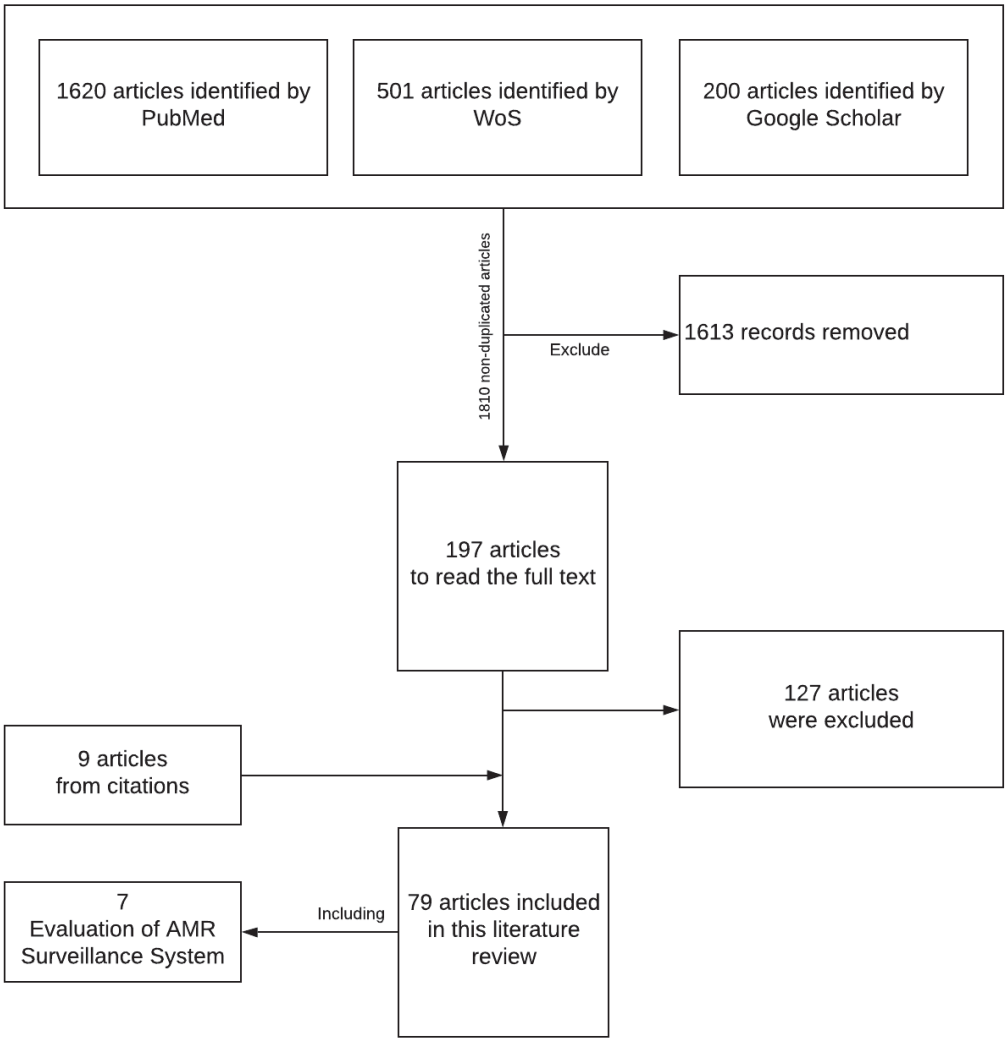


Figure 1.1: PRISMA flow chart diagram of articles selection process in the systematic review

1.3.2. AMR surveillance systems in general

The AMRSS described in this review were started between 1986 and 2011, including 33 still ongoing at the date of publication. The median duration of international active and sentinel AMRSS was 3 years (IQR 2 – 7 years) and 4 (IQR 2 -5) years for passive systems (figure 1.2). National-scale AMRSS had a median of 4 (IQR 2 – 6) and 6 (IQR 3.5 – 7.5) years for active and passive systems, respectively.

Among the 79 systems included in the analysis, the most common objectives were: monitoring trends in infection and resistance (48/79 systems), followed by studying the susceptibility pattern for targeted antimicrobials (22/79 systems). The objective of linking AMR with different sectors was described in 6 systems, including 3 systems investigating the link with AMC and three with food, animal production and admission ward.

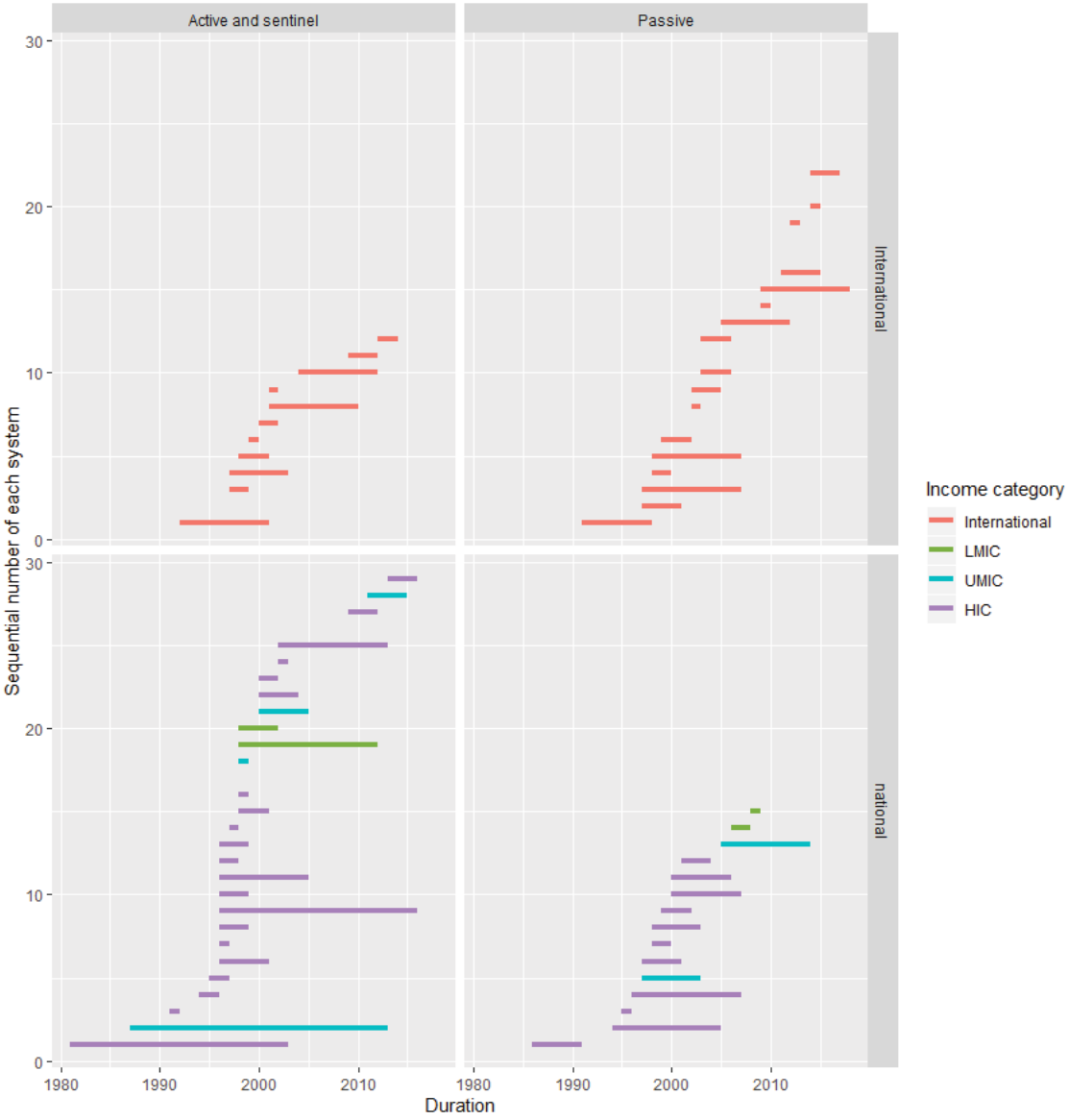


Figure 1.2: Timeline of the published AMRSS from the start to the end date of the surveillance programs or to the year of article publication. LMIC: Low and middle income country; UMIC: Upper middle income country; HIC: High income country

1.3.3. AMR surveillance systems in humans

Among the 75 AMRSS in humans or both humans and animals, 40 and 35 were systems on a national and international scale, respectively. AMC data was collected in 16 systems.

Thirteen international AMRSS collected existing data; 21 acquired new data and one used data from a literature review. The systems that acquired new data used reference laboratories to analyse isolates sent from the participating medical centres or hospitals. Western Europe and Northern America were the two most often represented regions in the surveillance programs. Out of the 40 national systems focusing on humans, 29 systems were based in high-income countries and 11 systems in LMICs (classifications based on world-bank stratifications) [75].

1.3.4. Hospital-based AMRSS

As the overall objective of this thesis focuses on the hospital-based AMRSS, the main analysis focused on 71 such AMRSS (including laboratory and medical centres) (table 1.1; from S01 to S71). These included 34 active, 33 passive and 4 sentinel surveillance systems (table 1.2). The United States were the leading country with 7 national-scaled AMRSS, followed by France (4 AMRSS) (table 1.1). Twenty AMRSS were deployed in more than one continent (including 6 active and 14 passive surveillance systems). Supplementary figures 1a to 1i represent location of countries participating in the largest international systems (S02, S12, S21, S05, S10, S09 and S14).

The most frequently described objectives were monitoring trends in infection and resistance (43 systems), followed by studying the susceptibility pattern of targeted antimicrobials (20 systems) and early alert for novel resistant strains (6 systems) (figure 1.3).

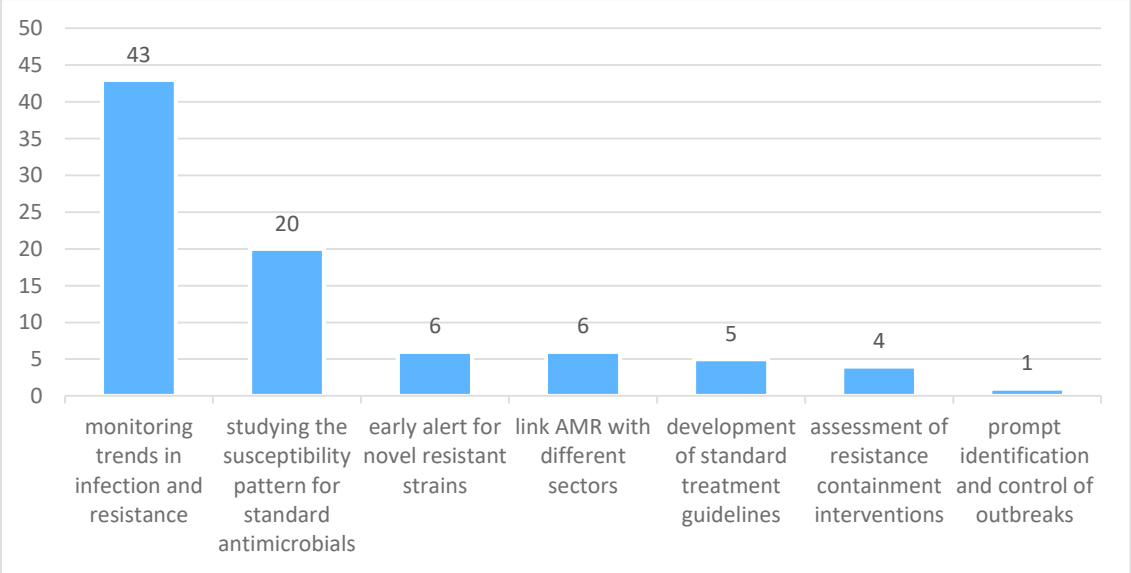


Figure 1.3: Distribution of objectives of AMR surveillance systems. Number of systems were showed.

The number of hospitals in each AMRSS varied from 1 to more than 600. There were four surveillance systems conducting surveillance on food safety together with AMR in humans. AMC data were collected in 14 systems (19%). All these systems were based in Europe and North America. Among them, 12 systems were at national level and two at international level.

There were 9 surveillance systems focusing on one bacterium (4 *N. gonorrhoeae*, 3 *S. aureus*, 1 *A. baumannii* and 1 *S. pneumoniae*). Three of four *N. gonorrhoeae* surveillance systems were sentinel. Enteric pathogens were the most frequent group of bacteria under surveillance (4 systems), followed by respiratory tract pathogens (3 systems). Anaerobes (S52 and S46) and fungi (*Candida spp.*) (S21) were also monitored.

Laboratory quality control was implemented in 35 (49%) systems. Internal and external quality control supports reliability of test results [76]. Among these 35 systems, internal quality control using reference strains was reported in 25 systems: 13 using American Type Culture Collection (ATCC) reference strains [77], and 12 others using other reference strains. Ten systems implemented an External Quality Assessment (EQA) program to ensure quality and comparability across laboratories.

The CLSI performance standards for AST were used in 44 systems. The version of CLSI varied from 1998 to 2013 depending on the systems. The EUCAST performance standard was used as single breakpoint in 6 systems. Two programs in Europe, EARSS and its successor EARS-Net (S07 and S09) collected data from various countries, which used EUCAST, CLSI and local standards to interpret their data. Five systems used two breakpoints to interpret one dataset to validate the results. Two systems in France (S61 and S62) and two in Sweden (S69 and S70) used only their national breakpoint.

Table 1.1: AMRSS identified from the literature review until 31/12/2017

Code	Surveillance system name	Country	Level	Type of surveillance	Start	Duration	Surveillance target
S01	Chemotherapy Alliance for Neutropenics and the Control of Emerging Resistance [78]	North America	International	active	2000	3	Human
S02	International Network for the Study and Prevention of Emerging Antimicrobial Resistance [79]	US and Europe	International	passive	1998	3	Human
S03	Programme to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) [80]	US and Europe	International	passive	2012	1	Human
S04	A study of typhoid fever in five Asian countries: disease burden and implications for controls [81]	Asia	International	passive	2001	1	Human
S05	Central Asia and European Surveillance of Antimicrobial Resistance [82]	Asia and Europe	International	passive	2011	5	Human
S06	Surveillance network for the enteric infections Salmonella and VTEC O157 [83]	Europe	International	active	1997	3	Human
S07	European Antimicrobial Resistance Surveillance System [84]	Europe	International	active	1998	4	Human
S08	European Surveillance of Antibiotic Resistance [85]	Europe	International	sentinel	1999	2	Human
S09	European Antimicrobial Resistance Surveillance Network [86]	Europe	International	active	2001	10	Human
S10	The European Gonococcal Antimicrobial Surveillance Programme [54]	Europe	International	sentinel	2009	4	Human
S11	WHO Western Pacific Regional Programme for Surveillance of Antimicrobial Resistance [87]	World	International	passive	1991	8	Human

S12	The Alexander Project [88]	World	International	active	1992	10	Human
S13	Study on Antimicrobial Resistance in Staphylococcus aureus [89]	World	International	active	1996	1	Human
S14	SENTRY Antimicrobial Surveillance [90]	World	International	passive	1997	5	Human
S15	Meropenem Yearly Susceptibility Test Information Collection [91]	World	International	active	1997	7	Human
S16	ARTEMIS Global Antifungal Surveillance Programme [92]	World	International	passive	1997	11	Human
S17	International Nosocomial Infection Control Consortium (INICC) [93]	World	International	passive	1998	10	Human
S18	Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin [94]	World	International	passive	1999	4	Human
S19	Pan-European Antimicrobial Resistance Using Local Surveillance (PEARLS), Wyeth Pharmaceuticals [95]	World	International	sentinel	2001	2	Human
S20	NosoMed Pilot Survey in the Eastern Mediterranean Area [96]	World	International	passive	2002	2	Human
S21	Antimicrobial Resistance Epidemiological Survey on Cystitis [97]	World	International	passive	2003	4	Human
S22	TARGETed Surveillance Study [98]	World	International	passive	2003	1	Human
S23	Tigecycline Evaluation and Surveillance Trial (TEST) [99]	World	International	active	2004	9	Human
S24	International Daptomycin Surveillance Programmes [100]	World	International	passive	2005	8	Human
S25	Community-Acquired Respiratory Tract Infection Pathogen Surveillance (CARTIPS) [101]	World	International	passive	2009	2	Human
S26	ResistanceMap [102]	World	International	passive	2009	10	Human
S27	Assessing Worldwide Antimicrobial Resistance and Evaluation Programme (AWARE) [103]	World	International	passive	2012	1	Human
S28	International Network For Optimal Resistance Monitoring (INFORM) [104]	World	International	active	2012	3	Human

S29	In Vitro Activity of Oral Antimicrobial Agents against Pathogens Associated with Community-Acquired Upper Respiratory Tract and Urinary Tract Infections [105]	World	International	passive	2012	2	Human
S30	Minocycline activity tested against Acinetobacter baumannii complex, Stenotrophomonas maltophilia and Burkholderia cepacia species complex isolates [106]	World	International	active	2013	1	Human
S31	Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) [107]	World	International	passive	2014	2	Human
S32	International Solithromycin Surveillance Programmes [108]	World	International	passive	2014	1	Human
S33	Surveillance of antimicrobial resistance at a tertiary hospital in Tanzania [55]	Tanzania	national	active	1998	5	Human
S34	RESISTNET Surveillance Program in Brazil [109]	Brazil	national	active	1998	2	Human
S35	Canada surveillance of antimicrobial resistance in respiratory tract pathogens [110]	Canada	national	active	1994	3	Human
S36	Canadian Integrated Program for Antimicrobial Resistance Surveillance [111]	Canada	national	active	2002	12	Both
S37	Gonococcal Isolate Surveillance Project [112]	US	national	passive	1986	6	Human
S38	New Jersey AMR surveillance [113]	US	national	active	1991	2	Human
S39	National Antimicrobial Resistance Monitoring System [114]	US	national	active	1996	6	Both
S40	Intensive Care Antimicrobial Resistance Epidemiology [115]	US	national	active	1996	2	Human
S41	AFHSC-GEIS network [116]	US	national	active	1998	2	Human
S42	Drug-resistant Streptococcus pneumoniae surveillance [117]	US	national	active	1998	1	Human
S43	Antimicrobial Resistance Monitoring and Research [118]	US	national	active	2009	4	Human

S44	China Gonococcal Antimicrobial Susceptibility Programme [119]	China	national	sentinel	1987	27	Human
S45	CHINET surveillance system [120]	China	national	passive	2005	10	Human
S46	AMR surveillance network Indian Council of Medical Research [121]	India	national	passive	2008	2	Human
S47	Japan nosocomial infections surveillance [122]	Japan	national	passive	2000	8	Human
S48	Korean Nationwide Surveillance of Antimicrobial Resistance [123]	South Korea	national	active	1997	2	Human
S49	Nepalese AMR programme [124]	Nepal	national	active	1998	15	Human
S50	MRSA multi-centre surveillance [125]	Pakistan	national	passive	2006	3	Human
S51	Laboratory-based Antimicrobial Drug Resistance surveillance program [126]	Singapore	national	active	2006	1	Human
S52	Taiwan Surveillance of Antimicrobial Resistance [127]	Taiwan	national	passive	1998	3	Human
S53	National Antimicrobial Resistance Surveillance Thailand [128]	Thailand	national	active	2000	6	Human
S54	Australian Gonococcal Surveillance Programme [52]	Australia	national	active	1981	23	Human
S55	The surveillance network (TSN) in Australia [129]	Australia	national	active	1998	4	Human
S56	Passive surveillance of antimicrobial resistance in Queensland public hospitals [130]	Australia	national	Active	2002	2	Human
S57	Bulgarian Surveillance Tracking Antimicrobial Resistance [131]	Bulgaria	national	passive	1997	7	Human
S58	Surveillance for Antimicrobial Resistance in Croatia [132]	Croatia	national	active	1996	4	Human
S59	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme [45]	Denmark	national	active	1996	21	Both
S60	English Surveillance Programme for Antimicrobial Utilization and Resistance [133]	UK	national	active	2013	4	Human

S61	ABU and ABR surveillance system in CHU de Besançon [134]	France	national	passive	1998	6	Human
S62	Network of private medical analysis laboratories [135]	France	national	active	2000	5	Human
S63	Surveillance of antimicrobial use and antimicrobial resistance in intensive care units [136,137]	Germany	national	active	2000	3	Human
S64	The Greek Network for the Surveillance of Antimicrobial Resistance [138]	Greece	national	passive	1995	2	Human
S65	Hungarian ABR monitoring system [139]	Hungary	national	passive	1997	5	Both
S66	Infectious diseases Surveillance Information System [53]	Netherlands	national	passive	1996	12	Human
S67	Norwegian monitoring program of antimicrobial resistance in feed, food, and animals [46]	Norway	national	passive	2000	7	Human
S68	Susceptibility to the Antimicrobials Used in the Community in España [140]	Spain	national	active	1996	4	Human
S69	The Swedish Strategic Programme Against Antibiotic Resistance [141]	Sweden	national	passive	1994	12	Both
S70	Surveillance of antibiotic resistance in ICUs in southeastern Sweden [142]	Sweden	national	active	1995	3	Human
S71	Surveillance of MRSA bacteraemia in the UK [143]	UK	national	passive	2001	4	Human
S72	Community-Based Surveillance of Antimicrobial Use and Resistance in Resource-Constrained Settings [144]	Asia and Africa	International	passive	2002	4	Human
S73	Bacterial Infections and Antibiotic-Resistant Diseases Among Young Children in Low Income Countries [145]	Asia and Africa	International	passive	2014	4	Human
S74	Antibiotic Resistance in the Mediterranean Region [146]	Mediterranean	International	passive	2003	4	Human

S75	Colombian Integrated Program for Antimicrobial Resistance Surveillance [147]	Colombia	national	active	2011	4	Animal
S76	Foodborne Diseases Active Surveillance Network [148]	US	national	active	1996	10	Human
S77	Japanese Veterinary Antimicrobial Resistance Monitoring Program [149]	Japan	national	passive	1999	4	Animal
S78	Surveillance of antimicrobial resistance in bacteria from animal [150]	France	national	active	1996	12	Animal
S79	VAV surveillance network [151]	Spain	national	active	1996	6	Animal

Note: S01 to S71: hospital-based AMRSS; S72-S79: other AMRSS

Table 1.2: Summary of the main characteristics of AMRSS worldwide

Characteristic	Category	n (%)
Surveillance level	National	39 (55)
	International	32 (45)
Type of surveillance	Active	34 (48)
	Passive	33 (46)
	Sentinel	4 (6)
Pathogen included	*Neisseria gonorrhoeae*	4 (6)
	Acinetobacter baumannii	1 (1)
	Staphylococcus aureus	3 (4)
	Streptococcus pneumoniae	1 (1)
	S. aureus, E. coli, K. pneumoniae	1 (1)
	Gram-negative bacteria	1 (1)
	S. aureus / S. pneumoniae and other Gram-positive bacteria	2 (3)
	Enteric bacteria	4 (6)
	Respiratory tract bacteria	3 (4)
	Enterobacteriaceae	2 (3)
	Campylobacter	1 (1)
	Candida	1 (1)
	All microbiological data	47 (67)
Antimicrobial consumption data	Collect new data	12 (17)
	Use data from other sources	2 (3)
	No antimicrobial consumption data	57 (80)

Standard for AST interpretation	CLSI	44 (62)
	EUCAST	6 (8)
	Local standard	3 (4)
	CLSI and EUCAST	2 (3)
	CLSI and local standard	3 (4)
	CLSI, EUCAST and local standard	2 (3)
	Unspecified	11 (15)
Indicators of resistance	Proportion of resistant isolates	61 (86)
	Proportion of resistance in population	3 (4)
	Number of resistant cases	1 (1)
	Unspecified	6 (8)
Denominator data	Number of tested isolates	56 (79)
	Number of admission and tested isolates	4 (6)
	Number of negative results and tested isolates	1 (1)
	Number of blood culture, bed capacity, admission and tested isolates	4 (6)
	Unspecified	6 (8)
Clinical information	Yes	18 (25)
	No	53 (75)
Data de-duplication	Yes	29 (41)
	Unspecified	42 (59)
Types of microbiologic sample	Blood	3 (4)
	Blood and cerebrospinal fluid	3 (4)
	Bloodstream, skin, respiratory, urinary tract	1 (1)
	Sputum	1 (1)
	Urine	1 (1)
	Stool	1 (1)

	All	58 (82)
	Unspecified	3 (4)
Performing AST location	In reference/central laboratory	20 (28)
	In local laboratory	51 (72)
Quality control	External Quality Assessment	10 (14)
	Reference strains	13 (18)
	Yes (but method unspecified)	12 (17)
	Unspecified	36 (51)

Once isolates were collected, they were either analysed in the laboratory of participating hospitals/medical centres (51 systems – 70%), or they were sent to a central laboratory for analysis (20 systems – 30%).

Sixty-one AMRSS calculated resistant proportions among tested isolates and three systems estimated the resistant proportion in the population where population information was collected. Sixty-five AMRSS collected the number of isolates as denominator data, among them two systems also collected number of negative results and 8 systems collected other denominators (number of admissions, bed capacity, number of blood cultures). One fourth (18 AMRSS) collected the clinical information of patients. The lack of clinical and denominator information did not allow the analysis of the origins of the resistant isolates.

The relation between the type of surveillance, the location of performing AST and the scale of AMRSS with other characteristics are shown in the cross tables (table 1.3). In general, active surveillance systems were more likely to be organised at national than international level (24 (62%) versus 10 (31%)). The AMRSS which analysed the isolates in a central laboratory were more likely to focus on specific pathogens than those analysing in a local laboratory (13 (65%) versus 17 (34%)). The former systems also performed data de-duplication more frequently (12 (60%)) than the latter (17 (34%)). More national AMRSS collected antimicrobial consumption data than international systems (10 (26%) versus 4 (13%)).

Table 1.3: Characteristics of AMRSS by type of surveillance (active versus passive); by laboratory location and by surveillance level. Chi-squared test was used to compare two groups.

	Type of surveillance		
	Active (n=34)	Passive (n=33)	p-value
Laboratory location: reference/central laboratory	8 (24%)	10 (30%)	0.73
Antimicrobial consumption	7 (21%)	7 (21%)	1.00
Data de-duplication	14 (41%)	13 (39%)	1.00
Specific pathogen	13 (38%)	9 (27%)	0.49
Quality control	15 (44%)	18 (55%)	0.54
Clinical information	9 (26%)	8 (24%)	1.00
	Laboratory location		
	In reference/central laboratory (n=20)	In local laboratory (n=51)	p-value
Antimicrobial consumption	2 (10%)	12 (24%)	0.34
Data de-duplication	12 (60%)	17 (34%)	0.07
Specific pathogen	13 (65%)	17 (34%)	0.03
Quality control	10 (50%)	25 (50%)	1.00
Clinical information	7 (35%)	11 (22%)	0.39
	Surveillance level		
	International (n=32)	National (n=39)	p-value
Active surveillance	10 (31%)	24 (62%)	0.02
Laboratory location: reference/central laboratory	12 (38%)	8 (21%)	0.19
Antimicrobial consumption	4 (13%)	10 (26%)	0.28
Data de-duplication	11 (34%)	18 (46%)	0.45
Specific pathogen	18 (56%)	12 (31%)	0.05
Quality control	18 (56%)	18 (46%)	0.54
Clinical information	7 (22%)	11 (28%)	0.74

Note: p-value is calculated from chi-squared test for the difference between two proportions

Evaluation of AMR surveillance system

Evaluation of performance, process and cost was reported for seven AMR surveillance systems (table 1.1 - S10, S33, S38, S39, S42, S54 and S66). Performance evaluation assessed the effectiveness aspects of the surveillance systems, while process evaluation measured how well the systems were structured and functioned. Altogether, the seven evaluations assessed 13 different attributes [59] (table 1.4) . Representativeness was the

most frequently assessed attribute (evaluated in three systems), followed by timeliness, bias, completeness of reporting and cost (two systems each) (figure 1.4).

Two systems in Australia (S54) and the Netherlands (S66) reported using the updated guidelines for evaluating public health surveillance systems from US CDC [59] in their evaluation, other evaluations assessed the attributes according to their needs without using any guidelines. The evaluations used various quantitative and qualitative methods for assessment of the attributes. All but one evaluation assessed two or three attributes, only S02 performed a full performance evaluation using the six effectiveness attributes.

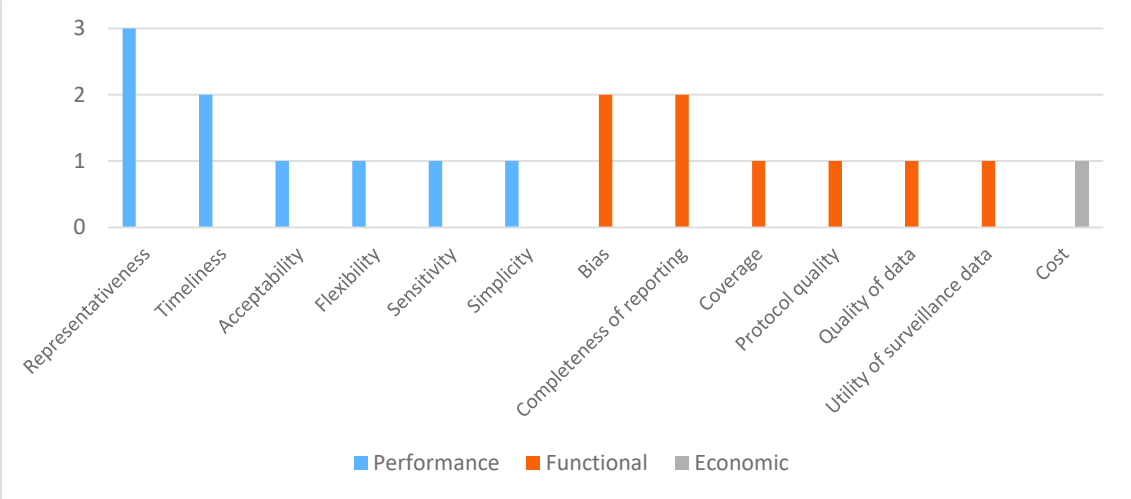


Figure 1.4: Frequency of the type of evaluation attributes used in AMRSS evaluation worldwide

Table 1.4: AMRSS evaluation methods and results

Attribute name	AMRSS Code	Attribute definition in the evaluation	Evaluation method	Attribute assessment results
Representativeness	S54	An AMRSS that is representative accurately describes the resistance pattern over time and its distribution in the population by place and person	Calculate the proportion of number of isolates tested by this system with the total number of gonococcal notifications between 1995 and 2003	Between 1995 and 2003, the total isolates tested annually by Australian Gonococcal Surveillance Programme averaged 63.1% of the total gonococcal notifications in Australia
	S66	Did not define	Compare between all early warning signals of this surveillance system and outbreaks notified by other networks.	Participation was voluntary, which resulted in a non-representative sample of medical microbiology laboratories for the Netherlands.
	S38	The validity of an isolate-based surveillance in estimating rates of infection	Determine the correlation of the number MRSA blood isolates from the surveillance system and the number reported by the hospital for September 1991.	Correlation coefficient r = 0.78, statistically significant. The AMRSS represented well the population.
Sensitivity	S54	The proportion of AMR cases detected by the surveillance system	Examine whether the AGSP tests enough isolates to detect changes in AMR	Over 3,000 isolates were tested each year nationally, but it was difficult to assess whether this number is sufficient to detect significant changes in gonococcal AMR rates in sub-populations.

Simplicity	S54	The simplicity of an AMRSS refers to both its structure and ease of operation	Assess the flow of data in the system (collection, transmission, analysis and reporting)	The surveillance system was relatively simple as all the reference laboratories use standardised testing methods and the common case definition. There was a clear mechanism for data flow through the system.
Timeliness	S54	Timeliness reflects the speed between steps in an AMRSS	Assess the flow of data in the system (collection, transmission, analysis and reporting)	The system had continuously reported on a quarterly and annual basis within six months of the end of the reporting period. This is adequate for reporting on AMR trends.
	S42	The classification of average time to complete reporting.	Compare the median time between specimen collection with the completion of reference laboratory testing for Active Bacterial Core surveillance (ABCs) or reporting to the health department of Knox County (KOHs) and conventional reporting (was 3 weeks).	Time to release report of ABCs and KOHs were 4 and 1 months, respectively. These components were slower than conventional reporting which had weekly reporting.
Bias	S33	The selection bias in favour of patients with infections caused by resistant organisms	Self-estimation of how well the rural population is represented	Study's sample represented poorly the rural population
	S39	The selection bias towards dirty facilities in AMR surveillance in animal	Calculate a contaminated fraction to present the possibility of cross-contamination. Higher fraction, more possibility of overestimate the resistant proportion	No data

	S10	Completeness of data reporting is presented for collection periods	Calculate percentage of records that has information of each variable (gender, age, mode of transmission, HIV status…).	Gender and age (99%); Mode of transmission (57%); HIV status (35%)
Completeness of reporting	S42	Did not define	Capture-recapture analysis: Cases with invasive *S. pneumoniae* were cross-checked between two components by using available patient identifiers. Total cases were combined from two components: Active Bacterial Core surveillance (ABCs) and Knox County Health Department surveillance program (KOHs).	ABCs component captured 86% of non-duplicated isolates. KOHs component captured 89%.
Cost	S33	The monetary value of implementing the surveillance program	Calculate direct and indirect cost	Direct cost: 1000€/PC Indirect cost: 100€/month/site
	S42	Annual cost to maintain the surveillance system	Direct and indirect costs were estimated for 1998 on the basis of interviews with relevant personnel from the different surveillance systems.	The annual cost of the ABCs and KOHs components were an estimated $30,000 and $5,000/year, respectively.
Acceptability	S54	Acceptability reflects the willingness of persons and organizations to participate in the surveillance system	Assessed through survey-based consultation with stakeholders of this surveillance system (reference laboratories, clinics, public health officials, WHO)	The acceptability of the system is high for the contributors to the system, where all reference laboratories have participated continually over the last 25 years.
Flexibility	S54	The capacity of an AMRSS in adapting to changing information needs or operating conditions with little	Identify examples of the system's ability to adapt to changes in testing methods	The network has had to adapt to some challenges (e.g. using new molecular based methods to diagnose gonococcal

		additional time, personnel, or allocated funds.		infections and molecular based methods to diagnose gonococcal infections).
Level of coverage	S10	number of isolates tested compared to the number of reported cases	Calculate the ratio of number of isolates tested compared to the number of reported cases as part of the enhanced epidemiological surveillance of STI in 2010.	Number of isolates tested ranged from 1% (United Kingdom and Hungary) to 81% (Portugal).
Protocol quality	S39	The level of consistent protocol between laboratories for isolation of organisms	Compare the sampling, transporting and reporting activities of local laboratories with the standard protocols of program.	Human data lack a rigorous sampling plan and suffer from irregular compliance.
Quality of data	S66	Did not define	Examine the percentage of error and unknown data.	The evaluation revealed that the quality of the data was insufficient.
Utility of surveillance data	S38	The usefulness of data in describing institutional risk factors for increased rates of nosocomial infection.	Stepwise multiple linear regression analysis was used to evaluate the mean annual rate of MRSA blood isolates as the dependent variable with continuous and categorical independent variables of interest.	Significant linear relationship between population density and mean annual MRSA blood isolate rate.

1.4. Discussion

In this review, we outlined the key aspects of AMR surveillance systems that have been implemented and published worldwide and summarized the performance of the systems for which an evaluation was reported. The number of AMR surveillance systems has increased substantially in the last two decades, particularly more systems at an international scale and more systems employing an active approach at the national scale. This review also highlighted several limitations within AMRSS worldwide. Firstly, the microbiological and epidemiological capacities of health-care facilities in these systems need strengthening; this issue was discussed explicitly in 12 systems (17%). Second, a lack of reliable methods for excluding duplicate isolates, as shown in 42 systems (59%), without specification of de-duplication could lead to bias and an overestimation of the resistant proportions. Furthermore, the collection of microbiologic samples was heterogeneous among the systems, therefore data aggregation and comparison between hospitals or laboratories are not feasible, as mentioned in S27, S19 and S11. Thus, the value of an AMRSS is restricted primarily to the participating hospitals, laboratories or medical centres in using AMR surveillance data for improvement of patient care and supporting interventions to control AMR. Next, even though several international AMR surveillance programs were in place, there was a lack of a formal framework for collaboration among surveillance programs worldwide. As an example, in the European Antimicrobial Resistance Surveillance Network (S09), the Central Asia and European Surveillance of Antimicrobial Resistance (S05) or WHO Western Pacific Regional Programme for Surveillance of Antimicrobial Resistance (S11), the requirements for data collection and quality were different. This can pose a challenge for any efforts to combine or share the data between the programs. Last, the evaluation framework for AMRSS evaluation were also highly variable. There is currently no standard evaluation framework developed specifically for surveillance systems in AMR.

An important finding of this review was the gap in the evaluation of the AMRSS including performance evaluation, despite many efforts to implement surveillance as one of the important tools in controlling AMR. This finding is consistent with the general lack of evaluation of animal and human health surveillance systems worldwide [57,62]. Among the 79 reported systems, only 7 had performed an evaluation using a limited number of evaluation attributes. The methodologies for evaluation of the surveillance systems were highly heterogeneous, therefore it was not feasible to compare the performance of AMRSS worldwide. This problem might be due to the lack of a systematic methodology for surveillance evaluation, which has

been discussed in a recent project for the development of SurvTool (a tool for the integrated evaluation of animal health surveillance systems) [152]. The development of this tool aims to provide detailed and structured information on the available methods and relevance according to a specific evaluation question and context for animal health surveillance, which could also be applied to AMR surveillance.

Representativeness was by far the most frequently assessed attribute. As recommended by the US CDC updated guidelines for surveillance system evaluation, representativeness should be assessed by comparing the reported events to the actual events [59]. However, the latter is generally unknown; and each study used different type of information available for the same targeted geographical area to evaluate this attribute. S54 used the total number of gonococcal notifications in the previous eight years in Australia while S66 and S38 used data on resistant cases notified by other networks in same year of surveillance for comparison.

Definitions of the attributes under evaluation were also different across the systems in some aspects. An example was for the attribute of completeness of reporting which had different meanings in the two evaluations under which it was evaluated (S42 and S10). The European Gonococcal Antimicrobial Surveillance Programme (S10) defined this as the percentage of records that has information of each collected variable in the system, while the Innovative Surveillance system for Drug-resistant *S. pneumoniae* (S42) defined this as the percentage of invasive cases which were captured by the surveillance component in comparison with a conventional system. The definition used as in the evaluation of S42 was more similar to the attribute of representativeness assessed in S66 and S38 mentioned above.

Timeliness, which is also a critical attribute in AMRSS as it will influence the rapidity of the treatment and/or control action, was only assessed in two systems. S54 assessed timeliness by evaluating the flow of data in the system (collection, transmission, analysis and reporting) and S42 assessed it by comparing the data processing duration between two components of the system. The fixed timeline in data collation on a quarterly basis and in release of data report on a semi-annual basis in S54 might have improved the timeliness of the system, and more importantly this timeline was considered to be acceptable by the stakeholders. Therefore, assessment of timeliness should be based on the responses by the stakeholders who benefit from the surveillance system.

Cost of implementation was the only financial attribute that was assessed in these surveillance systems (S42 and S33). The costs reported in these studies were costs of equipment and human

resources. As noted in one study (S33), it was difficult to distinguish between the costs of running surveillance activities from the costs of running the daily laboratory activities (such as susceptibility testing and data entry and analysis). The benefits and cost savings from AMR surveillance systems were also not assessed in these studies. To support further implementation especially in resource-restricted settings, more data on costs of setting up and running AMR surveillance programs should be collected and published.

There was a lack of data on AMC collected as part of the reviewed AMR surveillance systems. In the analysis of two systems, the authors used AMC data from other surveillance programs. The analysis from S61 demonstrated the use of time-series graphs to show the possible association between ABC and the emergence of AMR. Other systems that collected AMC data only showed Defined Daily Dose/1000 bed-days [153] and no investigations were reported in these analyses on the link between AMC and AMR. Monitoring both AMC and AMR is important as identified in the WHO's Global Action Plan [36]. In addition, monitoring of antimicrobial use should be incorporated in or linked with the AMR surveillance system in order to evaluate the impact of any interventions to control AMR through improving antimicrobial consumption practices in the targeted population.

The choice of denominator data was important in the surveillance of AMR as this allows a comparison in the resistance prevalence between participating sites (clinics, hospitals or nations). This has also been identified in the report by Rempel *et al.,* who did an assessment on 22 surveillance systems to investigate their validity: all studies used appropriate denominator data and case definitions [154]. An AMRSS had appropriate denominator and case definition if this choice protected against bias [154]. Denominator information may be useful for estimating the prevalence of specific resistance profiles in the human and animal population.

Although this review specifically targeted the AMRSS that were published in academic literature, I have also searched the references and the reports from public health agencies. In fact, 40/79 systems were at national scale, and some papers that I included were the reports from these government agencies. The search process I used was valid because it follows a systematic process with reproducible steps, and through this process I could identify the papers and reports that contain required information for evaluating the characteristics, strengths and weaknesses of each system. There might be some systems that I have missed during this process, however I believe this might be due to the fact that there is not enough information

available about these systems, and thus including them would not improve significantly the conclusion of my analysis.

1.5. Conclusion

This review resumed the key elements of AMR surveillance systems over the world and the methods and results of AMR surveillance system evaluation. The findings from this review show that although AMRSS have been increasingly implemented in many countries, a number of limitations exist in the surveillance protocols that can affect the validity and usefulness of the generated surveillance data. These are issues in microbiological and epidemiological capacity, data de-duplication, heterogeneity in data collection and quality, and a lack of evaluation in most of the AMRSS. A lack of an evaluation framework was also found among the limited number of studies, which performed evaluation on a few performance attributes. This review highlighted the need for systematic evaluation to be carried out to assess AMRSS performance and for developing specific methods building on from current evaluation guidelines with additional attributes specific for AMR surveillance.

Chapter 2

Application of SurvTool and OASIS to evaluate the VINARES network for surveillance of antimicrobial resistance

2.1. Introduction

Antimicrobial resistance (AMR) among common bacterial pathogens is recognized as a global health threat, leading to a significant increase in healthcare costs, treatment failures and deaths [155]. This issue is more pressing in low- and middle-income countries (LMICs), including Viet Nam. While exact data and evidence are scarce from LMICs, the burden of resistant infections is disproportionate to the countries' resources, [31]. Surveillance has been indicated as one of the important strategies in Global and in National Action Plans to contribute to combating AMR including in Viet Nam [156].

According to WHO, surveillance of antimicrobial resistance is the continuous, systematic collection, analysis and interpretation of AMR data needed for the planning, implementation, and evaluation of public health practice. AMR surveillance allows the early detection of public health emergencies, to observe trends over time and to evaluate the impact of an intervention. AMR surveillance data inform local clinical decision making and guidelines and allow priorities to be set and can inform public health policy and strategies [39]. A surveillance system is composed of one or several surveillance components – one component is defined as a single surveillance activity used to investigate the occurrence of one or more hazards [157].

Bax *et al.* [65] mentioned the multiple difficulties of AMR surveillance in the structure of study, the selection of host populations to be sampled and the choice of sampling methods and organisms. The testing method and cut-offs for susceptibility used for antimicrobial susceptibility testing (AST) is also important and needs to be standardized. The statistical handling of surveillance data is challenging and sustainable funding is a great concern in surveillance.

In order to optimize the use of available resources, timely and relevant evaluation of AMR surveillance systems (AMRSS) needs to be performed. Evaluation can inform planning a new or re-designing the existing surveillance system, to ensure reaching the objectives and to take the appropriate corrective actions.

There have been very few evaluation frameworks designated to evaluate surveillance systems for AMR specifically. AMR surveillance was a part/activity in a framework [62], or was considered as a general public health surveillance system. From a public health perspective, there have been a number of guidelines and tools developed for evaluating surveillance systems. In 1988, the US CDC published Guidelines for Evaluating Surveillance Systems to ensure that problems of public health importance are being monitored efficiently and effectively [37]. US CDC's Guidelines for Evaluating Surveillance Systems were updated in 2001 to address the need of integrating surveillance and health information systems and changes in the objectives of public health surveillance to facilitate the response of public health to emerging health threats.

In 2008, the Health Metrics Network - a global health partnership focused on strengthening health information systems in low- and middle-income countries, hosted by the World Health Organization (WHO) – provided an assessment tool for assessing National Health Information Systems. This tool assesses the inputs and outcomes of a surveillance system, builds consensus around the priority needs, informs stakeholders and ensures the comparable assessment findings [158].

WHO introduced a multi-stage rapid assessment analytical tool to assess the AMR situation in countries in 2011 [159]. This tool was used to determine the extent to which effective practices and structures to tackle AMR were already in place and where gaps remained. Authorities in each country were invited to complete the questionnaires themselves.

In 2012, the European Centre for Disease Prevention and Control (ECDC) published a handbook, which serves as guidance for infectious diseases surveillance system evaluation and data quality monitoring and supports self-assessment of surveillance systems at various levels from local to national in order to provide accurate and timely information for decision-making [160].

In 2015, WHO introduced the Global Antimicrobial Resistance Surveillance System (GLASS). GLASS aims to enable standardized, comparable and validated AMR data collection and analysis and sharing of AMR data across countries to inform decision-making and action [6]. It provides a list of indicators for monitoring and evaluating GLASS implementation of each country.

In 2016, the Food and Agriculture Organisation of the UN (FAO) provided the Assessment Tool for Laboratories and Antimicrobial resistance Surveillance Systems (ATLASS) in order to support countries in assessing and improving their national AMR surveillance system in the food and agriculture sectors [161]. This tool generates a baseline, and classifies a "stage" for AMR laboratory capacity detection, AMR surveillance, and information dissemination.

Since 1988, a number of national and international efforts have been made to implement AMR surveillance in Viet Nam, at different scales (table 2.1). The National Program for Surveillance of Antibiotic Resistance (NPSAR), implemented by the Vietnamese Ministry of Health (MoH), was the first national surveillance program for AMR [162,163]. Under this program, common bacteria causing infections (including *S. aureus*, *E. coli*, *Salmonella spp.*, *Shigella spp.*, *P. aeruginosa*...) in all specimens in both in-patients and out-patients under a passive component were isolated and antimicrobial susceptibility tests were performed. MRSA, ESBL and Vancomycin-Resistant Enterococci (VRE). An active component determined the pathogenic bacteria in healthy children in communities (nasal *S. pneumoniae*, nasal *H. influenzae*, rectal *E. coli* and oral *S. aureus*) and their antibiotic sensitivity pattern.

The number of participating hospitals increased from 9 in 1988 to 30 in 1993. This program was stopped in 2006. In 2008, the Global Antibiotic Resistance Partnership (GARP) and the Oxford University Clinical Research Unit Viet Nam (OUCRU) collaborated with the Viet Nam MoH to set up a new antibiotic resistance surveillance program. A cross-sectional study was performed to collect antibiotic resistance and antibiotic purchasing data from 15 participating hospitals in 2008-2009 [164]. From 2009 to 2011, another initiative, the Surveillance of Antibiotic Resistance (SOAR) program was implemented in 11 hospital across Viet Nam,

focusing on AMR among respiratory pathogens [165]. Isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* were obtained from clinical materials taken from adult and paediatric patients with community-acquired respiratory infections.

In 2012, the Viet Nam Resistance (VINARES) project was launched. A hospital network was established and surveillance data on antimicrobial resistance and antibiotic consumption were collected from this network in two time periods: 2012-2013 (VINARES 1) and 2016-2017 (VINARES 2), which could be considered two components of this surveillance system. VINARES 1 was implemented as a collaboration between the MoH, Vietnamese Infectious Diseases Society, OUCRU and Linköping University, Sweden, together with 16 hospitals across the country [166]. VINARES 2 collected data for the 2016-2017 period as part of a UK/Viet Nam Partner Driven Collaboration entitled "Towards an evidence based National Action Plan on Antimicrobial Resistance in Viet Nam". Thirteen hospitals participated in the network in VINARES 2, all of which also participated in VINARES 1. The primary aim of VINARES 2 was to create an evidence informed methodology and well governed working processes to develop and implement policies and guidelines for controlling AMR in Viet Nam. Large surveillance datasets have been submitted to the network in these two periods; however there has not been any formal evaluation of the performance and effectiveness of these two surveillance projects.

Table 2.1: Objectives of NPSAR, GARP, SOAR and VINARES projects in Viet Nam

Surveillance component	Objective	Surveillance type	Duration	Hospital number	Surveillance procedure
NPSAR	Monitoring antibiotic resistance among microbiology laboratories. Developing national action plan to improve antibiotic prescribing and use.	Passive and active	1988-2006	31	All participant hospitals submitted annual data directly to Department of Therapy (1988-1990) and Department of Drugs and Medical Devices (1990-2006) of MoH. There were nine annual trainings for laboratory technicians in all (n = 24) provincial hospitals.Community samples were collected in healthy children (nasal *S. pneumoniae*, nasal *Haemophilus influenza*, rectal *E. coli*, oral *S. aureus*).This project issued 6 research yearbooks every two or three years.
GARP	Addressing the challenge of antibiotic resistance by developing actionable policy proposals. Monitoring AMR in hospitals	Passive	2009	15	A cross-sectional study was performed to collect antibiotic resistance and purchasing data. Hospitals carried out antimicrobial susceptibility testing (AST) then submitted annual result to MoH in paper form. OUCRU was in charge of analysis of data and producing a report. One report was issued after the study.
SOAR	Surveillance of antimicrobial resistance of key respiratory pathogens	Active	2011	11	*S. pneumoniae* and *H. influenzae* isolates were collected from adult and paediatric patients with community-acquired respiratory infections from 11 different centres in Viet Nam. AST was centrally performed.
VINARES	Collecting national-wide AMR data in hospitals	Passive	2012-2013 2016-2017	16 (2012-2013) 13 (2016-2017)	The Viet Nam Resistance network (VINARES) was launched in 2012 as a collaboration between the MoH, the Vietnamese Infectious Diseases Society, OUCRU and Linköping University,

	Sweden. Reported data including AST results from bacterial isolates from clinical specimens were sent monthly to OUCRU.

The hospital network for AMR surveillance established as VINARES has been recognized by the MoH as the National AMR Surveillance Network in 2016 and data collection is ongoing [167]. The network is currently supported by a Fleming Fund country grant and by the Global Health Security Agenda, with contributions from WHO, US CDC, PATH, FHI360 and OUCRU. It is important to perform a thorough assessment of the quality and effectiveness of VINARES 1 and 2 to understand the strengths and weaknesses of this hospital surveillance network and identify the areas for improvement to support the organization and implementation of an improved national surveillance system.

The objective of this study is to evaluate the AMR surveillance system in Viet Nam based on the VINARES project, comparing the two periods of 2012-2013 and 2016-2017 by assessing its strengths, weaknesses, effectiveness and implementation costs and to provide meaningful recommendations for its improvement.

2.2. Methods

2.2.1. Evaluation approach and framework

SurvTool [152] was used to establish the framework to evaluate AMR surveillance system in Viet Nam. A number of approaches are available for evaluating surveillance systems [60,158,168,169], however, most of these had the limitation that they lacked the level of detail and flexibility needed for practical implementation [62]. SurvTool was developed to provide a practical approach for evaluation of surveillance systems. It was built within the RISKSUR project, an EU-funded project from 2012 to 2015 delivered by the RISKSUR consortium (www.fp7-risksur.eu). Within this project, decision support tools (software which supports analysts and decision makers in making better and faster decisions) were developed that can be used to evaluate surveillance systems, based on an interdisciplinary approach. The development of SurvTool was built on existing evaluation frameworks, methods and tools available in the literature [62] and incorporating inputs from experts. The main objective of SurvTool was to guide users in practically planning and implementing an integrated evaluation of surveillance systems [152].

Specifically, SurvTool helps the user to establish an evaluation context, including surveillance description, evaluation questions and suggestion of assessment methods [170]. This tool was used to: 1) describe the surveillance system and its components under evaluation; 2) identify the most relevant evaluation questions based on the specific context and decision-makers requirement and 3) identify the most relevant evaluation attributes to assess and the method to

do so. An evaluation attribute is a criterion that measures a specific functionality or effectiveness of the surveillance system.

To date, SurvTool has been applied mostly in animal health surveillance [171,172]. However, SurvTool can support evaluation of surveillance systems with multiple objectives such as prevalence estimation and case finding, or demonstration of freedom from disease or early case detection. It could be applied on endemic, sporadic or emerging diseases and also to AMR surveillance (www.survtools.org).

We evaluated the antimicrobial susceptibility testing (AST) data submitted by participating hospitals in VINARES 1 and VINARES 2. For denominator data, we used data from the annual health statistics of Viet Nam to calculate the effectiveness of AMR surveillance system in Viet Nam in the timeframe between 2012-2013 and 2016-2017. The proportions of resistant priority pathogens against relevant antibiotics were summarized by region and hospital type, separately. The antimicrobial susceptibility data come from microbiological laboratories of VINARES 1 and 2. We received the data in WHONET format [173] and imported into the R program for the descriptive analysis. The cost data was extracted from official budget documents of VINARES project stored on the OUCRU server. These data were available for OUCRU staff only. Cost analysis was done in Microsoft Excel.

2.2.2. Qualitative assessment of the surveillance system using OASIS tool

To assess the evaluation attributes, we used OASIS (Outil d'Analyse de Systèmes d'Information en Santé - a French acronym that translates as 'analysis tool for surveillance systems in human and animal health'); a qualitative assessment tool for assessment of strengths and weaknesses of surveillance systems based on 78 criteria describing the situation and operation of a surveillance system [174].

OASIS was developed by ten epidemiologists, developers and users of assessment methods and surveillance system managers from the French Agency for Food, Environmental and Occupational Health Safety (ANSES) [175]. OASIS combines three methods, including surveillance network assessment tools, critical control points assessment method and the US CDC Guidelines for Evaluating Surveillance Systems to develop a complete and standardized surveillance system assessment tool [175]. It standardizes the results and gives a better comparison of surveillance systems. OASIS was initially developed as an assessment tool of surveillance systems on zoonoses and animal diseases, but it can also be applied for general health surveillance systems.

The OASIS questionnaire includes 78 questions representing the functional parts of a surveillance system, and is used to collect information to support the scoring of the assessment criteria. These assessment criteria are categorized in ten sections according to the structure and activities of a surveillance system. Based on the information collected, each criterion is scored from 0 to 3 according to the level of completion of the system and scores are added up for each section; a higher score reflects better performance. These sections include:

- Objectives and scope of surveillance: assess the relevance of surveillance objectives, level of detail, accuracy,
- Central organization: assess the structure and operation of central unit,
- Hospital organization: assess the structure and operation of participant hospitals,
- Laboratory: assess the integration of laboratory in the surveillance system, the quality assessment of laboratory and accuracy of test,
- Surveillance tools: assess the standardization of surveillance protocols, measurement tools and data collection,
- Surveillance procedure: assess the active/passive component of surveillance system,
- Data management: assess the adequacy of the data management system,
- Training: assess the frequency and quality of training,
- Communication: assess the communication between the central unit and hospitals, technical support of central unit and the publication of results,
- Evaluation: assess the evaluation of performance of system and the implementation of improvement.

The OASIS evaluation tool has three outputs. The first and second output of OASIS provide a summary of the strengths and weaknesses of above ten sections and the contribution of each assessment criterion of the surveillance system. These aim to provide a general view of the structure and operation of the surveillance system and help to quickly identify areas for improvement. The third output provides the assessment results for ten attributes defined specifically by WHO and US CDC for an AMR surveillance system to represent the influence of the system's organization and design on its performance. Each attribute is represented by a numerical value of 0-100 by combining the scores assessed for all assessment criteria contributing to the attribute. The results of the 10 attributes are visualized in a radar chart demonstrating the strengths and weaknesses of the surveillance system.

For our evaluation, we defined the ten attributes as follows:

- Sensitivity: refers to the proportion of resistant cases detected by the surveillance system to all resistant cases in Vietnamese hospitals for each pathogen – antimicrobial combination,
- Specificity: refers to the proportion of non-resistant cases detected by the surveillance system for each pathogen – antimicrobial combination,
- Representativeness: how accurately the surveillance system describes the occurrence of AMR in the population by place and person,
- Timeliness: reflects the speed between steps in the surveillance system
- Flexibility: ability to adapt to changing information needs or operating conditions with little additional time, personnel or allocated funds.
- Reliability: ability to properly collect, manage, and provide data of the surveillance system without failure
- Stability: refers to the reliability and availability (the ability to be operational when it is needed) of the surveillance system
- Acceptability: reflects the willingness of persons and organizations to participate in the surveillance system;
- Simplicity: the surveillance system should be as simple as possible in both its structure and ease of operation while still meeting its objectives;
- Usefulness: the surveillance system is useful if it contributes to the prevention, control and improved understanding of AMR.

OASIS has been applied mostly to animal health, but also to human health and AMR surveillance [176]. As an example, OASIS was used for the evaluation of a surveillance network of antimicrobial resistance in pathogenic bacteria from animal origin of 59 laboratories in France 2009) [175]. The surveillance system collected electronic or paper-based results of antibiograms from laboratories. The network was coordinated by two laboratories in Lyon and Ploufragan–Plouzané, France. The first assessment output displayed a global, good operation of the surveillance network, except for the surveillance procedures. It also identified the main areas for improvement in central and field institutional organization, training, and evaluation. The second output highlighted mainly a lack of representativeness and an improvement margin for sensitivity, specificity and flexibility.

In this study, we applied this OASIS questionnaire to VINARES 1 and 2, each considered as one component of the surveillance system in Viet Nam. I used the OASIS questionnaire to

interview one lab staff and one coordinator who were directly involved in the projects. Data were also collected from official documents and publications of these projects.

2.2.3. Quantitative assessment of the effectiveness attributes

The results of SurvTool indicated the effectiveness attributes that the evaluation should focus on. We selected only five effectiveness attributes that are relevant for the surveillance system under evaluation in answering our research questions and based on expert opinion. These include sensitivity, coverage, representativeness, timeliness and cost. The description and assessment method for each of these five attributes are described in table 2.2.

These assessments will be carried out separately for the following pathogen – antimicrobial combinations: *A. baumannii* - imipenem; *P. aeruginosa* - imipenem; *E. coli* - imipenem; *E. coli* – ESBL; *K. pneumoniae* - imipenem; *K. pneumoniae* – ESBL; *S. aureus* – MRSA. These combinations are suggested by WHO [177] and were the most common in VINARES.

Table 2.2: Description of the effectiveness attributes and their quantitative assessment methods

Attribute Name	Description	Assessment method
Sensitivity	Surveillance sensitivity refers to the ability of the surveillance system to detect cases; AMR surveillance sensitivity refers to the proportion of individual inpatients having a resistant bacterial isolate that the surveillance system is able to detect.	The number of patients with an infection caused by a resistant isolate detected in VINARES divided by the total number of patients with an infection caused by a resistant isolate in all hospitals in Viet Nam. We defined a case as a patient diagnosed to carry a resistant bacterial isolate, i.e. doctor decided based on clinical presentation of that patient and the AST returned a result of resistance, specific for each of the following pathogen – antimicrobial combinations: *A. baumannii* - imipenem; *P. aeruginosa* - imipenem; *E. coli* - imipenem; *E. coli* – ESBL; *K. pneumoniae* - imipenem; *K. pneumoniae* – ESBL; *S. aureus* – MRSA. Therefore, $$Sensitivity = \frac{N_R}{N_A}$$ N_R and N_A are the number of de-duplicated resistant isolates detected by VINARES and the number of patients carrying a resistant isolate in Viet Nam, respectively. N_A was unknown, therefore we estimated this by summing up the products of the estimated average number of patients carrying a resistant isolate and the number of hospitals by each category): $$N_A = \sum_{i=1}^{3} k_i * N_{Ri}$$ Where the value of i varies refers to the type of hospital (national (i = 1), specialized (i = 2) and provincial (i = 3, including district)); k_i is number of hospitals of type *i*; N_{Ri} is average number of cases

		having a resistant isolate for a specific pathogen – antimicrobial combination in a hospital of type *i*, estimated from VINARES data. The numbers of hospitals in the periods 2012 and 2016 were obtained from the 2012 and 2015 health statistics yearbook of the MoH.
Coverage	The proportion of the target population that was included in the surveillance; the target population in VINARES is all hospital inpatients.	Dividing the number of patients tested in VINARES and number of all patients in Viet Nam during the same period. In this analysis, we estimated coverage using three measures that can present the target population including the number of inpatients, the number of patient days, and the number of hospitals.
Representativeness	The extent to which the features of the population of interest are reflected by the population included in the surveillance activity.	The distribution of bacteria by region will be compared with the distribution of population and of area.
Timeliness	Timeliness is usually defined as the time between any two defined steps in a surveillance system, the time points chosen are likely to vary depending on the purpose of the surveillance activity.	The duration of data collection, transmission and report issue will be calculated. In this study, timeliness was assessed using four criteria: • time from antimicrobial susceptibility testing in laboratory to data collection to OUCRU; • time from requirement of laboratories to data technical support from OUCRU; • monthly External Quality Assessment (EQA) participation; and • time to report the data.

Costs	Costs of the initial implementation and running of surveillance system.	Implementation and annual cost were estimated from the total cost. This cost depends on the type of hospital. The total costs were obtained from financial documents of each surveillance project. A discount rate of 5% was applied so that the cost in different time points could be comparable*. The average cost-effectiveness ratio (ACER) will be used to compare the cost per outcome unit. ACER of one AMRSS represents cost per one effectiveness unit and it can be obtained by dividing the net cost of surveillance by the effectiveness: $$ACER = \frac{Total\ Cost}{Outcome}$$ The cost for one hospital, one collected isolate, one resistant isolate, one priority specimen, one priority bacterial isolate, one workshop or training and one report or newsletter of each surveillance project were calculated. Following GLASS recommendations [50], priority specimens include: blood, urine, stool, cerebrospinal fluid, vaginal swabs, nasopharyngeal swabs, pus, wound swabs and sputum; priority bacteria [177] include: *E.coli*, *Klebsiella spp.*, *Acinetobacter spp.*, *P. aeruginosa*, *S. aureus*, *Enterobacter spp.*, *S. pneumoniae*, *H. influenzae* and *E. faecium*.

*People often put more value to current rather than future costs and effects. Therefore, economic evaluations need to discount the costs and benefits by adjusting the value of these by a discount rate for the future time when they occur. O'Mahony et al. [178] recommends countries with a differential discounting policy to also report outcomes for equal discounting at rates of 3 and 5%.

2.2.4. Evaluation protocol

Of concern, while assessing the technical effectiveness of the AMR surveillance system in Viet Nam, were low sensitivity, bias and overestimation of the resistant proportions among community acquired infections (CAI) caused by the passive nature of the surveillance (i.e. collect all data generated by the microbiology laboratories, with limited clinical metadata). This may lead to biases as microbiological diagnosis is underused in most LMICs, it's biased towards more severe or unresponsive infections, and it may render inadequate results due to antibiotic use prior to sampling and this cannot be assessed well because no clinical metadata are included in the surveillance here.

The cost of the system was also considered. SurvTool provided an evaluation protocol based on the specific evaluation needs and context of AMR surveillance in Viet Nam (table 2.3). Based on the outputs of SurvTool, one functional attribute was quantified (surveillance system organization) to assess the strengths and weaknesses of the system and the impact of the system function on its effectiveness and 4 effectiveness attributes (sensitivity, coverage, representativeness and timeliness) to compare the efficacy of the 2 components over the 2 different periods.

Table 2.3: AMRSS evaluation context in Viet Nam

Context elements	Description
Alternative strategies to consider?	Increase number of hospitals & change ratio of hospital types
Are you considering risk-based options?	No
Do you have a budget constraint for the surveillance system/components?	Yes
Do you know the current cost of your system and/or components?	Yes
Do you want to evaluate the whole system or some components in the system?	The whole system strengths and weaknesses; the effectiveness of the different components
Evaluation criteria	Effectiveness, cost, non-monetary benefit
Evaluation method	Least cost analysis
Evaluation question	Assess the costs and effectiveness of surveillance components (out of two or more) to determine which achieves a defined effectiveness target at least cost, the effectiveness needs to be determined
Geographical area	Viet Nam
Hazard name	Antibiotic resistance of priority bacteria

Hazard situation	Endemic
Legal requirements	(Not Set)
Stakeholder concerns about current approach	Low sensitivity and bias and overestimate resistant proportion among CAI
Strengths and weaknesses of the current surveillance approach?	Strengths: collect multiple pathogen - antimicrobial susceptibility, easy, cheap; Weaknesses: low coverage and do not separate infection origin (HAI or CAI)
Surveillance components to evaluate	VINARES 1 and 2
Surveillance objective	Estimate prevalence
Will you consider the costs of surveillance in your evaluation	Yes

CAI: Community-acquired infection; HAI: Hospital-acquired infection

2.3. Results

2.3.1. Descriptive analysis of AMR surveillance system in Viet Nam

VINARES 1 and VINARES 2 were two passive surveillance components based on the same hospital network, which aimed to collect routine AST results of selected hospitals across the entire country. All pathogens in all types of samples were collected and the laboratory results were submitted to the system. Both components had similar objectives: (1) to detect the proportion of resistant isolates in order to give recommendations for empiric therapy and (2) to monitor the prevalence of these resistant isolates to generate knowledge on the AMR situation in hospitals to trigger control actions on treatment used or on antibiotic use such as changes of practices and/or behaviours. These two components also used a similar surveillance protocol as described in table 2.4.

The components varied in the number, type and location of the hospitals included in the surveillance activities: 16 for VINARES 1 and 13 for VINARES 2 (Figure 2.1). Three northern hospitals participated in VINARES 1 but did not participate in VINARES 2. The provincial hospital type was the largest group (7 hospitals); followed by specialized hospital (5 hospitals in 2012-13 and 3 hospitals in 2016-17) (table 2.5). Two specialized hospitals covered the Southern region in two periods; while three were in the Northern region in first period and only one in second period (Supplementary table S2.1).

Table 2.4: VINARES protocols from SurvTool outputs

Characteristic	**Description**
Surveillance System Name	AMRSS VIET NAM
Hazard Name	Antibiotic resistance of priority pathogen – antimicrobial combinations
Based on the current disease status, what is the primary surveillance objective?	Estimate resistant proportions
a) Why is surveillance necessary	Protect public health
b) What will it accomplish	To inform the selection of intervention measures
Geographical Area	Viet Nam
Data collecting target	Patient's antibiogram
Component name	VINARES 1 / VINARES 2
Target Species	Human
Geographical Area Covered	Viet Nam
Data Collection Point	Clinical Microbiology laboratory
Study Type	Passive surveillance
Type of data collected	AST results generated from positive clinical specimens
Target unit level	Hospital
Sampling unit	Individuals
Sampling design	Multiple stage
Notes / Comments	Stratified hospital sampling, all patients/hospital
Number of units in your target population	16 (VINARES 1) / 13 (VINARES 2)
Number of secondary units in your target population	100-10000
Describe who are the agents who will collect samples/ information.	Microbiology labs
Consider whether a data/sample collection protocol is available, or needs to be prepared.	Passive surveillance: Doctor prescribes sampling a patient for microbiological diagnosis, all data from the lab are collected
What will be the frequency of data/sample collection?	Continuous
Consider whether a data/sample transfer protocol is available.	Yes
Describe the frequency	Monthly collection of data from hospitals
Consider whether training is needed for data transfer.	Yes (software training)

Microbiological analysis performed by	Laboratory staff
Analysis method	AST method: Disk diffusion, MIC, E-Test
Sample analysis frequency	Right after receiving sample from doctor
Expected load of samples to be analysed monthly?	Depend on hospital
Epidemiological data collected	No
Results disseminator	OUCRU
Target of results dissemination	MoH and hospitals
Results dissemination method	Annual report

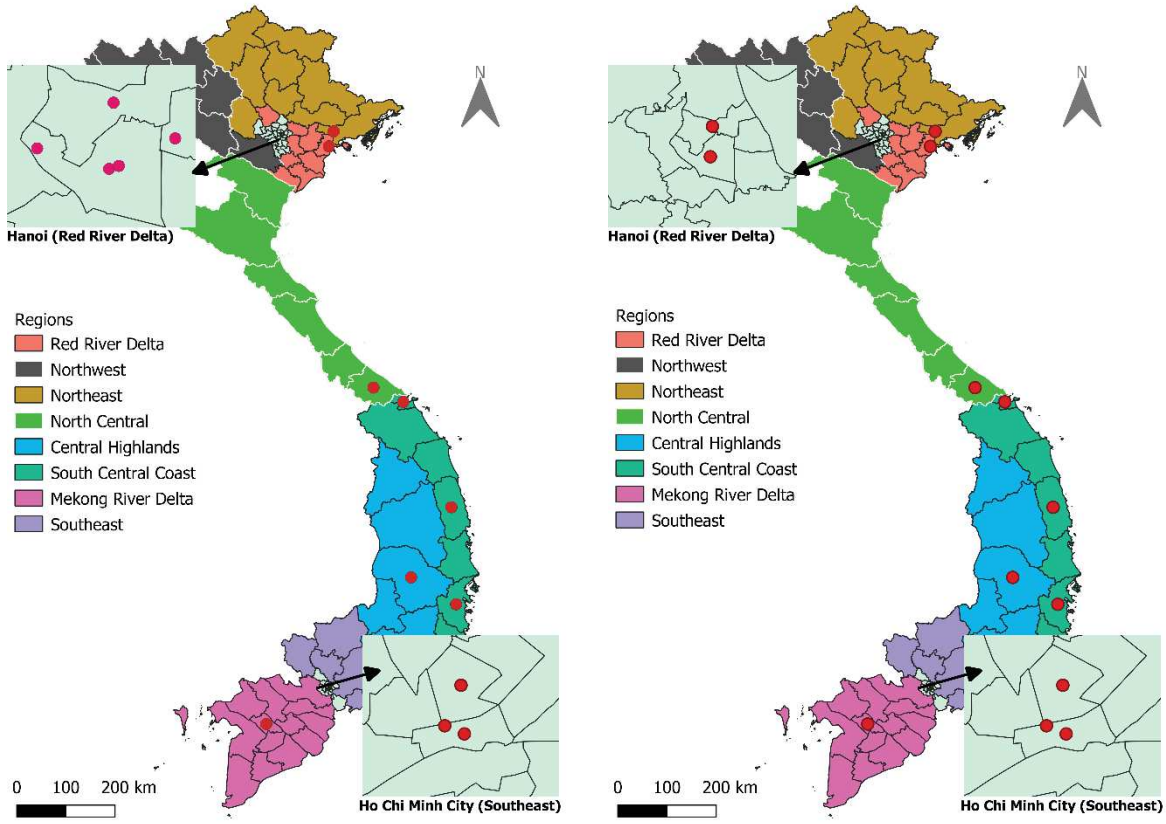


Figure 2.1: Location of hospitals in VINARES 1 and VINARES 2 components

Table 2.5: Distribution of hospitals in VINARES 1 and VINARES 2 components by region and by hospital type

n	VINARES 1 (16 hospitals)	VINARES 2 (13 hospitals)
Region		
Red River Delta	6	3
Northeast	1	1
North Central	1	1
South Central Coast	3	3
Central Highlands	1	1
Southeast	3	3
Mekong Delta River	1	1
Hospital type		
National	4	3
Provincial	7	7
Paediatric	2	1
Surgical	1	0
Tropical disease	2	2

In this surveillance system AST results from bacteria isolated from patients admitted to hospital were collected. Specimens were collected from patients as part of clinical care only, not for surveillance purposes. The microbiology lab conducted AST also as per standard of care only, not for surveillance purposes. AST results were submitted to the coordinating centre (including OUCRU and the National Hospital for Tropical Diseases (NHTD)) every month (for VINARES 1) or every three months (for VINARES 2). OUCRU provided technical support to the laboratories to improve quality and capacity and distributed UK-NEQAS EQA panels. A report for each cycle of surveillance was shared with MoH and other international institutions in Viet Nam including WHO and the United States Centers for Disease Control and Prevention. Figure 2.2 illustrates actors and their actions in the system.

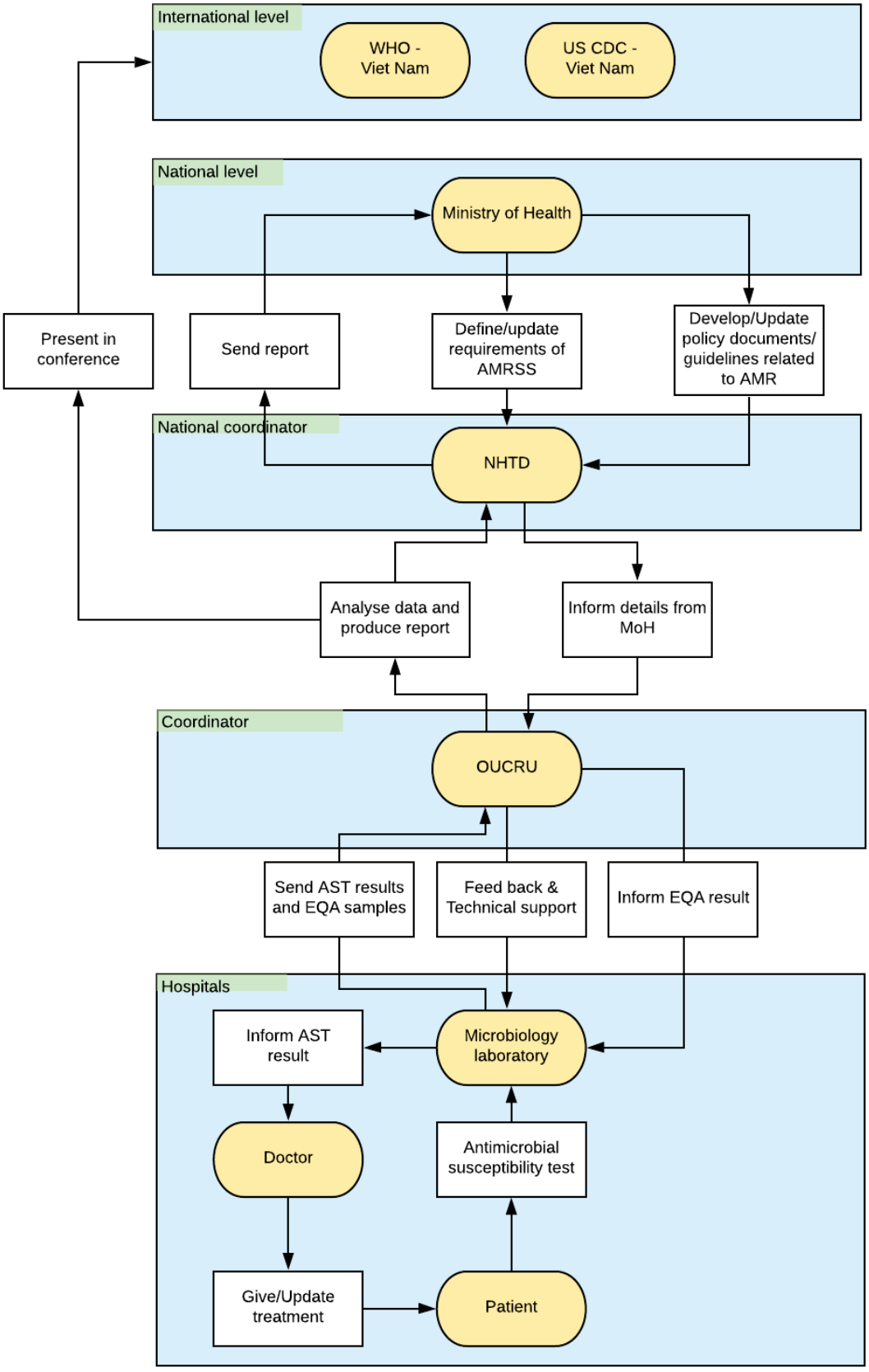


Figure 2.2: Organization of AMRSS in Viet Nam

2.3.1.1. Strengths and weaknesses of the surveillance system

Strengths and weaknesses were assessed for the 10 critical aspects of the AMR system surveillance in Viet Nam (Table 6). Surveillance procedures with passive components were found to be the most limiting aspect of the current system (22% satisfaction) which confirmed the need to assess the performances of the system components to improve its design.

Table 2.6: Strengths and weaknesses of the 10 critical aspects of the AMRSS in Viet Nam

Critical aspect	Score (out of 100)	Description
Objectives	100	The objectives were fully described and appear in an official document.
Central organization	67	There was a steering committee consisting of representatives from MoH, NHTD, Hospital for Tropical Diseases of Ho Chi Minh City and OUCRU in which the role of each member was defined. But this committee did not include all partners and the meeting frequency of the committee was low.
Field institutional organization (Participating hospital)	79	Hospitals worked independently, with minimum supervision from the central organization. The human and financial resources of the field units were sufficient. There was a common data management procedure for all hospitals. This network covered only a part of the country. The role of the hospital staffs was included in an official document but no coordination meeting was organized.
Laboratory	74	All laboratory staffs were well trained and received support from central unit. However, submitting data was not timely.
Surveillance tools	74	There was a comprehensive and formalized protocol for AMR surveillance. Sensitivity and specificity of AST method was good, but there was not a tracking/recording tool for cases with unclear results.
Surveillance procedures	30	VINARES achieved a good score for the passive surveillance components. However, due to having no active component, the score was lower.
Data management	48	Material and financial resources for data management and analysis were provided adequately. However, the data validation procedure was not established and data was not analysed regularly.
Training	93	Initial training was implemented for all laboratory staffs when joining the surveillance system and advanced training was carried out regularly. Material and resources for training were sufficiently

		provided by the central organization as reported in the staff interviews.
Communication	71	Information bulletin was disseminated every quarter, but only one report and no scientific article was released in the end of surveillance component. The assessments in the form of reports, annual meetings, or regular summaries were not returned systematically to hospitals
Evaluation	0	The central organization did not implement an evaluation for the surveillance system. The performance of the system was not reviewed and no corrective measure was applied.

2.3.1.2. Influence of the system design on its performance

The second output of OASIS indicates the overall influence that the system design and organization have on the ten performance attributes. The percentage associated with a performance attribute represents its level of functionality corresponding to the quality of the organization and design of the system (figure 2.3). The current system organization was found to impact most its flexibility (35%); representativeness (42%), timeliness (57%) and sensitivity (65%); specificity acceptability and reliability were also impacted (Table 2.7). The system was relatively strong in terms of stability, utility, and simplicity. Table 2.7 describes the problems identified in the system that have affected its performance attributes.

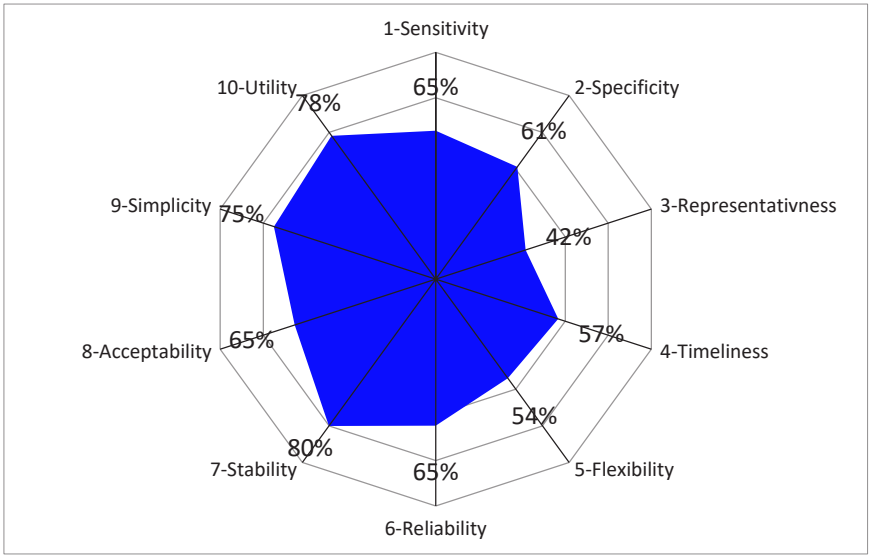


Figure 2.3: Impact of the AMR surveillance system process in Viet Nam on the 10 quality performance attributes as assessed by OASIS tool

Table 2.7: Problems of the AMRSS that affects its performance attributes

Attribute	Reduction (%)	Problems that affects the system's attributes
Representativeness	58	No active surveillance for inpatients in the country. The passive surveillance network did not cover the whole country. Only big national and provincial hospitals participated in the surveillance network, causing a sampling bias.
Flexibility	46	The flexibility of system was low because no system evaluation was performed. As a consequence, the strengths and weaknesses were not identified and the central unit could not have any corrective measures.
Timeliness	43	Hospitals did not adhere to the deadline of submitting AST results to the central unit, so the analysis and report were also delayed. A dedicated support team was not available. The questions and problems of hospitals in the network were not solved in time (e.g. technical issues with computers.
Specificity	28	Advanced training was organized regularly There was not any awareness raising programs for data sources in surveillance network.
Sensitivity	31	Advanced training was organized to maintain the quality of performance of staffs and fix problems timely. No active surveillance was available so the probability to detect new and rare AMR was low. The report was not returned systematically to participants
Reliability	35	Quality control was applied to assure the accuracy of microbiological results. The verification of data submitted from hospitals was not performed regularly by OUCRU. System evaluation was not performed to have corrective measures. Analysis deadlines at the hospitals (including formalization, standardization, verification, transfer of results) to the central unit were not adhered. It could lead to data loss problems or persisting unsolved issues.
Acceptability	35	The enthusiasm of hospitals diminished because the reports and scientific articles on surveillance results were not released regularly. The report on AST results was returned to hospitals only once per year. The financial and material resources for hospitals were not highly adequate.
Simplicity	25	The central unit role has been defined, but not all partners participated in it. The definition of AMR case was not very simple.

Utility	22	Data exploitation was not performed regularly, so the surveillance unit could not give feedback. Moreover, the reports and scientific articles on surveillance results were not released regularly, so the participants did not receive much benefit from the surveillance system.
Stability	20	Human resource: the number of people who worked full time for the central unit was not sufficient. Sampling sites: the surveillance network did not cover the whole country. Result dissemination: the reports and scientific articles on surveillance results were not released regularly.

2.3.2. Coverage and Representativeness

The number of isolates that were analysed and for which data were submitted increased from 25,742 in VINARES 1 to 42,553 in VINARES 2. Coverage was estimated using three indicators: the number of inpatients, the number of patient-days per year, and the number of hospitals in the network. These indicators are not perfect denominators to evaluate coverage, however they are the best indicators with data available.

Data in VINARES were collected by a survey at the beginning of project. The denominator (Viet Nam's data) was obtained from national statistics yearbook [179]. The analysis was done for 2012 only, 2016 data were not available. Table 2.8 indicates that the coverage of VINARES 2 was lower than VINARES 1, but both were lower than 5%. Considering the number of inpatients and patient days, the coverage of VINARES 1 was 6.4% and 8.2% respectively, higher than the coverage of the number of hospitals.

Table 2.8: Coverage of VINARES 1 and VINARES 2 based on number of inpatients, number of patient days and number of hospitals

	VINARES 1	Viet Nam 2012	Coverage of VINARES 1 (%)	VINARES 2	Viet Nam 2016	Coverage of VINARES 2 (%)
Number of inpatients	849 306	13 187 559	6.4%	NA		
Number of patient days	7 424 372	90 872 997	8.2%	NA		
Number of hospitals[(a)]	16	492 (18 : 145: 329)	3.3%	13	576 (23 : 188: 365)	2.2%

(a): national (including general and leprosy hospitals), specialized, provincial (including general and leprosy hospitals), other branches and private hospitals were taken in account. other branches and private hospitals are considered as provincial hospitals.

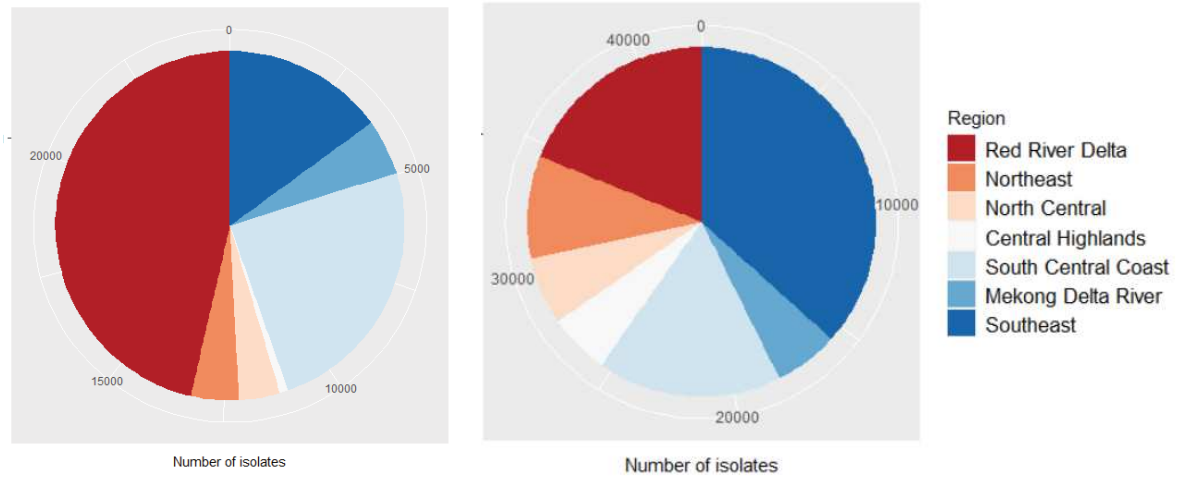
The representativeness of isolate collection by region was assessed by comparing the distribution of *E. coli*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* in VINARES with the distribution of population and with area of each region. The results of VINARES highlighted the important contribution of the Red River Delta and the Southeastern region in two periods. Table 2.9 shows the Red River Delta contributed from 37% to 52% of isolates in 2012-2013 period, while this region occupied 21% of population and 5% of area. In 2016-2017 period, the Southeastern region contributed a very high *P. aeruginosa* proportion. The Mekong Delta's population and area occupied a large proportion of Viet Nam, however it contributed less than 10% of isolates. The North-western region did not contribute any isolate. The contribution of the Central Highlands and Southeastern regions were decreased the most due to the fact that three hospitals in Red River Delta withdrew from the network (figure 2.4).

Table 2.9: Distribution of bacteria by region (Red River Delta : Northeast : Northwest : North Central : South Central : Central Highlands : Southeast : Mekong Delta River)

Percentage (%)	**VINARES 1**	**Viet Nam 2012**	**VINARES 2**	**Viet Nam 2016**
E. coli[(a)]	45 : 4 : 0 : 4 : 26 : 2 : 16 : 3 (n=4437)	Population[(b)]	28 : 2 : 0 : 1 : 12 : 1 : 6 : 3	Population[(b)]
K. pneumoniae [(a)]	45 : 2 : 0 : 3 : 30 : 1 : 13 : 6 (n=2206)	21 : 7 : 6 : 13 : 11 : 5 : 20 : 17	45 : 2 : 0 : 3 : 30 : 1 : 13 : 6	22 : 7 : 6 : 12 : 10 : 6 : 18 : 19
A. baumannii [(a)]	37 : 0 : 0 : 4 : 27 : 1 : 25 : 6 (n=1668)	Area	37 : 0 : 0 : 4 : 27 : 1 : 25 : 6	Area
P. aeruginosa[(a)]	52 : 4 : 0 : 3 : 22 : 1 : 12 : 5 (n=2326)	5 : 14 : 16 : 15 : 13 : 16 : 7 : 12	13 : 6 : 0 : 5 : 16 : 4 : 53 : 4	5 : 14 : 16 : 15 : 13 : 16 : 7 : 12

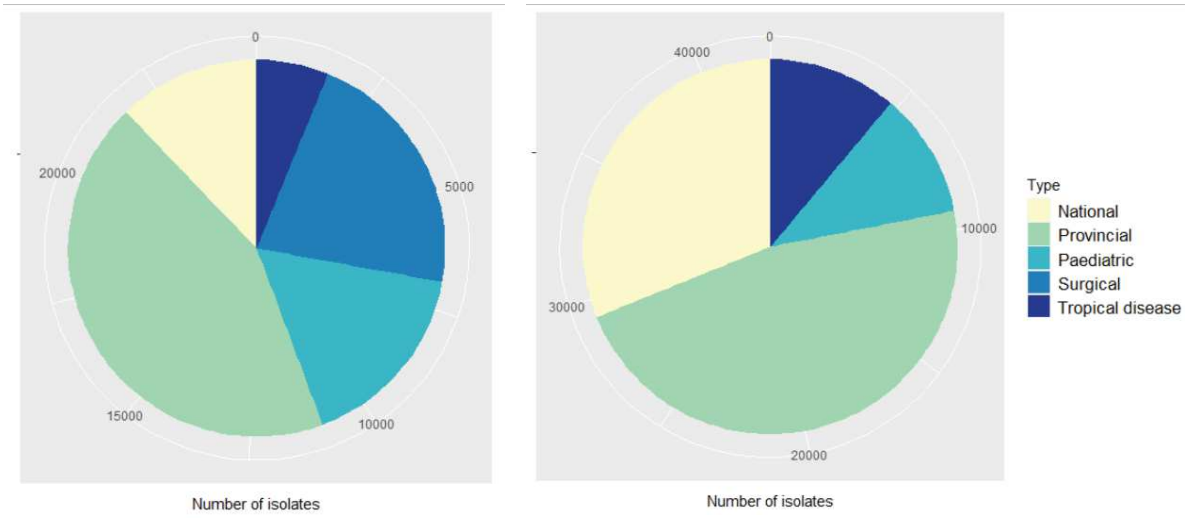
Note: NA: Not available; [(a)]: Distribution of bacteria [(b)]: Distribution of population and area by region

Provincial hospitals had a similar contribution to the total number of isolates between the 2 periods (40%) (figure 2.5). The contribution of the national hospitals increased in VINARES 2 both in number and percentage of isolates, despite their reduced number in this component. Surgical hospitals contributed more than 20% of isolates in 2012 but it did not participate in VINARES 2, that could have led to a bias in the result.



A - VINARES 1 B - VINARES 2

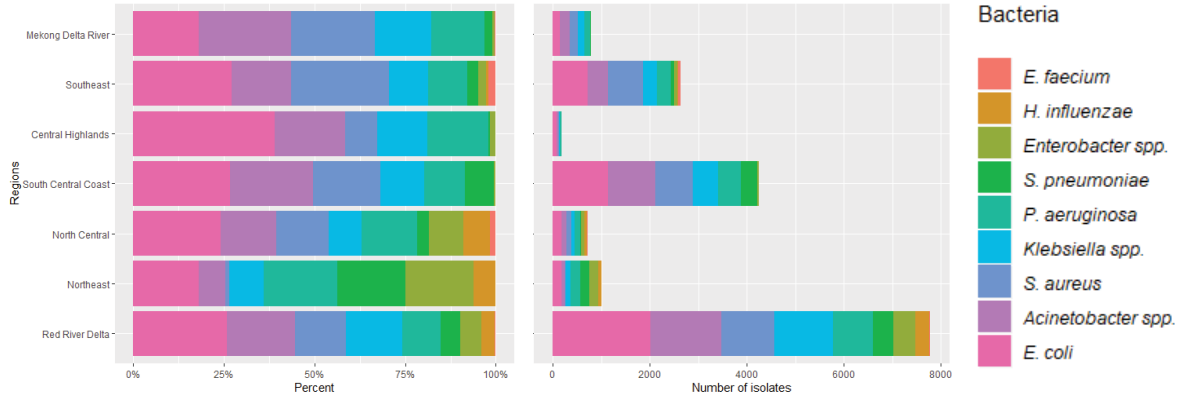
Figure 2.4: Number of isolates detected per region by the AMRSS components: A- VINARES 1; B- VINARES 2



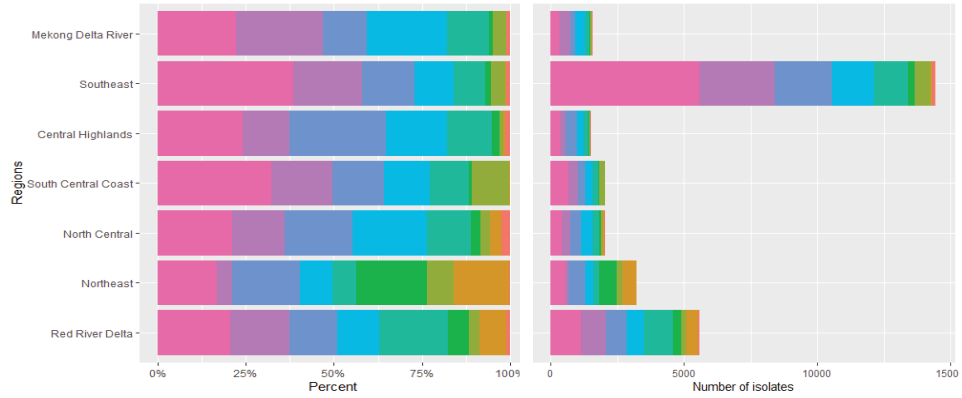
A - VINARES 1 B - VINARES 2

Figure 2.5: Number of isolates detected per hospital type by the AMRSS components: A- VINARES 1; B- VINARES 2

E. coli, Klebsiella spp. and *Acinetobacter spp.* were the most frequently isolated bacteria. They were mostly detected in the Red River Delta and Southeastern regions, where the two largest cities of Viet Nam (Hanoi and Ho Chi Minh city) are located. The proportion of these bacteria in the Centre and the South were higher than in the North (figure 2.6 – VINARES 1(a) and (b)). Between VINARES 1 and 2, the Central Highlands and Mekong Delta regions contributed the least to the number of priority bacteria isolates, which is line with their lower contribution to the total number of isolates to the system (figure 2.4).



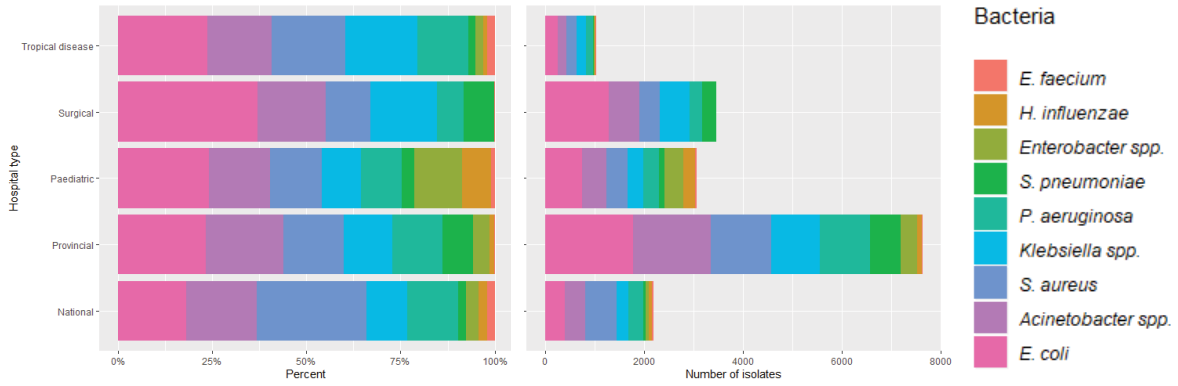
VINARES 1 (a) VINARES 1 (b)



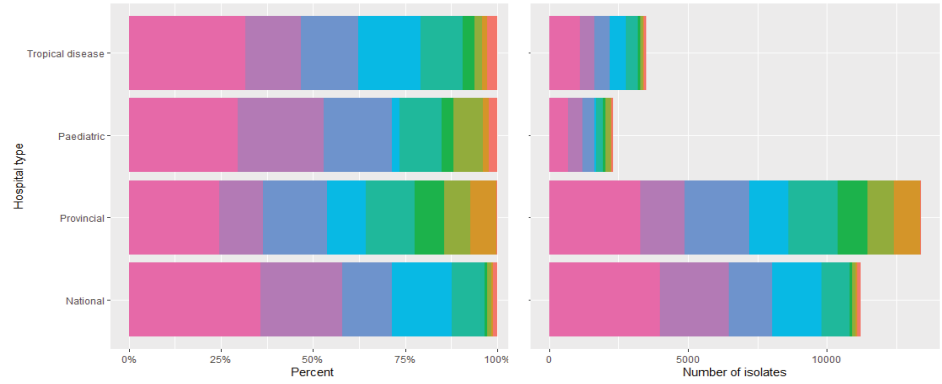
VINARES 2 (a) VINARES 2 (b)

Figure 2.6: Number and percentage of priority bacteria by region in VINARES 1 and VINARES 2 projects

Seven provincial hospitals reported around 40% of total priority bacteria. The proportions of bacteria were similar across species at the provincial hospitals; the distribution was more heterogeneous at the national level (figure 2.7). The contribution of *E. coli* and *Klebsiella spp.* bacteria in the surgical hospital was the highest (figure 2.5a) which could lead to a bias in their detection in VINARES 2 component which has no representation of this hospital type. However, the surgical hospital did not provide a representative detection of all the priority bacteria (no detection of *E. faecium*, *H. influenzae* and *S. pneumonia* in such hospitals).



VINARES 1(a) VINARES 1(b)



VINARES 2(a)

VINARES 2(b)

Figure 2.7: Number of priority isolates by hospital type in VINARES 1 and VINARES 2 projects

2.3.3. Timeliness

Timeliness was assessed using four criteria as described in table 2.10. Most of laboratories sent antimicrobial susceptibility testing data on time (monthly in VINARES 1 and quarterly in VINARES 2). The feedback or support for data management was prompt. Laboratories participated monthly EQA; among them 14 laboratories always sent assessment results on time. The information bulletin was published quarterly in VINARES 1, containing updated information to all laboratories. No information bulletin was sent in VINARES 2.

Table 2.10. Evaluation of timeliness of VINARES surveillance component activities

Time of activity	**VINARES 1**	**VINARES 2**
Time from resistance detection in laboratory to data collection to OUCRU	90% lab sent data monthly; 10% sent data up to 3 months	All laboratories sent data within 3-6 months
Data technical support from OUCRU	Within 1 week since requirement	Within 1 week since requirement
Monthly EQA participation	14/ 16 laboratories uploaded result on time	12/ 13 laboratories uploaded result on time
Report	Quarterly information bulletin Annual report (2013) Paper (2016, 2019)	No information bulletin; Annual report (2017)

2.3.4. Sensitivity

We used the number of hospitals (table 8) and the estimated average number of resistant isolates per type of hospitals to calculate the denominator. From the statistical yearbook, there were 492 and 576 national, specialized and provincial hospitals for 2012 and 2016, respectively [179]. Table 2.11

summaries the sensitivities of seven pathogen – antimicrobial combinations in VINARES. The sensitivities are in the 2-5% range and stay similar between two periods.

Table 2.11: Estimated average number of resistant bacterial isolates in a hospital, number of resistant isolates in VINARES 1 and 2 (N_R), estimated number of resistant isolates in Viet Nam (N_A) and sensitivity of each pathogen – antimicrobial combination

	Number of resistant isolates in a hospital			N_R	N_A	Sensitivity
VINARES 1	type 1 (National)	type 2 (Specific)	type 3 (Provincial)			
A. baumannii - imipenem	123	63	25	1004	19574	5%
P. aeruginosa - imipenem	62	256	86	1766	66530	3%
E. coli - imipenem	115	287	192	2972	106853	3%
E. coli - ESBL	42	309	99	1929	78132	2%
K. pneumoniae - imipenem	27	122	74	1093	42522	3%
K. pneumoniae – ESBL	89	163	74	1526	49583	3%
S. aureus - MRSA	64	128	110	1584	55902	3%
VINARES 2						
A. baumannii - imipenem	640	135	60	2745	62000	4%
P. aeruginosa - imipenem	147	97	93	1383	55562	2%
E. coli - imipenem	140	18	30	684	17554	4%
E. coli - ESBL	715	132	220	4081	121561	3%
K. pneumoniae - imipenem	147	55	40	886	28321	3%
K. pneumoniae – ESBL	177	49	71	1175	39198	3%
S. aureus - MRSA	275	190	61	1822	64310	3%

N_R: number of resistant isolates in VINARES 1 and 2; N_A: and estimated number of resistant isolates in Viet Nam

2.3.5. System costs

The implementation cost of VINARES 1 was 434,000 USD. Applying discount rate of 5% for 4 years later, the equivalent cost in 2016 was 434,000*(1.05^4) = 528,000 thousand USD. VINARES 2's cost was 379000 USD. Table 2.12 shows the outcome of each component and cost for each outcome unit. In general, the VINARES 2 component had lower cost for one outcome.

Table 2.12: Cost per one outcome unit of the AMRSS

	VINARES 1 (528000 USD)		VINARES 2 (379000 USD)	
Outcome	Number of outcomes	ACER[(a)]	Number of outcomes	ACER
Laboratory	16	33000	13	29154
Collected isolates	33084	16	75051	5
Isolates for analysis	25742	21	42553	9
Priority specimen	14737	36	31308	12
Priority bacteria	17369	30	26001	14.6
Workshop and trainings	4	132000	4	94750
Report and newsletter	5	105600	1	379000

(a) ACER: average cost-effectiveness ratio

2.4. Discussion

In this study we used SurvTool and OASIS to assess the AMR surveillance system in Viet Nam in the period 2012-2017 through the VINARES components, and we pointed out the strengths and weaknesses of the system and identified the aspects that could be improved. These areas for improvements can be applied to the current national AMR surveillance system because it is based on VINARES in terms of methods and participating sites.

Overall, the system organization was correctly established with clear objectives and a well-defined technical committee who led the system to perform in the right directions. However, the timeliness and flexibility of the system could be improved by a higher frequency of meetings and communication flow between the central unit and the participating hospitals. As shown in this evaluation, the low frequency of meetings in VINARES led to slow responses and feedback to issues from the central unit, thus the timeliness and flexibility attributes were significantly decreased.

The quality of laboratory activities was assured because of the fully provided resources and well-qualified staffs. But the delay in submitting data from the lab staff might be a reason of

declining the timeliness of surveillance system. In addition, data management and analysis were done manually. Data transferring by email was dependent mostly on the hospitals. Another issue was the lack of formalized data processing procedures that affected the simplicity and flexibility of the system, e.g. it was difficult for a new staff to take over the work.

The acceptability and enthusiasm of hospitals were negatively affected by the frequency of data exploitation and reporting. All above laboratory and data issues could be improved significantly by establishing an automated system: data submitting reminder, data validation, analysis and reporting. The communication and support should be easier to increase the timeliness and acceptability. Email and telephone communication were not enough to describe all issues and feedback. An internet-based communication system might be implemented to have an efficient discussion.

One important objective of AMR surveillance systems is to provide accurate estimates of the resistant proportions of priority pathogens to inform control actions and to guide empirical therapy. The surveillance components evaluated here include a good representativeness of hospitals in terms of hospital types and geographic areas, and therefore AMR data collected from this system can provide a representative picture of the AMR situation of the country. One limitation was that the network did not include smaller hospitals such as district hospitals; one might expect that the level of resistance is lower in these smaller hospitals. However, due to limited or non-existent microbiology laboratory capacity in the smaller hospitals, we do not have data to understand the actual AMR prevalence in these settings. In addition, with the objectives of AMR surveillance in the VINARES project, it was not feasible to set up active surveillance components to enhance the sensitivity and the ability to detect rare resistance. Based on the outputs of the evaluation using SurvTool and OASIS, the score for sensitivity and specificity of the surveillance system was reduced due to lack of an active surveillance component, however, this output is only applicable when future AMR surveillance systems are required to detect rare resistance and subtle changes in the number of resistant cases in the country. Establishing an active surveillance system for AMR can be resource-consuming and need to be considered carefully depending on the primary objectives of the surveillance [66]. In this evaluation, sensitivity was estimated using the assumption that the numbers of resistant patients were similar all the hospitals of a given type. In addition, the surveillance cost only included the costs contributed by the VINARES project and did not take into account any other investment costs by the participating hospitals. These factors should be taken into consideration when applying similar assessment to other surveillance systems.

In this evaluation, sensitivity was estimated using the assumption that the numbers of resistant patients were similar all the hospitals of a given type. In addition, the surveillance cost only included the costs contributed by the VINARES project and did not take into account any other investment costs by the participating hospitals. These factors should be taken into consideration when applying similar assessment to other surveillance systems.

This evaluation is the first evaluation of the AMR surveillance system in Viet Nam. Since this was done after the VINARES projects have completed, most assessments were conducted retrospectively. In the future, in order to improve the performance of the surveillance systems, evaluation protocols should be developed and integrated from early on to provide feedback in time for improvement and enable the systematic and timely corrections.

One limitation of this evaluation was the lack of good data to adequately perform assessments of the effectiveness attributes. As a result, alternatives of data sources were used which were mostly of poor quality in attempt to analyse some of these attributes. For example, representativeness was assessed by the number of regions in network. We did not have data for further assessment of representativeness in each bacteria or disease. Likewise, the sensitivity assessment might be biased toward underestimation as the hospitals in the surveillance network were major secondary and tertiary hospitals of Viet Nam and the proportion of resistant cases among patients might be higher than the overall proportion in the country. Sensitivity was lower among *E. coli* and *K. pneumoniae* – these bacteria are found commonly as pathogens in the community - and was higher among *A. baumannii* – bacteria found frequently as pathogens in ICU because the coverage of provincial hospitals in VINARES was lower than national and specialized hospitals. It is therefore premature and difficult to interpret and draw any conclusions on these attributes.

Regarding the costs of the surveillance system, the VINARES 2 cost per outcome unit was lower than in VINARES 1 for two reasons. VINARES 2's total cost was lower than VINARES 1 as it was inherited from VINARES 1. No investment on initial setting up such as network settlement, materials and training were required for VINARES 2. Moreover, there were more patients who had samples collected and AST done in 2016 than in 2012 which explained the lower cost per isolate in the 2016 period.

This is the first study which applied the SurvTool for the evaluation of AMR surveillance systems in human health. In comparison with an evaluation of gonococcal AMR surveillance in Australia which was carried out in 2005 using the guidelines for the evaluation of

surveillance systems developed by US CDC [52], this study had different definition of effectiveness attributes, although this guideline proposed the same performance attributes that were already mentioned in SurvTool. The simplicity, flexibility, sensitivity, representativeness, timeliness and acceptability attributes were evaluated. Similar to our study, their evaluation did not have control data to quantify sensitivity in terms of probability of detection; but the sensitivity was assessed differently - by comparing the increasing resistant cases in the surveillance system with the report from a reference laboratory. The timeliness was simply assessed by representing the frequency of releasing the report: quarterly and annual reports within six months of the end of the reporting period. According to WHO, this frequency was adequate for reporting AMR trends [180]. So, the annual report of AMRSS of Viet Nam could be considered as not sufficient.

In comparison with other AMRSS reviewed previously, the VINARES surveillance system shared a similar limitation in terms of a lack of population data in order to have accurate assessments. VINARES had similar timeliness in terms of feedback, data update and reporting in comparison to S42 and S54. VINARES targeted a wider range of pathogens, type of hospitals and regions of Viet Nam, unlike the previous systems that only targeted a specific pathogen (e.g. S54) or only included a type of medical laboratories (e.g. S66). Regarding the estimated coverage, VINARES appeared to have a lower coverage than some other AMRSS including S54 and S38.

Since 2016, this network of hospitals has been officially recognized as the national surveillance network for AMR by the MoH in Viet Nam (decision 6211) with continuing EQA, surveillance protocols and data submission portal in development. This set-up should allow the national network to start operating smoothly based on the strengths of VINARES. The organization and objectives of the AMR surveillance system in the VINARES period 2012-2013 and 2016-2017 were well defined. The surveillance tool and training as set up in VINARES was sufficient for a sustainable AMR surveillance system in a low-resourced setting such as Viet Nam.

Two areas for improvement that might be applied to the current national surveillance system are: (1) to develop and establish an automatic data management and reporting system along the surveillance process to improve the passive detection and reporting of AMR and (2) to develop an adapted evaluation protocol to systematically and regularly assess the performance and effectiveness of the surveillance system.

Since 2016, the national surveillance network is led by the Medical Services Administration within the Viet Nam MoH and has received support through the Fleming Fund pilot grant (held by OUCRU) and the Global Health Security Agenda with US CDC and PATH as main partners. The Fleming Fund country grant replaced the pilot grant funding and is held by FHI360 with subcontracts to PATH and OUCRU. Recently, three university hospitals (in the north, central and south of Viet Nam) were added to the network. Regular laboratory trainings have been conducted by OUCRU and its host, the National Hospital for Tropical Diseases. Monthly UK-NEQAS panels for identification and AST are distributed and results are collected by OUCRU. Failure to submit the right result is fed back and discussed with the labs and extra training is conducted where needed. PATH has developed a website and portal for sites to submit AMR data from WHONET and all laboratories have been provided with laptops with WHONET translated into Vietnamese installed. A ministerial committee is developing a surveillance protocol based on GLASS, with relevant vaccine-preventable and locally relevant pathogens added, with the aim to also collect sufficient clinical metadata for the data to inform clinical decision-making and treatment guidelines.

To increase the utility of AMR surveillance data, a pilot research project "A Clinically-Oriented Antimicrobial Resistance Surveillance Network) (ACORN) has been initiated recently in the Oxford Tropical Network (OUCRU and Mahidol Oxford Tropical Medicine Research Unit- MORU) aiming to establish an efficient and pragmatic protocol compatible with GLASS to capture clinical data for linking with microbiology data in the surveillance system in Viet Nam, Cambodia and Laos [181,182].

2.5. Conclusion

This evaluation reveals the strengths and weaknesses of VINARES's surveillance system in two periods. It could be a reference for researchers and public health organizations in establishing an efficient AMRSS. The type of hospitals has an effect on the efficacy of AMRSS. The objective of the system was clear, central and hospital units were well structured, and the surveillance protocol was consistent over time; all of these factors allow trends in AMR over time to be identified. Although VINARES has low coverage and sensitivity based on the comparison with the national statistics, the structure of VINARES could be considered sufficient to capture the overall AMR situation in a LMIC setting such as Viet Nam. The result suggests appropriately building a core network of participant hospitals can help to increase the effectiveness and decrease the cost per income unit. Further evaluation should be undertaken to optimize the effectiveness of AMRSS based on the backbone of VINARES as it is now the national surveillance system for AMR in Viet Nam.

Chapter 3

Antimicrobial susceptibility testing results of VINARES project in two periods: 2012-2013 and 2016-2017

During the time of implementation, the VINARES project generated AMR data for two time periods: 2012-2013 and 2016-2017. These datasets are important in providing an understanding of the overall AMR patterns for infection-causing bacteria in the hospitals in the network, informing clinical treatment in practice and supporting design and evaluation of control interventions. For my PhD thesis, these data are necessary as baseline data inputs to evaluate the VINARES surveillance system and optimize the AMR surveillance systems through modelling the effectiveness and costs of hypothetical surveillance systems in chapter 4.

This chapter presents the work of analysing these two datasets that have formed two peer-reviewed articles, one has been published in Journal of Global Antimicrobial Resistance [183] and one will be submitted soon.

3.1. Antimicrobial susceptibility testing and antibiotic consumption results from 16 hospitals in Viet Nam- the VINARES project, 2012-2013.

3.1.1. Introduction

Antimicrobial resistance (AMR) among common bacterial pathogens is recognized as a global health threat, leading to a significant increase in healthcare costs, treatment failures and deaths [155]. The issue is more pressing in low- and middle-income countries (LMICs) like Viet Nam where the burden of resistant infections is disproportionate, while data and evidence on the exact burden and epidemiology are scarce [31].

Overuse and inappropriate use of antibiotics is an important driver for the emergence and spread of AMR. The World Health Organization (WHO) has introduced a six-point policy package on World Health Day 2011, including surveillance of antimicrobial resistance and use and rational antimicrobial use [184], which served as the framework for the Global and most National Action Plans of member states. WHO also published a comprehensive set of recommendations to track antimicrobial use and resistance in bacteria, and to ensure a better use of antibiotics and reduce antimicrobial use in animal husbandry [64]. In Viet Nam, there is substantial overuse of antimicrobial drugs, both in the animal health sector and in hospitals and the community in the human health sector [185][164]. An observational study of antibiotic sales in northern Viet Nam showed high proportions of transactions at pharmacies that included antibiotics: 24% in the urban sites and 30% in the rural sites, the large majority without prescription [186].

Since 1988, a number of national and international efforts have been made to implement AMR surveillance in Viet Nam, at different scales. Table 3.1.1 describes the objectives, scale and results of each project.

The Viet Nam Resistance network (VINARES) was launched in 2012 as a collaboration between the Ministry of Health, the Vietnamese Infectious Diseases Society, the Oxford University Clinical Research Unit-Viet Nam (OUCRU) and Linköping University, Sweden together with 16 hospitals across the country [166]. Here we describe the Antimicrobial Sensitivity Testing (AST) results from isolates from clinical specimens from the microbiology laboratories and the antimicrobial consumption data from the pharmacies from the VINARES hospitals between October 2012 and September 2013. These results provide an update on earlier results published in the situation analysis ([164]) and allow for recommendations of

improvement of data collection to use as evidence for design and implementation of targeted interventions to tackle antibacterial overuse and resistance in Viet Nam.

3.1.2. Methods

Data collection

The VINARES network was described previously [166]. Sixteen hospitals were included, among which seven in the northern, three in the central and six in the southern region of Viet Nam; including 7 national and 9 provincial level hospitals; 2 tropical diseases, 2 paediatric and one surgical hospital(s) (figure 3.1.1). Antibiotic consumption was reported monthly by pharmacy department. Each department was provided with a laptop and an Excel file to enter the detail antibiotic consumption in ICU ward and in whole hospital. In few cases, patients had to buy outside medicine that was not available in pharmacy department (e.g. colistin). We ignored this situation but it did not affect to the result as it was very rare.

A baseline laboratory assessment was conducted at the 16 participating hospitals. Laboratories were provided with American Type Culture Collection (ATCC) reference strains for internal quality control and were enrolled to the monthly UK-NEQAS identification and AST external quality assessment programme. Each laboratory performed identification and susceptibility test on an isolate sent monthly by UK-NEQAS and uploaded the result on their website. UK-NEQAS assessed the test results and returned the report to OUCRU. Each microbiology laboratory was also provided a laptop, surveillance database software (WHONET) [173], and up-to-date Vietnamese-translated Clinical Laboratory Standards Institute (CLSI) guidelines (M100-S22) [73]. Staff from all participating sites were trained during several workshops on microbiology methods and the use of WHONET. A helpdesk was set up to address any issues throughout the project. Reported data including AST results from bacterial isolates from clinical specimens sent in for routine diagnostics and hospital-wide antibiotic consumption in the 16 participating hospitals were sent monthly from October 2012 to September 2013. AST results were entered manually into WHONET or exported from automated AST as VITEK2 (bioMérieux, Marcy l'Étoile, France) or LABCONN (Labsoft, Viet Nam) using BacLink (provided with WHONET). There were four hospitals that used automated systems, 11 used manual and one used both. A configuration file was developed for each laboratory to convert data. Both AST and antimicrobial usage data were submitted regularly or on request by email.

Table 3.1.1: Objectives, scale and results of AMR surveillance projects which were implemented between 1990-2017 in Viet Nam .

Project	Year	Scale	Vietnamese sites	Description	Result of program
NPSAR (former ASTS) [162] [163]	1988 – 2006	Viet Nam	9 (in 1988) 31 (1993)	NPSAR – implemented by MoH - was a national surveillance program for AMR. Bacteria causing infectious diseases in in-patients and out-patients were isolated and tested for antimicrobial susceptibility.	*Escherichia coli* producing ESBL: 7.7% (42/548) *Klebsiella pneumoniae* producing ESBL: 23.7% (115/485)
ANSORP [32]	1996	Asia	1	Children's Hospital 2, HCMC, participated in a project of surveillance for pneumococcal resistance among clinical *Streptococcus pneumoniae* isolates that were collected from 14 centres in 11 countries in Asia and the Middle East between 2000 and 2001.	Proportion of penicillin non-susceptibility *S. pneumoniae* (71.4%) in Viet Nam, highest among participant countries. Amoxicillin/clavulanic acid (AMC) resistance rate was 22.2%.
ANSORP [33]	2004 - 2006	Asia	1	A prospective, multinational surveillance study with molecular typing analysis that was performed to understand the changing epidemiology of *Staphylococcus aureus* infections in Asian countries.	University of Medicine and Pharmacy in HCMC, Viet Nam reported hospital- and community-acquired *S. aureus* were 74.1% and 30.1%, respectively. Second highest rates of MRSA among participants, lower than Sri Lanka.
Multi-centre	2008-2009	Global	3	This study assessed the variation in management and adherence to treatment guidelines of *S. aureus* bacteraemia treated consecutively over one year in eight centres in	80 patients (19%) from Viet Nam had methicillin-resistant *S. aureus* bacteraemia.

evaluation study on *S. aureus* bacteremia [187]				the United Kingdom, three in Viet Nam and one in Nepal.	
GARP[164]	2009	Global	15	GARP-Viet Nam and Oxford University Clinical Research Unit (OUCRU) collaborated with the Vietnamese MoH to set up new antibiotic resistance surveillance program. A cross-sectional study was performed to collect antibiotic resistance and antibiotic use data from 15 participating hospitals 2009.	*E. coli* resistant to cefuroxime (30-80%), to SXT from 60-80%. *E. coli* and *K. pneumoniae* producing ESBL were 15%-57% and 7%-73%, respectively. 40% of *Pseudomonas aeruginosa* and 60% of *Acinetobacter spp.* were resistant to ceftazidime.
SOAR [165]	2009-2011	Global	11	A study on AMR surveillance of respiratory pathogens. Isolates of *S. pneumoniae* and *H. influenzae* were obtained from clinical materials taken from adults and paediatric patients with community-acquired respiratory infections.	47.8% and 93.1% of *S. pneumoniae* were non-susceptible to penicillin and resistant to azithromycin. 40.5% of *Haemophilus influenzae* produced β-lactamase. Resistances to AMC for *S. pneumoniae* and *H. influenzae* were low (3.1% and 2.6%, respectively).
SMART [188]	2009 – 2011	Global	4	A study on antimicrobial susceptibility rates in aerobic Gram-negative bacteria causing intra-	ESBL positive in *E. coli* and *K. pneumoniae* were 48.1% and 39.5%, respectively.7.7% of 13

	abdominal infections in Viet Nam (2 sites in HCMC and 2 sites in Hanoi).	*P. aeruginosa* isolates were resistant to ceftazidime but none to ciprofloxacin.

AMR: Antimicrobial Resistance; NPSAR: National Program for Surveillance in Antimicrobial Resistance; ASTS: Antimicrobial Sensitivity Testing Study; MoH: Ministry of Health; ESBL: Extended spectrum beta-lactamase; AMC: Amoxicillin/clavulanic acid; ANSORP: Asian Network for Surveillance of Resistant Pathogens; HCMC: Ho Chi Minh City; MRSA: Methicillin-resistant Staphylococcus aureus; GARP: Global Antibiotic Resistance Partnership; SXT: Trimethoprim/sulfamethoxazole; SOAR: Survey of Antibiotic Resistance; SMART: Study for Monitoring Antimicrobial Resistance Trends.

All duplicate isolates for the same patient (identical specimen type and bacterium) in the AST dataset were excluded following WHO recommendations [39]. Results obtained by disk diffusion (DD) and minimum inhibitory concentration (MIC) methods were combined. If both were performed the MIC result was used. Reported resistance rates are the proportion of bacteria with the AST showing resistance (result = R). Intermediate susceptible isolates (result = I) were not considered as resistant. Results were accepted, analysed and reported as is, and generally no confirmatory testing of unexpected results or rare phenotypes in reference or central laboratories was performed according to current practice in most LMICs.

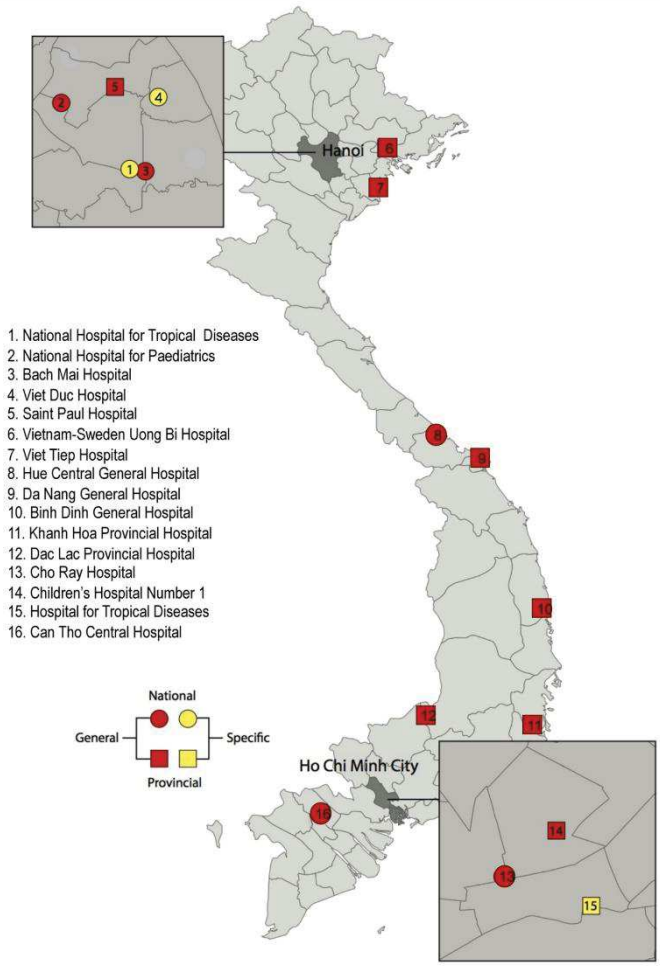


Figure 3.1.1: Location, speciality, and type of the 16 participating hospitals in the VINARES 2012-2013 project. Source: doi:10.1371/journal.pmed.1001429.g001

Data analysis

The number and proportion of nine indicator bacteria (*Acinetobacter spp.*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella spp.*, *Staphylococcus aureus*, *Enterobacter spp.*, *Enterococcus faecium* and *Streptococcus pneumoniae*) were described overall, by patient age group, sex and specimen type.

An *S. aureus* isolate was counted as MRSA if it tested resistant to oxacillin or cefoxitin in screening. Similarly, *S. pneumoniae* isolates were counted as reduced susceptible to penicillin if resistance to oxacillin by disk diffusion was reported (also if unconfirmed by MIC testing). Resistance rates were reported for all specimens combined and for a subgroup of invasive isolates from blood and cerebrospinal fluid (CSF). The proportion assessed by disk diffusion or MIC was reported if applicable. A sample was considered resistant to an antibiotic class if it was resistant to at least one antibiotic agent in that class as per CLSI guidelines.

The antibiotic consumption was summarized in number of Defined Daily Dose per 1 000 bed days (DDD/1000 patient-days). The Defined Daily Dose is the assumed average maintenance dose per day for a drug used for its main indication in adults, which can be obtained from the WHO Antimicrobial DDD Quick Reference List [153]. The DDD/1000 patient-days was calculated by antibiotic class and did not depend on bed size of hospital.

For each pathogen – antimicrobial combination, the resistant proportion was calculated as the ratio between the number of resistant isolates and number of tested isolates for that drug. All hospitals were anonymized and coded from H1 to H16. R software (version 3.1.11) was used for the analysis [189].

3.1.3. Results

3.1.3.1. Distribution of bacteria and antibiotics

AST results were reported for 26,808 isolates from the VINARES network between October 2012 and September 2013. After de-duplication and removal of fungi, 24,732 bacterial isolates were included in the analysis.

The most commonly isolated organisms were: *E. coli* (4,437 isolates, 18%), *Klebsiella spp.* (3,290 isolates, 13%) – including 2,206 *K. pneumoniae* isolates (9%), *Acinetobacter spp.* (2,895 isolates, 12%) – including 1,668 *A. baumannii* isolates (7%), *P. aeruginosa* (2,326 isolates, 9%), *S. aureus* (2,039 isolates, 8%), *Enterobacter spp.* (1,067 isolates, 4%), *S. pneumoniae* (813 isolates, 3%), *H. influenzae* (404 isolates, 2%) *E. faecium* (98 isolates, 1%). Gram-negative bacteria accounted for 69% (17,065 isolates) and Gram-positive for 31% (7,667 isolates). Sputum was the most frequently reported specimen (3,625 isolates, 15%); followed by blood (3,222 isolates, 13%). Eleven percent of total isolates were recovered from blood and CSF.

The distribution of isolates by gender and age of patient and type of specimen for the nine indicator bacteria is summarized in supplementary table S3.1.1. Among 17,369 common bacteria (*E. coli, K. pneumoniae, A. baumannii, P. aeruginosa, S. aureus*, *Enterobacter spp., S. pneumoniae*, *H. influenza* and *E. faecium*), a higher proportion was isolated from male (66%) than from female patients (34%), reflecting the usual hospital population in Viet Nam. *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *Acinetobacter spp.* (including *A. baumannii*) were mainly reported from adults aged over 20, while *S. aureus* and *S. pneumoniae* were more commonly reported from children aged 10 years or less.

The distribution of bacteria was stratified by hospitals and by region separately (figure 3.1.2). *Acinetobacter spp.* were found mostly in two major general hospitals (H2 and H4). *H. influenzae* was isolated mainly from children, with more than 50% from one paediatric hospital (H11). The proportion of *E. coli* was similar across the three regions and, overall, the pathogen distribution appeared similar across regions too.

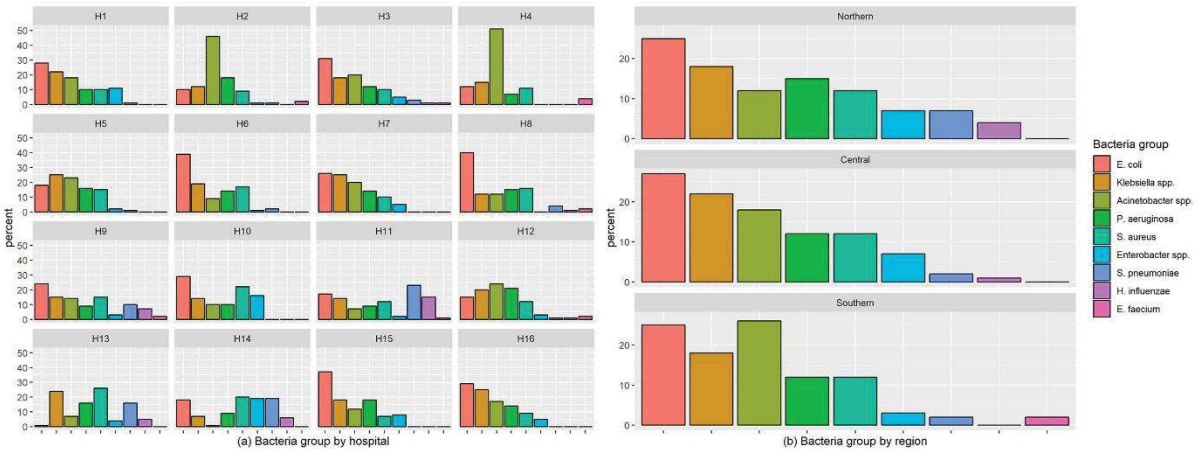


Figure 3.1.2: Percentage of bacteria by hospitals (a) and by regions (b) of 16 hospitals in VINARES 2012-2013 project.

Antibiotic consumption was summarized by hospital and region separately. One hospital (H2) did not provide consumption data. The average antibiotic consumption was 918 DDD/1,000 patient-days per hospital. Hospitals in the central and southern region had similar antibiotic consumption rates (1,079 and 1,026 DDD/1000 patient-days, respectively), while a lower rate was reported on average from hospitals in the northern region (799 DDD/1000 patient-days, after excluding a paediatric hospital). Most commonly used antibiotics were third-generation cephalosporins (223 DDD/1000 patient-days, 24%), fluoroquinolones (151 DDD/1000 patient-days, 16%), second-generation cephalosporins (112 DDD/1000 patient-days, 12%), penicillin combinations (111 DDD/1000 patient-days, 12%), followed by aminoglycosides (54 DDD/1000 patient-days, 6%), penicillins with extended spectrum (53 DDD/1000 patient-days,

6%), fourth-generation cephalosporins (49 DDD/1000 patient-days, 5%), carbapenems (35 DDD/1000 patient-days, 4%) and glycopeptides (10 DDD/1000 patient-days, 1%). Overall, third-generation cephalosporins were the largest group in all regions, followed by fluoroquinolones (figure 3.1.3). Two thirds of second-generation cephalosporins were used in the central region.

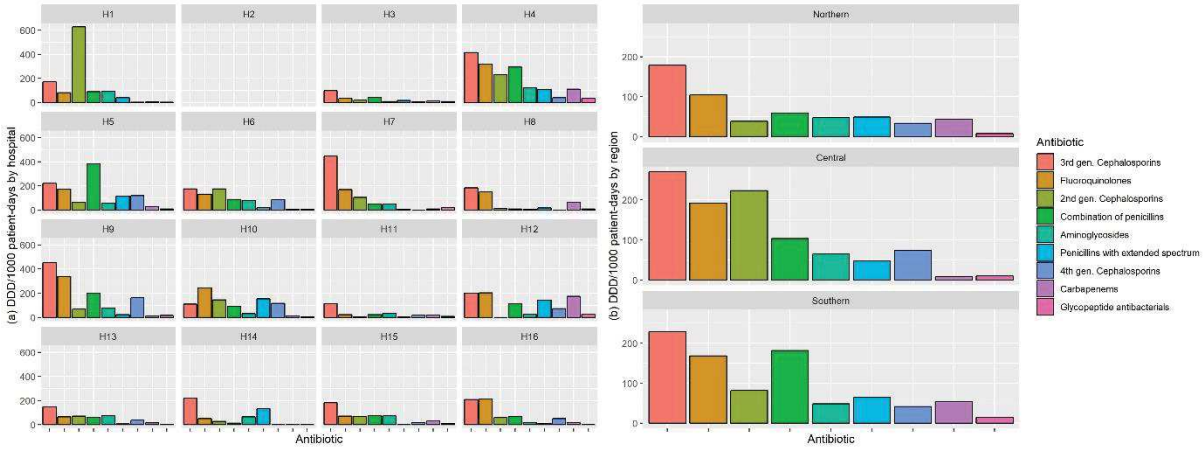


Figure 3.1.3: Antibiotic consumption in number of Defined Daily Dose / 1000 patient-days by hospitals and regions, collected from 15 hospitals of VINARES 2012-2013 period. One hospitals did not provide data.

3.1.3.2. Antimicrobial susceptibilities

General

The proportion of isolates having AST varied by hospital; more ASTs were performed at national hospitals than in provincial hospitals (supplementary table S3.1.2). Vancomycin-susceptibility test for *E. faecium* and imipenem-susceptibility test for *P. aeruginosa* were the most frequently carried out across the hospitals (98% and 76%, respectively). Four hospitals (H3, H4, H8, H12) had tested more than 95% of reported isolates.

Figure 3.1.4 illustrated the resistant proportions of each pathogen – antimicrobial combination and its relationship with the amount of antibiotic used and the number of isolates. Second-generation cephalosporins are not included in figure 3.1.4 because most hospitals did not test for these. More than 50% of Enterobacteriaceae were resistant to third-generation cephalosporins and fluoroquinolones. Carbapenem-resistant proportions were highest among *Acinetobacter spp.* (around 75%), followed by *P. aeruginosa* (around 50%) and lowest in Enterobacteriaceae (around 25%). *S. aureus* and *E. faecium* were susceptible to vancomycin, but the susceptibility results of *E. faecium* should be interpreted with caution because of the low numbers. *S. pneumoniae* was susceptible while nearly 50% of *H. influenzae* were resistant to combinations of penicillins.

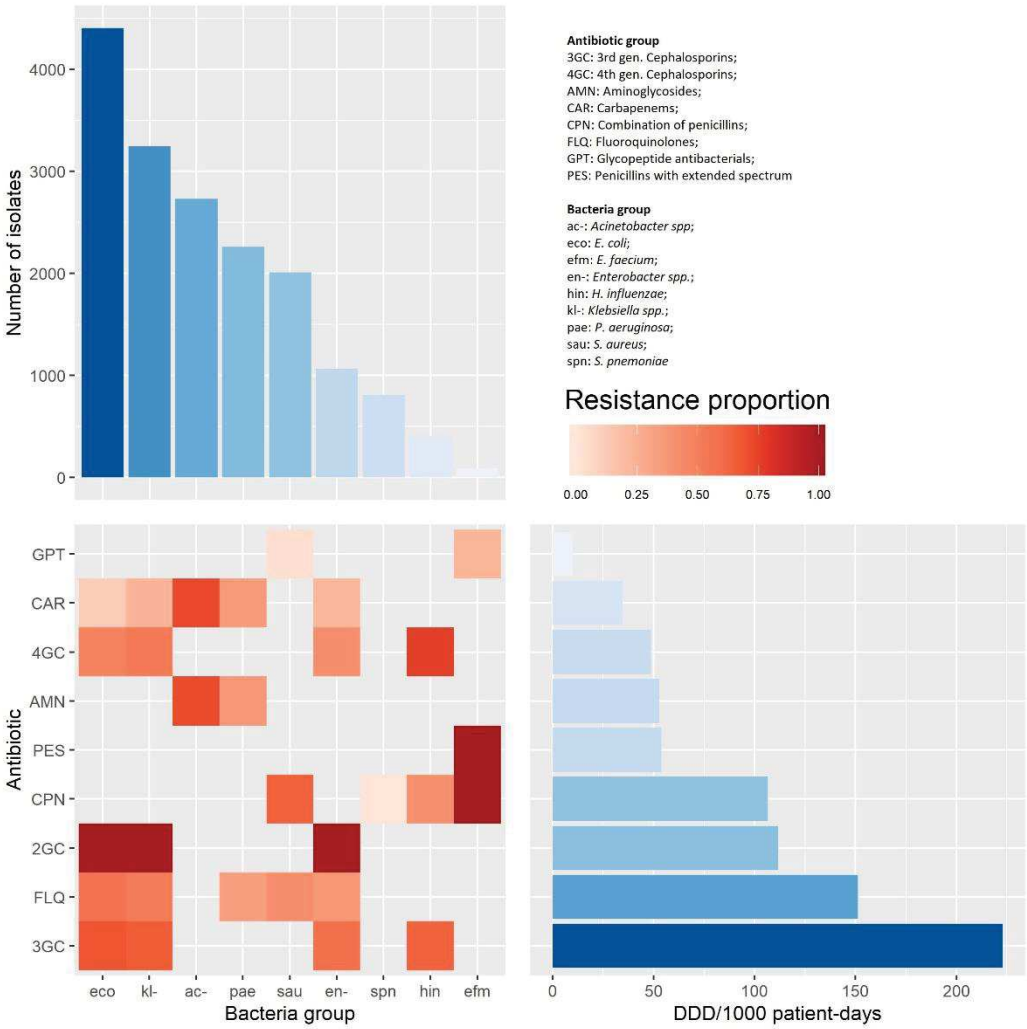


Figure 3.1.4: Resistant proportion, number of isolates and number of Defined Daily Dose/1000 patient-days per antibiotic group of 15 hospitals in VINARES 2012-2013 project.

For each pathogen – antimicrobial combination, the resistant proportion was shown in bottom left figure; the number of isolates for each organism was in top left and the number of DDD/1000 patient-days of antibiotic group was in bottom right. The resistant proportion was calculated for 15 hospitals that provided antibiotic consumption data. DDD/1000 patient-days figure illustrates the amount of antibiotic used for all bacterial treatment, not for any specific bacteria. Untested or clinically irrelevant pathogen – antimicrobial combinations were not shown.

AST results of Gram-positive bacteria

Table 3.1.2 showed AST result for *S. aureus*, *S. pneumoniae* and *E. faecium*. *S. aureus* was isolated from 2,039 specimens. 258 (13%) were from blood and CSF. Among 1,580 tested, 1,098 (69%) S. *aureus* isolates were identified as MRSA. Similar resistance rates were observed for isolates from blood and CSF isolates from all specimens. D-test for induced

clindamycin resistance was not separately reported, therefore resistance may be underestimated.

Results from 813 *S. pneumoniae* isolates included 87 from blood and CSF. 99% (353/358) ceftriaxone, 39% (86/221) penicillin and 54% (349/641) vancomycin susceptibility tests were done / confirmed using E-tests. 115/344 isolates (33%) of *S. pneumoniae* showed reduced susceptibility to penicillin; the corresponding percentage in blood and CSF isolates was 7/30 (23%). *S. pneumoniae* susceptibility to penicillin was screened using oxacillin disks; 86 isolates were confirmed by penicillin MIC test. Out of 194 oxacillin disk diffusion results showing resistance, 87 (45%) were not confirmed by penicillin susceptibility test. Regarding blood and CSF specimens, there were 6 isolates confirmed by penicillin MIC test, and they were all susceptible. 10 isolates (2%) of *S. pneumoniae* were resistant to vancomycin (2/10 of resistant isolates were confirmed by E-test). These results were not confirmed in a reference laboratory or molecularly, and this should be interpreted with caution.

Among 98 *E. faecium* isolates, only one amoxicillin susceptibility test was done. 78% of isolates were vancomycin susceptible while the proportion of normal-level gentamicin-susceptibility was lower than 50%.

Antimicrobial susceptibility testing results of VINARES project: 2012-2013

Table 3.1.2: Antimicrobial susceptibility results of *S. aureus*, *S. pneumoniae* and *E. faecium* isolated in 16 hospitals of the VINARES 2012-2013 project

Resistance	*S. aureus*		*S. pneumoniae*		*E. faecium*	
/ Tested isolates (%)	All specimens	Blood and CSF	All specimens	Blood and CSF	All specimens	Blood and CSF
	(n = 2039)	(n = 258)	(n = 813)	(n = 87)	(n = 98)	(n = 24)
MRSA	1098/1580 (69)	145/197 (74)				
Vancomycin	22/823 (3)	2/135 (1)	10/641 (2)	1/74 (1)	21/96 (22)	3/24 (12)
Ciprofloxacin	456/1277 (36)	71/189 (38)	2/12 (17)	0/0 (NT)		
Erythromycin	985/1315 (75)	103/143 (72)	246/289 (85)	26/29 (90)		
Clindamycin	639/907 (70)	74/118 (63)				
Gentamicin	435/1155 (38)	55/135 (41)			26/46 (57)	8/9 (89)
Levofloxacin	333/852 (39)	40/125 (32)				
SXT	261/1156 (23)	41/141 (29)				
Penicillin			115/344 (33)*	7/30 (22)**		
Ceftriaxone			90/358 (25)	9/52 (17)		
Amoxicillin					1/1 (100)	0/0 (NT)

CSF: Cerebrospinal fluid; MRSA: Methicillin-resistant Staphylococcus aureus; SXT: Trimethoprim/sulfamethoxazole; * screened with oxacillin, 86 isolated were confirmed by MIC method and only one isolate was resistant to penicillin; ** screened with oxacillin, only 6 isolates was confirmed by MIC method and all were susceptible to penicillin; Untested or clinically irrelevant pathogen – antimicrobial combinations were not shown

AST results of Gram-negative bacteria

Enterobacteriaceae's susceptibility for amikacin, cefotaxime, ciprofloxacin, gentamicin, imipenem, tobramycin and trimethoprim / sulfamethoxazole are shown in table 3.1.3. Among the 4,437 *E. coli* submitted, 527 (12%) were from blood and CSF and 992 (23%) from urine. More than 80% of ASTs for *E. coli* were carried out by disk diffusion. Resistance was above 50% for third-generation cephalosporins and fluoroquinolones. Lower resistance levels were seen for imipenem and amikacin. Resistance rates among all isolates were generally higher than proportions observed in blood and CSF isolates ($p < 0.0001$ for cefotaxime and ciprofloxacin; $p = 0.03$ for SXT).

Of the 3,290 available *Klebsiella spp.* isolates, 2,206 were *K. pneumoniae*. Resistance rates to third-generation cephalosporins and carbapenems were 68% and 16%, respectively. Similar to *E. coli,* proportions of resistance to cefotaxime, ciprofloxacin and SXT were also lower among blood and CSF than all isolates ($p < 0.0001$ for all).

Among the 1,067 *Enterobacter spp.* isolates (82 from blood and CSF) 21% of isolates were resistant to carbapenems.

Table 3.1.4 showed the AST results of *Acinetobacter spp*., *P. aeruginosa* and *H. influenzae*. Results from 2 895 *Acinetobacter spp*. (including 1,668 *A. baumannii*) were submitted. Data on colistin was available from only one hospital and 2 of 333 isolates were found to be resistant. Results showed very high resistant proportions for all antibiotics, from 68% (amikacin) to 77% (ceftazidime). Resistant proportions of *Acinetobacter spp.* for imipenem and amikacin in blood and CSF were lower than in other specimens ($p < 0.0001$ for both).

Of the 2,326 *P. aeruginosa* isolates submitted, 154 were from blood and CSF. The resistance rate to ceftazidime was 33%, similar to blood and CSF specimens. 33% of isolates were resistant to imipenem while 39% were aminoglycosides-resistant. Blood isolates had lower aminoglycosides-resistance levels in comparison with all isolates ($p=0.04$).

H. influenzae was isolated from 404 specimens; including 10 from blood and CSF. 160 (71%) isolates were resistant to ampicillin. The resistance rate to amoxicillin/clavulanic acid (AMC) and cefotaxime were 39% and 44%, respectively.

Antimicrobial susceptibility testing results of VINARES project: 2012-2013

Table 3.1.3: Antimicrobial susceptibility results of *E. coli, Klebsiella spp., Enterobacter spp.* isolated in 16 hospitals of VINARES 2012-2013 project

Resistance / Tested isolates (%)	*E. coli*		*Klebsiella spp.*		*Enterobacter spp.*	
	All specimens (n = 4437)	Blood and CSF (n = 527)	All specimens (n = 3 290)	Blood and CSF (n = 413)	All specimens (n = 1067)	Blood and CSF (n = 82)
Amikacin	321/2936 (11)	36/394 (9)	638/2 163 (29)	61/329 (19)	149/768 (19)	11/58 (19)
Cefotaxime	2342/4192 (56)	240/514 (47)	1479/2227 (66)	101/190 (53)	483/802 (60)	25/48 (52)
Ciprofloxacin	1758/3052 (58)	188/397 (47)	1222/2305 (53)	139/332 (42)	277/741 (37)	28/63 (44)
Gentamicin	1285/2655 (48)	111/282 (39)	1042/1989 (52)	99/233 (42)	294/760 (39)	21/47 (45)
Imipenem	180/2977 (6)	15/403 (4)	393/2 294 (17)	64/361 (18)	144/665 (22)	12/70 (17)
SXT	1994/2803 (71)	196/298 (66)	1242/2007 (62)	118/236 (50)	360/709 (51)	24/51 (47)
Tobramycin	502/1309 (38)	52/247 (21)	588/1377 (43)	65/236 (28)	142/386 (37)	16/48 (33)

CSF: Cerebrospinal fluid; SXT: Trimethoprim/sulfamethoxazole

Antimicrobial susceptibility testing results of VINARES project: 2012-2013

Table 3.1.4: Antimicrobial susceptibility results of *Acinetobacter spp., P. aeruginosa*, *H. influenzae* isolated in the VINARES 2012-2013 project

Resistance	*Acinetobacter spp.*		*P. aeruginosa*		*H. influenzae*	
/ Tested isolates (%)	All specimens (n = 2895)	Blood and CSF (n = 313)	All specimens (n = 2326)	Blood and CSF (n = 154)	All specimens (n = 404)	Blood and CSF (n = 10)
Amikacin	1347/1993 (68)	82/188 (44)	329/1556 (21)	13/82 (16)		
Cefotaxime					118/270 (44)	5/10 (50)
Ciprofloxacin	1298/1733 (75)	74/207 (36)	496/1527 (32)	33/120 (28)	17/269 (6)	0/10 (0)
Gentamicin	1385/1837 (75)	130/214 (61)	566/1456 (39)	33/106 (31)		
Imipenem	1495/2138 (70)	110/244 (45)	578/1765 (33)	36/129 (28)	33/341 (10)	0/10 (0)
SXT	1258/1799 (70)	86/192 (45)			46/60 (77)	3/5 (60)
Ceftazidime	1650/2146 (77)	124/242 (51)	602/1826 (33)	43/133 (32)		
TCC	771/1128 (68)	47/141 (33)				
AMC					109/276 (39)	2/5 (40)
Erythromycin					3/3 (100)	0/0 (NT)
Ampicillin					160/226 (71)	3/5 (60)

CSF: Cerebrospinal fluid; SXT: Trimethoprim/sulfamethoxazole; TCC: Ticarcillin/clavulanic acid; AMC: Amoxicillin/clavulanic acid.

3.1.4. Discussion

We describe the AST and antibiotic usage results reported from the VINARES network in Viet Nam between 2012 and 2013. Overall, the data showed high proportions of AMR among all tested bacteria across all hospitals in the network. Our results also show large variations in the resistant proportions between hospitals. This highlights the importance of continuous monitoring of local antibiotic use and bacterial resistance - one of the core strategies in the National Action Plan on combatting drug resistance [156]. Overall, we find lower proportions of resistance in samples taken among isolates from blood and CSF samples, likely reflecting different proportions of hospital acquired isolates among sample-types.

Cephalosporins, fluoroquinolones and penicillin covered 70% antibiotic use. Hospitals were more likely to use fluoroquinolones and less likely to use cephalosporins in 2012 (16%) than in 2008 (11%) [185]. This may be explained by the change of antimicrobial susceptibility between the two periods.

The antibiotic use DDD/1000 patient-days provides a rough indication that 91% of patients in hospitals were on antibiotic treatment. However, DDD/1000 patient-days is not an appropriate measure to study the impact of antimicrobial stewardship because DDD/1000 patient-days can be misrepresented by use of combination therapy or use of higher dosages for certain indications or guided by therapeutic drug monitoring (not yet practiced in Viet Nam). This biases towards higher DDD/1000 patient-days, and thus an overestimate of antibiotic use. As evidence of these biases in DDD/1000 patient-days measurements, a monthly point prevalence study conducted in ICUs within VINARES reported that the proportion of patients receiving antibiotics at survey time was 85% (2787 of 3287) and that 60% of patients were prescribed more than one antibiotic [190]. This result was higher compared to the point-prevalence conducted in 2008 (67% (5104 of 7571) of patients receiving antibiotics) [185]. Two possible explanations were that 16/36 participating sites of the previous study were district-level hospitals with an expected lower usage and that there has been an increase of usage of antibiotic in hospitals over time. The global report of antibiotic consumption also stated an increase of 20-25 DDD/1000 patient-days in Viet Nam in 2010-2015 period [191].

The number of days of antimicrobial therapy (DOT) can be used along with DDD/1000 patient-days to report antibiotic consumption practices in hospital, which offers more clinical relevance [192]. DOT reports the administration of a single agent on a given day regardless of the number of doses administered or dosage concentration [193], and this avoids the overestimation of

usage. DDD/1000 patient-days allows the comparison of antibiotic use across countries and hospitals, while DOT could make conclusions about the relative use of one antibiotic compared with another [193]. The measurement of DOT might be difficult for most of hospitals [192]. The measurement of antibiotic use by DDD/1000 patient-days and DOT per 1000 patient-days were dissimilar because the administered dose is dissimilar from the DDD recommended by the WHO, according to a study on 130 hospitals in US [193].

We reported similar levels of resistance among four gram-negative bacteria including *E. coli*, *K. pneumoniae, P. aeruginosa* and *Acinetobacter spp.* compared to the GARP situation analysis [164]. Further studies to evaluate the changes in antibiotic consumption and the likely effect on resistance levels at hospitals are warranted to prioritize targets of intervention. In addition, linking microbiology and susceptibility data with clinical data should be aimed for in this surveillance network to allow assessment of the origin of the infection (community versus hospital acquired) for better informing evidence-based guidelines.

In the GARP situation analysis, an MRSA proportion of between 30 to 64% was reported [164]. An evaluation from 2008-2009 in three hospitals in Viet Nam revealed an MRSA proportion of 19% in 80 patients with *S. aureus* bacteraemia [187]; while here we report 61% of MRSA in blood and CSF specimens. Better and more comprehensive surveillance methodology may explain the higher proportions of MRSA bacteraemia. In VINARES, all MRSA tests were done by oxacillin or cefoxitin disc diffusion test, which is a reliable proxy for detection of MRSA [194].

More than 50% of *S. pneumoniae* were non-susceptible to penicillin. This was also confirmed in a recent review by WHO [8], showing the result of penicillin non-susceptibility from 47-48% in 2 countries in the South-East Asia and 17-64% in 10 countries of Western Pacific region. However, the extent of the problem is uncertain to determine partly due to variations in how reduced susceptibility is being reported and large proportions of intermediate results. The SOAR study reported 48% (138/289) of penicillin-non-susceptibility among *S. pneumoniae* [165].

Carbapenems were still mostly active against the tested Enterobacteriaceae. Compared to 2009, there was a slight increase of resistance to imipenem among *E. coli* (from 2% to 6%) and *Klebsiella pneumoniae* (from 10% to 17%) [164]. Most imipenem-susceptibility tests for Enterobacteriaceae were done by disk diffusion, but this may not be as reliable as the broth microdilution or other methods [195]. *Klebsiella spp.* showed increased resistance to third-

generation cephalosporins in comparison with 2009 situation analysis study (from 40% to 66%). Fourth-generation of cephalosporins also had less effect on these species. For *E. coli*, we showed similarly high resistant proportions to the conventional agents used for treatment such as SXT and third-generation cephalosporins in comparison with the 2009 situation analysis (from 60-80%) [164]. These data showed the persistent and increasing problem of Enterobacteriaceae resistance to third-generation cephalosporins in the hospital settings. Even though resistance to carbapenems in our report is still low, the levels tend to increase in comparison with the 2009 situation analysis and are likely to continue increasing unless effective interventions are undertaken.

P. aeruginosa was still susceptible to ceftazidime, ciprofloxacin and imipenem with a resistant proportion around 30%. The 2009 situation analysis showed similar proportions, around 40% resistance to ceftazidime and ciprofloxacin in 2009 [164]. Data from VINARES are more likely to reflect the actual resistant proportiongiven the improved and quality assessed microbiological and reporting practices. *P. aeruginosa* was among the three most common aetiologies of hospital acquired infections in ICUs in Viet Nam in the same period [190]. This point prevalence survey showed higher resistant proportions of *P. aeruginosa* to carbapenems (55.7%) compared to our surveillance results, reflecting the larger burden of resistance in the ICU settings.

In our study, *Acinetobacter spp.* also showed 70% resistance to imipenem, while the proportion reported in the 2009 situation analysis was only 40% [164]. High carbapenem resistance in these organisms raised a great concern for treatment alternatives, as colistin is usually the last resort and an increase in colistin resistance is likely to happen. Colistin resistance was only assessed at one hospital in our network, and 0.6% of 333 tested isolates showed resistance using E-test / VITEK (which are not the recommended standard). Higher levels of carbapenems (85%) and colistin (1.3 [n=78] and 31.6% [n=38]) resistance were reported from two hospitals (of the three provincial and university hospitals participating in VINARES) in southern Viet Nam in another study from 2012-2014 [196].

VINARES reported higher AMC resistance *H. influenzae* in comparison to SOAR (39% and 2.6%, respectively). This could be the result of increasing rate over time, or due to large overlap between participating hospitals. The SOAR samples were came from outpatients, whereas ours were from samples sent to the microbiology laboratories. As microbiology is underutilised in Viet Nam (and other LMICs) this probably represents a population with more advanced

infections or a more extensive history of pre-treatment and thus selection of resistance pathogens. This is very illustrative of how the current AMR surveillance overestimates resistance because of this underuse and lack of clinical metadata and denominators.

AST was not conducted for all reported isolates and this could have introduced bias in the reported resistant proportions. Three explanations can be given: first, some ASTs are only indicated based on the results of another (e.g. in *S. aureus* vancomycin was only tested for MRSA); second, ASTs may have been only indicated when the isolates were suspected to be the etiological pathogen causing clinical manifestations; and third, ASTs may have been ordered because of failure in empirical treatment.

For future efforts to conduct antimicrobial resistance surveillance and to provide more useful data for guiding local clinical treatment and public health research, it is important for clinical microbiology laboratories to be strengthened and better utilized. Currently, the number of samples coming to the laboratory is low in comparison with the number of admitted patients. It is likely that the more severe patients, transferred patients, patients failing primary treatment and patients with hospital acquired infections are overrepresented among patients from whom samples are sent to the laboratory. Clear clinical diagnostic and treatment guidelines, with consistent microbiological testing on suspicion of infectious aetiology, could partially overcome this bias. Clinical data should also be considered to be part of the surveillance data. This could include clinical syndrome, date of admission, transfer status and antibiotic use while sampled.

3.1.5. Conclusion

This project demonstrates an initiative with a large network of hospitals to monitor AMR in Viet Nam. Resistant proportions to common antibiotics in 16 hospitals were remarkably high, most have increased since the 2009 situation analysis. Policy development for pharmacies both in hospitals and in the community requires a structured solution to address this problem. AMR surveillance could be improved by enhancing capacity of clinical microbiologists through advanced training and upgrading WHONET program with more control of data entry and a pre-defined global configuration. Clinical data should be included in the reports from the hospitals in the future. External quality assurance is also recommended for all testing performed in the laboratory.

3.2. Antimicrobial susceptibility testing results from 13 hospitals in Viet Nam – the VINARES project, 2016-2017

3.2.1. Introduction

In a 2015 estimate based on data from the European Antimicrobial Resistance Surveillance Network (EARS-Net), over 33,000 people die each year in the European Union as a direct consequence of a drug resistant bacterial infection [197]. Data in low- and middle-income countries are rare, but a recent estimate from Thailand that 19,122 of 45,209 (43%) deaths in patients with hospital-acquired infection due to multiple drug resistance (MDR) bacteria suggests these number may be higher [25].

In their 2014 review, Rossolini *et al.* indicated an out-of-control crisis for Gram-negative pathogens particularly with the worrisome emergence and spread of carbapenem-resistant Enterobacteriaceae, especially in the hospital environment, while Gram-positive pathogens appear to be relatively under control [198].

In May 2015, the World Health Assembly adopted a Global Action Plan on Antimicrobial Resistance, which highlighted the need to improve awareness and understanding of antimicrobial resistance and to strengthen the knowledge and evidence-based decisions through surveillance and research [36]. The review by the World Health Organisation (WHO) pointed out the lack of a global consensus on methodology and data collection for AMR surveillance. In addition, routine surveillance often uses samples from severe cases including those with hospital acquired infections and those with treatment failure, leading to an under-representation of samples from patients with community-acquired infections (CAI) and failure of the data to properly inform treatment guidelines [8]. As a response to this situation, WHO introduced that same year the Global Antimicrobial Resistance Surveillance System (GLASS). GLASS aims to enable standardized, comparable and validated AMR data collection and analysis, and sharing of AMR data across countries to inform decision-making and action [39].

AMR surveillance activities were initiated in Viet Nam in 1988 with several specific programs as summarised previously [183], including VINARES, a network of 16 hospitals throughout the country collecting data on antimicrobial consumption, susceptibility testing results and hospital-acquired infection prevalence [166,183,190,199].

These projects highlighted high proportions of resistance among several WHO GLASS priority pathogens: carbapenem-resistant *Acinetobacter baumannii* (40% in the Global Antibiotic

Resistance Partnership (GARP) in 2009 [164] and 70% in VINARES in 2012 [183]); *Escherichia coli* and *Klebsiella pneumoniae* producing extended spectrum beta-lactamase (ESBL, 30% and 43% in 2009, respectively); carbapenem-resistant *E. coli* (2% in 2009 [164] and 6% in 2012 [183]) ; carbapenem-resistant *K. pneumoniae* (10% in 2009 [164] and 17% in 2012 [183]); Methicillin-Resistant *Staphylococcus aureus* (MRSA), reported at 30.1% for hospital-acquired infections in 2004 [33] and at 69% in 2012 [183].

In 2013, the Viet Nam Ministry of Health published its national action plan on AMR, including strengthening and improving the national surveillance system on the use of antimicrobials and drug resistance [156]. In 2015, Viet Nam received a pilot funding from the Fleming Fund to establish a National AMR surveillance network and reference laboratory [199]. The VINARES network was recognised in 2016 by the Ministry of Health as the national AMR surveillance network and will continue to receive support from the Fleming Fund as part of the country grant for Viet Nam. The national AMR surveillance network also receives support from the US Centres for Disease Control and Prevention (US CDC) and Program for Appropriate Technology in Health (PATH) as part of the Global Health Security Agenda. A surveillance protocol based on GLASS and the Fleming Fund roadmap is being developed by the Ministry of Health with support from US CDC, WHO and Oxford University Clinical Research Unit (OUCRU). Data collection as part of a project on development on evidence based guidelines restarted in 2016 [199].

In this paper, we present the Antimicrobial Susceptibility Testing (AST) results from isolates from clinical specimens from 13 microbiology laboratories participating in VINARES between June 2016 and May 2017. These results provide an insight in the dynamics of AMR and an update on the earlier results published based on data from the VINARES for the 2012-2013 period [183].

3.2.2. Methods

3.2.2.1. Data collection

The VINARES network was described previously [166,183]. In 2016-2017, 13 hospitals (7 provincial, 3 specialised and 3 national) continued participating in the network of which 4 were in the northern, 5 in the central and 4 in the southern region. Among these, there was 1 paediatric and 2 infectious diseases hospitals (figure 3.2.1).

WHONET was used for data entry, management and analysis [173]. Routine AST data at the participating laboratories was entered into WHONET 5.6 by hospital technicians or was

exported from automated systems including VITEK2 (bioMérieux, Marcy l'Étoile, France) or Phoenix automated microbiology system (BD Diagnostic Systems, Sparks, MD) using LABCONN (LabSoft, Viet Nam). Raw data files were extracted and submitted by email to OUCRU. Files were converted to WHONET format using BacLink, a free tool included in WHONET [200]. All data files were combined in a single file. Data files were checked for common errors and compatibility (language and file structure).

3.2.2.2. Statistical analysis

For the current report, we focused on eleven priority pathogens: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp.*, *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae, Salmonella spp.* and *Shigella spp.* [177]. Data were de-duplicated, so that one isolate represents one patient. Only the first isolate per patient, per pathogen, per reporting period, per stratification level (hospital) was included. This also minimizes bias associated with reporting of repeated cultures [39]. Local specimen types were converted into specimen types understood by WHONET.

AST results were categorised according to Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines as follows: susceptible, intermediate, resistant and unknown. Intermediate susceptibility was not considered resistant, unless otherwise indicated. For each pathogen and antimicrobial under surveillance, the proportion of patients with growth of resistant bacteria was calculated in all specimens, and separately in specimens from Intensive Care Units (ICU), invasive specimens (blood and cerebrospinal fluid (CSF)) or stool specimens (for *Shigella spp.* and *Salmonella spp.*). AST results were interpreted by WHONET (version 5.6), then summarized in the R software [189].

MRSA was assessed by oxacillin and cefoxitin screening. As not all hospitals used molecular or other confirmation testing, an *S. aureus* isolate was considered MRSA if it was resistant to one of these two antimicrobials. In 2012-13, reduced susceptibility to penicillin in *S. pneumoniae* was mostly detected using oxacillin screening [183]. In 2016-17 this was more commonly done directly by penicillin susceptibility testing using both disk diffusion and MIC in automated systems.

We included five antibiotic classes in the current report: carbapenems (imipenem, meropenem and ertapenem), aminoglycosides (amikacin, gentamicin and tobramycin), fluoroquinolones

(ciprofloxacin and levofloxacin), macrolides (azithromycin, erythromycin and clindamycin) and cephalosporins (ceftriaxone and cefepime).

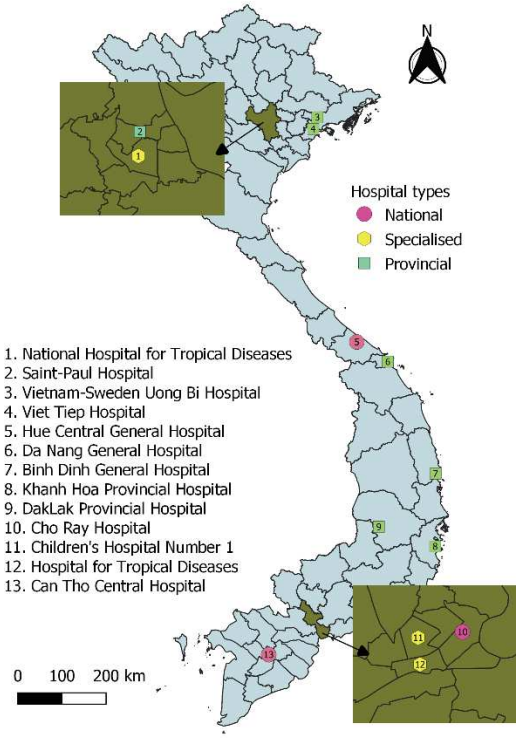


Figure 3.2.1: Location, speciality, and type of the 13 participating hospitals in the VINARES 2016-2017 project.

An analysis of antibiotic resistance by hospital type was carried out. Three hospital types were considered: national and provincial level general and specialised hospitals, as shown in figure 3.2.1. Among the 16 hospitals participating in VINARES 2012-2013, three (one national and two specialised, all in the northern region) did not participate in 2016-2017 period. Data of each hospital type were pooled and analysed. This analysis served to compare susceptibility between hospital types. Only the pathogen-antimicrobial combinations with the highest sample numbers were selected, including imipenem-resistant *A. baumannii*, *E. coli*, ESBL-producing *E. coli* and MRSA.

3.2.3. Results

Distribution of bacteria and antibiotics

Between May 2016 and April 2017, hospitals submitted results from 75,051 specimens. Among them, 22,752 records were unknown or reported no growth, 48,084 were Gram-negative and -

positive bacteria, 882 were fungi, 1,454 were anaerobes, 1,864 were mycobacteria and 15 were parasites.

After removal of negative cultures, fungi, anaerobes, mycobacteria and parasites and deduplication, 42,553 isolates were included in this analysis; including 30,222 (71%) Gram-negative and 12,331 (29%) Gram-positive bacteria. Among all isolates, 8,793 (21%) were from ICUs and 7,439 (18%) were from invasive infections.

E. coli and *S. aureus* were the most frequently detected species with 9,092 (21%) and 4,833 isolates (11.3%), respectively; followed by *K. pneumoniae* (3,870 isolates – 9%) and *A. baumannii* (3,710 isolates – 9%). Bacteria were mainly isolated from sputum (8,798 isolates – 21%), blood (7,118 isolates – 17%) and urine (5,202 isolates – 12%); 321 isolates (1%) were from cerebrospinal fluid (CSF).

3.2.3.1. Susceptibility of Gram-positive bacteria

Antimicrobial susceptibility testing results of bacteria in all specimens, in invasive specimens or stool and in ICU specimens were shown in table 3.2.1 to 3.2.3, respectively.

Since not all isolates were tested for all listed antibiotics, the denominator of each susceptibility test was different and smaller than the number of isolates collected. There were 4,833 *S. aureus* isolates, including 715 (15%) from blood and CSF and 690 (14%) from ICU. 73% (1,824/2,510 isolates) of *S. aureus* were MRSA, 71% (372/521) in blood and CSF and 69% (185/270) in ICU. The non-susceptible vancomycin proportion was low (2% (45/2,680) in all specimens and 1% (7/565) in blood and CSF). No confirmatory testing for vancomycin was reported. The proportion resistant to macrolides was 83% (3,861/4,661) in all specimens and 79% (545/693) in blood and CSF.

E. faecium was isolated from 296 specimens, 51 (17%) from blood and CSF and 65 (22%) from specimens collected in ICU. 34/46 isolates (74%) were aminoglycoside-resistant. 99/290 isolates (34%) of *E. faecium* were resistant to vancomycin (VRE) (19% of VRE tests were done by MIC method). 22 of 64 isolates (36%) from ICU were reported as vancomycin-resistant. 78% of *E. faecium* isolated from blood and CSF were high level resistant to aminoglycosides, however the number of isolates from blood and CSF was very low (n=9).

1367 *S. pneumoniae* were isolated; including 160 from blood and CSF and 184 from specimens collected in ICU. The penicillin-resistant *S. pneumoniae* proportion was 83% (657/794) in all specimens, but much lower in blood and CSF (42%, 42/100 isolates) and among isolates from

specimens collected in ICU (51%, 42/83 isolates). 691/794 (87%) of penicillin susceptibility tests were done by MIC method. 58/356 (16%) *S. pneumoniae* isolates were cephalosporins-resistant; resistance rate was lower among ICU isolates (11%, 10/94). Two isolates (0.2%) were recorded as resistant against vancomycin, none of them were from blood/ CSF or ICU.

3.2.3.2. Susceptibility of Gram-negative bacteria

Proportion of *K. pneumoniae* isolated from ICUs was 28% (1,069/3,870), 11% (1,016/9,092 isolates) for *E. coli* and 17% (230/1,322) for *Enterobacter spp.*

The proportion of *E. coli* carrying ESBL was 59% (4,085/6,953) and 40% (1,186/2,958) in *K. pneumoniae*. Carbapenem-resistance among *E. coli, Enterobacter spp.* and *K. pneumoniae* were 11% (961/8,830), 27% (1,049/3,816) and 29% (376/1,298), respectively. Trimethoprim/sulfamethoxazole-resistant *Enterobacteriaceae* ranged from 47% (215/454) of *K. pneumoniae* in blood and CSF to 76% (700/925) of *E. coli* in ICU.

The number of isolates of *A. baumannii* and *P. aeruginosa* were similar. A high proportion of *A. baumannii* and *P. aeruginosa* isolates were from ICU (32% (1,176/3,710) and 33% (1,158/3,461), respectively). Ceftazidime-resistant proportions of *A. baumannii* in all specimens and in ICU were 2,743/3,298 (83%) and 866/958 (90%). These resistant proportions in *P. aeruginosa* were 1,378/3,231 (43%) and 574/1,062 (54%). Carbapenem-resistant proportions of *A. baumannii* and *P. aeruginosa* were 79% (2,855/3,622) and 45% (1,514/3,376), respectively.

Of 1,085 *H. influenzae* isolates submitted, 146 were from ICU and 12 were from blood and CSF. The proportion of ampicillin-resistant *H. influenzae* was 88% (804/911) among all isolates; this proportion was higher among isolates collected on ICU (92/98 isolates – 94%). Three percent (18/664) of *H. influenzae* isolates were cephalosporins-resistant, while none were found resistant to carbapenems.

Salmonella spp. and *Shigella spp.* susceptibility were investigated in all specimens and in stool. Among 277 isolates of *Salmonella spp.*, there were 32 isolates from stool; only 18 isolates from ICU (table 4). Fluoroquinolones-resistant *Salmonella spp.* in all specimens and in stool were 7% (18/253 and 11% (3/27), respectively. Among 53 *Shigella spp.* isolates, 70% came from stool. 7/46 (15%) of *Shigella spp.* were fluoroquinolone-resistant.

3.2.3.3. Susceptibility by hospital type

The carbapenems- and cephalosporins resistant, ESBL and MRSA of *A. baumannii*, *E. coli* and *S. aureus* in national, provincial general and specialised hospitals are compared as the number of tests of these pathogen-antimicrobial combinations were high enough to produce reliable result. The detail is shown in supplementary table S3.2.1. *A. baumannii* had the highest carbapenem resistant proportion in national, followed by specialised and provincial hospitals (Chi-squared test, $p < 0.0001$). *E. coli* showed a different ESBL positive proportion between national and provincial hospitals (Chi-squared test, $p < 0.0001$). MRSA proportions increased from provincial, to specialised, to national hospitals (Chi-squared test, $p < 0.0001$).

Antimicrobial susceptibility testing results of VINARES project: 2016-2017

Table 3.2.1: Antimicrobial susceptibility testing results of 11 bacteria in all specimens of 13 hospitals in VINARES 2016-2017 project

Resistant / Tested (%)	*A. baumannii* (N=3710)	*E. coli* (N=9092)	*E. faecium* (N=296)	*Enterobacter spp.* (N=1322)	*H. influenzae* (N=1085)	*K. pneumoniae* (N=3870)	*P. aeruginosa* (N=3461)	*S. aureus* (N=4833)	*S. pneumoniae* (N=1367)	*Salmonella spp.* (N=277)	*Shigella spp.* (N=53)
Carbapenem	2855/3622 (79)	961/8830 (11)		376/1298 (29)	0/1065 (0)	1049/3816 (27)	1514/3376 (45)			1/195 (1)	1/19 (5)
Aminoglycosides	2686/3641 (74)	4188/8785 (48)	34/46 (74)	637/1297 (49)		1756/3780 (46)	1457/3389 (43)	1674/4090 (41)		48/78 (62)	4/5 (80)
Fluoroquinolones	2929/3589 (82)	5813/8682 (67)		484/1271 (38)	7/909 (1)	1593/3619 (44)	1435/3357 (43)	1720/4618 (37)	31/1117 (3)	18/253 (7)	7/46 (15)
Cephalosporins	2969/3549 (84)	5441/8195 (66)		675/1192 (57)	18/664 (3)	1995/3732 (53)	1392/3058 (46)		58/356 (16)	20/217 (9)	8/26 (31)
Macrolides	25/29 (86)		249/262 (95)		4/1015 (0)			3861/4661 (83)	1234/1317 (94)	53/137 (39)	2/3 (67)
ESBL		4085/6953 (59)		276/467 (59)		1186/2958 (40)					
MRSA								1824/2510 (73)			
Penicillin			111/124 (90)					2347/2400 (98)	657/794 (83)		
SXT		5704/7843 (73)	73/77 (95)	467/929 (50)	429/470 (91)	1753/3348 (52)	1329/1388 (96)	1021/4158 (25)	886/1069 (83)	39/237 (16)	44/50 (88)
AMC		1476/3251 (45)		461/604 (76)	271/358 (76)	1080/1999 (54)					

Antimicrobial susceptibility testing results of VINARES project: 2016-2017

Ampicillin	5547/5938 (93)	228/253 (90)	476/510 (93)	804/911 (88)	2563/2622 (98)		57/64 (89)	2/21 (10)	104/252 (41)	35/46 (76)
TCC	1317/2947 (45)		297/671 (44)		863/1449 (60)	1097/2160 (51)				
Azithromycin							307/370 (83)	65/73 (89)	3/63 (5)	1/2 (50)
Vancomycin		91/290 (31)					45/2680 (2)*	16/1229 (1)		

ESBL: extended-spectrum β-lactamase; MRSA: Methicillin-resistant Staphylococcus aureus; SXT: Trimethoprim/Sulfamethoxazole; AMC: amoxicillin clavulanic acid; TCC: Ticarcillin/Clavulanic Acid; *: Resistant and Intermediate

Table 3.2.2: Antimicrobial susceptibility testing results of 11 bacteria in blood and CSF (in stool for *Salmonella spp.* and *Shigella spp.*) of 13 hospitals in VINARES 2016-2017 project

Resistant / Tested (%)	*A. baumannii* (N=187)	*E. coli* (N=1535)	*E. faecium* (N=51)	*Enterobacter spp.* (N=77)	*H. influenzae* (N=12)	*K. pneumoniae* (N=482)	*P. aeruginosa* (N=142)	*S. aureus* (N=715)	*S. pneumoniae* (N=160)	*Salmonella spp.* (N=32)**	*Shigella spp.* (N=37)**
Carbapenem	110/183 (60)	116/1483 (8)		20/77 (26)	0/11 (0)	109/476 (23)	54/139 (39)			0/19 (0)	1/14 (7)
Aminoglycosides	107/185 (58)	637/1471 (43)	7/9 (78)	35/75 (47)		195/470 (41)	48/138 (35)	294/637 (46)			
Fluoroquinolones	96/182 (53)	953/1475 (65)		24/76 (32)	0/9 (0)	177/459 (39)	37/138 (27)	297/689 (43)	2/143 (1)	3/27 (11)	4/31 (13)
Cephalosporins	118/178 (66)	931/1402 (66)		37/66 (56)	0/11 (0)	221/471 (47)	47/120 (39)		17/125 (14)	4/28 (14)	7/21 (33)
Macrolides	1/1 (100)		46/48 (96)		0/4 (0)			545/693 (79)	140/152 (92)	1/5 (20)	2/3 (67)
ESBL		655/1107 (59)		7/16 (44)		128/365 (35)					
MRSA								372/521 (71)			
Penicillin			19/22 (86)					490/504 (97)	42/100 (42)		
SXT		935/1377 (68)	20/20 (100)	29/57 (51)	5/8 (62)	215/454 (47)	74/82 (90)	233/661 (35)	107/134 (80)	6/30 (20)	31/34 (91)

Antimicrobial susceptibility testing results of VINARES project: 2016-2017

AMC	180/577 (31)		26/32 (81)	1/5 (20)	112/285 (39)					
Ampicillin	928/1028 (90)	37/40 (92)	21/23 (91)	7/8 (88)	278/287 (97)				14/31 (45)	23/33 (70)
TCC	169/356 (47)		14/45 (31)		115/195 (59)	46/110 (42)				
Azithromycin							30/40 (75)	14/21 (67)	1/5 (20)	1/2 (50)
Vancomycin		13/51 (25)					7/565 (1)*	4/148 (3)		

ESBL: extended-spectrum β-lactamase; MRSA: Methicillin-resistant Staphylococcus aureus; SXT: Trimethoprim/Sulfamethoxazole; AMC: amoxicillin clavulanic acid; TCC: Ticarcillin/Clavulanic Acid; *: Resistant and Intermediate; **: sample collected in stool

Table 3.2.3: Antimicrobial susceptibility testing results of 11 bacteria isolated from ICU specimens of 13 hospitals in VINARES 2016-2017 project

Resistant / Tested (%)	*A. baumannii* (N=1176)	*E. coli* (N=1016)	*E. faecium* (N=65)	*Enterobacter spp.* (N=230)	*H. influenzae* (N=146)	*K. pneumoniae* (N=1069)	*P. aeruginosa* (N=1158)	*S. aureus* (N=690)	*S. pneumoniae* (N=184)	*Salmonella spp.* (N=18)	*Shigella spp.* (N=10)
Carbapenem	976/1132 (86)	146/1004 (15)		96/229 (42)	0/146 (0)	415/1051 (39)	664/1128 (59)			0/12 (0)	0/1 (0)
Aminoglycosides	962/1135 (85)	422/998 (42)	6/6 (100)	128/229 (56)		632/1032 (61)	604/1136 (53)	250/468 (53)		2/5 (40)	1/1 (100)
Fluoroquinolones	958/1103 (87)	568/950 (60)		120/224 (54)	6/117 (5)	570/973 (59)	597/1126 (53)	331/647 (51)	2/137 (1)	2/17 (12)	2/7 (29)
Cephalosporins	992/1076 (92)	579/925 (63)		139/201 (69)	2/48 (4)	726/1033 (70)	554/1014 (55)		10/94 (11)	1/16 (6)	3/4 (75)
Macrolides	17/18 (94)		57/59 (97)		3/134 (2)			548/660 (83)	154/167 (92)	1/6 (17)	2/3 (67)
ESBL		435/716 (61)		62/82 (76)		424/780 (54)					
MRSA								185/270 (69)			
Penicillin			20/24 (83)					313/324 (97)	42/83 (51)		
SXT		700/925 (76)	2/2 (100)	121/204 (59)	111/120 (92)	629/937 (67)	332/351 (95)	116/615 (19)	103/130 (79)	5/18 (28)	10/10 (100)

Antimicrobial susceptibility testing results of VINARES project: 2016-2017

AMC	259/489 (53)		52/58 (90)	64/94 (68)	527/781 (67)					
Ampicillin	556/584 (95)	50/54 (93)	123/126 (98)	92/98 (94)	696/704 (99)				10/17 (59)	10/10 (100)
TCC	313/646 (48)		85/158 (54)		491/696 (71)	436/693 (63)				
Azithromycin							101/123 (82)	7/10 (70)	1/6 (17)	1/2 (50)
Vancomycin		22/64 (35)					17/340 (5)*	1/146 (1)		

ESBL: extended-spectrum β-lactamase; MRSA: Methicillin-resistant Staphylococcus aureus; SXT: Trimethoprim/Sulfamethoxazole; AMC: amoxicillin clavulanic acid; TCC: Ticarcillin/Clavulanic Acid; *: Resistant and Intermediate

3.2.3.4. Comparison with data from VINARES 2012-2013

Here we compare susceptibility of priority bacteria-antimicrobial combinations between the two periods of VINARES (2012-2013 versus 2016-2017). Laboratories used similar protocols in the two periods, including antimicrobial susceptibility testing methods using translated CLSI guidelines and data collection procedures. Laboratories were enrolled in the UK-NEQAS external quality assessment programme during both data collection periods. Since the VINARES 2016-2017 had 13 hospitals, we calculated the antimicrobial susceptibility result of VINARES 2012-2013 in whole dataset and in a subset of 13 hospitals. Supplementary table S3.2.2 showed resistant proportions of priority pathogen-antimicrobial combinations between the two periods.

The number of isolates submitted in the 2016-2017 period was twice as high as in the 2012-2013 period. Overall, antimicrobial resistant proportions were higher in 2016-2017 for almost all pathogen-antimicrobial combinations of interest including imipenem-resistant *A. baumannii*, *P. aeruginosa* and Enterobacteriaceae.

Resistant proportions for 13 pathogen-antimicrobial combinations of 13 hospitals that participated in both periods (2012-13, 2016-17) are shown in figure 3.2.2. Most hospitals had higher imipenem-resistant *A. baumannii*, *K. pneumoniae, P. aeruginosa* and penicillin non-susceptible *S. pneumoniae* proportions in the second period. ESBL positive Enterobacteriaceae were lower in the second period. No trends for vancomycin-resistant *E. faecium*, ceftriaxone-resistant Enterobacteriaceae and MRSA were seen. Proportions of vancomycin-intermediate and resistant *S. aureus* were small in both time periods of VINARES.

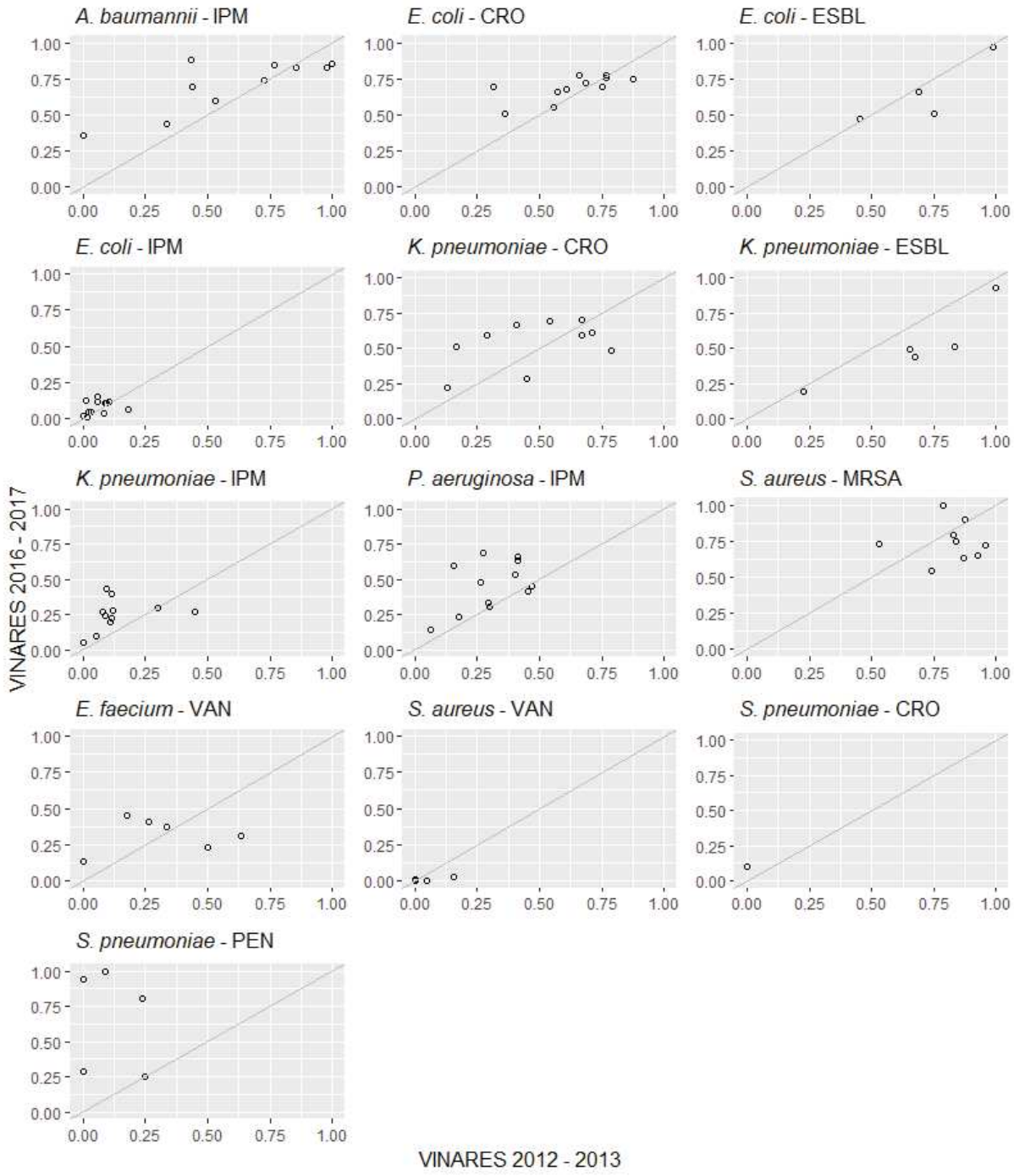


Figure 3.2.2: Resistant proportions of 13 pathogen-antimicrobial combinations from 13 hospitals that participated in two VINARES periods. Resistant proportion for each pathogen-antimicrobial combination by hospital in two periods is represented by a dot. A reference line is added in the figure. A dot above this line indicates a higher resistant proportion in the second period than in the first period. *H .influenzae* - ampicillin was not included in the figure because all *H. influenzae* isolates in 2012 were from the hospitals that did not submit results 2016-17. IPM: imipenem, CRO: ceftriaxone, VAN: vancomycin, PEN: penicillin

3.2.4. Discussion

In this paper, we describe the antimicrobial susceptibility testing results from 13 laboratories within the VINARES network in 2016-2017. Overall, we found high proportions of resistance among all tested priority bacteria and these proportions were generally higher than those reported for 2012-2013.

Proportions of carbapenem-resistant Gram-negative pathogens increased gradually in the VINARES hospitals. Carbapenem-resistant *A. baumannii* rose up over the years: 40% reported from the GARP report in 2009 [164]; 70% (1495/2138) from the VINARES in 2012-2013 and 79% in the 2016-2017 period. A similar observation can be found with carbapenem-resistant *P. aeruginosa* (30%, 33% and 45%, respectively).

In the 2012 point prevalence survey in 16 hospitals' ICU in Viet Nam, Phu et *al.* reported that the two most common pathogens of hospital acquired infections (HAI) were *A. baumannii* (24%) and *P. aeruginosa* (14%) [190]. This report showed carbapenem resistance in patients having HAI was most common in *A. baumannii* (89% [149/167]) and *P. aeruginosa* (56% [49/88]) [190], similar to our VINARES 2016 data.

The proportions of MRSA remained consistently about 70% in both data periods in VINARES, higher than the one reported from the GARP in 2009 (from 17% to 63% in hospitals) [164] and from the Antimicrobial Sensitivity Testing Study program in 2006 (42%) [201].

Vancomycin-intermediate and resistant *S. aureus* remained negligible and stable over the two time periods of VINARES with no trend observed. Vancomycin-resistance among *S. aureus* was not confirmed molecularly and we are unsure of the significance of these findings

The decrease in ESBL detection among Enterobacteriaceae is mostly due to changes in use of detection methods. This difference, looking at the denominators for testing between 2012 and 2016, is more likely an artefact of increased ESBL testing using VITEK2 or other automated systems than a signal of a decrease of ESBL circulation. In 2012-13 ESBL confirmation was only done on a proportion of ceftriaxone resistant isolates in most sites, whereas in 2016-17 a number of sites had switched to using automated systems and almost all isolates were screened for ESBL production.

An increasing trend of penicillin non-susceptible *S. pneumoniae* could not be described properly for the period between 2012-2013 and 2016-2017 as different methods were used for assessment. There was a change from oxacillin disk diffusion screening in 2012 to penicillin

susceptibility test in 2016 across sites. The ANSORP study from 2000 to 2001 reported 91% of penicillin non-susceptible *S. pneumoniae* [32] in Viet Nam, but it may not represent the true prevalence of the entire country because samples were taken in only one hospital in Ho Chi Minh city.

A result from the SOAR study (2009-2011) in 11 centres in Viet Nam reported that 51% (100/195) of *H. influenzae* were resistant against ampicillin [165]. In our VINARES data, ampicillin resistant proportions increased further from 71% in 2012-2013 to 88% in 2016-2017.

Despite a lower number of hospitals participating in the surveillance network in the second period than in the first period, the number of isolates submitted was significantly higher in the second period. This reflects the increase in the use of microbiology over the time (doctors have increasingly collected specimens for diagnostics) and the improvement in microbiology capacity in all hospitals.

We have attempted to assess the associations between the level of antibiotic use and resistance rates. However, due to the small number of data time points (about 12 months on average) and the high variability in the data, it was difficult to identify significant associations and any underlying trends.

The isolates included in VINARES were from the routine clinical specimens, and therefore the rates of isolation and resistance might over-represent patients with severe infections especially when empiric treatment has failed. In addition, these rates may also over-represent the patients with hospital-acquired infections, especially those who have stayed for a long period in hospital and have an increased risk of infection. In addition, these estimated rates were only specific to the hospitalized patient population, and thus unlikely to represent the bacteria circulating in the community where there can be asymptomatic carriers and people with mild infections that do not require hospital admission.

The results highlight the difference between national and provincial hospitals. Previous studies [202–204] showed that the proportion of patients with hospital-acquired infection was higher in the national than in provincial hospitals. As bacteria associated with hospital acquired infections are usually more resistant, this may partially explain this difference. Also, patients with resistant bacterial infections or patients unresponsive to therapy because of resistance are more likely to be transferred to national level hospitals.

Limitations

VINARES collected isolate-based data (surveillance approaches based solely on laboratory data), without epidemiological, clinical, and population-level data. Currently, GLASS accepts both isolate-based and sample-based data, but it encourages countries to collect and report sample-based data, which can provide stratified and therefore more useful information [39]. Current data collected in VINARES do not allow to differentiate between hospital or community acquired infections. Therefore, resistant proportions may be inflated when trying to use data to inform empiric treatment for community acquired infections. Sample- or case-based data collection may provide potential solutions for this issue.

A standardized sampling and data collection strategy across the whole surveillance network is important to minimize selection bias, enhance representativeness and interpretation of the results, and allow inference of the results to the country representativeness [39]. The change in the participation of hospitals had impact on the overall resistant proportions.

3.2.5. Conclusion

We show the results from a successful continuation of a large AMR surveillance network in Viet Nam. The data show alarmingly high and increasing resistant proportions in important organisms causing infections in Viet Nam. However, resistant proportions varied across hospital types in the network. The results may not reflect the true AMR prevalence in Viet Nam as there may be biases in sample selection for AST and data on whether isolates were hospital or community acquired were not collected here. Affordable and scalable ways to adopt a sample-or case-based approach across the network should be explored. Clinical data should also be included in the reports from the hospitals to help provide more informative interpretations of the surveillance data.

Chapter 4

Optimizing cost and effectiveness of AMRSS

4.1. Introduction

As part of the strategies in the National and Global Action Plan to combat AMR, surveillance systems have been established in many countries for the systematic collection and analysis of AMR data. These systems should be able to inform local treatment guidelines and clinical decision-making, track changes in resistance patterns over time and space, detect emergence of important resistance mechanisms for public health actions and support in outbreak notification and investigation, benchmark for measuring intervention and inform the development and implementation of policy and interventions [37],[27]. However, in the health budget constrained context in LMICs such as Viet Nam, the implementation of AMR surveillance system will have to compete for scarce resources with many other healthcare related and other programmes and interventions. More evidence is required to inform policy makers on the effectiveness of AMR surveillance system and the costs to set up, maintain and expand the system.

Assessing the cost and effectiveness of a public health surveillance system in general is particularly challenging because different criteria need to be considered to describe the system, including the surveillance objectives, utility and technical performance attributes. As a result, very few economic evaluation studies have been conducted [205]. In our recent review including 79 studies reporting on AMR surveillance systems around the world, there were only seven studies describing the results of evaluating performance and only two reported the costs of implementation of these surveillance systems [52–55,113,114,117]. These studies evaluated

a number of performance attributes such as representativeness, timeliness, sensitivity and level of coverage. However, none systematically assessed the system performance by varying the system structure to identify the optimal design and in relation to the costs being invested on these systems.

In Viet Nam, the National AMR Surveillance Network has been formally established in 2016 and consists of 16 hospitals of three types: national level general hospitals which are directly managed under the Ministry of Health (MoH), provincial level general hospitals which are managed by Provincial Departments of Health (DoH) in the respective province, and specialized (infectious diseases) hospitals which are managed either by MoH or DoH [167]. This national network originated from the VINARES network with the same surveillance structure and protocol [166]. VINARES was launched in 2012 and collected data on AMR for the 2012-2013 and 2016-2017 time periods. We have previously used SurvTool [152] and OASIS [175] to systematically evaluate the organization and performance of the AMR surveillance system in Viet Nam in these two VINARES periods to identify the strengths and weaknesses of this system and identify further improvement areas to support the performance of the National AMR Surveillance Network. Based on the output of surveillance evaluation framework in chapter 2 and expert opinions, we identified that the precision, bias, sensitivity, representativeness and coverage are the important performance attributes for the AMR surveillance network in Viet Nam. These attributes can vary when the structure of the network changes, for example in terms of the number of hospitals participating in the network or the distribution of the hospitals by types.

One of the important objectives of the hospital-based AMR surveillance network is to provide accurate data on the resistance patterns of common bacterial pathogens to inform local antibiotic treatment guidelines and guide empiric treatment for doctors in hospitals in Viet Nam. However, as shown in our evaluation of the VINARES network, the current surveillance system is unable to distinguish the origin of infection in terms of community-acquired infection (CAI) or hospital-acquired infection (HAI). The current system for data submission does not include relevant clinical information to distinguish these. From the current surveillance system only the averaged resistant proportions can be estimated, which is likely to be overestimated for CAI but under-estimated for HAI, as the resistant proportion among HAI associated pathogens is generally higher than among CAI [202–204]. Consequently, using the resistant proportions to guide clinical treatment may lead to an overuse of broad-spectrum antibiotics to cover for the presumed high resistance levels among CAI. In order to interpret the AMR data

from the current surveillance system, we aimed to develop a mechanism to estimate the resistant proportions for CAI and HAI patients.

This study aims to evaluate the effectiveness and costs of hypothetical AMR surveillance systems (AMRSS) in order to identify options for an optimal system where performance can be maximized to achieve the most accurate estimate for outcome while maintaining the affordable costs of investment. Evaluation of AMRSS in chapter 2 showed that the cost of the national AMR surveillance system is dependent on the number and distributions of hospitals by types participating in the network. Adding an additional hospital might increase the benefits but also increase the costs for establishing and maintaining the system. The question we try to answer from this model-based evaluation is which combination of hospitals for the national surveillance system can provide a good value for money for the government to invest. In the other words, which combination will be most cost-effective from a health systems perspective. We used modelling methods to evaluate four effectiveness attributes: Mean Squared Error (precision and bias) of the resistant proportions, sensitivity, representativeness and coverage of AMRSS. In order to evaluate the accuracy of the resistant proportions among bacteria causing CAIs, we first developed an algorithm to predict this proportion based on VINARES data and data from other studies. We then used this predicted value of resistant proportions for CAI in our effectiveness evaluation. The results from this study are important as the represent the first practical evidence on the costs and effectiveness of AMR surveillance to inform the government and policy makers in further implementation of the National AMR Surveillance Network.

4.2. Methods

We conducted a model-based evaluation of a hypothetical AMR surveillance system that was built with the same characteristics as the VINARES network established in 2012-2013 and the current National AMR Surveillance Network, which originated from VINARES. All values for the parameters in the models were obtained from the VINARES surveillance dataset and project documents for cost data. To deal with the lack of data on the origin of infection, we used a classification model derived from an external training dataset to predict the HAI/CAI status of each pathogen (having a non-duplicated isolate) in the VINARES dataset. However, there are very few studies identifying the origin of bacterial infections in hospitals that represent the general hospitalized patient population. We could only identify one such external dataset for *K. pneumoniae,* therefore we decided to run our evaluation analysis for this bacterium only. We chose to focus on carbapenem-resistant *K. pneumoniae* (based on the

imipenem-resistant *K. pneumoniae* data) because this is an important indicator for antibiotic resistance in Viet Nam and a critical priority pathogen-antimicrobial combination recommended by WHO [177]. In addition, the number of isolates for this combination was large compared to other combinations which would help increase the statistical power for our analyses. The number of ESBL *K. pneumoniae* was small to give an accurate result. Therefore, for the remaining of this chapter, our analyses and results refer to *K. pneumoniae* - carbapenem combination.

We used the following assumptions:

- Three types of hospitals are included in the AMR surveillance system: national, specialized and provincial. For simplicity, we assumed that hospitals were similar to one another within each type of hospital regarding hospital size (patient admissions, bed capacity), proportion of CAI/HAI in patients with infection and resistant proportions in CAI/HAI patients. In addition, we also assumed that the proportion of resistant infections among CAI was similar in all hospital types, while that among HAI varied by type of hospitals.
- The number of CAI patients in the participating hospitals in each hospital type followed a Poisson distribution. There were three distinct distributions in three hospital types. The number of HAI patients of three hospital types also followed three distinct Poisson distributions.
- The number of patients carrying resistant isolates among CAI in each hospital type followed a Binomial distribution. Therefore, there were three Binomial distributions for the number of patients carrying resistant isolates among CAI, and three for HAI.

Previous studies supported these assumptions: GARP report [164] showed the similar *E.coli* producing ESBL were not different (p-value > 0.05) between specialized hospitals; Imipenem-resistant *K. pneumoniae* were similar in national hospitals (they did not provide detailed data to calculate p-value). VINARES 2012-2013 data confirmed the imipenem-resistant *S. pneumoniae* were similar between provincial hospitals ($p > 0.05$); and the same conclusions were found for specialized hospitals ($p > 0.05$).

In each simulation process, the number of CAI/HAI patients and the number of patients carrying resistant isolates were varied randomly using the baseline input data from VINARES surveillance network. This process could be applied for other AMRSS by importing its baseline data to produce the optimal AMRSS.

In the first section, we classified the infection origin of VINARES patients in one of two categories (CAI or HAI). By definition, an infection was defined as a hospital-associated infection present on the day of the survey if the onset of symptoms was on Day 3 of hospitalization or later (day of admission = Day 1) or if the patient presented with an infection but was discharged less than 48 hours from the same or another hospital [206]. CAI was defined as an infection that does not fit the criteria for a HAI [207]. However, we could not classify VINARES patients using these definitions because the surveillance system does not collect information on the date admission. It only collected information on age, sex, type of specimen, specimen collection date, and ward sending the specimen. We developed a classification model (see below) to predict the HAI/CAI status of each patient based on these types of information.

Next, we developed the calculation formula for 4 indicators: Mean Squared Error (MSE), Sensitivity, Representativeness and Coverage to evaluate the effectiveness of a surveillance network. These indicators were selected based on the literature review of AMR surveillance systems in the world and evaluation of the VINARES surveillance network. Lower MSE, and higher sensitivity, coverage and representativeness were preferred.

Baseline surveillance cost was calculated from VINARES document. Using this data, annual surveillance cost formula was developed for an AMRSS having an arbitrary number of hospitals.

In the last section we describe the methods used to generate the number of patients and the number of resistant cases of one hospital in a hypothetical AMRSS; and the methods to calculate MSE via simulation.

4.2.1. Classification model for CAI/HAI status

In this part, we used machine learning terms as following:

- Training: a process of training a model involves a learning algorithm with a dataset (training data) to learn from. The algorithm finds patterns in the training data that map the input data attributes to the answer (which is available in training data). Training provides a model that captures these patterns.
- Training dataset: a sample of data used to fit the model. The training data must contain the correct answer (the infection origin in this study) which we want to predict.
- Testing: a process of using a testing dataset to evaluate how well the final algorithm was trained with the training dataset.

- Testing dataset: a dataset that is independent of the training dataset, but that is assumed to follow the same probability distribution as the training dataset.
- Validation: a process of frequent evaluation of a model in order to tune model parameters.
- Validation dataset: The sample of data used to validate the model in the validation process.
- Model accuracy: The overall agreement rate averaged over cross-validation iterations
- Model sensitivity: measures the proportion of actual CAI that are correctly identified. In the classification, CAI was assigned as a "positive" or "event" value and HAI was a "negative" or "no event" value. The sensitivity definition mentioned here had a different meaning with the sensitivity of AMRSS which mentioned in chapter 2 and the effectiveness attribute formula (paragraph 2.3).
- Model specificity: measures the proportion of actual HAI that are correctly identified.
- Model positive predictive value: proportion of true CAI results in CAI returned by the classification
- Model F1 score: the harmony average of positive predictive value and sensitivity [208]

For training our classification model, we used a dataset containing information on 278 *K. pneumoniae* isolates recovered from patients admitted to the National Hospital for Tropical Diseases between 2007-2011 in which similar data were collected as in the VINARES, but also including the HAI/CAI status of each patient.

Machine learning algorithms were used to develop the classification model from the *K. pneumoniae* dataset. The models were used to identify the set of predictors that explained variation in the outcome (HAI vs CAI) the most. For validation, each model was applied to the testing dataset (a subset of training dataset) in order to quantify the quality of the predictors in terms of four quality variables: accuracy, sensitivity, specificity and F1 score.

4.2.1.1. Classification algorithms

Classification is an algorithm that maps the input data to a specific category. We selected 5 commonly used classification algorithms to develop the possible prediction models. These were selected after a test run was applied for 8 popular methods and the ones that achieved convergence with training data were selected (table 4.1).The other methods which were tested but did not work were: Support Vector Machines with Linear Kernel, AdaBoost Classification Trees and Linear Discriminant Analysis [209].

Table 4.1: Description, strength, weakness and implementation of potential classification algorithms

Classification algorithms	Description	Strength	Weakness	Implementation in R
Naïve Bayes	This algorithm is based on applying Bayes' theorem, with strong (naïve) independence assumptions between the features, which returns the probability of outcome when the predictors are known.	This algorithm requires a small amount of training data to estimate the necessary parameters. Naive Bayes classifiers are extremely fast compared to more sophisticated methods.	Rarely one of the best algorithms in terms of quality of predictions	Function: naive_bayes Package: naive_bayes
Boosted Logistic Regression	LogitBoost fits an additive logistic regression model by stage wise optimization of the binomial log-likelihood [210]	Powerful classification technique with remarkable success on a wide variety of problems, especially in higher dimensions [211]	High bias	Function: LogitBoost Package: caTools
Random Forest	This is an ensemble method based on decision trees where, for each tree, both observations and features are sampled. This model learns from various over grown trees and a final decision is made based on the majority [212].	It manages overfitting very well	Time consuming	Function: rf Package: randomForest
Gradient boosting machine	This method is similar to Random Forest, except that it is sequential and the features of each tree are weighted according to the performance of the previous tree.	This algorithm has high predictive accuracy and handles missing data.	Prone to over-fitting and computationally intensive.	Function: gbm_h2o Package: h2o

K-Nearest Neighbours	This classification algorithm determines the outcome of an observation based on the outcome values of similar observations.	This algorithm has ease to interpret output, great calculation time and good predictive power [213]	The classes with the more frequent examples tend to dominate the prediction of the new observation	Function: knn Package: class

4.2.1.2. Data

We determined the origin of infection of patients with results on antimicrobial susceptibility testing in VINARES 2012-2013 dataset. Information about this project and the resistant proportions of key pathogen – antimicrobial combinations have described in our published paper [183]. VINARES collected data on 4 groups of variables: patient information (sex, age); hospital data (hospital, ward), specimen (specimen type, collection date) and microbiology (bacteria name, antimicrobial susceptibility).

The training data was collected from patients admitted to the National Hospital for Tropical Diseases (Hanoi) who had cultures positive with *K. pneumoniae*. Data were collected retrospectively for the period from 2007 to 2009 and prospectively from 2009 to 2011 [214]. CAI contributed 56% (156 isolates), 58% (90 patients) of CAI patients were between 40 and 60 years old (table 4.2). The proportions of critical care and other wards were similar in CAI (52% versus 48%), while it had a large difference in HAI (88% critical care versus 12% other wards). Blood and sputum were the specimens that *K. pneumoniae* was cultured from most frequently, with sputum being by far the most common specimen in HAI (88%).

Table 4.2: Distribution of predictors in CAI and HAI in training dataset

Characteristic	Summary statistic (n (%))	
	CAI (N=156)	HAI (N=122)
Age Category		
- (10,20]	5/156 (3)	10/122 (8)
- (20,40]	34/156 (22)	40/122 (33)
- (40,60]	90/156 (58)	41/122 (34)
- (60,100]	27/156 (17)	31/122 (25)
Ward		
- Critical Care	81/156 (52)	107/122 (88)
- Other	75/156 (48)	15/122 (12)
Specimen		
- Blood	53/156 (34)	9/122 (7)
- CSF	6/156 (4)	1/122 (1)
- Pus	21/156 (13)	2/122 (2)
- Sputum	64/156 (41)	107/122 (88)
- Urine	10/156 (6)	3/122 (2)
- Other	2/156 (1)	0/122 (0)

4.2.1.3. Implementation

A model consisted of predictors and an algorithm to classify the dependent variable into one of the possible classes. From the training dataset, there were only 3 predictors that were the same as in VINARES and therefore were evaluated: age category, ward of hospitalisation, and specimen type. We evaluated 3 model combinations:

- One variable only: Age category or ward or specimen type,
- Two variables: Age category and specimen type; Age category and ward; ward and specimen type,
- Three variables: age category, ward and specimen type.

Training datasets were split in two subsets: one subset for model training (90% of observations) and one (10% of observations) for validation.

Five classification algorithms were applied for 7 combinations of predictors generating 35 models. Each model was assessed for four quality variables: accuracy, sensitivity, specificity and F1 score.

A principal component analysis (PCA) was conducted to determine which model had highest quality variables overall. PCA produced a score that represented value of these variables, higher score implied a better model. The models having positive scores were combined in an ensemble model aggregating the prediction from these models to generate a final prediction with a reduced prediction error (assuming the base models are independent). The combination method used the score of each model produced from the PCA as a weight for that model in the ensemble model, following the steps below:

- Choose best models which have positive score produced by PCA
- Classify infection origin of VINARES patients using these models
- Assign a value of 1 to CAI and 0 to HAI status
- Calculate round average of HAI/CAI status for each patient from these models, using the PCA score as a weight

Analysis was done using R [189]. The classification model was built using the *caret* (version 6.0-85) package. PCA was performed using the *factoextra* (version 1.0.6) package. Other relevant packages used are listed in table 4.1.

4.2.2. Calculate hospital parameters

After classifying patients as having HAI and CAI in each hospital, the parameters of one hospital for the target pathogen – antimicrobial combination were calculated. These parameters include the number of isolates stratified by HAI/CAI status and the resistant proportion in isolates with HAI or CAI status. We assumed that the resistant proportion among CAI is the same for all hospitals and the proportion among HAI is dependent on the type of hospital.

4.2.3. Effectiveness attribute formulas

To characterize the effectiveness of a surveillance network, we considered 4 indicators: Mean Squared Error, Sensitivity, Representativeness and Coverage. These indicators were selected based on the literature review of AMR surveillance systems and evaluation of the VINARES surveillance network.

- MSE indicates how the estimator of resistant proportion is closely around the resistant proportion in CAI.
- Sensitivity represents the percentage of resistant cases that the AMRSS can detect among all resistant cases in Vietnamese hospitals.
- Coverage calculates the percentage of patients that the AMRSS can reach among all patients in Vietnamese hospitals.
- Representativeness describes how the sample in the AMRSS reflects the whole patient population in all hospitals in Viet Nam.

The absolute value of sensitivity and coverage cannot be calculated as the denominator (data from all Vietnamese hospitals) are generally unknown. The ratio of these statistics will be calculated instead to compare the quality of two AMRSS.

A hospital will be characterized by four parameters (n_c, n_h, p_c, p_h) where

- n_c are the number community-acquired infection patients;
- n_h is the number of hospital-acquired infection patients;
- p_c is the proportion of resistance among patients with community-acquired infection;
- p_h is the prevalence of resistance among patients with hospital-acquired infection.

Based on the results from our literature review (Chapter 1) and our evaluation of the VINARES surveillance network (Chapter 2), we can characterize an AMRSS by the number of hospitals

of each type: AMRSS (t_1, t_2, t_3). National, specialized and provincial hospitals are indicated from 1 to 3, with t_1, t_2 and t_3 indicating the number of hospitals of each type.

4.2.3.1. Mean Squared Error

Definition

By definition, the Mean Squared Error (MSE) expresses the average squared difference between the estimated values and the true values. The MSE can be written as the sum of the variance of the estimator and the squared bias of the estimator [215]. Therefore, the MSE represents the precision and bias of the estimator.

In this study, MSE of the resistant proportions among CAI was calculated. Our aim was to estimate the precision and bias of estimator $\hat{p}_c$ (the estimated value of p_c based on the data in each AMRSS) of p_c in terms of MSE. It was the expected value of the squared of the difference between the estimator $\hat{p}_c$ of resistant proportion in CAI from AMRSS and the expected p_c from the community.

$$MSE = E[(p_c - \hat{p}_c)^2]$$

MSE formula when having one hospital in the system

In absence of information on n_c, n_h and p_h, the best estimator of p_c we can get is

$$\hat{p_c} = \frac{R}{N} = \frac{n_c p_c + n_h p_h}{n_c + n_h}, \text{where}$$

$\hat{p}_c$ was the overall resistant proportion of one pathogen-antimicrobial combination (*K. pneumoniae* – carbapenem in this chapter) in the AMRSS. *R* and *N* are the number of resistant cases and total number of cases for the target pathogen – antimicrobial combination, respectively.

By definition,

$$\text{MSE}(\hat{p_c}) = \text{Var}(\hat{p_c}) + \text{Bias}(\hat{p_c})^2 = \frac{\hat{p_c}(1-\hat{p_c})}{n_c + n_h} + (\hat{p_c} - p_c)^2$$

where Var and Bias is the variance and bias of the estimator.

MSE formula when having *k* hospitals in the system

If we consider *k* hospitals, each hospital *i* is characterized by four parameters $(n_{ci}, n_{hi}, p_c, p_{hi})$. The resistant proportion among CAI (p_c) is assumed to be the same across all hospitals.

The average resistant proportion now reads:

$$\hat{p_c} = \frac{R}{N} = \frac{\sum_{1 \le i \le k}(n_{ci}p_c + n_{hi}p_{hi})}{\sum_{1 \le i \le k}(n_{ci} + n_{hi})}$$

The total number R of patients infected with a resistant pathogen and the total number N of patients can be split by hospital type and by origin of infection.

$$R = \sum_{l=1}^{3}\sum_{j=1}^{t_i} n_{clj}p_c + \sum_{l=1}^{3}\sum_{j=1}^{t_i} n_{hlj}p_{hlj} \quad (1)$$

$$N = \sum_{l=1}^{3}\sum_{j=1}^{t_i} n_{clj} + \sum_{l=1}^{3}\sum_{j=1}^{t_i} n_{hlj}$$

where $l = 1 \to 3$ corresponding to the three types of hospitals: national, specialized and provincial, respectively. t_1, t_2 and t_3 are number of national, specialized and provincial hospitals so that

$$t_1 + t_2 + t_3 = k$$

The variance of the estimated resistant proportion reads

$$\mathrm{Var}(\hat{p_c}) = Var\left(\frac{R}{N}\right) = \frac{1}{N^2}Var(R)$$

In formula (1), the number of resistant cases in CAI $n_{clj}p_c$ follows a binomial distribution B(n_{clj}, p_c) with n_{clj} trials and probability of event p_c. The number of resistant cases in HAI $n_{hlj}p_{hlj}$ is also a binomial distribution B(n_{hlj}, p_{hlj}). Therefore, R is the sum of $2 * 3 * (t_1 + t_2 + t_3) = 6k$ binomial variables. Specifically,

$$R = Expected\ Value(\sum_{l=1}^{3}\sum_{j=1}^{t_l}(Binomial_{clj}(n_{clj}, p_c) + Binomial_{hlj}(n_{hlj}, p_{hlj}))$$

So, the variance of R:

$$Var(R) = Var(\sum_{l=1}^{3}\sum_{j=1}^{t_l}(Binomial_{clj}(n_{clj}, p_c) + Binomial_{hlj}(n_{hlj}, p_{hlj}))$$

Under the assumption that these distributions are independent, the variance of the sum is the sum of variances, thus:

$$Var(R) = \sum_{l=1}^{3}\sum_{j=1}^{t_l}\left(Var\left(Binomial_{clj}(n_{clj}, p_c)\right) + Var\left(Binomial_{hlj}(n_{hlj}, p_{hlj})\right)\right)$$

$$Var(R) = \sum_{l=1}^{3}\sum_{j=1}^{t_l}\left(p_c(1-p_c)n_{clj} + p_{hlj}(1-p_{hlj})n_{hlj}\right)$$

Therefore,

$$\mathrm{MSE}(\hat{p_c}) = \mathrm{Var}(\hat{p_c}) + \mathrm{Bias}(\hat{p_c})^2 = \frac{Var(R)}{N^2} + (\hat{p_c} - p_c)^2 \quad (2)$$

Simulation process for MSE

In this section I explain how I run Monte Carlo simulations in order to numerically validate the MSE formula that I derived analytical in the section above. For that, I first describe the algorithm used to generate random AMRSSs and, then, how I compare the simulations with the analytical formula derived above.

Hypothetical AMRSS generation

We denoted an AMRSS (t_1, t_2, t_3) to describe an AMRSS by three numbers: t_1, t_2 and t_3 which are number of national, specialized and provincial hospitals respectively, and k as the total number of hospitals $(t_1 + t_2 + t_3 = k)$;

We generated the AMRSSs by varying t_1, t_2, and t_3.

For a given AMRSS (t_1, t_2, t_3), the following procedure was applied for the l^{th} hospital (l from 1 to k) to generate the number of HAI/CAI patients and resistant proportions:

- Generate the number of HAI and CAI patients:
    - Determining the distribution of number of HAI and CAI following a Poisson distribution with an average count of annual patients as estimated from VINARES. Random numbers were drawn from this distribution. Then the maximum likelihood of this distribution's parameter was calculated from data points.
    - Generating a random data point which follows this Poisson distribution with the above maximum likelihood parameter
- Generate resistant proportion in HAI and CAI patients using corresponding data points of VINARES by:
    - Determining resistant proportion in HAI and CAI. First, we assumed it follows a binomial distribution with an average count of annual patients and the proportion

of resistant infections as estimated from VINARES. Then the maximum likelihood of this distribution's parameter was calculated from data points.

- Generating a random data point which follows this binomial distribution with the above maximum likelihood parameter

MSE calculation:

For a given AMRSS (t_1, t_2, t_3), its MSE was calculated by:

i. Generating the number of HAI and CAI patients and resistant proportions of HAI/CAI patients as described above
ii. Calculate MSE using formula (1)
iii. Repeat 20 times of steps i and ii to have 20 MSE values, then calculate average of MSE.

Validation of MSE formula

The MSE formula was validated by simulations by comparing the MSE value obtained by formula against the values obtained by simulation. For a specific number of hospitals in AMRSS, we generated a random combination of national, specialized and provincial hospitals. The data was simulated 1000 times to get 1000 MSE values; then the mean of these values was compared with the MSE value obtained by the formula using the Student t-test (figure 4.1). This process repeated for different numbers of hospitals in AMRSS.

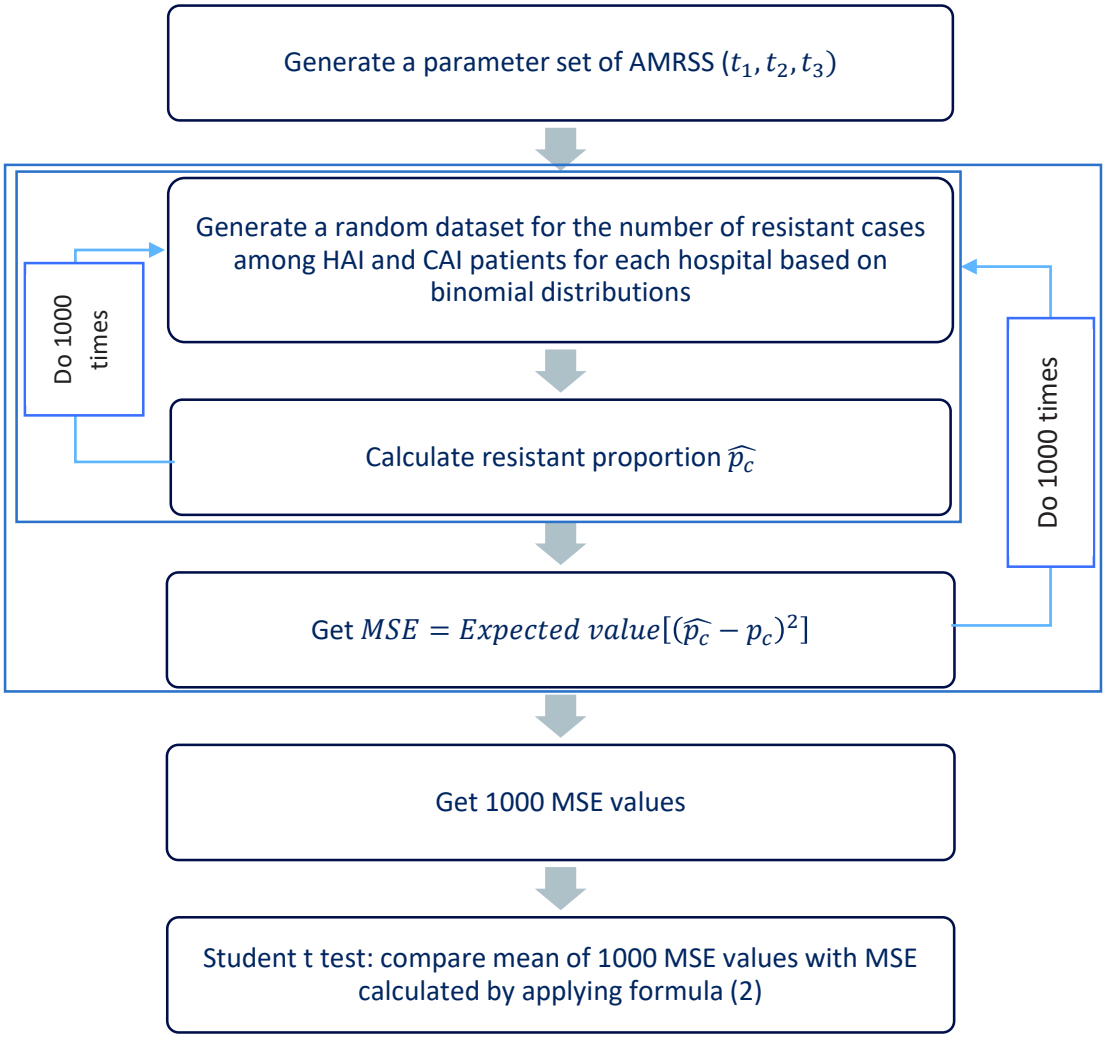


Figure 4.1: Simulation process to validate the MSE formula

4.2.3.2. Sensitivity Ratio

The sensitivity of two successive AMRSS were compared by assessing the ratio of their sensitivities. By definition, sensitivity is the proportion of patients infected with a resistant pathogen for the specific pathogen - antimicrobial combination that the surveillance system is able to detect among all resistant cases in all Vietnamese hospitals.

We calculated the sensitivity ratios for all resistant cases regardless of HAI/CAI status.

Assuming S_1 and S_2 are the sensitivities of two AMRSS, from the definition of sensitivity, the ratio of sensitivity of AMRSS 1 having k_1 hospitals and AMRSS 2 having k_2 hospitals are:

$$R_S = \frac{S_1}{S_2} = \frac{number\ of\ resistant\ cases\ covered\ by\ AMRSS\ 1}{number\ of\ resistant\ cases\ covered\ by\ AMRSS\ 2}$$

$$R_S = \frac{\sum_{1 \le i \le k_1}(n_{c_1 i} p_c + n_{h_1 i} p_{h_1 i})}{\sum_{1 \le j \le k_2}(n_{c_2 i} p_c + n_{h_2 i} p_{h_2 i})}$$

where

$n_{c_j i}$ and $n_{h_j i}$ are the number of CAI and HAI patients and $p_{h_1 i}$ is the resistant proportion in hospital i of AMRSS j.

4.2.3.3. Coverage Ratio

Coverage of one AMRSS is calculated by dividing the number of patients having antimicrobial susceptibility test (AST) per year reached by the AMRSS by the total number of patients having AST per year in all Vietnamese hospitals.

For a fixed budget, higher AMRSS' coverage was better. However, the denominator (number of patients having AST in all Vietnamese hospitals) is unknown, we cannot determine the coverage proportion.

Therefore, we calculated coverage ratio of AMRSS 1 having k_1 hospitals and AMRSS 2 having k_2 hospitals as follows:

$$R_C = \frac{Number\ of\ AST\ covered\ by\ AMRSS\ 1}{Number\ of\ AST\ covered\ by\ AMRSS\ 2}$$

$$R_C = \frac{\sum_{1 \le i \le k_1}(n_{c_1 i} + n_{h_1 i})}{\sum_{1 \le j \le k_2}(n_{c_2 i} + n_{h_2 i})}$$

where

$n_{c_1 i}$ and $n_{h_1 i}$ were number of CAI and HAI patients in hospital i of AMRSS 1.

$n_{c_2 j}$ and $n_{h_2 j}$ were number of CAI and HAI patients in hospital j of AMRSS 2.

4.2.3.4. Representativeness

Representativeness describes how the patients covered under the AMRSS reflected the overall patient population. In this study, the distribution of number of hospitals in each type was chosen as the indicator of representativeness of an AMRSS.

The distribution of number of hospitals in each type of Viet Nam in 2016 was used as the reference.

The goodness of fit of each AMRSS was measured by the chi-squared statistic:

$$\chi^2 = \sum_{i=1}^{3} \frac{(O_i - E_i)^2}{{E_i}^2}$$

O_i and E_i were number of patients covered under an AMRSS and total number of patients in each hospital type.

Chi-squared value χ^2 was used to compare the representativeness of two AMRSS. The smaller χ^2, the more representative that AMRSS had.

4.2.3.5. Generalized linear model assessment of effectiveness

A generalized linear model (GLM) was applied for MSE, sensitivity ratio and coverage ratio in function of number of hospitals. Theses effectiveness values were log transformed before applying the models. There were two models:

- Effectiveness in function of number of hospitals in general: *log(effectiveness) ~ number of hospitals*

$$\log(MSE) = \beta_{10} + \beta_{11}k$$

- Effectiveness in function of number of hospitals in each type: *log(effectiveness) ~ number of national + number of specialized + number of provincial hospitals*

$$\log(MSE) = \beta_{20} + \beta_{21}t_1 + \beta_{22}t_2 + \beta_{23}t_3$$

The coefficient of GLM and the 95% CI were re-transformed to the linear scale in order to represent the change of effectiveness when one more hospital was added in one AMRSS.

This analysis was performed in R.

4.2.4. Cost assessment

4.2.4.1. Cost data

Yearly cost per hospital was calculated based on information collected from VINARES surveillance network's documents. Cost depends on the role of hospital: reference or participating hospital. There were two reference hospitals in the system (National Hospital for Tropical Diseases in the North and Hospital for Tropical Diseases in the South), which were in

charge of coordination between hospitals, OUCRU and MoH; and worked as reference laboratory. Both reference and participating hospitals provided AST data.

VINARES' surveillance costs were separated in three groups: cost for central unit, cost for reference hospitals and cost for participating hospitals.

To calculate the estimated costs for adding one hospital in the surveillance network, costs were split in two categories: fixed and variable costs. Fixed costs were assumed to last for 5 years, while variable cost was calculated by year. By dividing the cost in two categories, an annual cost could be calculated. Fixed costs included all materials, meetings and trainings, website, and data management that were invested at the beginning to set up the surveillance system. Variable costs were on-going cost items including salary, annual meeting and refresh training.

Other activities in VINARES surveillance network that were not related to the set-up and maintenance of the AMR surveillance system were excluded (e.g. point prevalence survey and antibiotic usage surveillance).

4.2.4.2. Cost formula

We assumed that each AMRSS had 1 central unit and 2 reference hospitals and a varying number of participating hospitals. The VINARES had two reference hospitals, which were located in the north and the south of Viet Nam. This is required following the usual administrative and operational division in the healthcare system in the country. Therefore, we kept both of them in all hypothetical AMRSS. Therefore, the total cost of AMRSS for one year is the sum of the costs for 1 central unit, for 2 reference hospitals and for all the participating hospitals. We assumed that the cost of one AMRSS having 1 central unit and two reference hospitals is:

$$TC = \ Cost\ of\ Central\ Unit + 2 * Cost\ for\ Reference\ Hospitals + k * Cost\ for\ partipating\ hospitals$$

TC: total cost, *k*: number of participating hospitals

We presented the improvement in effectiveness attributes (for example, the increase in the accuracy of resistant proportion among CAI patients by a percentage of reduction in MSE) for a given amount of costs invested. This can help the government to make the decision on which hospitals to include in the surveillance system under a specified budget to improve its effectiveness.

4.3. Results

4.3.1. Proportions of VINARES patients by origin of infection

We generated 35 classification models with 3 predictors (age category, ward of hospitalisation and specimen type), using 5 algorithms (Naïve Bayes, Boosted Logistic, K-Nearest Neighbours, Random Forest and Gradient boosting) (Table 4.3). Each model was evaluated by 4 quality statistics (Accuracy, sensitivity, specificity and F1 score). The generated models had scores for accuracy (0.55 to 0.77), sensitivity (0.34 to 0.80), specificity (0.35 to 0.88) and F1 score (0.45 to 0.79) (table 4.3).

We used these models to predict the proportion of isolates by origin of infection (CAI or HAI) in VINARES data. The estimated proportions of CAI isolates from these models were from 0% to 98%, while those for HAI isolates from 2% to 100%.

Principal component analysis (PCA) on four quality statistics performed to measure the quality of 35 models generated the scores in 4 dimensions. Two dimensions of PCA that represent the largest amount of variation (97.6%) of the 4 quality statistics are presented in figure 4.2. The PCA indicates that the gradient boosting and naïve Bayes models, which fall in the right of the 2-dimension plane achieved highest quality overall.

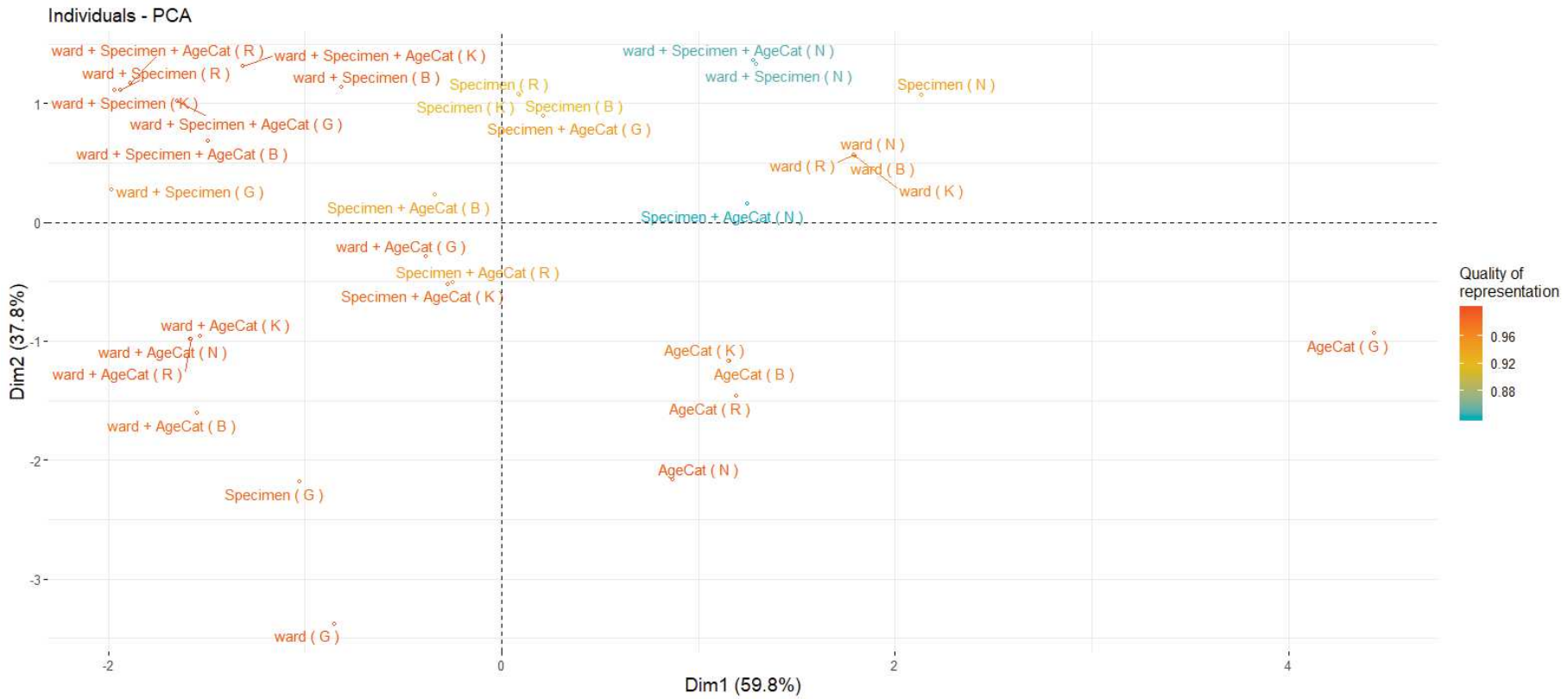


Figure 4.2: Models in two dimensions of principal component analysis coloured by their quality of representation (the importance of a component for a given observation, represented by squared cosine (cos^2) - squared distance of the observation to the origin). Abbreviations for algorithms: Naïve Bayes (N), Boosted Logistic Regression (B), Random Forest (R), Gradient boosting machine (G) and K-Nearest Neighbours (K).

Table 4.3: Quality statistics and the HAI/CAI classification results for VINARES

Predictors	Algorithm	Quality statistics				Classification results for VINARES n(%)		Score
		Accuracy	Sensitivity	Specificity	F1	CAI	HAI	
Age category	Gradient boosting (G)	0.55	0.34	0.78	0.44	0	1601	4.44
Specimen	Naïve Bayes (N)	0.70	0.43	0.88	0.56	1241	360	2.14
Ward	K-Nearest Neighbours (K)	0.65	0.48	0.88	0.61	1271	330	1.80
Ward	Boosted Logistic (B)	0.65	0.48	0.88	0.61	1271	330	1.80
Ward	Naïve Bayes (N)	0.65	0.48	0.88	0.61	1271	330	1.79
Ward	Random Forest (R)	0.66	0.48	0.88	0.61	1271	330	1.79
Ward + Specimen	Naïve Bayes (N)	0.74	0.47	0.86	0.60	1556	45	1.29
Ward + Specimen + Age category	Naïve Bayes (N)	0.74	0.47	0.86	0.60	1351	250	1.28
Specimen + Age category	Naïve Bayes (N)	0.69	0.51	0.75	0.60	1354	247	1.25
Age category	Random Forest (R)	0.61	0.58	0.63	0.62	526	1075	1.19
Age category	Boosted Logistic (B)	0.61	0.58	0.66	0.63	526	1075	1.16
Age category	K-Nearest Neighbours (K)	0.61	0.58	0.66	0.63	526	1075	1.15
Age category	Naïve Bayes (N)	0.60	0.62	0.53	0.63	619	982	0.87
Specimen + Age category	Gradient boosting (G)	0.71	0.58	0.85	0.69	1354	247	0.21
Specimen	Boosted Logistic (B)	0.72	0.59	0.88	0.70	1241	360	0.09
Specimen	K-Nearest Neighbours (K)	0.72	0.59	0.88	0.70	1241	360	0.09
Specimen	Random Forest (R)	0.72	0.59	0.88	0.70	1241	360	0.09
Specimen + Age category	Random Forest (R)	0.68	0.66	0.69	0.70	1354	247	-0.25
Specimen + Age category	K-Nearest Neighbours (K)	0.68	0.67	0.68	0.69	1306	295	-0.27
Specimen + Age category	Boosted Logistic (B)	0.71	0.64	0.75	0.70	1334	267	-0.34
Ward + Age category	Gradient boosting (G)	0.69	0.67	0.70	0.70	1381	220	-0.38

Ward + Specimen	Boosted Logistic (B)	0.75	0.65	0.84	0.74	1241	360	-0.81
Ward	Gradient boosting (G)	0.60	0.80	0.35	0.69	1271	330	-0.85
Specimen	Gradient boosting (G)	0.65	0.78	0.46	0.71	1241	360	-1.03
Ward + Specimen + Age category	K-Nearest Neighbours (K)	0.77	0.69	0.84	0.76	1395	206	-1.32
Ward + Specimen + Age category	Boosted Logistic (B)	0.75	0.73	0.78	0.76	1479	122	-1.49
Ward + Age category	K-Nearest Neighbours (K)	0.70	0.78	0.59	0.75	1381	220	-1.54
Ward + Age category	Boosted Logistic (B)	0.69	0.80	0.51	0.73	1317	284	-1.55
Ward + Age category	Random Forest (R)	0.70	0.79	0.59	0.75	1381	220	-1.58
Ward + Age category	Naïve Bayes (N)	0.70	0.79	0.59	0.75	1381	220	-1.58
Ward + Specimen + Age category	Gradient boosting (G)	0.77	0.73	0.80	0.77	1368	233	-1.65
Ward + Specimen + Age category	Random Forest (R)	0.78	0.74	0.82	0.79	1395	206	-1.89
Ward + Specimen	Random Forest (R)	0.78	0.75	0.81	0.79	1556	45	-1.94
Ward + Specimen	K-Nearest Neighbours (K)	0.78	0.75	0.81	0.79	1556	45	-1.97
Ward + Specimen	Gradient boosting (G)	0.77	0.77	0.69	0.77	1556	45	-1.99

F1: harmony average of positive predictive value and sensitivity; CAI: community acquired infection; HAI: hospital acquired infection. A higher score represents a better model.

Based on the PCA result, we selected 17 models having positive scores to predict the CAI/HAI status for VINARES isolates. We assembled these models assigning a weight for each model in order to generate a more accurate prediction of CAI/HAI status for each patient isolate in the VINARES dataset. PCA scores of each model was used as a weight (table 4.3). The final assembled model classifies 1216 (76%) of VINARES patients as having a CAI and 385 (24%) having HAI. These proportions varied by type of specimens and ward (table 4.4). The proportion of CAI was 42% among patients aged from 40-60 years, while patients more than 60 years old presented the largest group in HAI (62%). Critical care ward presented a low proportion in CAI (13%) but higher in HAI (45%). Sputum contributed 67% of specimen in HAI.

Table 4.4: Distribution of age, admission ward and specimen in CAI and HAI for VINARES patients

Characteristic	Summary statistic (n(%))	
	CAI (N=1216)	HAI (N=385)
Age category		
- (10,20]	68/1216 (6)	25/385 (6)
- (20,40]	238/1216 (20)	109/385 (28)
- (40,60]	515/1216 (42)	11/385 (3)
- (60,100]	395/1216 (32)	240/385 (62)
Ward		
- Critical Care	158/1216 (13)	172/385 (45)
- Other	1058/1216 (87)	213/385 (55)
Specimen		
- Blood	122/1216 (10)	7/385 (2)
- CSF	26/1216 (2)	1/385 (0)
- Pus	140/1216 (12)	4/385 (1)
- Sputum	103/1216 (8)	257/385 (67)
- Urine	84/1216 (7)	1/385 (0)
- Other	741/1216 (61)	115/385 (30)

4.3.2. Parameters for hospitals participating in surveillance network

Estimated values for the number of patients and number of resistant cases in CAI and HAI of each hospital participating in the surveillance network are presented in table 4.5. For each type of hospitals, the average number of patients (defined as having one *K. pneumoniae* isolate) was calculated. Specialized hospitals had the highest number of *K. pneumoniae* patients for CAI. The estimated carbapenem-resistant proportion of *K. pneumoniae* for CAI was 9%, and from 9% to 15% for HAI depending the type of hospitals.

Table 4.5: Parameters of one hospital of VINARES

Hospital type	All patients with *K. pneumoniae* isolate (n (sd))		Proportion of patients having carbapenem-resistant *K. pneumoniae* (% (sd))	
	CAI	HAI	CAI	HAI
National	45 (17)	24 (13)	9 (1)	15 (2)
Specialized	98 (66)	7 (4)	9 (1)	14 (4)
Provincial	39 (20)	34 (18)	9 (1)	9 (2)

4.3.3. Number of hospitals

The effectiveness measurements were performed on a set of simulated AMR surveillance systems (AMRSS). Each simulated AMRSS consists of national, specialized and provincial hospitals. We varied the number for each type of hospitals as follows:

- Number of national hospitals: from 1 to 30
- Number of specialized hospitals: from 1 to 30
- Number of provincial hospitals: from 1 to 40

The maximum total number of hospitals hypothetically participating in the national surveillance network was set at 100. The higher number of hospitals in an AMRSS was not realistic and it caused high computational time for the modelling process.

The actual number of provincial hospitals is higher than national and specialized hospitals in Viet Nam. Therefore, we set the maximum for the number of provincial hospitals as 40 while that for national and specialized hospitals was 30.

For each number of hospitals participating in the AMRSS, there can be different combinations of national, specialized and provincial hospitals. The total number of hospitals in one hypothetical AMRSS can vary from 4 to 100. However, for AMRSS that have 70 hospitals, the results were biased due to lack of combinations of three hospital types, which made it difficult

to interpret. Therefore, we restricted our simulations to the AMRSS with up to 70 hospitals. We also excluded the combinations with the number of hospitals below 11 for a better precision. Finally, only AMRSS having 12 to 70 hospitals were included in the analysis.

4.3.4. Effectiveness attributes: results from simulation

4.3.4.1. Mean Squared Error

Validation of MSE formula

Simulation was initially performed for AMRSS having 3-100 hospitals. Only those with 11 to 70 hospitals were then included for the analysis because of the wide variation in simulation results for the number of hospitals below 11 and above 70.

MSE values were estimated using formula (2) and by simulation method. Values returned by simulation were consistent with the values calculated by formula (Student t test returns all p-value > 0.05). Figure 4.3 illustrated the MSE produced by formula against the MSE obtained by simulation. Formula based MSE values were all in the 95% CI of the simulation based MSE values. This indicates the validity of MSE formula to be used as a measure for precision and bias in the proportions of resistance in CAI generated from the hypothetical AMRSS.

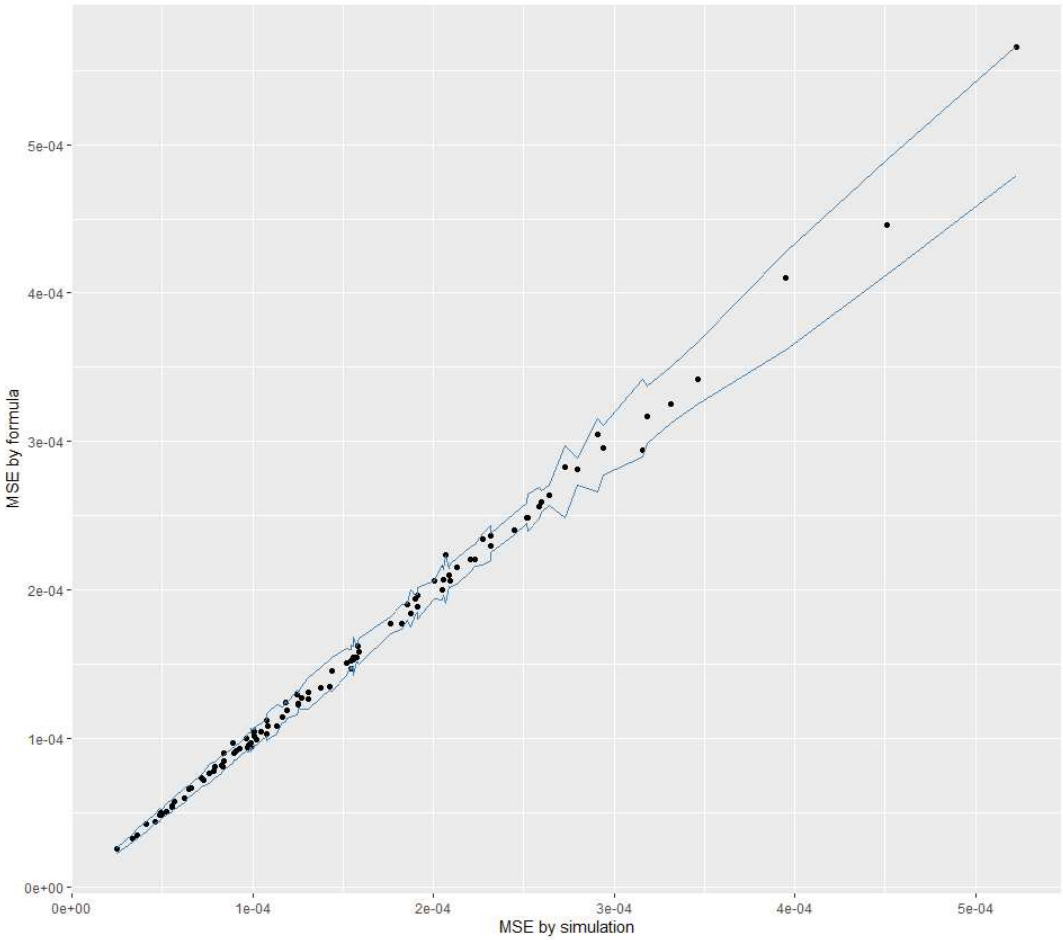


Figure 4.3: MSE obtained by formula and by simulation in hypothetical AMRSS with different number of hospitals. In one AMRSS, the number of hospitals for each of the three hospital types were randomly chosen. 95% CI of simulated MSE is also displayed. The CI ranges were randomly increased or decreased because of random combination of hospital types in different AMRSS.

Mean Squared Error of VINARES

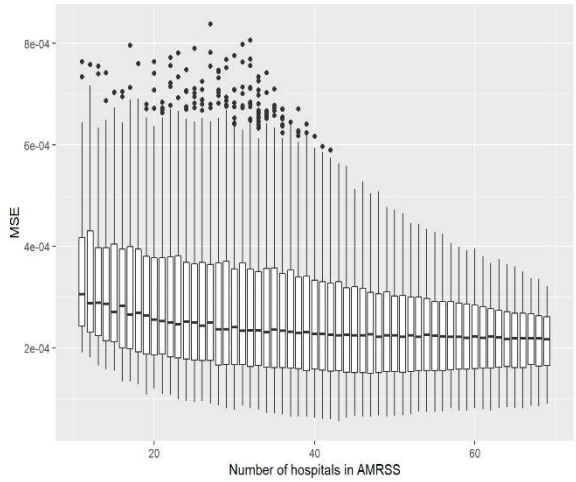
The mean squared error of resistant proportion for CAI in the data collected in VINARES 2012-2013 is 2.27×10^{-4}. The VINARES 2012-2013 consisted of 4 national hospitals, 5 specialized hospitals and 7 provincial hospitals.

Mean Squared Error of simulated AMRSS

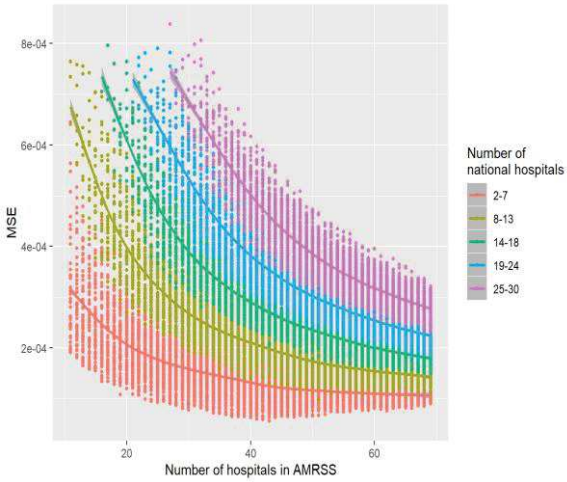
MSE of the simulated AMRSS varies from 0.55×10^{-4} to 8.38×10^{-4}, with a median of 2.28×10^{-4} [IQR 1.61×10^{-4} – 3.04×10^{-4}]. Figure 4.4 (A) illustrates the overall decreasing trend of MSE when increasing the number of hospitals, while figure 4.4 (B)-(D) classify MSE by number of national, specialized and provincial hospitals, respectively. The number of hospitals was categorized into five intervals for each hospital type.

Overall, MSE decreases while the number of hospitals increases. This trend remains even when stratifying by the number of national hospitals, however the higher number of national hospitals, the higher value of MSE (meaning less accuracy). On the other hand, a higher number of specialized or provincial hospitals result in a lower value of MSE.

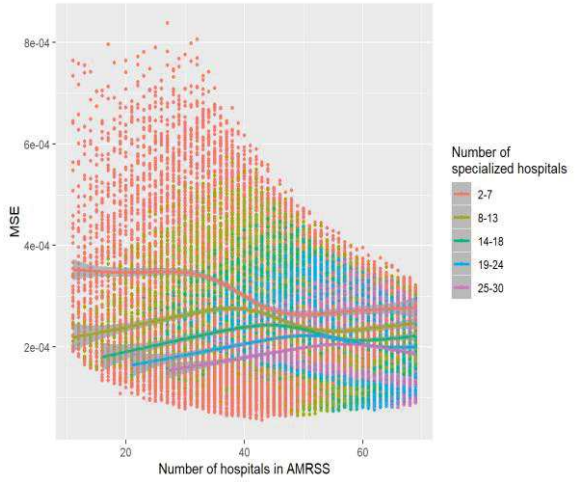
When stratified by the proportion of hospitals (q1: 0 to 33%, q2: 34% to 66%, q3: 67% to 100%) by each type of hospital (national-specialized-provincial), we found that MSE value was lower when the proportion of national hospitals was in the q1 range (figure 4.5 (A)). Particularly, the MSE values were lowest in the q1-q1-q3 combination, with national and specialized hospitals ranging between 0-33% and provincial hospitals contributing more than 67%. The lowest MSE point in this combination was when the total number of hospitals was 43.



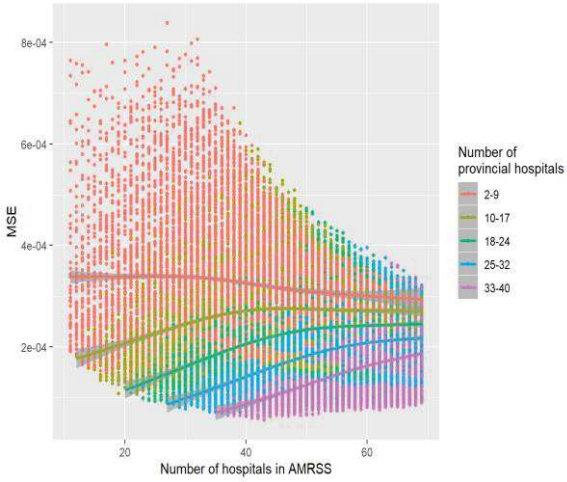
(A) Variation of MSE depending on the number of hospitals. Each boxplot showed the variation of MSE of different combinations for one number of hospitals.



(B) MSE values were categorized by group of number of national hospitals.

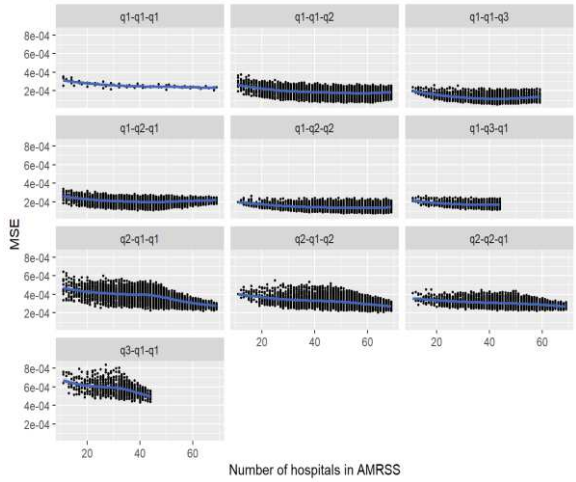


(C) MSE values were categorized by group of number of specialized hospitals.

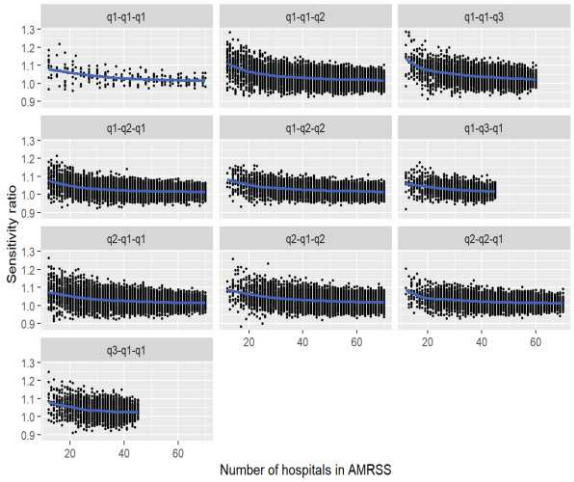


(D) MSE values were categorized by group of number of provincial hospitals.

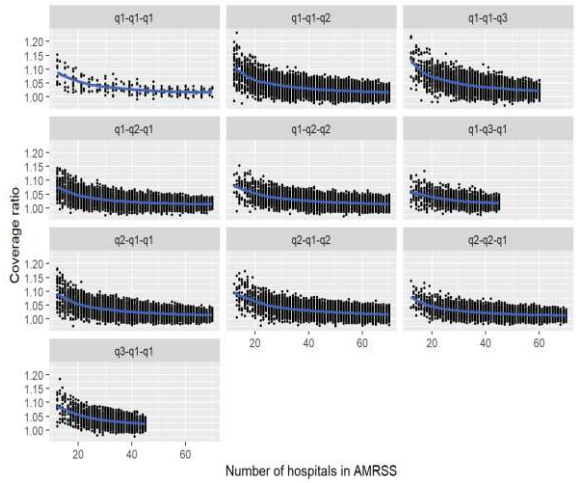
Figure 4.4: Variation of MSE in function of number of hospitals (A), and by type of hospitals (B)-(D). Smooth lines estimate the trend of MSE. The smooth lines in figure (B)-(D) represented the average of MSE of each group with similar number of hospitals.



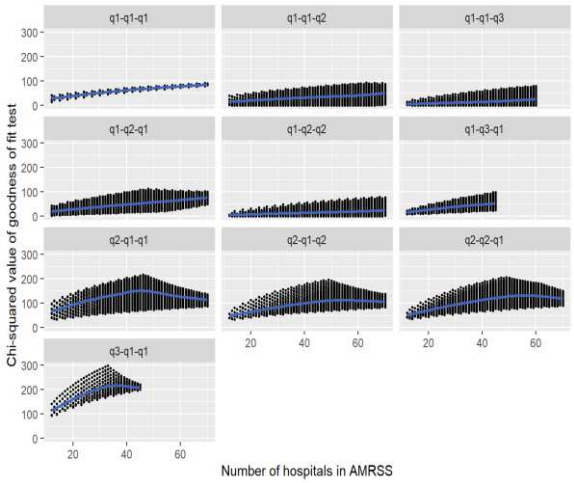
(A) MSE



(B) Sensitivity ratio of two successive AMRSS (x-axis is number of hospitals in former AMRSS)



(C) Coverage ratio of two successive AMRSS (x-axis is number of hospitals in former AMRSS)



(D) Representativeness

Figure 4.5: MSE, sensitivity ratio, coverage ratio and representativeness stratified by proportion of hospitals for each hospital type. Number of hospitals in one type was categorized by their contribution into three intervals: 0 to 33% (q1), 34% to 66% (q2), 67% to 100% (q3) of the total number of hospitals in the AMRSS.

Linear regression was performed to regress the logarithm of MSE against the number of hospitals. First regression analysis took into account the total number of hospitals and the second used the number of hospitals in each type as three covariables (table 4.6). Overall, when adding one more hospital, MSE will decrease 0.6% (CI 0.6% - 0.7%). Stratified by type of hospitals, adding one specialized or one provincial will reduce MSE by 1.8% (CI 1.8% - 1.8%) and 2.2% (CI 2.2% - 2.2%), respectively. On the other hand, adding one national hospital will increase MSE by 3.5% (CI 3.4% - 3.5%).

Table 4.6: Regression of logarithm of MSE, sensitivity ratio and coverage ratio against the number of hospitals. Coefficient and coefficient interval (CI) are exponentialized.

		Coefficient	Low CI	High CI	p-value
MSE					
Log(MSE) ~ number of hospitals	Hospital number	0.994	0.993	0.994	< 0.0001
Log(MSE) ~ number of national + specialized + provincial hospitals	National	1.035	1.034	1.035	< 0.0001
	Specialized	0.982	0.982	0.982	< 0.0001
	Provincial	0.978	0.978	0.978	< 0.0001
Sensitivity ratio					
Log(Sensitivity ratio) ~ number of hospitals	Hospital number	0.999	0.999	0.999	< 0.0001
Log(Sensitivity ratio) ~ number of national + specialized + provincial hospitals	National	0.999	0.999	0.999	< 0.0001
	Specialized	0.999	0.999	0.999	< 0.0001
	Provincial	0.999	0.999	0.999	< 0.0001
Coverage ratio					
Log(Coverage ratio) ~ number of hospitals	Hospital number	0.999	0.999	0.999	< 0.0001
Log(Coverage ratio) ~ number of national + specialized + provincial hospitals	National	0.999	0.999	0.999	< 0.0001
	Specialized	0.999	0.999	0.999	< 0.0001
	Provincial	0.999	0.999	0.999	< 0.0001

4.3.4.2. Sensitivity and coverage ratio

The sensitivity ratio of two successive AMRSS varies from 0.88 to 1.29, with a median of 1.02 (IQR 1.00 – 1.04). In general, the sensitivity ratio was higher than 1 (Student t-test p-value < 0.0001), which indicates that the sensitivity increases when adding one more hospital. The sensitivity ratios are different between type of hospitals (figure 4.5).

Similar observations were found for coverage. The coverage ratio of two successive AMRSS varies from 0.97 to 1.23, with median 1.02 (IQR 1.01 – 1.03). The coverage ratio was higher than 1 (Student t-test p-value < 0.0001), which indicates that coverage increases when adding one more hospital. The coverage ratios are also different between type of hospitals (figure 4.6).

The coefficients of sensitivity ratio and coverage ratio in the regression against the total number of hospital and type of hospital were 0.999 for both (table 4.6), indicating that the sensitivity ratio and coverage ratio were smaller when adding one more hospital. In other words, the percentage of increasing sensitivity and coverage decreased 0.1%. In average, sensitivity and coverage increased 1.09 times when adding 1 hospital into an AMRSS having 11 hospitals, but this increase was 1.05 times when adding 1 hospital to an AMRSS having 20 hospitals.

The results showed sensitivity ratio and coverage ratio could be smaller than 1. This happened when $AMRSS_k$ had mainly provincial hospitals (which usually have smaller numbers of specimens) and $AMRSS_{k+1}$ consisted of mostly specialized hospitals (which usually have larger numbers of specimens).

Figure 4.5 (B-C) did not show much difference in sensitivity ratio and coverage ratio when stratifying by the proportions of hospitals in each hospital type.

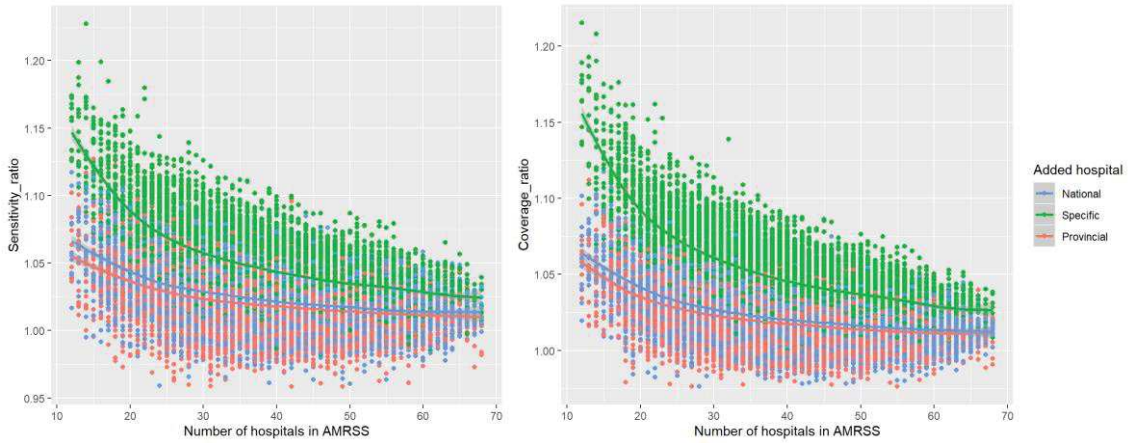


Figure 4.6: Variation of sensitivity and coverage ratio by hospital type. Smooth lines represented average of sensitivity ratio when number of hospitals increase.

4.3.4.3. Representativeness

Chi-square values of the Pearson goodness-of-fit test represented the level of representativeness in the distribution of hospitals in a hypothetical AMRSS in comparison with the distribution of hospitals in Viet Nam. A lower chi-square value signified a higher level of representativeness.

The number of national : specialized : provincial hospitals in Viet Nam 2012 was 18 : 145: 329 (approximated 1 : 8 : 18) and was used as reference distribution.

Chi-square value for each AMRSS against the reference distribution was shown in figure 4.5 (D).

Table 4.7 presents the chi-square statistic of the National : Specialized : Provincial combination that has the highest level of representativeness for a specific number of hospitals in a hypothetical AMRSS (table 4.7). The combination of 1 national, 7 specialized and 17 provincial hospitals could be considered to provide the highest level of representativeness.

Table 4.7: Combination of hospital types of the most representative AMRSS for a given total number of hospitals based on the value of Chi-square statistic

Number of hospitals	Number of hospitals by hospital type (National **:** Specialized **:** Provincial)	Chi-square statistic
12	1 : 3 : 8	0.76
13	1 : 4 : 8	0.61
14	1 : 4 : 9	0.46
15	1 : 4 : 10	0.39
16	1 : 5 : 10	0.34
17	1 : 5 : 11	0.23
18	1 : 5 : 12	0.18
19	1 : 6 : 12	0.19
20	1 : 6 : 13	0.11
25	1 : 7 : 17	0.03
30	1 : 9 : 20	0.01
40	1 : 12 : 27	0.14
50	2 : 15 : 33	0.02
60	2 : 18 : 40	0.02
70	3 : 26 : 41	1.89

4.3.5. Cost and effectiveness assessment

The total cost of surveillance for VINARES 2012-2013 was 386 thousand USD for 24 months. This cost was broken down in specific cost items (table 4.8). The cost for central unit, a reference and participating hospital were 38,000, 21,300 and 7,300 USD per year, respectively. Using these costs as input to our analysis of simulated AMRSS, we estimated that for an added hospital, the annual cost for the simulated AMRSS will be increased by 7300 USD regardless of type of hospital.

Table 4.8: Detail costs of surveillance for 24 months in VINARES 2012-2013

Cost item	Cost allocated to	Total cost	Total cost/year	Annual cost / hospital	Type of cost	Comments

Labour - central unit	Central unit	73560	36780	36780	Variable	Cost for 2 years
Labour - reference hospital	Reference hospital	24600	12300	6150	Variable	Cost for 2 years
Labour - participating hospital	Hospital	34272	17136	1069	Variable	
Equipment	Hospital	23100	4620	289	Fixed	
Consumable	Reference hospital	15700	15700	7850	Variable	
Travel - initial training	Hospital	64800	12960	810	Fixed	
Travel - site support and monitoring	Hospital	28500	28500	1781	Variable	Implementation for 1 year
Training - initial	Hospital	36800	7360	460	Fixed	
Training - annual refresh	Hospital			230	Variable	Estimated to be half of the initial training
Approval and initial admin costs	Central unit	14624	2925	183	Fixed	
EQA	Hospital	7429	7429	1061	Variable	Only 7 hospitals participated in EQA
Guidelines and updates	Central unit	9429	1886	118	Fixed	
Website	Central unit	10000	2000	125	Fixed	
Data management/ analysis/ reporting	Central unit	11571	11571	723	Variable	First year implementation
Data entry	Hospital	24000	24000	1500	Variable	First year implementation
Site evaluation	Hospital	8000	1600	100	Fixed	

EQA: External Quality Assessment

4.3.5.1. Cost and Effectiveness

In the regression analysis of MSE against costs, MSE will decrease when the cost goes up (figure 4.6). For one million USD per year added in the surveillance system to expand the network, MSE will decrease by 81% (CI 80% - 82%, p-value < 0.0001) (table 4.9).

Table 4.9: Percentage of reduction of MSE when cost of AMRSS increases

Added cost (USD)	MSE reduced (%)	CI (%)	p-value
10 000	0.8	0.7 – 0.8	< 0.0001
100 000	8.1	7.4 – 8.4	< 0.0001
500 000	34.2	32.1 – 36.2	< 0.0001

Higher costs increased sensitivity and coverage, however the percentage of increase in sensitivity and coverage were lower as the cost increases, reflected in the decreasing trend in their ratio (figure 4.7). MSE reduces quickly at the beginning, however change in MSE slope decreases when the added cost reaches above 1 million USD. At the same time sensitivity ratio goes down gradually. With 830 000 USD added in the AMRSS, MSE will decrease 50%.

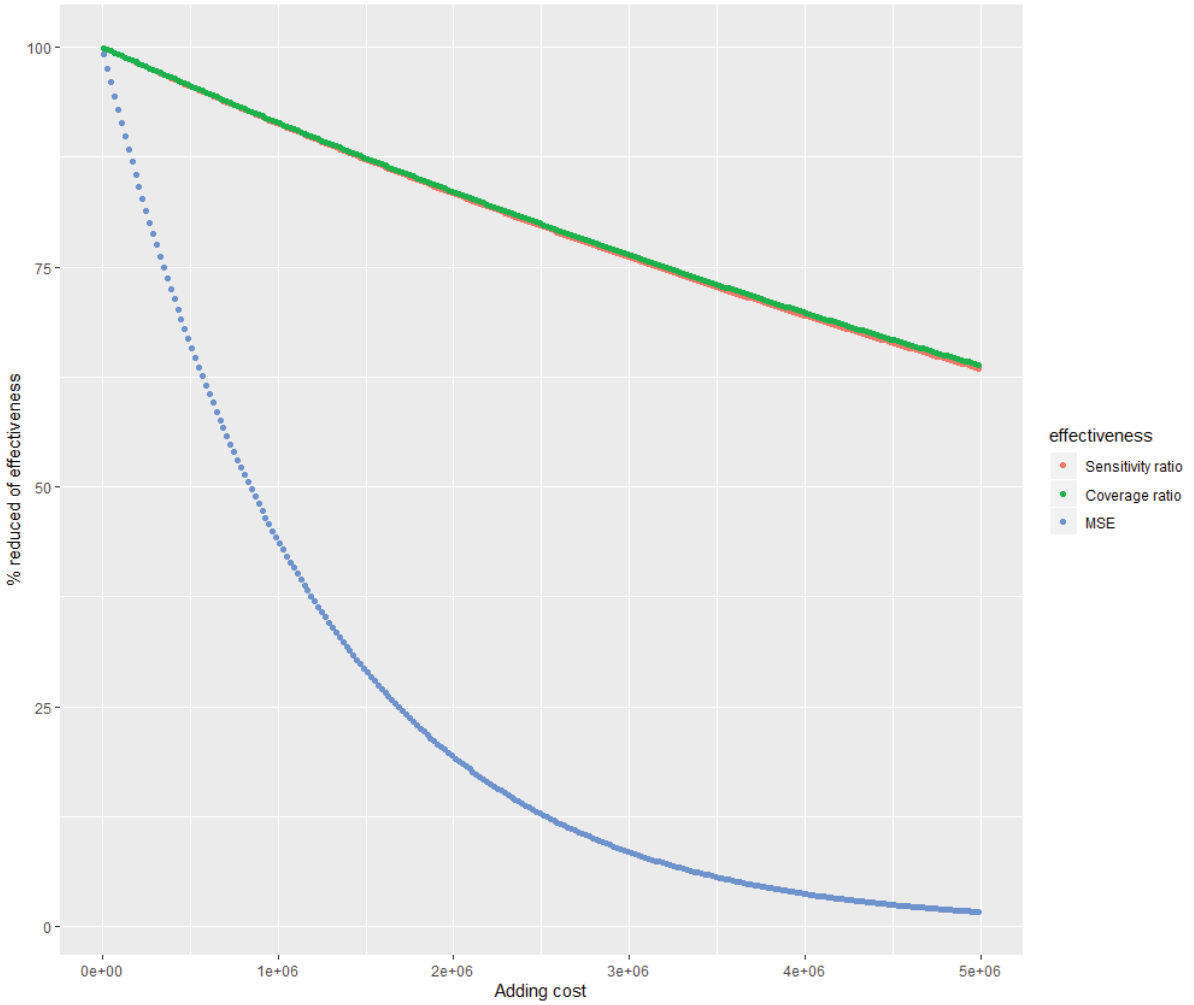


Figure 4.7: Reduction of MSE and sensitivity ratio (%) when adding annual cost to one AMRSS

4.3.5.2. Choosing the optimal AMRSS

For a given priority pathogen – antimicrobial combination, with a given amount of budget, the number of hospitals can be determined using the above described effectiveness attributes. For

a given number of hospitals, we can identify which combination of national-specialized-provincial hospitals returns the lowest MSE, highest sensitivity and highest representativeness.

The procedure for choosing the optimal AMRSS for a given number of hospitals is in following priority: MSE, sensitivity and representativeness. For given number of hospitals, the AMRSS having to 10% of the smallest MSE values and top 10% of highest numbers of patients infected by resistant pathogens (which represents sensitivity) were selected. Then the combination having the lowest Chi-square statistic (which implies the highest level of representativeness) can be considered optimal. Coverage is not taken into account in this selection because it has high correlation with sensitivity.

Table 4.10 presented the combinations of hospitals by type that had the highest level of representativeness after we conducted the selection procedure above for each given total number of hospitals in the AMRSS. We compared these combinations to the combination set up in VINARES, which is also the same in the current National AMR Surveillance Network. For each given number of hospitals in total, the decision maker can choose the best hospital combination as in this table. Higher number of hospitals in total overall resulted in a better AMRSS, but also higher cost needs to be invested.

Table 4.10: List of best AMRSS by number of hospitals after selection based on MSE, sensitivity and representativeness

Total number of hospitals	Number of hospitals by type[(a)]	Cost of AMRSS ($)	Sensitivity Increase (%)	Coverage Increase (%)	MSE Decrease (%)	Cost Increase (%)
12	1 : 6 : 5	153 600	107	111	90	84
13	1 : 5 : 7	160 900	109	106	87	88
14	1 : 4 : 9	168 200	103	103	80	92
15	1 : 4 : 10	175 500	104	109	72	96
16	1 : 5 : 10	182 800	118	119	64	100
16(*)	**04:05:07**	**182 800**	**100**	**100**	**100**	**100**
17	1 : 5 : 11	190 100	123	126	71	104
18	1 : 11 : 6	197 400	166	175	70	108
19	1 : 7 : 11	204 700	152	153	69	112
20	1 : 7 : 12	212 000	154	155	61	116
25	1 : 12 : 12	248 500	214	220	58	136
30	1 : 7 : 22	285 000	191	204	43	156
40	2 : 11 : 27	358 000	277	292	42	196
50	1 : 13 : 36	431 000	342	352	38	236
60	1 : 19 : 40	504 000	435	448	36	276
70	1 : 29 : 40	577 000	546	574	37	316

(a) (National : Specialized : Provincial); (*) Reference combination, which was the combination of hospitals set up in VINARES in 2012 and remains the same in the current National AMR Surveillance Network. The percentage of increase/decrease in effectiveness attributes was compared to this reference combination.

4.4. Discussion

In Viet Nam, the current national AMR surveillance system aims to monitor the proportion of resistant isolates obtained from patients presenting at hospitals in order to give specific recommendations for empiric therapy and assess the AMR prevalence to support control actions. In this study, using a subset of the dataset on carbapenem-resistant *K. pneumoniae* isolates from the VINARES network in 2012-2013 as baseline, we evaluated the effectiveness and costs of AMR surveillance systems by varying the number of participating hospitals by three types of hospitals (national, specialized and provincial). Incremental changes in costs and benefits from increasing an additional hospital to the network were compared between the simulated systems to identify the optimal combinations of hospitals for a given number of hospitals in a given budget allocated for AMR surveillance. We assessed the four effectiveness attributes that represent the outcomes of the surveillance system: accuracy of resistant proportion for CAI causing bacteria using MSE, sensitivity of the system to detect resistant cases, representativeness in describing the patient population and coverage which reflects the proportion of patient population reached by the system. Since denominator data is lacking, we evaluated ratios of attributes of two successive simulated systems to determine the systems with optimal hospital combinations for MSE, sensitivity and coverage.

Since one key objective of the national AMR surveillance system is to provide accurate estimates of resistant proportions among patients with community acquired infections presenting to hospital to guide empiric treatment, MSE can be used as an important criterion in choosing the most effective structure for the surveillance system. We found that adding a hospital does not always decrease the MSE (or increase the accuracy) of CAI specific resistant proportions. While expanding to an additional specialized or provincial hospital tend to increase accuracy, adding a national hospital appears to decrease the accuracy of the resistance estimates. This might be because the predicted values for HAI and CAI for specialized and provincial hospitals were highly variable due to the quality of training data, therefore an increase in the number in these hospital types can help reduce the amount of bias for the resistant proportion. However, the highest level of representativeness was indicated in the combinations with lower number of national hospitals. This is valid because the number of

national hospitals is much smaller compared to the number of other hospital types in Viet Nam overall. Therefore, considering both MSE and representativeness, the best combination of hospitals is still likely to be those with lower number of national hospitals.

In the previous and current surveillance networks clinical data that can support the separate reporting of resistant proportions in CAI and HAI causing bacteria is not collected. This has restricted the effective use of surveillance data in informing guidelines development and guiding empiric treatment in local hospitals in Viet Nam. We overcome this difficulty by identifying a predictive model using different approaches and estimate the resistant proportions separately for CAI and HAI from the VINARES surveillance data. Data from a previous study [214] were used to build the model to predict CAI/HAI status in VINARES data. We estimated 24% of isolates included in the VINARES surveillance during 2012-2013 were from HAI patients. There was limited data on the prevalence of HAI in hospitals in Viet Nam. A prevalence survey in the same period of VINARES in adult ICU settings in 14 hospitals showed a HAI prevalence ranging from 5.6% to 60.9% with an average of 29.5% [11]. Another study in 2014-2016 in a hospital for tropical diseases also reported a proportion of 23.4% in the observed patients contracting HAI in an adult ICU [12]. The overall hospital-wide rate is much lower, as shown in some reports from non-peer reviewed literature (below 5%) [216,217]. Our estimate of HAI proportions in VINARES data using predictive modelling was rather high, closer to the average range reported in ICUs. However, this high estimate might be because of the overrepresentation of severe infections in the routine antimicrobial susceptibility testing data submitted to the surveillance network. Patients who had specimens collected for microbiological investigations are usually those with more severe illness or who don't respond to treatment. With the estimated proportion of 24% of HAI and 76% of CAI in VINARES data, the estimated resistant proportion for *K. pneumoniae* was 9% in CAI and 9-15% in HAI depending on the type of hospital.

We used *K. pneumoniae* in our evaluation because this organism is among the most common organisms in the VINARES surveillance network and we also had available external datasets on *K. pneumoniae* with information on origin of infection for developing the predictive model. Carbapenem resistant *K. pneumoniae* is among the priority pathogen – antimicrobial combinations for surveillance and research and included in the GLASS implementation guidelines [13]. The proportion of carbapenem resistance reported for this organism in the above-mentioned prevalence survey in ICUs was 14.9%. No data was available for the resistance rate among non-ICU patients. The overall carbapenem resistance among

Klebsiella spp. in VINARES 2012-2013 was 17% for all specimens and 18% for invasive specimens [14]. Based on the predictive model developed from the external dataset collected in 2011 in the National Hospital for Tropical Diseases, which does not include a wide range of specimens and wards and was specific to only one hospital setting, our derived estimates for carbapenem resistant proportion were not much different between CAI and HAI. This estimation can be improved if a more representative external dataset is available.

Sensitivity and coverage always increase as the number of participating hospitals increases but quickly reach equilibrium when the increase is minimal considering the additional costs involved. Both effectiveness attributes display similar patterns in the results of simulation because there is some resemblance in how they were defined and calculated: the proportion of resistant cases detected by the surveillance network out of all resistant cases highly correlate with the proportion of patients covered under the surveillance out of the total population of patients in Viet Nam. Determining the sensitivity of a public health system usually requires additional data collection or access to an external data source on the health condition under surveillance. From a practical standpoint, a surveillance system does not need to have a high sensitivity to be useful, as long as it remains reasonably stable overtime in order to help identifying changes for response actions [37,59]. The stability of sensitivity over time depends mostly on the consistency of surveillance protocols and testing methods. The use of ratios in our evaluation of the simulated systems provides an alternative solution to evaluate relative change in these types of effectiveness attributes, with the assumption that the core surveillance protocols and testing methods remain stable as the system expands to additional hospitals.

The number of hospitals participating in the network affected the total cost of the surveillance system. Increasing the number of hospitals generally increase the effectiveness attributes, however a decision has to be made on the most cost-effective system in a limited health budget with many competing health priorities. A public health surveillance system should be designed and implemented to provide decision makers with valid and timely information at the lowest possible amount of resources consumed [218]. While these can be improved by optimizing the efficiency in the operating procedures and staff capacity and skills, having the right hospital combination with an appropriate number of hospitals can greatly improve the validity or the accuracy of the AMR data for guiding treatment and taking other control actions. It is important to note that the implementation of the VINARES surveillance network was donor funded to meet an immediate demand for data to inform AMR control actions led by the Ministry of Health. While the costs and benefits of surveillance systems often spill across

national borders and the support from international donors for capacity building is justified [218], governmental resources must be mobilized for a sustainable and strong national AMR surveillance system. Therefore, a full health economic evaluation of the national AMR surveillance system should be considered in future, including conducting additional data collections to measure the costs and effects as well as the possibility of developing an integrated surveillance system from a one-health approach to create synergies and minimize the system operating costs [43].

Due to the unavailability of data for classifying the origin of infection, we only conducted the analysis for one pathogen – antimicrobial combination to evaluate the effectiveness of a surveillance system that targets all pathogen – antimicrobial combinations tested in the routine microbiology from the participating hospitals. This limitation can be overcome in the future when more data are collected. In principle, our approach can be done to all priority pathogen – antimicrobial combinations provided that data on origin of infection is available. These data can be either integrated into the current surveillance system or coming from external data collection. Decisions on the optimal surveillance structure can be made based on the first priority drug resistant bacteria or a composite score for the key bacteria of public health importance in the country.

The AMRSS effectiveness models were assessed with input data including the type and number of hospitals, and the rates of resistance in community-acquired infections which depend on the types and quality of data available either within the surveillance dataset itself (if clinical information is integrated into the ARMSS) or from external datasets. Therefore it is not straightforward to predict about the expected changes for other types of bacteria. The risk characteristics for other bacterial infections can influence on the types of specimens collected. On the other hand, since all three types of hospitals are included in our models, the results of identifying the optimal hospital combinations are likely to remain in similar directions for other types of bacteria.

Within the scope of this thesis, we only evaluated the representativeness attribute using the simple approach of measuring the deviation in the distribution of hospitals in each hypothetical AMRSS in comparison with the nation-wide distribution of hospitals by types. This approach only took into account the variation between the types of hospitals. Using this approach, the most representative AMRSS were found to be those containing only one or two national hospitals. However, this might not be practical in reality as national hospitals deserve to have

more representativeness profile, given their contribution in the number of isolates and their impact on the overall work on AMR control in the country. Therefore, further work can be done to take into account other representativeness aspects including geographical representativeness, hospital size (bed capacity and annual number of admissions), and variation within each hospital type. Among hospitals within one type of hospitals, there can be a lot of variations in the HAI/CAI patterns as well as the resistance profiles. However, we could not integrate this level of details in our analyses due to lack of hospital specific data nation-wide.

The calculations in this chapter were based on VINARES data, therefore the results are likely to be valid for surveillance systems that have similar organizational structures and data collection protocols like VINARES. With a resource-limited setting such as Viet Nam and many other LMICs, this methodology can be applied because we usually have to optimize the surveillance system in a restricted budget. By substituting the corresponding baseline data (number of hospital types, number of patients with CAI/HAI, number of patients carrying resistant isolates), effectiveness attributes for these surveillance systems can be assessed to determine the most desirable structure.

In the next generation of AMR surveillance in Viet Nam, the origin of infection will be collected as part of the process for integrating clinical meta-data. Currently, a project called ACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network) is being implemented as a pilot protocol for case based AMR surveillance since 2019 in Viet Nam, Laos and Cambodia [181,182]. ACORN aims to develop an efficient clinically orientated AMR surveillance system and implement routine clinical care in hospitals in LMIC settings, and OUCRU and the National Hospital for Tropical Diseases are piloting this now in Viet Nam. Data from this pilot project will be used for our model to find the optimal setting for an extended AMRSS in the future. The surveillance protocol that the Ministry of Health is developing for the national AMR surveillance network will also include collection of some clinical metadata. With this addition, we will have the actual data for HAI/CAI patterns for each participating hospital in the network and will not need to perform CAI/HAI classification models as done in this chapter. However, the principles underlying these classification methods can still be applied to the datasets of other surveillance systems that still do not have clinical data particularly in LMIC settings.

The strengths in our analysis are the inclusion of three types of hospitals representing the main hospital types in Viet Nam and the availability of cost breakdowns for the implementation of

a hospital-based AMR surveillance network. With the assumption of homogeneity among hospitals within each hospital type, we were able to evaluate the effect of adding each type of hospital and the associated added costs on the performance of the whole surveillance network. This type of lab-based surveillance system can only include hospitals equipped with laboratory diagnostic capacity and therefore excludes smaller and lower-level healthcare facilities such as district hospitals. However, even when clinical information is integrated to the current surveillance system to have accurate data on origin of infection, AMR data from this lab-based surveillance system can only be used at the provincial and national levels and cannot be generalized to the patient population attending the primary healthcare facilities. Future AMR surveillance systems can consider the incorporation of community-based surveillance components, which can focus on important indicator bacteria and feasible options for specimen collection [144].

In conclusion, the effectiveness in terms of accuracy, sensitivity, coverage and representativeness of the current AMR surveillance system can be enhanced when adding more hospitals into the network. For a given health budget allocation for improving the national AMR surveillance network, optimal structures for hospital combination can be determined through our model-based evaluation approach and the most cost-effective option can be identified depending on the priorities for implementing and maintaining the system. Further economic evaluations should be considered to collect additional datasets for conducting full analyses and to explore the additional surveillance components to increase the utility of the surveillance data for public health actions.

General discussion, future directions and conclusion

Surveillance data are crucial to inform about the current situation, trends in time and space and as benchmark for implementing actions to control the spread of AMR locally and globally. Despite a number of initiatives to set up surveillance for AMR in Viet Nam and the recent recognition of the VINARES network as the National AMR Surveillance Network (2016, decision 6211 of MoH) [167], the effectiveness of this network has not been evaluated. Evaluation of surveillance systems is critical to ensure surveillance objectives are being achieved and to identify areas for improving the efficiency and effectiveness and for sustainability [57]. Therefore, I set out to systematically evaluate the existing AMR surveillance system (AMRSS) in Viet Nam using available data from VINARES and to assess the costs and effects of simulated AMRSS structure (number of hospitals of each type in the network) to determine the optimal combinations that can provide accurate estimates, by origin of infection, of the proportion of patients infected by resistant bacteria.

Since one of the aims of the AMR surveillance system in Viet Nam is to collect information to inform local treatment guidelines and clinical decision-making, one focus in this thesis was to identify an approach to predict the resistant proportions by origin of infection, i.e. hospital or community acquired.

My first hypothesis was that the current passive laboratory-based surveillance system overestimates the resistant proportions among community acquired infections (CAI) because (i) microbiology diagnostics are under-used and often reserved for more severe and unresponsive cases and no metadata are collected to distinguish between community- and

hospital-acquired infections (HAI), and (ii) proportion of antibiotic resistance in HAI is much higher than in CAI. My first research question was investigating whether we can estimate the proportion of resistance to inform local treatment guidelines for patients with CAI.

Secondly, I hypothesized that human and economic resources for AMR surveillance in Viet Nam are not adequately allocated. The result (resistant proportion) could be affected by the number of hospitals and the types of hospitals (national, specific and provincial) participating in the surveillance system. My second research was aimed at optimizing the effectiveness of the AMR surveillance system for a given budget allocation.

Review of AMR surveillance systems around the world

In my literature review (Chapter 1), I showed that the number of AMR surveillance systems globally has been increased substantially in the late 1990s; with most of the systems established after 2010 being passive international systems. These systems vary greatly in many aspects including surveillance objectives, target pathogens, number of participating hospitals, inclusion of reference / central laboratories, standards for interpretation of AST results, quality control measures, information on de-duplication, and integration of clinical information. These variations lead to difficulties when aggregating data and making comparisons across locations and regions.

There is also no standardized framework and guidelines for conducting evaluation of AMR surveillance systems. Such evaluations have also not been performed or reported in most of the AMR systems in this review. An evaluation was reported in less than 10% of the systems, focusing on few attributes such as representativeness, timeliness, bias, cost, coverage, and sensitivity. Depending on the health condition under surveillance, evaluation can focus on the attributes that are most relevant as also reflected in a systematic review on evaluation of animal and public health surveillance systems in the world previously [57].

From this review, I identified the key elements of an AMR surveillance system and the gaps and common issues in running these systems at local and international levels. The review also shows the gap in evaluation of AMR surveillance systems. Such a gap is critical to improve AMRSS performance and effectiveness and to ensure resources are adequately used to achieve the surveillance objectives. While there are generic guidelines for evaluating public health surveillance systems, these guidelines may not be specific enough to the context of AMR surveillance. AMR surveillance is different from surveillance of any specific disease because it is more complex with a wide range of targeted organisms, various types of specimens and

protocols for testing and quality control. One important aspect is that AMR surveillance plays an important role in helping to determine appropriate antibiotic treatments for patients whose illness requires antibiotic treatment [219]. Appropriate treatment (covering the suspected or detected pathogen) is not only beneficial at the individual patient level as it will improve the success of the treatment but in public health management of diseases and control of increasing AMR problems appropriate treatment (when indicated and not too broad) is also beneficial at population level by mitigating the spread of AMR.

The most common objectives in 48/79 surveillance systems in my review were to monitor trends in infection and resistance and study antimicrobial susceptibility patterns. The objective of developing treatment guidelines was explicitly stated in a small number (5) of systems, and two evaluated the bias in the estimated proportion of resistance in animal [114] or bias towards over-representation of resistant infections in the sampling protocol [55].

Information on how the effectiveness attributes of the surveillance systems were evaluated was poorly described in most studies, except for the systematic evaluation of the Australian Gonococcal Surveillance Programme [52]. Evaluation was often described as an add-on analysis rather than a systematic evaluation of the whole AMR surveillance system. In all studies, the context of surveillance was not described in detail.

Having gained an overview of the AMR surveillance systems and their evaluation worldwide, I focused my evaluation on the VINARES network in Viet Nam. This evaluation was conducted systematically to evaluate all aspects of the system organization and performance. A recent review of the existing approaches to evaluation of surveillance systems showed that most approaches were generic with broad recommendations and common steps for the evaluation process, including defining the surveillance system under evaluation, designing the evaluation process, implementing the evaluation, and drawing conclusions and recommendations [62].

Evaluation of AMR surveillance system in Viet Nam based on the VINARES network

I used SurvTool and OASIS to systematically evaluate the AMR surveillance system in Viet Nam. SurvTool helps the user to establish an evaluation context, including surveillance description, evaluation questions and suggestion of assessment methods. OASIS - a qualitative assessment tool for assessment of strengths and weaknesses of surveillance systems based on 78 criteria – can be used to assess the situation and operation of a surveillance system.

I chose the VINARES network because the current National AMR Surveillance Network in Viet Nam consists of the VINARES hospitals and essentially employs the same structure and protocols as VINARES. Using these tools, I assessed the surveillance system organization to identify the strengths and weaknesses of the system and the impact of the system function on its effectiveness.

I selected five attributes to assess, which were indicated in the outputs of SurvTool and that are relevant for the surveillance system under evaluation in answering our research questions. Based on expert opinion, I included four effectiveness attributes (sensitivity, coverage, representativeness and timeliness) and cost.

The VINARES network was operational as an AMRSS in 2012-13 and 2016-17. It then became the National AMR Surveillance System in 2016, and data collection resumed in 2018. There were 16 hospitals enrolled in the VINARES network in 2012: 4 national, 5 specialized and 7 provincial hospitals. In 2016, the number of hospitals submitting data was reduced to 13 with 3 national, 3 specialized and 7 provincial hospitals. The hospitals that dropped out of the network were large tertiary hospitals located in the capital city. Changes in the number of hospitals affected the surveillance data and the distribution of isolates of key organisms: 10% increase in the number of isolates from national hospitals in 2016-17 compared with 2012-13, while the proportion was the same for provincial hospitals in the 2 periods (44%). This could affect the accuracy of the estimated resistant proportions. As emphasized throughout this thesis, one important objective of AMR surveillance in Viet Nam is to gain accurate information on the resistance patterns to inform control actions and treatment. Therefore, it is important to identify the combinations of hospitals that provide data with low bias and high precision while saving the resources invested in the surveillance system.

The very limited amount of clinical metadata collected in the surveillance made the estimation of resistant proportions by origin of infection impossible. This is a concern for the use of surveillance data to help doctors in making decision for empiric treatment of their patients prior to sampling for microbiological diagnostics. The overall resistant proportion for all patients is likely to be biased towards hospital acquired and more severe or unresponsive patients, who are more likely to have drug resistant infections. While waiting for the integration of clinical data into the surveillance system, we aimed to model or estimate the proportions of resistance among CAI versus HAI from the surveillance data.

Under a passive surveillance protocol, laboratories at the hospitals in VINARES were asked to send data to the central unit following a specified timeframe (monthly in first and quarterly in second period); these data were AST results of the isolates recovered from specimens routinely collected by doctors and sent to the labs for diagnostics. This surveillance approach was effective in obtaining data from a large number of hospitals at a low cost using the existing health infrastructures. Passive surveillance is considered a relatively inexpensive strategy to gain health information from populations with a large geographical coverage, however this approach also poses issues in the control of data quality and timeliness because the system relies heavily on staff at the participating institutions to perform the required surveillance activity [218]. In VINARES, the data quality and consistency were assured by training, use of translated CLSI guidelines, ATCC strains for internal quality assurance, enrolment into UK-NEQAS for external quality assurance and standardized data submission using (translated) WHONET. But there was still a delay in data submission from the hospitals (10% of submissions were up to 3 months after the deadline), which affected the timeliness of the surveillance system. This and many other operational issues can be improved through regular and concurrent evaluation of the surveillance system to identify problems and implement prompt resolutions. Periodic evaluations may help ensure the system operates efficiently, information provided by the system is useful for public health practice, and health resources are spent appropriately for surveillance [220].

Resistant proportions: results from analysis of AST data from VINARES's surveillance network

Despite the limitations intrinsic to the passive surveillance approach and the absence of clinical metadata, the data collected in VINARES during the two periods 2012-2013 and 2016-2017 have provided a description of the resistant proportions of important bacteria – antibiotic combinations for each of the participating hospitals in the network and for all hospitals combined, stratified by sample (blood & CSF vs. other) and ward (ICU vs. non-ICU). These data are important to understand the distribution and magnitude of the AMR problem in hospitals in Viet Nam.

Resistance patterns varied greatly between the hospitals, and there were trends of increase of the resistant proportions over time between the two periods in some pathogen-antimicrobial combinations, and mixed results in other combinations. For example, imipenem-resistant proportions appeared to increase overtime for *K. pneumoniae,* while no such trend was

observed for MRSA and vancomycin-resistant *E. faecium*. Imipenem-resistant *A. baumannii* and *P. aeruginosa* were higher in second period of VINARES.

Such data can be used to inform local treatment guidelines at each hospital but direct use of these detected resistant proportions is limited considering the bias caused by the absence of clinical metadata and thus the inability to distinguish between hospital and community acquired origin of infection.

There are a number of priority pathogens recommended by GLASS [39] that are currently being monitored under the National AMR Surveillance Network. Comparison between the surveillance data and data from a point prevalence survey (PPS) in 15 ICUs in the VINARES network in 2012-2013 [190] for the key pathogens revealed striking differences. Imipenem resistance in the surveillance data was 70% for *A. baumannii* and 33% for *P. aeruginosa*, for all types of specimens combined (45% and 28% in blood and CSF). On the other hand, carbapenem resistance in HAI patients in the point prevalence survey was 87% and 56% for *A. baumannii* and *P. aeruginosa* respectively [221]. These large differences between the two data sources can be explained by the types of patients included, with the surveillance data including both CAI and HAI patients, the difference between ICU and non-ICU patients and the relative abundance of HAI among ICU patients, especially those receiving mechanical ventilation. This illustrates the likely effect of mixing the origin of infection on the resistance estimates, resulting in the overestimation of resistance among CAI patients as stated in my first research hypothesis.

For imipenem resistant *K. pneumoniae*, which was used as the target pathogen in the modelling study in chapter 4, the overall resistant proportion was 15% among all isolates in the VINARES surveillance data of 2012-2013. This was comparable to the proportion reported in the PPS [190]. Similarly, the proportion of *K. pneumoniae* resistant to third generation cephalosporins was 68% in the surveillance data in 2012-2013 and 72% in the PPS (p77) [221]. The surveillance data aimed to capture the resistance patterns for all patients with clinical specimens routinely collected (not distinguishing between CAI and HAI) while the PPS only targeted HAI patients in ICUs. The similarity in resistant proportion from surveillance data with that from the PPS is related to the over-representation of HAI isolates among the imipenem resistant *K. pneumoniae* isolates in the surveillance data and indicates the need to sample all patients with infection or requiring antibiotics for microbiological diagnostics, and not only severe or unresponsive patients..

Integration of clinical information as part of an AMR surveillance system from the beginning is urgently needed. If this could be done, data on resistant proportions will be more accurate and useful for control and treatment of infections. Until then, we have to determine how the surveillance data could be analysed to incorporate information on the origin of infection to make it more meaningful and effective.

Classifying origin of infection for VINARES surveillance data: results from classification models

Hospital and community acquired infections are intrinsically different in terms of causative pathogens, resistant proportions, patient populations and epidemiology. However, classification of an infection as community acquired or hospital acquired in practice is largely done based on the date of symptom onset. Those who developed symptoms before hospital admission for a disease are considered to have community-acquired infection while those developing symptoms after 48 hours or more of hospitalization are considered hospital acquired. Risk factors for HAI are complex; a recent systematic review reported the increased risk in patients with comorbidity, immunosuppression, surgery related factors, antibiotic use, ICU admission, and mechanical ventilation [222]. Older age was also linked to the increased risk of HAI, which was thought to be related to dysregulated immune function and increased susceptibility to infection in the elderly patients [223,224]. Finally, certain types of specimens are collected more often in patients with HAI than CAI; for example pneumonia is the most common type of HAI [190,225] and thus sputum or endotracheal specimens are collected more often among HAI than CAI patients. Therefore, the type of specimens can be used to help classify the CAI/HAI status of patient data.

To answer my first research question, I examined how to classify an individual patient as having CAI or HAI based on the observed data for the covariables collected in the surveillance system. Statistical modelling has been used as a common method for disease diagnosis, however this required prior assumptions and is less capable of dealing with massive complicated non-linear and dependent datasets generated from routine hospital information systems. I used classification models from machine learning with a combination of five classifiers including Naïve Bayes, which has been considered as a benchmark algorithm to be tried before other advanced techniques in the medical area [226]. The results from my analysis also showed Naïve Bayes classifier produced more high-quality models than other classifiers.

I only applied this approach to *K. pneumoniae*, as it was the only pathogen for which I could identify a suitable external dataset for use as training data. The resulting estimates for HAI proportions and imipenem resistance for this organism in the VINARES data were in the plausible ranges compared to other studies. In principle, this approach can be applied to any other pathogen – antimicrobial combination in the surveillance data that need to be evaluated, provided suitable external datasets are available. This depends on public health priorities and activities funded by local or international research funding sources. While integrating electronic clinical information from all participating hospitals into the national AMR surveillance system should be the long-term and sustainable way to go, funding smaller research to collect detailed clinical data for key bacteria at local hospitals can provide a short-term solution to enhance the clinical utility of the current AMR surveillance datasets.

Optimizing AMR surveillance system in Viet Nam

My second hypothesis was that the resources for the current AMR surveillance system are not adequately allocated to achieve the best outcome at a given budget. I evaluated this by simulating a large number of AMR surveillance systems with different combinations of hospitals containing national, specialized, and provincial hospitals and assessed their performance using the baseline values from the VINARES surveillance system in 2012-2013. The simulation results showed that the current AMR surveillance system should increase the proportions for specialized and provincial hospitals in order to increase the accuracy of resistant proportions and system representativeness. The initial set-up of VINARES included a higher proportion of national hospitals than that in the country. In addition, there is no single solution for the optimal combination of hospitals. Rather, it depends on the amount of budget that the government is willing to spend on AMR surveillance. The approach that I used to determine the cost and effectiveness of the systems can provide an answer on the option that would lead to the best outcomes in achieving the objectives of surveillance under a budget constraint.

Economic evaluation deals with costs and consequences and concerns choices to be made on the use of scarce resources [227]. Conventional healthcare evaluations often provide cost and effectiveness ratios among alternative healthcare programs, although there is an increasing debate that such ratios are not sufficient to make decisions on the optimal allocation of resources [228]. This is mainly because the costs and consequences often need to be narrowed down in order to calculate the ratios and therefore often failed to include many aspects influencing decision making in real-life practice. In my cost and effectiveness analysis, I did

not calculate the cost-effectiveness ratios because I did not compare the costs and effects of two distinctive surveillance programs with different surveillance approaches. The national AMR surveillance system has just been established using the structure of the VINARES hospital network with a passive laboratory-based surveillance approach. While the passive surveillance approach has inherent limitations due to the nature of voluntary or routine reporting systems [229], it is a long-term and low-cost solution suitable for LMIC settings such as Viet Nam. Therefore, the objective of the cost and effectiveness evaluation in my study was to optimize the effectiveness of the AMR surveillance system under a budget constraint (or a fixed budget).

Further work could be done to have a full economic evaluation of AMR surveillance providing evidence on the cost-effectiveness of different surveillance approaches, especially in the context where countries such as Viet Nam need to improve their surveillance methodologies in the roadmap to participate in the global case-based surveillance system (GLASS). GLASS aims to collect valid AMR data to monitor trends and burden as well as to inform local and national guidelines. The recommended surveillance approach in GLASS is more complex and time-consuming, but provides more reliable and less biased information than conventional laboratory-based surveillance systems [48]. Budget impact analysis might also be necessary to assess the affordability and to provide evidence on the non-healthcare costs that can support decision makers in rational resource allocation [230]. This is particularly required when moving toward a one-health approach as promoted by international organizations and formulated as a central recommendation of the Global Action Plan for AMR control [36].

Conclusions and recommendations for the next steps

Through a systematic evaluation of the AMR surveillance system in Viet Nam based on the VINARES network and application of modelling and simulation methods to evaluate the performance of hypothetical systems, this research showed a number of important results.

Firstly, the performance and effectiveness of the AMR surveillance system in Viet Nam was determined by the structure of the hospital network, the surveillance approach including the design of data collection protocols to include necessary metadata, the concurrent monitoring and prompt feedback of data to participating hospitals, and the integration of ongoing evaluation to timely identify issues and implement improvement resolutions.

Secondly, the AMR surveillance system has provided important data that help understand the AMR burden, support decision making in clinical treatment for patients and inform the design

and evaluation of controls actions in Viet Nam. However, AMR data from the surveillance system are likely to provide an over-estimation of the resistant proportions for infections acquired in the community and should be validated by external datasets before interpretation and used for treatment and control actions. Classification models can be useful in determining the origin of infection for the patients reported under the surveillance system.

Finally, the analysis showed that the current structure including 4 national, 5 specialized and 7 provincial hospitals is not optimal; increasing the proportions of specialized and provincial hospitals appears to improve the accuracy and representativeness of resistance data. The most effective combination of hospitals can be identified in a given budget allocated for AMR surveillance in the country.

In Viet Nam, the national AMR surveillance network was implemented since 2017 and continues to collect data using a protocol similar to VINARES. Currently, case-based AMR surveillance is an alternative approach recommended by GLASS, which can improve the utility of surveillance data in informing treatment guidelines and clinical practice, providing consistent and systematic data streams for analyses of the effectiveness of interventions and identifying high-risk populations and settings vulnerable to AMR infections [39].

Since 2019, OUCRU and the National Hospital for Tropical Diseases are piloting ACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network), with additional enrolment sites in Laos and Cambodia. ACORN combines clinical and laboratory data collection with direct feedback to local physicians [181,182]. Data from this pilot project will be used for our model to find the optimal setting for an extended AMRSS in the future.

Based on the results of this research and current situation in Viet Nam, the following recommendations are put forward for the next steps in improving the cost-effectiveness of AMR surveillance in Viet Nam and in other LMIC settings:

- Develop a feasible evaluation plan to be integrated to the current National AMR Surveillance Network to regularly monitor and improve the technical performance and efficiency of the system. Providing valid and timely information to decision makers at a lowest possible cost is the fundamental principle of any public health surveillance [218]. It is also equally important to ensure that data collected from the surveillance system are used appropriately and effectively to improve antibiotic treatment and to control AMR problems. This is well reiterated in the following quotation: "*The reason for collecting, analysing, and disseminating information on a disease is to control that*

disease. Collection and analysis should not be allowed to consume resources if action does not follow" [231].

- AMR surveillance is one of the important strategies in the National Action Plan to control AMR. Data from the AMR surveillance system should be used for design and evaluation of the national and local actions and interventions to tackle AMR issues including development of treatment guidelines and tools for doctors in local hospitals. This data should therefore be in an open-access format, which should be accessible for research and program implementation as well as local practitioners.

- The design of the current National AMR Surveillance protocol should be extended to include key clinical information of each patient, particularly information on the origin of infection to improve the utility of the AMR surveillance data in guiding treatment therapy and developing specific treatment guidelines. The feasibility of this extension should be evaluated carefully based on data from ACORN and the evidence implementing GLASS from other countries. In the meantime, separate research studies can also be conducted to determine the prevalence and resistance patterns of key pathogen – antimicrobial combinations for community acquired and hospital acquired infection. These datasets can be used for cross-validation of the AMR data collected from the national surveillance system or classification of these surveillance data by HAI/CAI status.

- Consider additional AMR surveillance components or alternatives including an active surveillance approach and an integrated one health surveillance approach. There needs to be more economic evaluation of these components including budget impact analysis to provide more evidence for policy makers in making decisions to allocate resources on the most effective options or combination of options within a constrained budget for AMR surveillance.

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Appendices

Chapter 1

Table S1.1: Completed checklist for systematic review of AMR surveillance systems worldwide – Chapter 1

Item	#	Item definition	Applicable in the thesis
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Not applicable for chapter format.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes. The statement is "to identify relevant technical and operational aspects and effectiveness attributes that could affect the performance of AMR surveillance systems around the world, and review the evaluation processes that have been used for these systems".
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes. This is a descriptive systematic review. We defined the time range of search for any published reports in English or French. Criteria for inclusion of reports were also described.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes, we listed the databases used for search.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Yes, the key words used for search were provided.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes, the process was described.

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	We described the data that were extracted, duplicates were also removed. For the purpose of this PhD, we only used information provided (published) in the reports, so we did not attempt to contact the authors for further information.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	We defined all variables in relation to the surveillance systems being reported in each of the paper.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	This is not applicable in this systematic review because we reviewed all information and synthesized all information descriptively.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	We only reported count and proportions.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	We only used a narrative approach to summarize the data.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable due to the nature of this review which is limited to a narrative review.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes, this was provided.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	A table of all reports on AMR surveillance systems was provided with citation and relevant characteristics.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not applicable.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable.

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Yes, we summarized the main findings and identified the gaps in the current literature on AMR surveillance systems worldwide.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Study-level limitations were mentioned throughout the discussion. We did not specifically discussed review-level limitations as this review includes all papers on AMR surveillance systems to the time of search and we did not examine the reporting bias in the published data.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Yes, these were reflected in the conclusion section of this chapter.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	This was described in my acknowledgement section for the whole thesis.

Checklist was from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

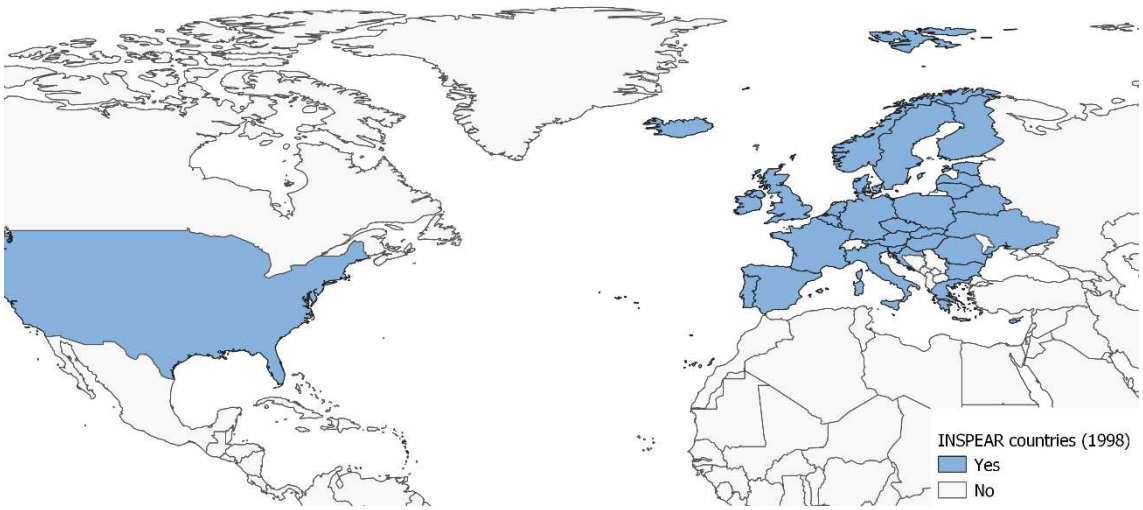

Figure 1a: AMRSS in INSPEAR program (1998)

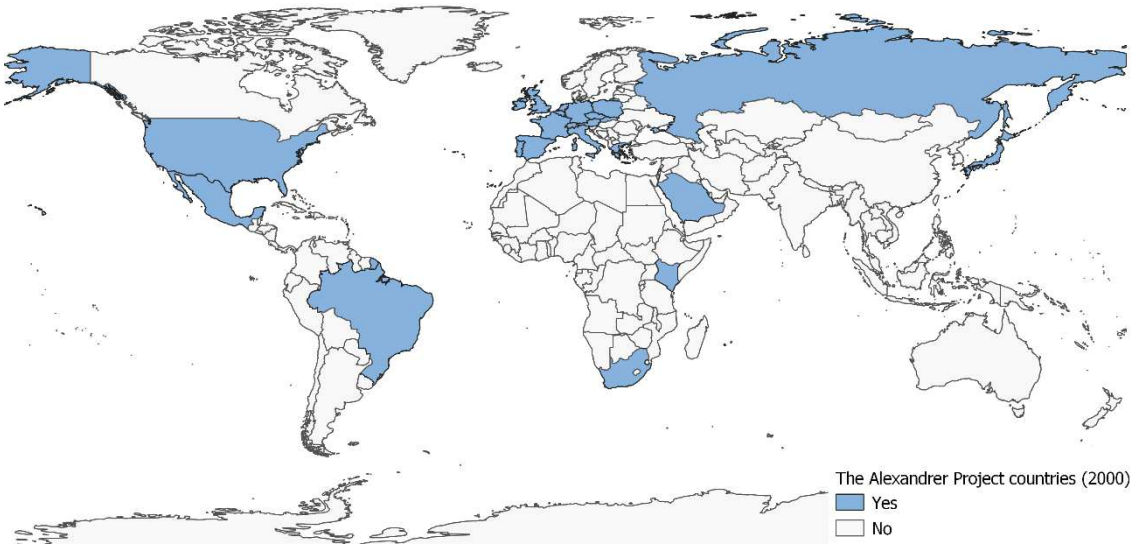

Figure 1b: AMRSS in Alexandrer Project (2000)

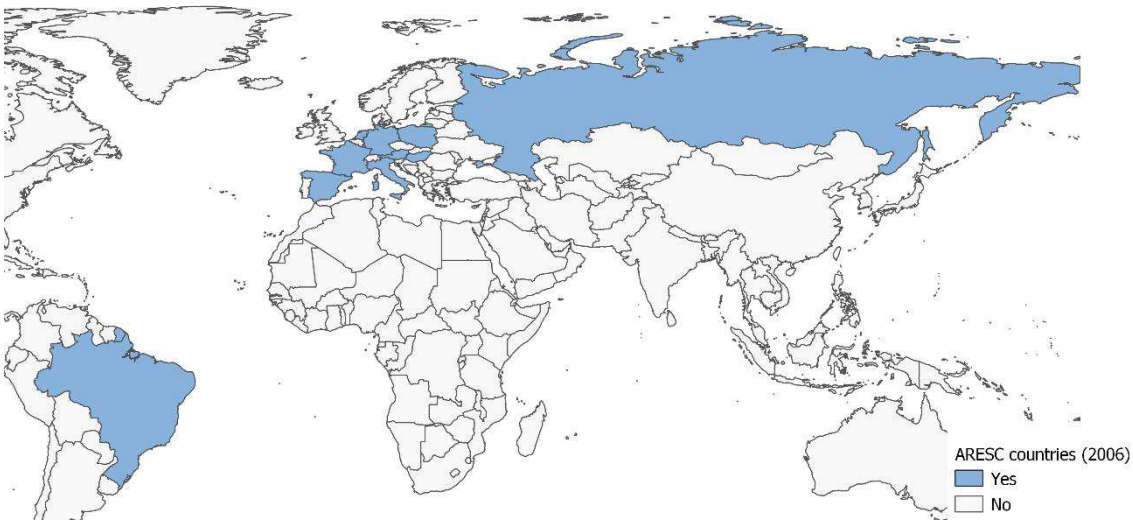

Figure 1c: AMRSS in ARESC program (2006)

Figure 1d: AMRSS in CAESAR program (2015)

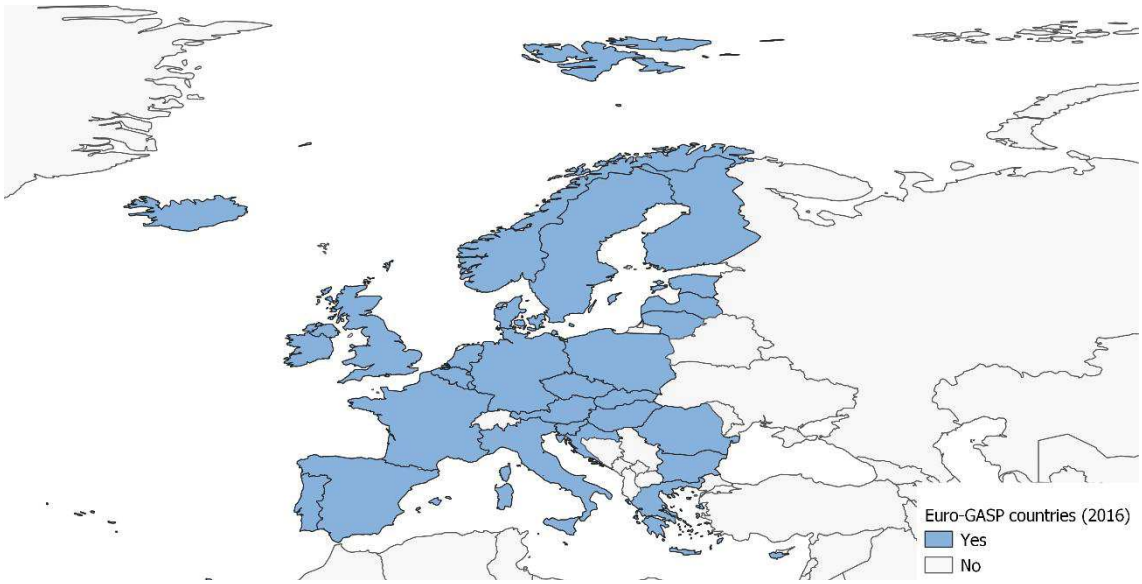

Figure 1e: AMRSS in Euro-GASP program (2016)

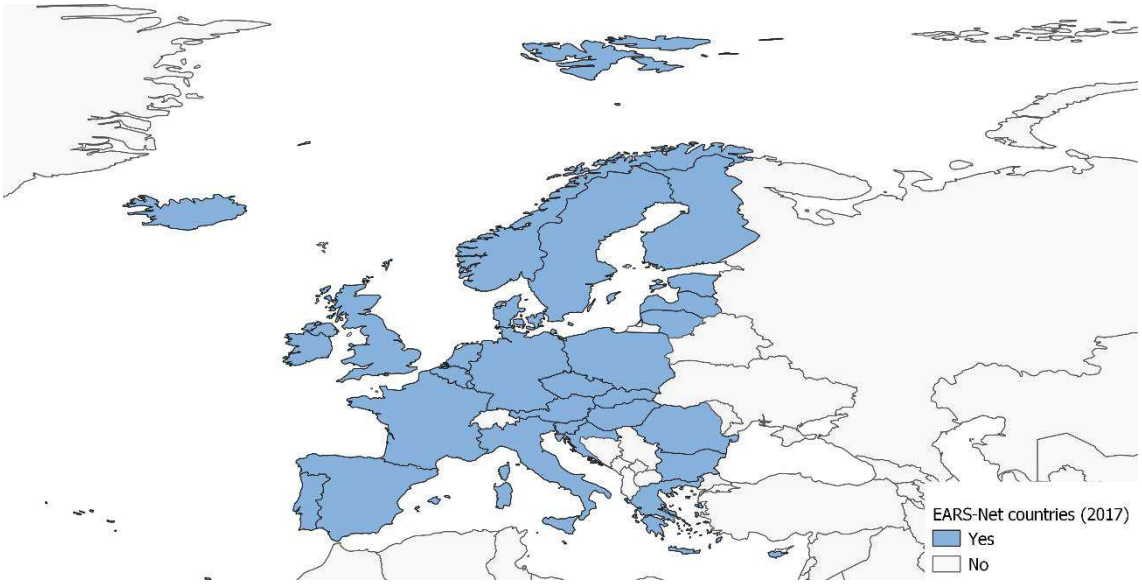

Figure 1f: AMRSS in EARS-Net program (2017)

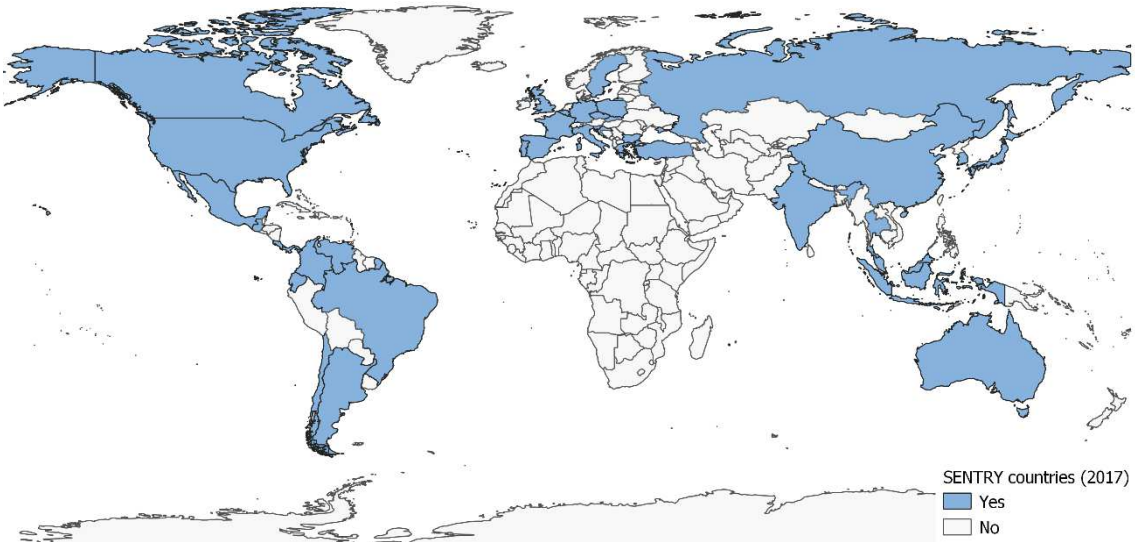

Figure 1g: AMRSS in SENTRY program (2017)

Chapter 2

Table S2.1: Specialized hospitals participating in VINARES surveillance system

Hospital	Period of VINARES	Type	Target population
National Hospital for Tropical Disease	2012 – 2013 2016 - 2017	Infectious disease	Patient in the north of Viet Nam
Hospital for Tropical Disease	2012 – 2013 2016 – 2017	Infectious disease	Patient in the south of Viet Nam
Children Hospital	2012 – 2013 2016 – 2017	Children	Patient in the south of Viet Nam
Viet Duc Hospital	2012 – 2013	Surgical	Patient in the north of Viet Nam
National Children's Hospital	2012 – 2013	Children	Patient in the north of Viet Nam

Chapter 3

Table S3.1.1: Patient and samples characteristics for the nine indicator bacteria

Characteristic n (%)	*Escherichia coli* (n = 4 437)	*Klebsiella spp.* (n = 3 290)	*Acinetobacter spp.* (n = 2 895)	*Pseudomonas aeruginosa* (n = 2 326)	*Staphylococcus aureus* (n = 2 039)	*Enterobacter spp.* (n = 1067)	*Streptococcus pneumoniae* (n = 813)	*Haemophilus influenzae* (n = 404)	*Enterococcus faecium* (n = 98)
Sex	**3 776**	**2 740**	**2 230**	**1 951**	**1713**	**988**	**633**	**396**	**58**
- Female	1 709 (45)	940 (34)	753 (34)	656 (34)	585 (34)	373 (38)	216 (34)	136 (34)	26 (45)
- Male	2 067 (55)	1 800 (66)	1 477 (66)	1 295 (66)	1 128 (66)	615 (62)	417 (66)	260 (66)	32 (55)
Age group	**4 339**	**2 944**	**2 427**	**2 273**	**1 779**	**1 029**	**480**	**177**	**62**
- 0 to 10 years	631 (15)	453 (15)	385 (16)	366 (16)	485 (27)	145 (14)	427 (89)	152 (86)	17 (27)
- 11 to 20 years	252 (6)	116 (4)	147 (6)	164 (7)	161 (9)	55 (5)	8 (2)	2 (1)	3 (5)
- 21 to 40 years	809 (19)	490 (17)	424 (17)	462 (20)	442 (25)	204 (20)	10 (2)	7 (4)	10 (16)
- 41 to 60 years	1 261 (29)	786 (27)	585 (24)	620 (27)	348 (20)	269 (26)	10 (2)	7 (4)	17 (27)
- 61 years or older	1 386 (32)	1 099 (37)	886 (37)	661 (29)	343 (19)	356 (35)	25 (5)	9 (5)	15 (24)
Specimen	**4 437**	**3 290**	**2 895**	**2 326**	**2039**	1067	**813**	**404**	**98**
- nasopharyngeal swab	6 (0)	15 (0)	6 (0)	11 (0)	28 (1)	12 (1)	11 (1)	0 (0)	0 (0)
- pus	555 (13)	243 (7)	148 (5)	225 (10)	538 (26)	92 (9)	10 (1)	5 (1)	14 (14)
- stool	143 (3)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	0 (0)	1 (0)	0 (0)
- urine	992 (22)	246 (7)	165 (6)	185 (8)	50 (2)	160 (15)	0 (0)	0 (0)	18 (18)
- vaginal swab	85 (2)	14 (0)	3 (0)	3 (0)	35 (2)	31 (3)	0 (0)	0 (0)	2 (2)
- wound swab	168 (4)	79 (2)	50 (2)	65 (3)	204 (10)	61 (6)	1 (0)	0 (0)	0 (0)
- blood	508 (11)	369 (11)	294 (10)	141 (6)	246 (12)	75 (7)	49 (6)	6 (1)	21 (21)
- CSF	19 (0.4)	44 (1)	19 (1)	13 (1)	12 (1)	7 (1)	38 (5)	4 (1)	3 (3)
- sputum	172 (4)	574 (17)	720 (25)	430 (18)	237 (12)	210 (20)	489 (60)	287 (71)	2 (2)
- others	1 789 (40)	1 706 (52)	1 490 (51)	1 251 (54)	687 (34)	419 (39)	215 (26)	101 (25)	38 (39)

Table S3.1.2: Number of percentages of antimicrobial susceptibility test of pathogen – antimicrobial combinations by hospital

Bacteria	Antibiotic	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	H15	H16
S. aureus	VAN	0/120(0)	13/17(76)	0/26(0)	70/70(100)	12/98(12)	0/18(0)	14/137(10)	29/29(100)	0/80(0)	0/99(0)	113/114(99)	0/80(0)	99/109(91)	54/201(27)	97/97(100)	0/57(0)
S. aureus	OXA	7/120(6)	0/17(0)	0/26(0)	70/70(100)	1/98(1)	0/18(0)	0/137(0)	29/29(100)	0/80(0)	0/99(0)	0/114(0)	0/80(0)	18/109(17)	0/201(0)	0/97(0)	0/57(0)
S. aureus	FOX	92/120(77)	16/17(94)	26/26(100)	70/70(100)	67/98(68)	0/18(0)	37/137(27)	29/29(100)	75/80(94)	60/99(61)	0/114(0)	76/80(95)	99/109(91)	143/201(71)	95/97(98)	57/57(100)
S. pneumoniae	PEN	0/13(0)		0/19(0)		0/4(0)	0/3(0)		6/7(86)	0/8(0)	0/2(0)	0/332(0)	0/10(0)	4/12(33)	75/186(40)	0/1(0)	0/1(0)
E. faecium	VAN		5/7(71)	2/2(100)	15/15(100)	2/2(100)			4/5(80)	8/9(89)		6/6(100)	13/13(100)			1/1(100)	
E. coli	IPM	317/338(94)	17/17(100)	160/161(99)	59/60(98)	68/119(57)	23/23(100)	159/428(37)	100/100(100)	155/156(99)	127/132(96)	162/162(100)	99/102(97)	0/10(0)	50/167(30)	226/414(55)	171/259(66)
E. coli	SXT	108/338(32)	11/17(65)	159/161(99)	56/60(93)	64/119(54)	9/23(39)	95/428(22)	100/100(100)	32/156(21)	60/132(45)	0/162(0)	100/102(98)	5/10(50)	100/167(60)	336/414(81)	253/259(98)
E. coli	TOB	112/338(33)	15/17(88)	0/161(0)	0/60(0)	108/119(91)	0/23(0)	186/428(43)	0/100(0)	2/156(1)	124/132(94)	161/162(99)	98/102(96)	0/10(0)	143/167(86)	0/414(0)	129/259(50)
Klebsiella spp.	IPM	188/204(92)	9/9(100)	34/34(100)	80/83(96)	93/184(51)	31/31(100)	45/140(32)	23/24(96)	96/96(100)	62/63(98)	142/143(99)	133/133(100)	71/78(91)	13/65(20)	109/175(62)	97/122(80)
Klebsiella spp.	SXT	72/204(35)	1/9(11)	34/34(100)	79/83(95)	100/184(54)	17/31(55)	33/140(24)	23/24(96)	26/96(27)	28/63(44)	0/143(0)	133/133(100)	52/78(67)	51/65(78)	144/175(82)	119/122(98)

Klebsiella spp.	TOB	70/204(34)	6/9(67)	0/34(0)	0/83(0)	173/184(94)	0/31(0)	57/140(41)	0/24(0)	3/96(3)	52/63(83)	142/143(99)	133/133(100)	72/78(92)	52/65(80)	0/175(0)	73/122(60)
Enterobacter spp.	IPM	106/114(93)		10/10(100)	1/1(100)	8/16(50)	1/1(100)	21/46(46)		22/22(100)	72/73(99)	22/22(100)	19/19(100)	19/20(95)	21/175(12)	64/98(65)	24/31(77)
Enterobacter spp.	SXT	36/114(32)		10/10(100)	1/1(100)	10/16(62)	0/1(0)	14/46(30)		5/22(23)	34/73(47)	0/22(0)	19/19(100)	15/20(75)	140/175(80)	85/98(87)	31/31(100)
Enterobacter spp.	TOB	35/114(31)		0/10(0)	0/1(0)	16/16(100)	0/1(0)	27/46(59)		2/22(9)	68/73(93)	22/22(100)	17/19(89)	19/20(95)	77/175(44)	0/98(0)	16/31(52)
Acinetobacter spp.	IPM	140/158(89)	14/14(100)	86/87(99)	302/302(100)	0/172(0)	15/15(100)	32/93(34)	15/15(100)	87/88(99)	46/47(98)	4/49(8)	160/161(99)	9/13(69)	1/11(9)	111/121(92)	44/59(75)
P. aeruginosa	IPM	66/80(82)	2/2(100)	46/46(100)	43/43(100)	0/113(0)	14/14(100)	28/115(24)	8/8(100)	52/53(98)	43/44(98)	51/51(100)	142/144(99)	46/50(92)	31/94(33)	154/163(94)	39/55(71)
H. influenzae	AMC			0/5(0)	0/1(0)			0/1(0)		2/7(29)		214/217(99)	7/8(88)	3/3(100)	0/61(0)		
H. influenzae	AMP			0/5(0)	1/1(100)			0/1(0)		0/7(0)		214/217(99)	0/8(0)	0/3(0)	0/61(0)		

Blank cells represent that no isolate was detected in that hospital; VAN: Vancomycin; OXA: Oxacillin; FOX: Cefoxitin; PEN: Penicillin; IPM: Imipenem; SXT: Trimethoprim/sulfamethoxazole; TOB: Tobramycin; AMC: Amoxicillin/clavulanic acid; AMP: Ampicillin; pathogen – antimicrobial combinations were selected using priority pathogen list recommended by World Health Organization (http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf).

Table S3.2.1: Antimicrobial susceptibility testing results by hospital type

Resistant / Tested (%)	*Acinetobacter spp.* (N=2469)			*E. coli* (N=4001)			*S. aureus* (N=1534)		
	National	Provincial	Specialised	National	Provincial	Specialised	National	Provincial	Specialised
Carbapenem	1979/2413 (82)	432/632 (68)	444/577 (77)	466/3801 (12)	370/3253 (11)	125/1776 (7)			
Cephalosporins	2053/2377 (86)	464/637 (73)	452/535 (84)	2670/3541 (75)	1730/2884 (60)	1041/1770 (59)			
ESBL				2145/3726 (58)	1541/2371 (65)	399/856 (47)			
MRSA							827/1032 (80)	425/677 (63)	572/801 (71)

Table S3.2.2: Resistant proportion of priority bacteria-antimicrobial combinations in all specimens and in blood and CSF, in 2012 and 2016. Decreasing resistant proportion were highlighted

*: Intermediate and Resistant; **: Screened with oxacillin

Resistant / Tested (%)	Bacteria	All specimens			Blood and CSF (stool for *Salmonella spp.* and *Shigella spp.*)		
		2012 (16 hospitals)	2012 (13 hospitals)	2016	2012 (16 hospitals)	2012 (13 hospitals)	2016
ESBL	*E. coli*	1337/1928 (69)	626/844 (74)	4085/6953 (59)	126/183 (69)	59/81 (73)	655/1107 (59)
ESBL	*K. pneumoniae*	887/1400 (63)	555/815 (68)	1186/2958 (40)	91/172 (53)	34/61 (56)	128/365 (35)
Imipenem	*A. baumannii*	1 495/2 138 (70)	1056/1584 (67)	2769/3551 (78)	110/244 (45)	85/205 (41)	100/178 (56)
Imipenem	*E. coli*	180/2 977 (6)	145/2111 (7)	687/8438 (8)	15/403 (4)	9/309 (3)	92/1410 (7)
Imipenem	*K. pneumoniae*	393/2 294 (17)	259/1697 (15)	891/3647 (24)	64/361 (18)	26/233 (11)	91/454 (20)
Imipenem	*P. aeruginosa*	578/1 765 (33)	322/996 (32)	1403/3220 (44)	36/129 (28)	22/88 (25)	49/135 (36)
MRSA	*S. aureus*	1 098/1 580 (69)	950/1303 (73)	1824/2510 (73)	145/197 (74)	130/171 (76)	372/521 (71)
Vancomycin*	*S. aureus*	28/823 (3.4)	10/372 (2)	45/2680 (2)	5/135 (3.7)	0/65 (0)	7/565 (1)
Penicillin	*S. pneumoniae*	115/344 (33)**	115/341 (34)**	657/794 (83)	7/30 (23) **	7/30 (23) ***	42/100 (42)
Vancomycin	*E. faecium*	20/79 (25)	20/79 (25)	91/290 (31)	2/14 (14)	2/14 (14)	**13/51 (25)**
Ampicillin	*H. influenzae*	160/226 (71)	1/1 (100)	804/911 (88)	3/5 (60)	1/1 (100)	7/8 (88)

Ceftriaxone	*E. coli*	2342/4 192 (56)	776/1472 (53)	5051/7049 (72)	240/514 (47)	114/234 (49)	912/1324 (69)
Ceftriaxone	*K. pneumoniae*	1479/2 227 (66)	626/1380 (45)	1912/3436 (56)	101/190 (53)	63/175 (36)	214/435 (49)
Ceftriaxone	*S. pneumoniae*	90/358 (25)	31/299 (10.4)	57/352 (16)	9/52 (17)	4/47 (8.5)	17/125 (14)

*: Intermediate and Resistant; **: Combination result of oxacillin screening and penicillin MIC test