



Evaluation and implementation of clinical decision support tools for antimicrobial stewardship

Nathan Peiffer-Smadja

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Evaluation and implementation of clinical decision support tools for antimicrobial stewardship

Par Nathan Peiffer-Smadja

**Thèse de doctorat de Santé Publique
Spécialité Recherches sur les services de santé**

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Title: Evaluation and implementation of clinical decision support tools for antimicrobial stewardship

Abstract:

Inappropriate prescription of antimicrobials impacts clinical outcomes and increases antimicrobial resistance. Antimicrobial stewardship interventions have been developed to improve the quality of antimicrobial prescribing. Among the interventions studied, clinical decision supports tools or systems (CDSS), whether digital or in paper format, may help optimize antimicrobial prescribing.

The overarching objective of this work was to assess and extend the implementation and use of existing decision support tools for antimicrobial prescribing. More specifically, the first part of the thesis aimed to expand the use of a CDSS to a new context, from high-income countries (HIC) to low- and middle-income countries (LMIC), the second part aimed to expand the use of decision support tools to a wider set of healthcare professionals by working with community pharmacists, and the third part aimed to provide a state of the art of the use of machine learning (ML) in CDSS for antimicrobial prescribing.

The first part of the thesis work consisted of a qualitative study analysing the potential benefits and risks of the extension of Antibioclc in West Africa, as well as the obstacles and facilitators to its development, its adaptation and its implementation in this context. Antibioclc is a free clinical decision support system (CDSS) for antimicrobial prescribing, targeting 37 common infectious diseases and used daily in primary care by more than 5,000 doctors in France. To this end, we organized a workshop in Burkina Faso in June 2019 which brought together 47 doctors representing 9 West African countries and 6 medical specialties. The participants considered that Antibioclc could improve patient care, encourage the development and updating of national antibiotic therapy recommendations and help develop capacities for the surveillance of infectious diseases in primary care. Participants stressed the need to adapt the tool to the local epidemiology of infectious diseases and antimicrobial resistance, and to include tuberculosis, HIV and malaria. The CDSS should be tailored to the availability of diagnostic tools and antibiotics in West Africa, as well as to the diversity of primary care structures in this region. The most frequently cited contextual barrier was the potential risk of increasing self-medication in West Africa.

The second part of this thesis aimed to study the utility of a paper-based decision tool developed by Public Health England for primary care doctors, if expanded to the community pharmacy setting for the management of urinary tract infections (UTI). This UTI leaflet includes prevention and antibiotic prescribing guidance. This qualitative study included individual interviews with Pharmacists, before and after the implementation of the UTI leaflet in 16 pharmacies in London and data from 50 service users via a detailed self-completed questionnaire. Community pharmacists recognised their important role in the management of community infections and in the prescription of antibiotics by pharmacists through Patient Group Directions. Although obstacles to the involvement of pharmacists were identified such as lack of access to the patient medical records, and lack of staff and training, these results reinforced the importance of decision support tools for antimicrobial prescribing as well as the development of an integrated management of community infections between pharmacists and doctors. In order to optimize the chances of success of CDSS, participants in each of the two studies strongly encouraged co-development of the tools with all stakeholders, including nurses, midwives and pharmacists, who are frequently involved in prescribing antimicrobials in primary care.

In the third part of the thesis, we carried out a review of the literature which analysed the development of machine learning CDSS in infectious diseases and in particular the current obstacles and limits to their large-scale use. ML-CDSS were limited by a low number of clinical variables used to guide de decision, by a small number of healthcare settings considered, by an evaluation restricted to technical performance and by a lack of integration into clinical practice.

This thesis provides insights for the development and implementation of low and high-tech decision support systems for antimicrobial prescribing in a primary care setting, both in low- and middle-income countries and in high-income countries. These results were rapidly used in in the response to the pandemic emergency by co-development of a CDSS for the management of COVID-19 in West Africa, which will subsequently be adapted to other infectious and tropical diseases.

Keywords: Clinical decision support system; Antimicrobial prescribing; West Africa; Implementation science; Antimicrobial Resistance; Co-design; Primary care

Titre : Évaluation et implémentation d'outils d'aide à la prescription antimicrobienne

Résumé :

La prescription inappropriée d'antimicrobiens impacte la prise en charge des patients et augmente la résistance antimicrobienne. De nombreuses interventions, dites de gouvernance antimicrobienne ("antimicrobial stewardship"), ont été développées afin d'optimiser la prescription antimicrobienne. Parmi les interventions étudiées, les outils ou systèmes d'aide à la prescription antimicrobienne, qu'ils soient digitaux ou sous format papier ("clinical decision support systems", CDSS), pourraient participer à l'amélioration de la prescription. Ce travail avait pour objectif d'évaluer et d'étendre la mise en place et l'utilisation d'outils existants d'aide à la prescription antimicrobienne en médecine humaine. Plus spécifiquement, la première partie de ce travail visait à étendre l'utilisation d'un CDSS à un nouveau contexte de soins, d'un pays à revenu élevé à des pays à revenu faible ou intermédiaire, la deuxième partie visait à étendre l'utilisation de CDSS à de nouveaux professionnels de santé, en l'occurrence les pharmaciens d'officine, et la troisième partie visait à décrire l'état de l'art en ce qui concerne l'utilisation de l'apprentissage automatique pour les systèmes d'aide à la prescription antimicrobienne.

La première partie de ce travail a consisté en une étude qualitative visant à analyser les bénéfices et les risques potentiels de l'extension d'Antibioclc en Afrique de l'Ouest, ainsi que les obstacles et les facilitateurs à son développement, son adaptation et son implémentation dans ce contexte. Antibioclc est un outil électronique gratuit d'aide à la prescription antibiotique, ciblant 37 maladies infectieuses courantes et utilisé quotidiennement par plus de 5000 médecins généralistes en France. Nous avons organisé un atelier au Burkina Faso en juin 2019 qui a rassemblé 47 médecins représentant 9 pays d'Afrique de l'Ouest et 6 spécialités médicales. Les participants ont estimé qu'Antibioclc pourrait améliorer la prise en charge des patients, encourager le développement et la mise à jour de recommandations nationales en antibiothérapie et permettre de développer les capacités de surveillance des pathologies infectieuses en soins primaires. Les participants ont souligné la nécessité d'adapter l'outil à l'épidémiologie locale des maladies infectieuses et de la résistance aux antimicrobiens, en ciblant notamment la tuberculose, le VIH et le paludisme. Il faudra également adapter cet outil à la diversité des structures de soins primaires en Afrique de l'Ouest et à la disponibilité des outils diagnostiques et des antibiotiques. L'obstacle le plus fréquemment cité était le risque potentiel d'augmenter l'automédication.

La deuxième partie de ce travail a visé à étudier le rôle potentiel des pharmaciens de ville dans la gestion des infections urinaires et la prescription antibiotique à travers une étude qualitative portant sur la mise en place d'un livret concernant les infections urinaires élaboré par Public Health England. Des entretiens individuels ont été réalisés avant et après la mise en place du livret dans 16 pharmacies à Londres et des questionnaires détaillés ont été remis à 50 patients. Les pharmaciens ont insisté sur l'importance de leur rôle dans la gestion des infections communautaires et dans la prescription antibiotique, encadrés par des protocoles locaux de prescription. Bien que des obstacles à leur implication aient été identifiés tels que l'absence d'accès au dossier médical, le manque de personnel ou de formation, ces résultats renforcent l'importance des outils d'aide à la prescription ainsi que d'une gestion coordonnée entre pharmaciens et médecins des infections communautaires. Afin d'optimiser les chances de succès de ces outils, les participants des deux premières parties du travail ont encouragé le co-développement de l'outil avec toutes les parties prenantes, y compris les infirmières, les sages-femmes et les pharmaciens, fréquemment impliqués dans la prescription d'antimicrobiens en soins primaires.

La troisième partie consiste en une revue de la littérature qui a permis de détailler le développement de l'apprentissage automatique ("machine learning") dans les outils d'aide à la décision en maladies infectieuses et notamment les obstacles et les limites actuels à leur utilisation à grande échelle. Les CDSS s'appuyant sur l'apprentissage automatique étaient limités par un faible nombre de variables cliniques utilisées pour l'aide à la décision, par un manque de diversité dans les contextes de soins étudiés, par une évaluation limitée aux performances techniques et par un manque d'intégration dans la pratique clinique.

Ce travail fournit des informations précieuses pour le développement et l'implémentation d'outils d'aide à la prescription antibiotique en soins primaires, aussi bien en Afrique de l'Ouest que dans des pays à revenu élevé. Ces résultats ont permis de co-développer dans un contexte d'urgence un outil électronique d'aide à la prise en charge de la COVID-19 en Afrique de l'Ouest, qui sera dans un second temps adapté aux autres maladies infectieuses et tropicales.

Mots clefs : Système d'aide à la décision clinique ; Outils d'aide à la prescription ; Antibiothérapie ; Afrique de l'Ouest ; Sciences de l'implémentation ; Résistance antimicrobienne ; Co-développement ; Soins primaires

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I. Main abbreviations

AMS: Antimicrobial Stewardship

AMR: Antimicrobial Resistance

CDSS: Clinical Decision Support System

CFIR: Consolidated Framework for Implementation Research

COVID-19: Coronavirus Diseases 2019

EPOC: Effective Practice and Organisation of Care

GP: General Practitioner

HIC: High-Income Country

HIV: Human Immunodeficiency Viruses

IQR: Interquartile Range

INSERM: Institut National de la Santé et de la Recherche Médicale (French National Institute for Health Research)

IP: Internet Protocol

IT: Information Technology

LMIC: Low and Middle-Income Country

MDG: Millennium Development Goals

MDR: Multi Drug Resistant

ML: Machine Learning

NAP: National Action Plan

PCR: Polymerase Chain Reaction

PGD: Patient Group Direction

PHE: Public Health England

SDG: Sustainable Development Goals

TB: Tuberculosis

UK: United Kingdom

UTI: Urinary Tract Infection

WHO: World Health Organisation

II. List of publications related to the thesis

Nathan Peiffer-Smadja, Rosalie Allison, Leah F Jones, Alison Holmes, Parvesh Patel, Donna M Lecky, Raheelah Ahmad, Cliodna AM McNulty. Preventing and Managing Urinary Tract Infections: Enhancing the Role of Community Pharmacists-A Mixed Methods Study. *Antibiotics (Basel)*. 2020 Sep 7;9(9):583. doi: 10.3390/antibiotics9090583. PMID: 32906824

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Tristan Delory, Pauline Jeanmougin, Sylvie Lariven, Jean-Pierre Aubert, Nathan Peiffer-Smadja, Pierre-Yves Boëlle, Elisabeth Bouvet, François-Xavier Lescure, Josselin Le Bel. A computerized decision support system (CDSS) for antibiotic prescription in primary care-Antibioptic: implementation, adoption and sustainable use in the era of extended antimicrobial resistance. *J Antimicrob Chemother*. 2020 Aug 1;75(8):2353-2362. doi: 10.1093/jac/dkaa167. PMID: 32357226

Nathan Peiffer-Smadja, Sarah Delliére, Christophe Rodriguez, Gabriel Birgand, François-Xavier Lescure, Slim Fourati, Etienne Ruppé. Machine learning in the clinical microbiology laboratory: has the time come for routine practice? *Clin Microbiol Infect*. 2020 Oct;26(10):1300-1309. doi: 10.1016/j.cmi.2020.02.006. Epub 2020 Feb 12. PMID: 32061795

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III. French summary

La résistance antimicrobienne est responsable de plus de 700 000 décès par an d'après l'OMS et ce chiffre pourrait atteindre 10 millions en 2050 si le phénomène se poursuivait avec la même croissance. La prescription inappropriée d'antimicrobiens nuit à la prise en charge clinique des patients et augmente la résistance antimicrobienne. De nombreuses interventions, dites de gouvernance antimicrobienne (« antimicrobial stewardship »), ont été développées afin d'optimiser la prescription antimicrobienne, l'objectif étant d'obtenir les meilleurs résultats cliniques tout en réduisant les effets indésirables des médicaments, la sélection d'organismes pathogènes et l'émergence de résistance. De nombreux facteurs contribuent à l'utilisation sous-optimale des antibiotiques, tels que le non-respect des recommandations par les professionnels de santé, l'absence de directives nationales concernant la prescription antimicrobienne dans certains pays, ou le comportement des usagers du système de santé. Dans les pays à revenu faible ou intermédiaire notamment, la prise d'antibiotiques sans ordonnance est considérée comme un facteur majeur d'utilisation inappropriée des antimicrobiens et d'émergence de résistance. Même si la grande majorité des prescriptions d'antibiotiques sont réalisées en soins primaires (jusqu'à 80 % en France par exemple), la majorité des interventions de gouvernance antimicrobienne prennent place dans le milieu hospitalier. Les interventions de gestion des antimicrobiens en médecine ambulatoire concernent principalement les infections respiratoires, et peu d'entre elles ont été répliquées ou ont obtenu des résultats durables après la fin des projets de recherche. Parmi les nombreuses interventions de gestion des antimicrobiens, les outils d'aide à la prescription antimicrobienne, qu'ils soient numériques ou sous format papier, pourraient participer à l'optimisation de la prescription. Les outils ou systèmes d'aide à la décision clinique sont des outils conçus pour fournir aux prescripteurs un accès rapide et simple à des informations essentielles à la prise de décision clinique. Les principales limites de ces outils d'aide à la décision sont leur mise en place, leur diffusion et leur utilisation sur le long terme dans la pratique de routine. Ce travail avait pour objectif d'évaluer et d'étendre la mise en place et l'utilisation d'outils d'aide à la prescription antimicrobienne en soins primaires. Plus spécifiquement, la première partie de ce travail visait à étendre l'utilisation d'un CDSS à un nouveau contexte de soins, d'un pays à revenu élevé à des pays à revenu faible ou intermédiaire, la deuxième partie visait à étendre l'utilisation de CDSS à de nouveaux professionnels de santé, en l'occurrence les pharmaciens d'officine, et la troisième partie visait à décrire l'état de l'art en ce qui concerne l'utilisation de l'apprentissage automatique pour les systèmes d'aide à la prescription antimicrobienne.

La première partie de ce travail visait à préparer la mise en place d'un outil électronique d'aide à la prescription antibiotique en Afrique de l'Ouest. Plus spécifiquement, il s'agissait de comprendre les bénéfices et les risques potentiels de cet outil, de déterminer les caractéristiques nécessaires à son succès, et d'analyser les obstacles et les facilitateurs à son développement, son adaptation et son implémentation. Puis, en s'appuyant sur ces données de co-créer avec des utilisateurs potentiels des solutions pour garantir l'utilisation et l'adoption durable d'un tel outil. À ces fins, nous avons organisé un atelier au Burkina Faso en juin 2019 qui a rassemblé 47 médecins représentant 9 pays d'Afrique de l'Ouest et 6 spécialités médicales. Cet atelier a débuté par une présentation d'un outil électronique d'aide à la prescription antibiotique (Antibioclic) suivie d'une table ronde avec tous les participants puis d'un questionnaire individuel avec des questions fermées et ouvertes. Antibioclic (<https://antibioclic.com>) est un exemple d'outil électronique d'aide à la prescription d'antimicrobiens largement utilisé en médecine générale en France. Il s'agit d'un outil développé en 2011, ciblant 37 maladies

infectieuses courantes, disponible gratuitement sur le web et en application smartphone sur iOS et Android. Les médecins peuvent saisir le diagnostic d'un patient sur le site ou l'application, puis répondre à un petit nombre de questions ciblées (âge, comorbidités, fonction rénale, allaitement, grossesse, etc.) et obtenir une recommandation adaptée aux besoins de leurs patients concernant le choix de l'antibiotique, la dose et la durée selon les recommandations nationales françaises. Antibioclc est mis à jour fréquemment et modifié dès qu'une nouvelle recommandation est publiée. Le nombre d'utilisateurs d'Antibioclc en France a régulièrement augmenté au cours des dernières années, passant d'un nombre médian de 414 utilisateurs par jour en 2012 à 5 365 utilisateurs par jour en 2018. L'application pour smartphone a été téléchargée 22 970 fois sur Android et 15 200 fois sur iOS. En 2018, plus de 3,5 millions de demandes ont été effectuées sur l'outil. L'architecture d'Antibioclc repose sur une méthode systématique de transformation des recommandations de pratique clinique en recommandations interprétables par ordinateur selon un arbre décisionnel semi-formel. Cette transformation se fait via un modèle de réseau de tâches où la prescription d'antibiotiques est décrite comme un processus avec un ensemble de tâches et de règles prédefinies pour obtenir une décision. La table ronde au Burkina Faso a été enregistrée et transcrise intégralement. Les données qualitatives obtenues lors de la table ronde et dans les questionnaires individuels ont été analysées à l'aide d'une analyse thématique inductive. Concernant l'utilisation d'outils électroniques dans la pratique médicale, la plupart des participants avaient accès à un smartphone lors des consultations (35/47, 74 %), mais seulement 49 % (23/47) avaient accès à un ordinateur et aucun n'utilisait d'outil d'aide à la prescription antibiotique. Les participants ont estimé qu'un outil électronique pourrait avoir un certain nombre d'avantages cliniques, notamment une amélioration de la prise en charge des patients, une meilleure adéquation aux recommandations d'antibiothérapie et une réduction de la résistance antibiotique. Ils ont aussi soulevé de potentiels avantages indirects liés à l'utilisation de cet outil comme celui d'encourager le développement et la mise à jour de recommandations nationales en antibiothérapie, d'accroître les connaissances des praticiens sur la prescription antibiotique ou de développer des capacités de surveillance des pathologies infectieuses en soins primaires. Les participants ont souligné la nécessité d'adapter l'outil à l'épidémiologie locale des maladies infectieuses et de la résistance aux antimicrobiens, à la diversité des structures de soins primaires en Afrique de l'Ouest ainsi qu'à la disponibilité des outils diagnostiques et des antibiotiques dans les pays concernés. Ils ont également suggéré d'ajouter à l'outil des recommandations personnalisées pour la tuberculose, le paludisme ou la prise en charge du VIH devant la prévalence de ces pathologies dans leur pratique clinique. L'obstacle contextuel le plus fréquemment cité était le risque potentiel d'augmenter l'automédication en Afrique de l'Ouest, où les antibiotiques peuvent souvent être achetés sans ordonnance. Le manque fréquent d'accès internet et à des ordinateurs constitue un autre obstacle qui pourrait être contourné par le développement d'une application mobile avec un mode hors-ligne. Une approche d'implémentation par étapes a été suggérée en démarrant et en évaluant l'utilisation de l'outil électronique sur un site pilote, suivie d'une diffusion à grande échelle à l'aide des réseaux professionnels et des médias sociaux. Cette étude fournit donc des informations précieuses pour le développement et l'implémentation d'un outil électronique d'aide à la prescription antibiotique en soins primaires en Afrique de l'Ouest.

La deuxième partie de ce travail visait à étudier le rôle potentiel des pharmaciens de ville dans la gestion des infections urinaires et la prescription antibiotique à travers une étude qualitative portant sur la mise en place d'un livret sur les infections urinaires élaboré par Public Health England. En effet, les infections urinaires sont les infections bactériennes les plus fréquemment rencontrées en médecine générale et constituent la principale source d'infection bactérienne invasive à *Escherichia coli*. Jusqu'à 50 % des femmes auront une infection urinaire au cours de

leur vie et 30 % d'entre elles auront des épisodes récurrents. Les infections urinaires imposent en règle générale la prescription d'antibiotique. Cependant, des recherches récentes suggèrent que la prescription d'antibiotiques dans les infections urinaires est sous-optimale. Le rôle que les pharmaciens de ville pourraient jouer dans l'amélioration de la prise en charge des infections urinaires a émergé ces dernières années. Nous avons ainsi mis en place un livret concernant les infections urinaires dans des pharmacies de ville en Angleterre. Ce livret avait pour objectif d'améliorer la gestion de ces infections et la prescription d'antibiotiques en améliorant le diagnostic et la prise en charge des infections urinaires, en facilitant la communication entre les usagers du service de santé et les pharmaciens, et en les éduquant sur les mesures de prévention des infections urinaires et la résistance aux antibiotiques. Les objectifs spécifiques de cette étude étaient d'explorer le point de vue des pharmaciens sur leur rôle de conseil aux patients atteints d'infections urinaires, d'évaluer la faisabilité et l'acceptabilité d'un outil d'aide à la décision dans le cadre des pharmacies de ville et de recueillir les opinions des usagers du service de santé qui demandent conseil en pharmacie. Nous avons inclus des pharmacies dans un arrondissement de Londres (Newham), échantillonées à dessein, ce qui a permis d'inclure des participants de statut socio-économique varié. La collecte des données s'est faite par le biais d'une enquête auprès des usagers du système de santé ($n = 51$), d'entretiens semi-structurés et questionnaires avant (16 entretiens, 22 questionnaires) et après (15 entretiens, 16 questionnaires) l'implémentation des livrets sur les infections urinaires. Les données ont été analysées de manière inductive à l'aide d'une analyse thématique et d'une tabulation descriptive des données quantitatives. Les résultats auprès des usagers du service de santé et des pharmaciens ont montré indépendamment qu'environ 25 à 30 % des patients se rendent d'abord dans une pharmacie pour des symptômes évocateurs d'infection urinaire. Les pharmaciens se sentaient à l'aise pour donner des conseils concernant les mesures hygiéno-diététiques nécessaires et pour orienter les patients vers les médecins généralistes. Ils considéraient que les officines offraient certains avantages pour les patients, à savoir leurs horaires d'ouverture étendus, leur ancrage local et la maîtrise fréquente des différentes langues parlées dans leur quartier. La majorité des usagers du système de santé ($n = 33, 65\%$) étaient également favorable à discuter de leur symptomatologie urinaire avec les pharmaciens. De façon plus générale, les pharmaciens d'officine ont insisté sur leur rôle important dans la prise en charge des infections communautaires et dans la prescription d'antibiotiques, encadrée par des protocoles locaux de prescription. Au Royaume-Uni, les « Patient Group Directions » (PGD) permettent en effet aux professionnels de santé non médecins de fournir et d'administrer sans ordonnance des médicaments ciblés à des groupes prédéfinis de patients. Alors même que les PGD permettent aux pharmaciens de fournir de la nitrofurantoïne pour certains patients atteints d'infections urinaires non compliquées, peu de recommandations ont été élaborées pour guider les pharmaciens dans la prise en charge globale des infections urinaires suspectées ou confirmées. Tous les pharmaciens participants ont souligné l'importance de l'utilisation d'un outil d'aide à la décision, par exemple le livret mis en place, aussi bien pour les patients venant en premier à la pharmacie que pour ceux venant se faire prescrire des antibiotiques après une consultation chez le médecin. La majorité des pharmaciens ($n=13, 81\%$) considéraient qu'un outil d'aide à la décision pourrait leur permettre de partager beaucoup plus d'informations et des informations plus précises concernant la prévention, les signaux d'alerte pour consulter un médecin généraliste et la résistance aux antimicrobiens. Parmi les suggestions, les pharmaciens ont demandé une version numérique de l'outil et une approche plus personnalisée pour chaque patient. Ils ont également proposé un QR code sur le livret papier qui pourrait être couplé à un outil électronique d'aide à la décision ou à une page Web d'information. Ils ont encouragé l'utilisation du livret ou d'un autre outil d'aide à la décision comme guide pour structurer la discussion avec les patients. Bien que des obstacles à l'implication des pharmaciens aient été identifiés comme le manque d'accès au dossier médical, le manque de personnel ou de

formation, ces résultats renforcent l'importance des outils d'aide à la prescription ainsi que la nécessité d'une gestion intégrée des infections entre pharmaciens et médecins. Afin de renforcer ces résultats, des entretiens qualitatifs semi-directifs ont également été menés avec des pharmaciens d'officine en France. Les participants ont été recrutés par le biais d'une organisation professionnelle de pharmaciens d'officine. Les entretiens ont été enregistrés, transcrits et analysés à l'aide d'une analyse thématique. Seize pharmaciens de ville ont participé à cette étude. Tous les participants avaient une bonne connaissance de la résistance aux antimicrobiens et pensaient que les pharmaciens de ville avaient un rôle important à jouer dans la lutte contre son expansion. Certains obstacles à la participation des pharmaciens d'officine à la gouvernance antimicrobienne ont été identifiés tels que les interactions difficiles avec les prescripteurs, le manque de temps, le manque d'accès aux dossiers médicaux des patients et l'absence de diagnostic mentionné sur les prescriptions d'antibiotiques. Une éducation renforcée des patients, des audits sur la prescription d'antibiotiques, une augmentation des tests rapides en pharmacie et une prescription retardée étaient autant d'interventions suggérées par les pharmaciens pour améliorer l'utilisation des antibiotiques en soins primaires. Parmi les stratégies citées par les participants pour faciliter la mise en œuvre de telles interventions étaient retrouvé la collaboration accrue entre pharmaciens et médecins généralistes, la mise en place de formations spécialisées ainsi que l'utilisation de systèmes d'aide à la décision clinique.

Afin d'optimiser les chances de succès d'un outil électronique d'aide à la prescription, les participants des trois études qualitatives décrites ont fortement encouragé le co-développement de l'outil avec toutes les parties prenantes, y compris les infirmières, les sages-femmes et les pharmaciens, qui sont fréquemment impliqués dans la prescription en soins primaires, notamment en Afrique de l'Ouest.

La troisième partie de ce travail visait à détailler le développement de l'apprentissage automatique ("machine learning") dans les outils d'aide à la décision en maladies infectieuses et notamment les obstacles et les limites actuelles à leur utilisation à grande échelle. L'apprentissage automatique (AM) permet l'analyse d'ensembles de données volumineux et complexes qui deviennent de plus en plus fréquents dans le domaine de la santé. Contrairement aux systèmes experts qui reposent sur la programmation d'un ensemble de règles, les systèmes d'AM sont capables de définir leurs propres règles directement à partir des données. Nous avons ainsi mené une revue narrative afin d'analyser les objectifs, les caractéristiques, le développement et les mesures de performance des systèmes d'AM pour diagnostiquer les maladies infectieuses, prédire la gravité et guider le traitement antimicrobien. Les références de cette revue ont été identifiées grâce à des recherches d'articles dans MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, ACM Digital Library, arXiv et IEEE Xplore Digital Library en utilisant une combinaison de mots-clés validée par un bibliothécaire spécialisé. Nous avons inclus les articles résultant de ces recherches et les références pertinentes citées dans ces articles jusqu'en juillet 2019. Au total, 75 articles avec 60 systèmes d'aide à la décision clinique s'appuyant sur l'AM ont été inclus. Dans l'ensemble, 37 (62 %) de ces systèmes se sont concentrés sur les infections bactériennes, 10 (17 %) sur les infections virales, neuf (15 %) sur la tuberculose et quatre (7 %) sur tous les types d'infection. Parmi les systèmes d'AM, 20 (33 %) portaient sur le diagnostic d'infection, 18 (30 %) sur la prédition, la détection précoce ou la stratification du sepsis, 13 (22 %) sur la prédition de la réponse au traitement, quatre (7 %) sur la prédition de la résistance aux antibiotiques, trois (5 %) sur le choix d'un traitement antibiotique et deux (3 %) sur le choix d'une thérapie antirétrovirale. Pour la grande majorité de ces systèmes ($n=58$, 97 %) l'apprentissage supervisé a été utilisé alors que pour deux d'entre eux (3 %) il s'agissait de l'apprentissage par renforcement. La plupart des systèmes d'AM trouvés dans la littérature ont

été développés pour les soins secondaires et tertiaires ($n=57$, 95 %) alors que seulement trois (5 %) ciblaient les soins primaires. De plus, seuls sept systèmes (12 %) étaient adaptés aux pays à revenu faible ou intermédiaire, dont six concernaient le VIH ou la tuberculose. Les données analysées étaient souvent limitées à un petit ensemble de variables et incluaient peu de variables cliniques pertinentes. L'évaluation de ces systèmes d'aide à la décision faisait défaut avec 57 systèmes (95 %) évalués par des mesures de performance telles que la sensibilité et la spécificité et seulement trois (5 %) évalués en pratique clinique. Le travail de la revue initiale a été étendu dans une seconde revue à l'utilisation de l'AM pour la microbiologie clinique. En utilisant une méthodologie similaire, 103 articles coporant 97 systèmes s'appuyant sur l'AM ont été inclus dans la seconde revue. Dans l'ensemble, 82 (85 %) de ces systèmes ciblaient les infections bactériennes, 11 (11 %) les infections parasitaires, neuf (9 %) les infections virales et trois (3 %) les infections fongiques. Plus précisément, 40 (41 %) systèmes s'appuyant sur l'AM se sont concentrés sur la détection, l'identification et la quantification des micro-organismes, 36 (37 %) ont évalué la sensibilité aux antimicrobiens, 21 (22 %) ont ciblé le diagnostic, la classification des maladies et la prédiction des résultats cliniques. Pour atteindre ces objectifs, les systèmes d'AM ont utilisé des sources de données très diverses : 21 (22 %) ont utilisé des données de séquençage du génome entier de micro-organismes, 19 (20 %) des données de microbiote obtenues par séquençage métagénomique, 19 (20 %) des images microscopiques, 17 (18 %) des données de spectroscopie, huit (8 %) des données issues de séquençage ciblé, six (6 %) des composés organiques volatils, quatre (4 %) des photographies de colonies bactériennes, quatre (4 %) des données de transcriptome, trois (3 %) des données de structure protéique et trois (3 %) des données cliniques. La grande majorité des systèmes de ML utilisaient l'apprentissage supervisé ($n=96$, 99 %), tandis que 6 (6 %) utilisaient l'apprentissage non supervisé. De la même manière que pour les maladies infectieuses, la plupart des articles ont été publiés à partir de données de pays à revenu élevé ($n=71$, 73 %) mais un nombre conséquent de systèmes ont été développés avec des données de pays à revenu faible ou intermédiaire ($n=36$, 37%). Parmi les systèmes analysés, 96 n'ont décrit que des mesures de performance telles que la sensibilité et la spécificité et un seul système d'AM était évalué dans la pratique clinique au Royaume-Uni.

De nombreux défis au développement mondial des systèmes d'aide à la décision clinique s'appuyant sur l'AM demeurent, allant de la taille et de la qualité des bases de données disponibles en médecine aux processus de validation et de commercialisation, en incluant les risques pour la sécurité et la confidentialité des données. Pour les maladies infectieuses de même que pour la microbiologie clinique, l'évaluation des systèmes d'apprentissage automatique était encore incomplète du point de vue clinique. Les futurs systèmes d'aide à la décision clinique s'appuyant sur l'AM devraient être développés dans des contextes de soins variés, y compris en soins primaires et dans les pays à revenu faible et intermédiaire qui sont actuellement sous-représentés. Cependant, le développement de systèmes d'aide à la décision s'appuyant sur l'AM peut être plus difficile en soins primaires où les données disponibles sont limitées et les bases de données sont rares. La même affirmation peut être faite pour les pays à revenu faible ou intermédiaire où l'extraction de données est difficile en raison du manque fréquent de système d'information clinique. Les futurs systèmes de décision clinique s'appuyant sur l'AM devraient être intégrés dans un processus structuré d'implémentation dans la pratique clinique. Concernant l'évaluation, les futures études impliquant les systèmes d'aide à la décision s'appuyant sur l'AM devraient dans l'idéal décrire des résultats cliniques après utilisation dans la pratique clinique de routine.

Les différentes parties de ce travail fournissent des informations précieuses pour le développement et l'implémentation d'outils d'aide à la prescription d'antibiotiques en soins primaires, aussi bien en Afrique de l'Ouest que dans des pays à revenus élevés. Ils renseignent

également sur la possibilité d'utiliser de façon efficace les outils d'apprentissage automatique pour exploiter les bases de données actuelles et améliorer les outils d'aide à la décision clinique. Ces travaux ont permis de co-développer un outil électronique d'aide à la prise en charge de la COVID-19 en Afrique de l'Ouest en réponse à l'urgence pandémique : Antibioclic Afrique. Le processus d'implémentation de cet outil est en cours et s'inspire des résultats obtenus dans les études décrites. L'objectif à moyen et long terme est d'étendre l'outil Antibioclic Afrique pour inclure des recommandations pour la gestion des infections bactériennes, virales et parasitaires, puis de conduire des études cliniques et microbiologiques afin d'évaluer l'impact d'Antibioclic Afrique. Enfin, en s'appuyant sur les travaux de revue menés sur l'apprentissage automatique, nous avons pour perspective de développer un système d'aide à la décision clinique capable de prédire le risque individuel d'infection à micro-organismes résistants chez des patients hospitalisés.

IV. Introduction

1. Antimicrobial resistance and antimicrobial stewardship

Antimicrobial resistance (AMR) is a global threat to public health, to the future of medicine and to society, considered as one of the 10 global health issues to track in 2021 according to the World Health Organisation (WHO).^(1,2) More than 700,000 deaths are attributable each year worldwide to antibiotic resistance,⁽³⁾ including more than 25,000 in Europe.⁽⁴⁾ More than 10 million deaths per year worldwide and more than 100,000 billion dollars in economic losses are predicted by 2050 if the growth of antibiotic resistance continues.⁽³⁾ In France, 158,000 infections and more than 11,000 deaths are attributable each year to resistant bacteria.⁽⁵⁾ The growing emergence of resistant bacteria raises concerns in the short and long term about the effectiveness of available antibiotics and could lead to situations of therapeutic failure. Indeed, the development of antimicrobial resistance regularly results in human infections with highly drug resistant bacteria which threatens the practice of basic surgical procedures as well as advancements in medicine.⁽⁶⁾

AMR affects both high-income countries (HICs) and low- and middle-income countries (LMICs).^(7,8) AMR was first included in a global action plan of WHO in 2015 which outlined the following six objectives: to improve awareness and understanding of antimicrobial resistance through effective communication, education and training; to strengthen the knowledge and evidence base through surveillance and research; to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions; to optimize the use of antimicrobial medicines in human and animal health. Indeed, the emergence of bacterial resistance is strongly correlated with the overuse and misuse of antibiotics in human and animal health.^(9–11) The repeated administration of antibiotics in humans or animals creates a selection pressure which promote mutations and exchanges of genetic material responsible for the acquisition of AMR by bacteria.⁽¹²⁾ In addition, antibiotics eliminate susceptible bacteria in the digestive flora of treated patients, thus making room for colonisation by resistant bacteria. Excessive and inappropriate use of antibiotics therefore presents collective consequences with risks of selection and transmission of resistant germs and

an increase in health expenditure, but also individual consequences with risks of treatment failure and drug toxicity for patients. Therefore, the prescription of antibiotics needs to be reasoned and requires an assessment of the benefit-risk balance for each patient and clinical situation. The above objectives have been translated in to National Action Plans (NAP) in more than a hundred countries, but implementation of plans is still variable and data are still lacking on what interventions might be the most effective to successfully implement the six objectives.

Inappropriate use of antibiotics includes non-use (absence of antimicrobial prescribing in situations that require it) overuse (antibiotic prescribing is frequent in situations that do not require antibiotic therapy), non-optimal use (delayed use, use of antibiotics that have a too broad or too narrow spectrum, the lack of adaptation of empiric antibiotic therapy to microbiological results, inappropriate route of administration, prescribing lower or higher dosages than the recommended dosages, too short or too long antibiotic therapies). Optimizing antimicrobial prescribing aims to achieve the best clinical outcomes while keeping to a minimum unintended consequences of anti-microbial use, including toxic effects, selection of pathogenic organisms, and the emergence of resistance.(13) Many factors contribute to the inappropriate use of antibiotics, such as the lack of compliance by healthcare professionals where recommendations do exist, the absence of guidelines for antimicrobial therapy in certain countries,(14) or the behaviour of service users.(15) In LMIC particularly, over the counter dispensing of antibiotics is considered a major driver of inappropriate use and AMR.(16,17) Interventions and actions to promote using antimicrobial responsibly are often gathered under the term “antimicrobial stewardship”.(18) Antimicrobial stewardship programs have been established for twenty years and are considered a key pillar of the fight for rationale use of antibiotics and for addressing AMR.

Multiple strategies are used in antimicrobial stewardship programs including, for example, the establishment of antimicrobial therapy teams evaluating and advising prescribing practices, multidisciplinary collaboration between clinical and microbiological teams, audits and feedback on practices, training as well as the use of clinical decision support tools.(18–20) Different taxonomies of AMS interventions have been proposed. The Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy for interventions related to antimicrobial prescribing included:(21)

- Audit and feedback defined as any summary of clinical performance of health care over a specified period of time.
- Education through meetings or distribution of educational materials.

- Educational outreach through academic detailing or review of individual patients with recommendation for change.
- Reminders provided verbally, or on paper, in the workplace environment (e.g., posters or messages printed on equipment) or on computer to prescribers.
- Structural: the influence on antibiotic prescribing of changing from paper to computerised records and of the introduction of new technology for rapid microbiology testing or measurement of inflammatory markers.

A Cochrane review on antimicrobial stewardship broadly divided interventions into two categories: actions that enable responsible antimicrobial use or actions that restrict inappropriate or unnecessary antimicrobial use.(20) Enabling interventions included e.g., audit and feedback, decision support tools, or educational outreach and restrictive interventions included selective reporting of laboratory susceptibilities, requiring prior authorizations or automatic stop orders.(18)

Antimicrobial stewardship interventions in hospitals have been shown to improve the quality of antimicrobial prescribing and lead to shorter treatment times, shorter hospital stays, and reduced colonization and infection with resistant bacteria.(20) A review found that behavioural change interventions for AMS could improve patient and microbiological outcomes and improve antimicrobial prescribing but there were large differences in improvement between various studies.(22) While the efficacy of antimicrobial stewardship interventions has been demonstrated in both hospital and community settings,(20,23,24) AMS interventions are not distributed equally among health contexts and countries. Indeed, interventions are rare and particularly difficult to implement in primary care.(25) This is the case in HICs as well as LMICs.(26) Yet antibiotic prescribing is mainly performed in outpatient care. Data suggest that 80-90% of all antibiotics used in humans are prescribed in primary care.(9) In France, more than 80% of antibiotics are prescribed in primary care and more than 75% of these prescriptions are made by general practitioners (GP).(27,28) Data on antimicrobial stewardship in ambulatory medicine mainly concern respiratory infections, and few of them have been replicated or sustained impact after the end of the initial research project.(29) A systematic review on interventions targeted at antibiotic prescribing in primary care found that the average effect size from these interventions tends to be limited, with most interventions achieving a modest reduction in total antibiotic prescribing.(30) It is therefore essential to explore new and sustainable avenues to improve the use of antibiotics in primary care.

2. Clinical decision support tools for antimicrobial prescribing

Among antimicrobial stewardship interventions, numerous clinical decision support tools for antimicrobial prescribing have been evaluated. Clinical decision support tools or systems (CDSS) are tools designed to provide the prescriber with rapid access to up-to-date information essential for making appropriate treatment decisions at the point of care.(31) These decision-support tools, accessible on paper or by computer or smartphone could facilitate the management of patients.(32) The 2019 English government report entitled "Contained and controlled - The UK's 20-year vision for antimicrobial resistance" specified that decision support systems should be part of future clinical management.(33) In the UK national action plan 2019-2024 to tackle antimicrobial resistance, one of the goals to be achieved in 2024 is to be able to report the percentage of antibiotic prescriptions guided by a diagnostic test or an electronic system.(34)

Multifaceted antimicrobial stewardship programs have often included decision support tools and materials such as patient facing infection management leaflets or computerised decision support systems.(35,36) Decision support systems have mostly been evaluated in the hospital setting and may bring sustained impact to decrease inappropriate prescriptions.(37) CDSS could become particularly interesting in the context of ambulatory and primary care where prescribers are not specifically trained in infectious diseases or infection prevention and control and can have difficulties obtaining specialised advice. Access to computers and smartphones as well as the computerisation of health systems have promoted the use of electronic-based or computerised decision support systems for medical practice. Electronic clinical decision support systems are part of one of the 13 urgent health challenges for the next decade according to the WHO report "Harnessing new technologies".(38) Of course, the use of CDSS in healthcare should be replaced in the wider context of sustainable development as described by the Sustainable Development Goals (SDG) which recognize that "ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality, and spur economic growth – all while tackling climate change and working to preserve our oceans and forests".(39)

The main limitation of decision support tools is their implementation, dissemination and long-term adoption.(40–42) CDSS for antimicrobial prescribing have often been developed and

implemented before carrying out an in-depth analysis of the needs, expectations and requirements of user physicians. This results in an overall limited adoption of CDSS in daily clinical practice.(40) However, if the objective is to improve clinical practice, physicians must follow the recommendations issued by the CDSS.(40,43,44) In order to devise a useful tool for its potential users effectively for use in clinical practice, it is essential to adapt it reliably and precisely to the context of care. The attitude of prescribers towards the technology (be it a favourable reception or reluctance) and the potential impact of CDSS on medical knowledge (e.g., risk of unlearning) are crucial questions to consider.

a. Primary care

Faced with the importance of antibiotic consumption in primary care and the growing problem of antibiotic resistance, there is an urgent need for interventions aimed at improving the use of antibiotics in community settings. These interventions must be tailored to the context of primary care and its actors.

In a systematic review focusing on CDSS for the management of antibiotics, the authors found 58 articles describing 38 CDSS.(40) Only 11 systems involved primary care and all of them only dealt with infections of a specific anatomical area (respiratory infections, urinary tract infections, etc.). None of the CDSS covered the full spectrum of infectious situations that may be encountered by general practitioners. The authors noted the heterogeneity of the evaluation methods of these tools and the difficulties in obtaining a sustainable adoption of the CDSS described. They also described a lack of prior assessment of user needs and expectations. Indeed, in a meta-synthesis of qualitative research on CDSS published in 2015, only 2 studies among 56 analysed CDSS that guided therapeutic decision-making. The authors identified some of the reasons and causes leading to difficulties in integrating CDSS into clinical work but did not find qualitative studies evaluating the requirements for the effective adoption of a CDSS. They also found that research related to the interaction between CDSS and prescribers including unintended consequences of CDSS was globally lacking.

France is one of the highest consumers of antibiotics in Europe.(9) In 2019, the consumption of antibiotics in France remained around 30% higher than the average overall consumption in Europe, making it necessary to continue the efforts made to improve the use of antibiotics.(45) In France, primary care represents more than 90% of total antibiotic consumption with 93% of

antibiotics dispensed in the community and 7% in health establishments. Among the antibiotics dispensed in the community, only 15% are prescribed by hospital doctors.(45) General practitioners (GPs) therefore represent the main prescribers of antibiotics in France with 9 out of 10 outpatient prescriptions for antibiotics from a GP and antibiotic therapy initiated every six consultations in general medicine.(46) Antibioclic (<https://antibioclic.com>) is an example of CDSS for antimicrobial prescribing widely used in primary care in France. It is a tool developed in 2011, targeting 37 common infectious diseases, freely available on the web and as a smartphone application on iOS and Android. Doctors can enter a patient's diagnosis on the site or app, then answer a small number of targeted questions (age, co-morbidities, kidney function, breastfeeding and pregnancy) and get a recommendation tailored to their patients' needs about antibiotic choice, dose and duration according to French national guidelines. Antibioclic is updated frequently and modified as soon as a new recommendation is published.

The number of Antibioclic users in France has steadily increased over the past few years, from a median number of 414 (IQR 245-494) users per day in 2012 to 5,365 (IQR 2,891-5,769) users per day in 2018. If we consider that each unique IP address corresponds to a user and that 80% of users are GPs, around 5,700 GPs use Antibioclic daily, or around 10% of the 58,140 GPs practicing in primary care in France.(47) The smartphone app was downloaded 22,970 times on Android and 15,200 times on iOS. In 2018, more than 3.5 million requests on the CDSS were made. The median level of satisfaction was 5/5 in a 2019 survey of 2,733 GPs.(47)

The architecture of Antibioclic is based on a systematic method of transforming clinical practice recommendations into computer-interpretable recommendations according to a semi-formal decision tree. This transformation is done via a task network model where the prescription of antibiotics is described as a process with a set of predefined tasks and rules to obtain a decision (Figure 1).(48) The Antibioclic committee is responsible for extracting and transforming clinical practice recommendations. After entering clinical information by the practitioner in the form of a selection from lists of characteristics, prescription advice is given.

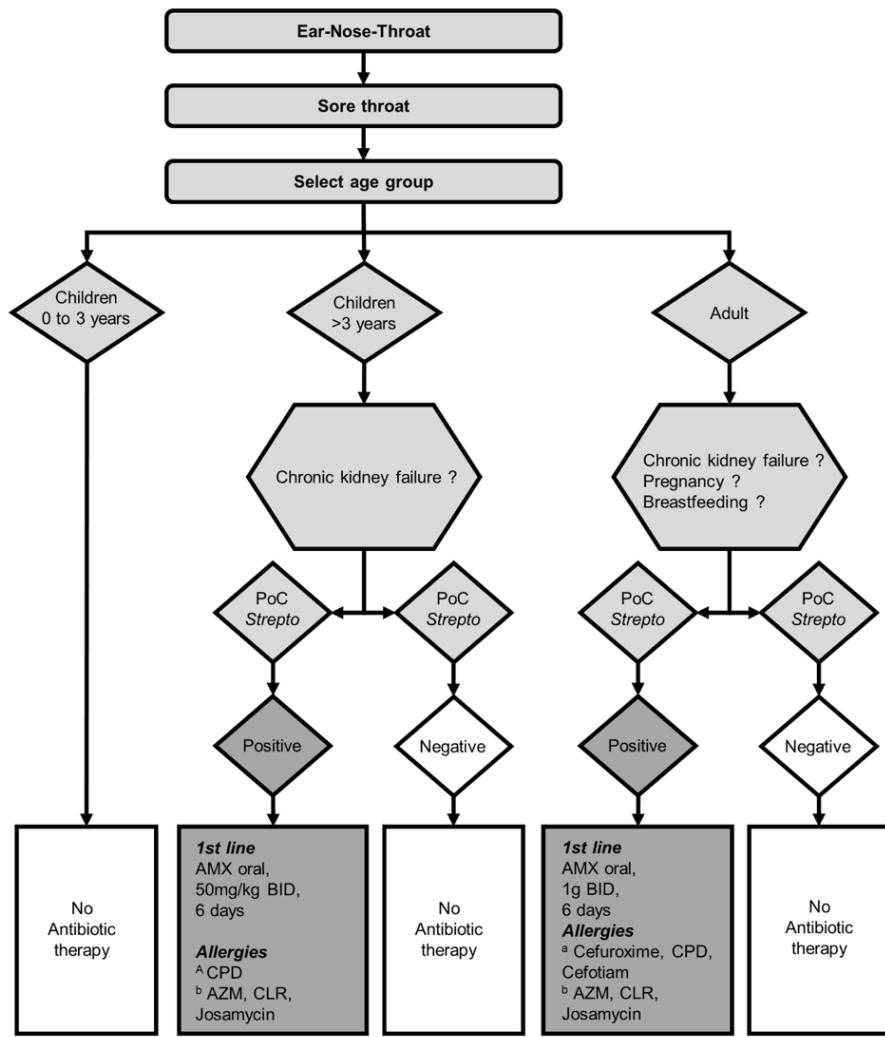


Figure 1. Example of the model for converting clinical practice recommendations into algorithmic recommendations for angina.

AMX: amoxicillin; CPD: cefpodoxime; AZM: azithromycin; CLR: clarithromycin; PoC Strepto: rapid test result for the presence of group A streptococci. Figure taken from the article by Delory et al.(47)

b. Community pharmacies

The use of antibiotics in primary care involves several health professionals. Among them, community pharmacists occupy a special place in the care process. They often fulfil the role of first interlocutor in primary care, thus being able to play a key role in orienting patients and coordinating care trajectories. In addition, they are also the last point of contact before patients initiate treatment. As privileged interlocutors for users because of their accessibility and availability, they play an essential role in the education of and advice to patients and the proper use of the drug. Pharmacists benefit from more geographic proximity to users. Indeed, the distribution of pharmacies often benefits from a balanced territorial network on the metropolitan territory, promoting access to primary care. In France, a report from the French Direction of Research, Evaluation, Studies, and Statistics (DREES) shows that pharmacists are among the health professionals best distributed throughout the national territory according to an indicator allowing to measure the geographical distribution of access to care according to supply and demand.(49)

As accessible health actors favoured by users, the missions of community pharmacists have also been expanding for several years in areas of public health and health promotion, including participation in vaccination campaigns,(21) Rapid Diagnostic Tests,(50) or the protocolised dispensation of treatments.(51) More recently, during the COVID-19 pandemic, pharmacists participated in the vaccine campaign against COVID-19 (52) and in the diagnostic management of COVID-19 by performing antigenic tests in pharmacies.(53) Recent changes in the regulations governing the activities of community pharmacists could lead to a greater strengthening of their role in the management of infections and the proper use of antibiotics, as can be observed in some countries. In the United Kingdom, for example, community pharmacists may have the role of prescriber in certain specific and predefined clinical situations. Patient Group Directions (PGD) authorise British pharmacists to dispense antibiotics without a doctor's prescription to patients with uncomplicated cystitis who present with specific clinical symptoms and fulfil inclusion criteria.(54) Several British and Australian studies have also looked at the good antimicrobial practices of pharmacists through their advisory activities and the opportunities for antimicrobial stewardship interventions in pharmacies,(55–60) in particular by issuing educational brochures, interprofessional cooperation (58,59) and deferred antibiotic prescriptions.(57,58) These studies reveal a significant potential for interventions at the community pharmacy level as well as a strong desire for participation on the part of most

pharmacists. However, community pharmacies are businesses operating on a for-profit basis and, as such, the issue of funding time spent interacting with the patients and not selling healthcare product is a crucial one.

The extension of the role of community pharmacists in antibiotic management and the controlled prescription of antibiotics in selected situations make them a target of interest for AMS interventions and in particular for the development of decision support tools. In a recent qualitative study in France involving 16 pharmacists, professionals described having been involved in AMS activities including per-unit antibiotic dispensing, rapid strep testing, delayed antibiotic prescribing and relying on CDSS checking antibiotic prescriptions compliance with guidelines (unpublished data). The majority of respondents in this study believed that the implementation in pharmacies of CDSS to display clinical practice guidelines could support pharmacists' prescription screening and assist potential audits of antibiotic prescribing in pharmacies. Some participants stressed the importance of integrating such tools with pharmacy management software.

c. Low- and middle-income countries

According to the WHO, the dissemination of electronic tools for clinical decision support in West Africa is currently limited.(61) The implementation of CDSS is influenced by the existing digital health environment at the national and global level. In 2005 the World Health Organisation (WHO) adopted a resolution laying the foundation of an e-health strategy and recognised its contribution to achieve Millennium Development Goals (MDG), notably in health system strengthening and extension of universal healthcare coverage.(62) Several toolkits and guidelines were developed by WHO to scale up and assess e-health initiatives and also provide technical assistance.(63) Although many e-health projects were developed in Sub-Saharan African but few of them were successful due to poor adherence and low uptake rate.(64) Fragmentation of initiatives, lack of coordination within the ecosystem, lack of monitoring and evaluation were identified as the main challenges for sustainable implementation of e-health initiatives.(65) Despite a global agenda for action in e-health, the scope of deployment of e-health initiatives at the country level, in line with national health priorities, is still relatively low. The WHO reported that only 7% of West African countries have implemented an effective digital health strategy.(66) Moreover, pre-implementation studies assessing micro and macro level influences are lacking. Considering the weight of socio-

economic factors in the misuse of antibiotics, multi-dimensional studies remain under-explored domains of study and are therefore needed.(67–69) Cross-cultural research associating international research centres are encouraged to overcome those barriers.(65) Globally, there is a need to develop antimicrobial stewardship interventions taking into account cultural and contextual determinants in different resource settings.(70,71)

Few studies have looked at CDSS for the prescription of antibiotics in LMICs and in West Africa. A recent review identified six tools for the management of febrile children in primary care.(72) A clinical algorithm for the management of childhood illnesses available on smartphones called e-ALMANACH was evaluated in Tanzania in a randomized controlled pilot study. It increased the detection of warning signals in children and decreased the prescription of antibiotics.(73) This result was confirmed in another controlled study with more than 1,400 children which showed that the use of e-ALMANACH reduced the prescription of antibiotics by 80%.(74) Another tool, e-POCT, an electronic algorithm using the results of Point of Care tests including CRP and procalcitonin, has reduced the failures of treatment of children with febrile illnesses compared to the use of the e-ALMANACH tool alone.(75,76)

Another study in Burkina Faso confirmed an overall positive attitude towards electronic decision support systems as well as the need for simplicity of the tools developed. However, the implementation of CDSS in West Africa meets specific challenges: for example, one team analysed the cost of implementing a CDSS for antenatal and delivery care in Africa and found that most costs resulted from recruiting and training nurses and midwives in the use of the CDSS.(77) Other obstacles such as lack of Information Technology (IT) infrastructure or limited availability of drugs and diagnostic tests have been identified.(78) Moreover many tools are integrated into medical file processing software, which are not easily accessible in LMICs and requiring, in addition to the cost of the software, the acquisition of hosting and maintenance servers.(79,80) These costs, if they are not anticipated, can limit the sustainability of CDSS in LMICs. Moreover, the dissemination of CDSS in LMICs has to be replaced in the wider context of antimicrobial prescribing in LMICs with specific challenges such as over the counter availability of antibiotics, lack of access to microbiological diagnosis or lack of trained healthcare professionals, to cite only a few.(17)

d. Machine learning decision support systems

Artificial intelligence research appeared in 1956 during the Dartmouth conference and has developed considerably since.(81) It is often defined as the study of "intelligent agents", or devices that analyse their environment and takes actions that maximize their chances of successfully achieving their goals. Electronic-based decision support systems in medicine began with the development of expert systems, based on rules captured from interviews with medical experts, and then translated and programmed.(82) The first medical expert system was developed in 1976 for infectious diseases and more specifically to suggest antibiotic regimens for severe bacterial infections. Expert systems derive their expertise from a more or less large number of predefined and manually programmed rules such as "if a patient has a suspicion of pyelonephritis, do an urine culture and begin a cephalosporin". The rules have to be acquired by interviewing medical experts, then translated and programmed rule by rule into the system. With about 450 rules, *Mycin*, the first CDSS in medicine, performed as well as some experts to identify bacteria causing severe infections and to recommend antibiotics. However, this approach proved to be difficult to adapt to real-world clinical decisions because of the volume of rules needed to gather experts' knowledge in difficult clinical decisions.

Modern AI switched from expert systems to machine learning (ML) systems.(82) In ML approaches, engineers program algorithms that can develop their own rules from the data that are available. Thus, ML systems replace the hand-coded rules by finding new rules derived from data. These systems can adapt to new circumstances or detect and extrapolate new patterns, thus extending their reach into unknown situations. The more data are given to machine learning algorithms, the more they can find and develop new rules and the more they improve their performance with regard to the task they are programmed to accomplish. Machine learning is based on many techniques, the best-known being deep learning which is based on artificial neural networks,(83) but others exist such as support vector machines or ensemble learning. ML systems are sometimes called data-intensive systems because, instead of using manually programmed rules, they need a large volume of data. Lately, the availability of health data has increased considerably with medical record management systems and the rise of connected devices and the optimal analysis and interpretation of this enormous volume of data, called big data, requires the computing power of machine learning.(84) This is one of the reasons why there is growing interest in machine learning clinical decision support systems.

Indeed, ML algorithms are being developed in many fields of medicine and have already started to be used in specialties that rely on and lend themselves to the accumulation of patient images such as radiology, pathology, dermatology or ophthalmology. In radiology, ML algorithms have been used to diagnose diverse diseases such as pneumothorax, fractures, heart enlargement or thyroid nodules on chest X-ray, CT scan or MRI.(85) One of the few real-life studies using a deep learning algorithm was shown to improve the ability of emergency medicine clinicians to accurately detect wrist fractures.(86) The IBM prototype for AI, Watson, identified pulmonary embolisms on computed tomography (CT) and detected abnormal wall motion on echocardiography.(87) The use of deep learning algorithms in dermatology have shown that machines could identify images with melanoma, basal or squamous cell carcinoma better than the majority of dermatologists.(88) The first FDA approval for an autonomous (without the need of a physician) ML algorithm took place in 2018 with IDx, a ML algorithm to detect "more than mild" diabetic retinopathy in retinal fundus photographs.(89) A recent review describes the development of deep learning in-depth, mostly for medical imaging.(90) Narrow tasks in which the context is predefined, such as image-processing tasks, are easier from an AI perspective. However, ML algorithms have also been developed for more complex tasks such as to help physicians for clinical decisions.(91) In pulmonology, an algorithm trained to identify COPD exacerbations and to predict the triage of patients could help pulmonologists.(92) In cardiology, the use of a ML-CDSS guided doctors to decide between coronary artery bypass surgery and percutaneous coronary intervention.(93) ML is also being tested in infectious diseases wherein most of the work focuses on research, drug development or clinical microbiology. ML algorithms are being developed to analyse bacterial genome and improve the prediction of resistance,(94,95) to analyse HIV genotype and predict susceptibility to antiretroviral drugs,(96) for surveillance purpose, such as the surveillance of healthcare-associated infections(97), to analyse patterns of epidemics(98) or to discover new antibacterial drugs or vaccines.(99–101) ML promises to improve decision-making in infectious diseases management as well.(102) ML has recently been applied to antimicrobial stewardship interventions and could help detecting inappropriate antimicrobial prescribing.(103) However, many challenges remain for the development of ML systems for clinical decisions. The gap in the implementation of ML systems is one of the challenges in the field of AI in healthcare and the pathway between development and routine use is long and fraught with obstacles, as emphasized by the non-adoption, abandonment, scale-up, spread and sustainability (NASS) framework for digital technologies.(104) The interpretability of ML systems is another challenge as healthcare professionals are less prone to adopt ML systems whose intrinsic

mechanisms they do not understand (the so-called ‘black box’).(105,106) Visualisation tools highlighting the variable or combination of variables that determined the output ought to be available for the prescriber and are an important parameter in future ML-CDSS.(107,108) ML-CDSS should also detail the trade-off that they apply between risk-taking and caution and show the confidence interval of their decisions and suggestions.(109) Controls have to ensure that ML-CDSS are registered on public databases and thoroughly evaluated independently of economic interest. The privacy protection of data,(110) cost-effectiveness research at the organisational and global level(42,111) and ethics discussion about accountability and liability when using ML-CDSS are other potential challenges to deal with.

3. Implementation science for clinical decision support tools

Implementation science is defined as “the scientific study of methods designed to promote the systematic adoption of research findings and other evidence-based practices into routine practice and thereby improve the quality and effectiveness of care”.(112) While many interventions have been developed for the improvement of clinical practices around the world, the literature shows a frequent failure to translate evidence into practice and suggests that the success of such interventions remains very dependent on the cultural, organizational and individual context.

Implementation science methods are thus based on an assessment of the local context, the definition of interventions adapted to this context, and the evaluation of the implementation process. Indeed, the implementation of appropriate antibiotic use interventions is often complex due to contextual barriers limiting their adoption by healthcare professionals.(113) These barriers can be structural, organizational or cultural at the same time, for example a lack of financial and human resources or difficulties of use and acceptance by health professionals.(114) Once applied to CDSS, the implementation sciences aim to optimize the adaptation of tools to the context, their usefulness, their efficiency, their cost, and above all their sustainable use by clinicians. Multiple interventions to implement AMS CDSS might be complementary and required to obtain significant impact on clinical outcomes.(115) Implementation sciences make it possible in particular to take into account different organizational levels, for example the user (micro), the hospital (meso), the health system (macro), as well as the interactions between the different layers of the health system, for

example between primary, secondary and tertiary care. Methods from implementation sciences can participate in lasting improvements through a qualitative assessment of the actors, barriers and levers of appropriate or unsuitable behaviour in the context of clinical practices. This perspective seems crucial to us in order to understand how prescribers can use CDSS and modify their clinical decision-making. The use of implementation science aims to optimize the integration of decision support systems into routine clinical practice, as well as their adoption and use by clinicians. (42) Implementation of CDSS

The barriers for the implementation of CDSS may be more important in the context of primary care. Indeed, antimicrobial stewardship interventions in the community come up against problems specific to the context of primary care such as a lack of updating of therapeutic practices (116,117) limited consultation times (118), uncertain diagnoses (119) and lack of systematic follow-up (118,120) as well as pressure to prescribe by patients and their families.(118,120,121) These issues constitute barriers to the implementation and therefore to the beneficial effects of these interventions on prescribing practices in community settings, despite a real need to optimise practices.

Many interventions that have been found to be effective in health services research studies fail to achieve significant patient benefit outcomes. Researchers working on public health interventions recognize the need to evaluate not only summative criteria but also formative criteria to determine to what extent the implementation of an intervention is effective in a specific context and can be transposed to other contexts. In order to facilitate the consideration of the success factors of the implementation of interventions, there are methodological frameworks, listing the main theoretical concepts to be taken into consideration during the development, implementation and evaluation of interventions. Indeed, implementation sciences rely on conceptual frameworks to study the different fields modulating the implementation, for example using the CFIR method (Consolidated Framework for Implementation Research).(122) CFIR provides a list of concepts that can be used to improve the implementation process and guide the assessment of obstacles and potential facilitators in the implementation of an innovation. The CFIR method details five areas, each of which can affect the implementation of an intervention:

1. The *intervention characteristics* describes the aspects of an intervention that can influence the success of an implementation. Eight sub-domains are described including the origin of the intervention, the relative advantages of the intervention, adaptability, cost or complexity.

2. The *outer setting* describes aspects of the environment that may influence the implementation. Four sub-areas are described including patient needs and resources, peer pressure or external incentives.
3. The *inner setting* describes the context of the internal aspects of implementation. Twelve sub-areas are described, including the culture of the target team, the commitment of the hierarchy or the enthusiasm for change.
4. The *individual characteristics* have five sub-areas related to individual characteristics such knowledge and beliefs about the intervention, individual relationship to change or individual relationship to the targeted structure.
5. The *implementation process* includes strategies or tactics that can influence implementation. Eight sub-areas are linked to the implementation process, including the commitment of personnel, the support of “champions” for the implementation or the process of reflection and evaluation.

Frameworks which also look at the inner and outer context and the process of change to specifically study the slow adoption of digital tools in health have also been developed such as the NASSS framework (non-adoption, abandonment, extension, dissemination, sustainability).(42) A theoretical framework, based on implementation research, has been proposed to design and evaluate antimicrobial stewardship interventions. It takes into account the rationale, setting, aims and features of the interventions and distinguish efficacy studies, effectiveness studies and implementation studies.(123) After a baseline assessment phase, implementation research frameworks make it possible to select the implementation techniques that best take into account the identified obstacles and levers. Planned implementation programmes thus inform the choice of the intervention components following an assessment of the likely barriers and facilitators.(22) Beyond technological innovations, organisational and structural change is often required to successfully implement CDSS in healthcare structures.(124) Tools have been proposed such as the implementation strategy matching tool that links barriers and facilitators to implementation strategies according to the 73 Expert Recommendations for Implementing Change (ERIC) implementation strategies. Indeed, the selection of implementation strategies may be facilitated by crossing the data obtained by the evaluation phase and a panel of strategies adapted to the identified obstacles and facilitators. Implementation research can guide the evaluation of the impact of interventions such as AMS interventions. While efficacy studies assess whether an AMS intervention produced the expected result under controlled conditions, effectiveness studies assess whether an AMS

intervention produced the expected result under ‘real-world’ pragmatic conditions and implementation studies assess the impact of an AMS programme in routine practice.(22)

4. Objectives

The overarching objective of this work was to use implementation science research to provide prescribers with useful and adapted tools to optimise antimicrobial prescribing in primary care. More specifically we aimed to analyse the potential for implementation of decision support tools for antimicrobial prescribing and antimicrobial stewardship involving different prescribers and health contexts, using low-tech and high-tech examples. More specifically, the first part of the thesis aimed to expand the use of a CDSS to a new context, from high-income countries (HIC) to low- and middle-income countries (LMIC), the second part aimed to expand the use of decision support tools to a wider set of healthcare professionals by working with community pharmacists, and the third part aimed to provide a state of the art of the use of machine learning (ML) in CDSS for antimicrobial prescribing.

The objective of the first study of this thesis was to study the requirements for a CDSS for antibiotic prescribing in primary care adapted to the context of West Africa and to analyse the barriers and facilitators to its use. We aimed to understand potential benefits and risks of implementing a CDSS and to ensure co-designed solutions.

The objective of the second study was to identify opportunities to implement a decision support tool for antimicrobial stewardship and to enhance the role of community pharmacists using a paper-based decision tool in community pharmacies.

Third, we aimed to provide a global overview of the use of machine learning in decision support systems for infectious and tropical diseases in the literature, as a preliminary work to the development of ML-CDSS for antimicrobial prescribing.

Figure 2 replaces the different objectives of the thesis on a simplified diagram representing some of the main steps for the success of a CDSS for antimicrobial prescribing.

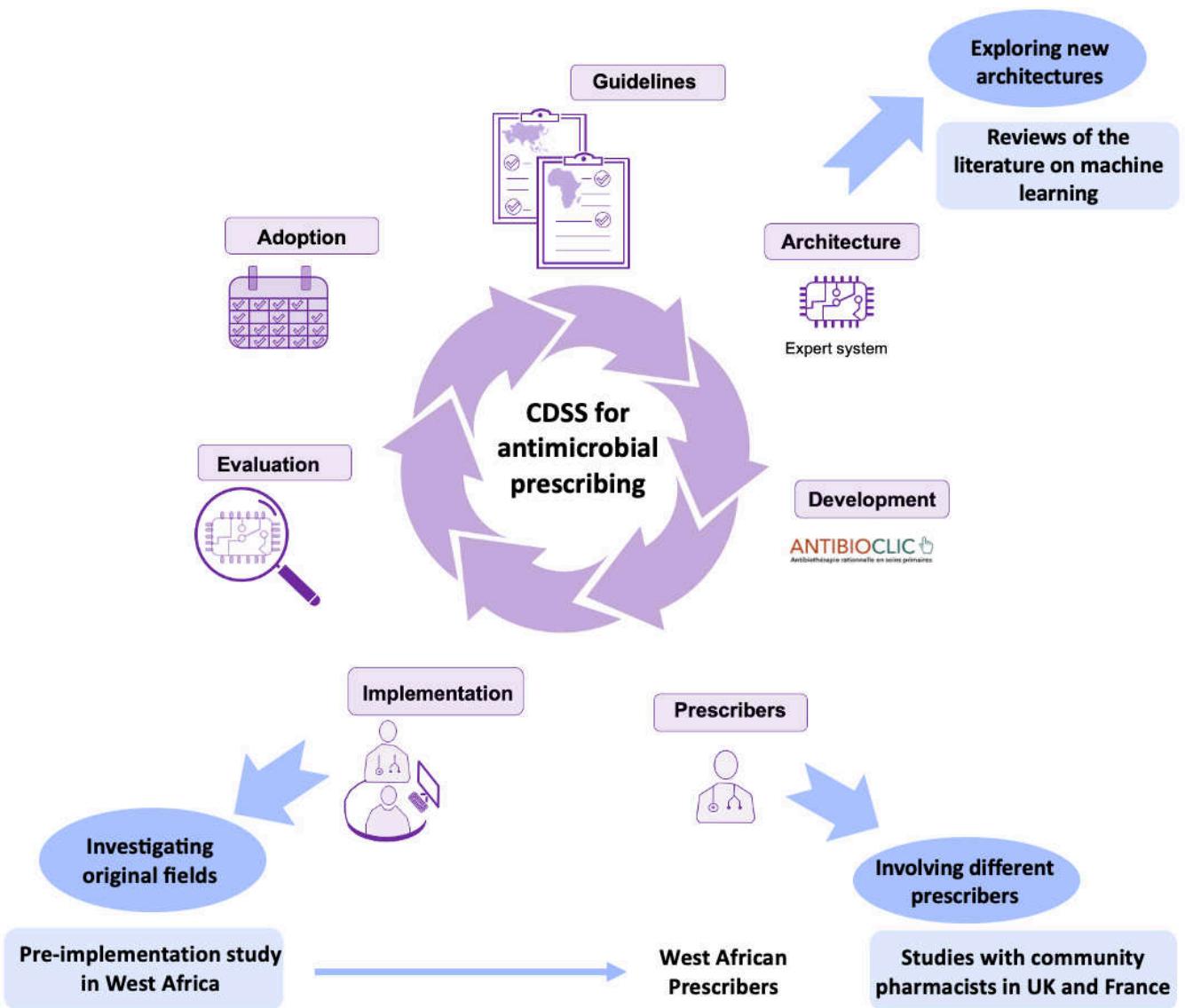


Figure 2. Specific objectives of the thesis on a diagram representing some of the necessary steps for a clinical decision support system for antimicrobial prescribing

V. Paving the way for the implementation of a decision support system for antibiotic prescribing in primary care in West Africa

1. Summary

The inappropriate use of antibiotics is well documented in both HICs and LMICs, it leads to poorer clinical outcomes and to an increase in antimicrobial resistance. The majority of antibiotics in human medicine are prescribed in primary care by practitioners who are not specialists in infectious diseases. In this study we describe the work of pre-implementation of an electronic CDSS for antimicrobial prescribing in West Africa. This work corresponds to an assessment of prescribers' needs and expectations for this type of tool and the discussion of further development in order to be able to co-design the CDSS best suited to the targeted care context and prescribers.

The objectives of this work were 1) to draw up an inventory of CDSS for antimicrobial prescribing in West Africa 2) to understand the potential benefits and risks of such a CDSS 3) to determine the necessary characteristics of this tool 4) to analyse the barriers and facilitators to its development, adaptation and implementation 5) to co-design solutions with potential users to ensure its sustainable use and adoption.

Towards these ends, we organized a workshop in Burkina Faso in June 2019 during the Interuniversity Diploma of Antibiotic Therapy in Sub-Saharan Africa. It began with the presentation of an existing French electronic CDSS for antimicrobial prescribing in primary care (Antibioclic) that provides personalized recommendations for 37 infectious diseases. We have chosen to present an example of an existing CDSS to the participants in order to make the discussions more concrete. The presentation was followed by a round table with all the participants and then an individual questionnaire with closed and open questions. The roundtable was recorded and then transcribed verbatim. Qualitative data were analysed using inductive thematic analysis on NVivo 12 software.

The workshop brought together 47 doctors representing 9 West African countries and 6 different medical specialties, mainly general medicine and microbiology. Regarding the use of electronic tools in medical practice, most participants had access to a smartphone during their consultations (n=35/47, 74%), but only 49% (n=23/47) had access to a computer and none used an electronic tool for antimicrobial prescribing. Participants felt that an electronic CDSS could have a number of clinical benefits, including improved clinical management, increased adequacy of antimicrobial prescribing with guidelines, and reduced antimicrobial resistance. They also raised potential indirect benefits linked to the use of this tool, such as encouraging the development and updating of national recommendations in antibiotic therapy, updating the knowledge of practitioners about antibiotic therapy or accelerating the development of surveillance capacities for infectious diseases in primary care. Participants underlined the need to adapt the CDSS to the local epidemiology of infectious diseases and antimicrobial resistance, to the diversity of primary care structures in West Africa as well as to the availability of diagnostic tools and antibiotics in the countries concerned. They also suggested adding personalized recommendations for tuberculosis, malaria and HIV management to the CDSS given the prevalence of these pathologies in their clinical practice. The most frequently cited contextual barrier was the potential risk of increasing self-medication in West Africa, where antibiotics, including antibiotics restricted to hospital use, can often be purchased without a prescription. Indeed, the participants considered that patients could potentially use the CDSS to choose an antibiotic themselves and thus avoid a consultation. In addition to regulating the distribution of antibiotics without a prescription, participants thus proposed restricting access to the CDSS to avoid this risk. The risk of losing patient confidence when consulting an electronic device was also mentioned and participants noted the lack of national recommendations guiding antibiotic therapy in some West African countries, which makes it more complex to develop a context-appropriate CDSS. In order to optimize the chances of success of an electronic decision support system, participants strongly encouraged the co-development of the tool with all stakeholders, including nurses, midwives and pharmacists, who are frequently involved in prescribing in primary care in West Africa. The frequent lack of internet and computer access is a barrier that could be overcome by developing a mobile application with an offline mode. A phased implementation approach was suggested by starting and evaluating the use of the electronic tool at a pilot site, followed by wide dissemination using professional networks and social media.

Most of the participants in the workshop were medical specialists in general medicine working in university hospitals in Burkina Faso. This bias is probably linked to the recruitment of participants via a university diploma organised by French and Burkina Faso universities. In the future, we must involve different prescribers in primary care such as nurses, midwives and doctors working in dispensaries in order to allow a broader vision of the prescription of antibiotics in primary care.(125) Indeed, prescribing habits can vary between professional groups and we wish to study the potential differences between prescribers regarding the needs and expectations of CDSS for antibiotic prescribing.(126,127) In addition, this work did not examine the governance system and public health priorities in the countries concerned, which may be important factors to consider before setting up a CDSS. Work has been done in European countries on governance to tackle antimicrobial resistance,(128) and there are relevant frameworks to assess this important factor.(129,130)

This study provided information for the development and implementation of an electronic tool to support antibiotic prescribing in primary care in low- and middle-income countries. CDSS in this context could help improve clinical management, optimize the use of antibiotics, reduce antimicrobial resistance and increase practitioner knowledge about antibiotic therapy but this potential impact needs to be evaluated in future clinical trials.

2. Article

Original Paper

Paving the Way for the Implementation of a Decision Support System for Antibiotic Prescribing in Primary Care in West Africa: Preimplementation and Co-Design Workshop With Physicians

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Abstract

Background: Suboptimal use of antibiotics is a driver of antimicrobial resistance (AMR). Clinical decision support systems (CDSS) can assist prescribers with rapid access to up-to-date information. In low- and middle-income countries (LMIC), the introduction of CDSS for antibiotic prescribing could have a measurable impact. However, interventions to implement them are challenging because of cultural and structural constraints, and their adoption and sustainability in routine clinical care are often limited. Preimplementation research is needed to ensure relevant adaptation and fit within the context of primary care in West Africa.

Objective: This study examined the requirements for a CDSS adapted to the context of primary care in West Africa, to analyze the barriers and facilitators of its implementation and adaptation, and to ensure co-designed solutions for its adaptation and sustainable use.

Methods: We organized a workshop in Burkina Faso in June 2019 with 47 health care professionals representing 9 West African countries and 6 medical specialties. The workshop began with a presentation of Antibioclic, a publicly funded CDSS for antibiotic



prescribing in primary care that provides personalized antibiotic recommendations for 37 infectious diseases. AntibioClic is freely available on the web and as a smartphone app (iOS, Android). The presentation was followed by a roundtable discussion and completion of a questionnaire with open-ended questions by participants. Qualitative data were analyzed using thematic analysis.

Results: Most of the participants had access to a smartphone during their clinical consultations (35/47, 74%), but only 49% (23/47) had access to a computer and none used CDSS for antibiotic prescribing. The participants considered that CDSS could have a number of benefits including updating the knowledge of practitioners on antibiotic prescribing, improving clinical care and reducing AMR, encouraging the establishment of national guidelines, and developing surveillance capabilities in primary care. The most frequently mentioned contextual barrier to implementing a CDSS was the potential risk of increasing self-medication in West Africa, where antibiotics can be bought without a prescription. The need for the CDSS to be tailored to the local epidemiology of infectious diseases and AMR was highlighted along with the availability of diagnostic tests and antibiotics using national guidelines where available. Participants endorsed co-design involving all stakeholders, including nurses, midwives, and pharmacists, as central to any introduction of CDSS. A phased approach was suggested by initiating and evaluating CDSS at a pilot site, followed by dissemination using professional networks and social media. The lack of widespread internet access and computers could be circumvented by a mobile app with an offline mode.

Conclusions: Our study provides valuable information for the development and implementation of a CDSS for antibiotic prescribing among primary care prescribers in LMICs and may, in turn, contribute to improving antibiotic use, clinical outcomes and decreasing AMR.

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KEYWORDS

decision support systems, clinical; antibiotic resistance, microbial; drug resistance, microbial; antibiotic stewardship; implementation science; Africa, Western; diffusion of innovation; medical informatics applications

Introduction

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a global threat that affects both high-income countries (HIC) and low- and middle-income countries (LMIC). The drivers of AMR, including antibiotic misuse, lack of infection prevention and control, and poor sanitation, particularly affect LMICs [1,2]. Data suggest that 80% to 90% of all antibiotics used in humans are prescribed in primary care [3]. Although antibiotic use has been increasing over the last decade in LMICs [2,4], antibiotic prescribing indicators in primary care for the African region deviate significantly from the World Health Organization's (WHO) reference targets [5]. Deviations from existing guidelines on antibiotic use, including delays and overuse, are linked both to patients' behavior and that of health care professionals [6,7]. There is thus a need to find interventions that could improve antibiotic prescribing in primary care to respond to the global threat of AMR.

Electronic Clinical Decision Support Systems

Electronic clinical decision support systems (CDSS) have been devised to provide prescribers with rapid access to updated information, which is required to make appropriate therapeutic decisions [8]. CDSS can be split into CDSS providing unsolicited information (eg, alerts for drug interactions) and CDSS providing solicited information (eg, diagnostic support systems). Computer representations of patient care guidelines are among commonly used CDSS [9,10]. They allow the prescriber to enter basic clinical information of a patient and access the diagnostic or therapeutic guidelines adapted to the patient's unique situation. Machine learning CDSS that find their own decision rules from the data are increasingly being developed and may replace knowledge-based CDSS in which

human experts define the decision rules in the future [11]. CDSS adapted in primary care have the potential to reduce overall antibiotic use and improve the appropriateness of antibiotic prescribing [12,13]. In LMICs, the introduction of such aids is in the early stages of development [14], but it could have a measurable impact within the context of sparse infectious diseases specialists. Primary care prescribers in LMICs often lack clinical practice guidelines adapted to their setting and do not have access to antimicrobial stewardship programs [15]. Although they may not have access to health care information systems, CDSS providing diagnostic guidance or easy access to therapeutic guidelines may help them make the right decision at the point-of-care [16]. Improving the adequacy of antibiotic prescribing might, in turn, lead to better clinical outcomes and decreased AMR. Moreover, CDSS have the potential to be implemented in multiple health facilities without recruiting new prescribers [17] and could optimize the utilization of resources that are scarce in LMICs.

Implementation of Clinical Decisions Support System in West Africa

Consequently, the development and implementation of CDSS that fit into clinical work might be part of interventions to mitigate against drivers of AMR in LMICs. However, the adaptation of CDSS for antibiotic prescribing in routine clinical care and their sustainability are often limited [10,18]. As is the case with many innovations in health care, multiple CDSS have been abandoned after their development and initial evaluation because of multiple factors, including the lack of preimplementation work [19]. Indeed, at the global level, the situation analysis for AMR in human health often lack the assessment of technological innovations [20]. Moreover, many CDSS failed to demonstrate a clinical impact because of the low uptake of the CDSS and poor adherence to the generated advice [21,22]. According to the WHO, the adaptation of



electronic CDSS is particularly low in LMICs [23]. Interventions to implement CDSS are challenging because of cultural and structural constraints, and these challenges are even more pronounced in primary care where prescribing can be done by a variety of health care professionals or when resources are limited [14,24]. West Africa hosts about 381 million people and includes 16 countries, among them some of the lowest income countries in the world [25,26]. French-speaking West African countries, including Benin, Burkina Faso, Cameroon, Chad, Ivory Coast, Republic of Congo, Guinea, Mali, Niger, Senegal, and Togo, were among the LMICs with the highest increase in global antibiotic consumption between 2000 and 2015 [2]. As highlighted by the WHO, countries in the African region are the least advanced regarding electronic and mobile health [23].

Objectives

Before developing or implementing a CDSS for antibiotic prescribing in West Africa, we need to understand the contextual, structural, and behavioral determinants that will facilitate or prevent the use of CDSS for antibiotic prescribing. Our study aimed to examine the requirements for a CDSS adapted to the context of primary care in West Africa and to analyze the barriers and facilitators of its implementation and adaptation by prescribers using qualitative methods during a preimplementation workshop.

Methods

Study Design

Our aims were (1) to understand the potential benefits and risks of a CDSS for antibiotic prescribing in primary care in West Africa, (2) to analyze the barriers and facilitators of its implementation, and (3) to ensure co-designed solutions for its adaptation and sustainable use. To this end, we organized a workshop with West African antibiotic prescribers that began with a presentation of Antibioptic, a CDSS for antibiotic prescribing currently widely used in France and freely available on the web and as a smartphone app (further details below). We chose to begin the workshop with an example of an existing CDSS rather than with a theoretical description of a CDSS for antibiotic prescribing. This strategy was considered by the organizing team as the most promising to elicit reactions among the participants. The main characteristics of a CDSS were presented, and the organizers went through a number of clinical scenarios on infectious diseases using Antibioptic. Then, the organizers moderated a roundtable discussion with all the participants. During this first-of-its-kind workshop, the participants generated barriers and facilitators to the use of a CDSS such as Antibioptic in West Africa and were asked to hypothesize if its use could lead to benefits or risks, including unexpected events. Participants were specifically asked to debate the challenges in the implementation and adaptation of a CDSS for antibiotic prescribing in West Africa and to co-design solutions.

Antibioptic—An Example of a Clinical Decision Support System for Antibiotic Prescribing

Antibioptic is a French CDSS for antibiotic prescribing in primary care, [27] targeting 37 common infectious diseases, freely available on the web and as a smartphone app on iOS and Android. It was codeveloped by general practitioners, specialists of infectious diseases, and engineers in 2011. Clinicians can enter the diagnosis of a patient on the website or app, they are then asked a few targeted questions (age group, comorbidities, renal function, breastfeeding, and pregnancy). Finally, they receive a tailored recommendation of antibiotic regimen, dose, and duration according to French national guidelines. [Multimedia Appendices 1](#) and [2](#) describe how to use Antibioptic respectively with slides or video in English. Antibioptic was developed using a systematic method to transform clinical practice guidelines from the French National Authority for Health and the French Infectious Diseases Society (SPILF) into decision trees in Antibioptic. Antibioptic is updated frequently and modified as soon as a new guideline is published. The number of Antibioptic users in France has steadily increased over the past years from a median (IQR) of 414 (245-494) a day in 2012 to 5365 (2891-5769) a day in 2018, without any saturation to date ([Multimedia Appendix 3](#)). The smartphone app has been downloaded 22,970 times on Android and 15,200 times on iOS. More details are described in a recent study [27].

Workshop Location and Participants

The 3-hour workshop to discuss the implementation and adaptation of a CDSS for antibiotic prescribing in West Africa was organized in Burkina Faso by 2 professors of infectious diseases, 1 from Burkina Faso (AP) and 1 from France (FL). To maximize participation and cost efficiency, the workshop took place during the French-speaking university course *Antibiologie et Antibiothérapie en Afrique Subsaharienne (Antibiotic therapy in Sub-Saharan Africa)* organized in Bobo-Dioulasso, Burkina Faso, on June 2019. This course lasts 5 weeks and is organized every year by the University Nazi Boni of Bobo-Dioulasso and the University of Montpellier. The course is open to West African health professionals working on AMR or antibiotic therapy, whether in primary, secondary, or tertiary care, with no selection among participants. Attendance to the workshop was voluntary for the participants of the course.

Electronic Questionnaire

After the roundtable discussion, an electronic questionnaire with closed- and open-ended questions was given to each participant ([Multimedia Appendix 4](#)). The questionnaire allowed the collection of in-depth individual data on the implementation and adaptation of a CDSS for antibiotic prescribing. The questionnaire was codeveloped by a multidisciplinary team including 6 members of the Antibioptic study team: infectious diseases clinicians (AP and FL), a microbiologist (AO), public health specialists (JB and GS) with experience in the West African context, and an implementation science and knowledge mobilization lecturer (RA). The first part collected demographic characteristics and information regarding the use of electronic tools for antibiotic prescribing. The second part displayed open-ended questions about potential outcomes and users of a

CDSS for antibiotic prescribing in West Africa and the challenges of its implementation and adaptation.

Data Analysis

Data from the closed-ended questions of the questionnaire were imported into R software version 3.2.4 (R Foundation for Statistical Computing). Numerical data are presented as absolute numbers, proportions, and median (IQR). The entire roundtable discussion was audio recorded and transcribed verbatim by the AMK France professional company. Data from the roundtable discussion and open-ended questions were analyzed using thematic analysis and were coded to identify key categories, which were developed into themes using NVivo 12 software (QSR International). The analysis of questionnaires and the roundtable discussion supported cross-validation and triangulation of the findings.

Ethical Considerations

Written consent was obtained from each participant. No distinguishable personal information was recorded, and all the data were analyzed anonymously. This survey was approved by the research ethics committee of Centre Muraz (Health Research Institute, Bobo-Dioulasso, Burkina Faso) and was compliant with the European General Data Protection Regulation.

Results

Participants

All 47 participants of the course, 19 women and 38 men with a median (IQR) age of 31 (30-38) years, participated in the workshop and completed the questionnaire (**Table 1**). Most of the participants (35/47, 74%) were from Burkina Faso, but 8 other West African countries were represented. Approximately half of the participants (24/47, 51%) worked in a university hospital, whereas the others worked in general hospitals (14/47, 30%), public health institutes (4/47, 9%), dispensary (1/47, 2%), private hospital (1/47, 2%), or pharmacies (1/47, 2%). The low number of participants working as primary care prescribers may be related to a more difficult access to university degrees. The specialty of the participants was general practice (21/47, 45%), microbiology (13/47, 28%), pharmacy (4/47, 9%), anesthesiology and intensive care (3/47, 6%), infectious diseases (2/47, 4%), and neurosurgery (2/47, 4%). Only 26% (12/47) of participants, all in Burkina Faso, stated that they used national guidelines to prescribe antibiotics. The others used French guidelines (20/47, 43%), WHO guidelines (20/47, 43%), or local hospital guidelines (4/47, 9%).

Table 1. Demographic characteristics of participants (N=47).

Characteristics	Values
Age (years), median (IQR)	31 (30-38)
Gender, n (%)	
Men	28 (60)
Women	19 (40)
Country of practice, n (%)	
Burkina Faso	35 (74)
Togo	3 (6)
Senegal	2 (4)
Mali	2 (4)
Gabon ^a	1 (2)
Guinea	1 (2)
Guinea-Bissau	1 (2)
Ivory Coast	1 (2)
Niger	1 (2)
Working structure, n (%)	
University hospital	24 (51)
General hospital	14 (30)
Public health institute	4 (9)
Dispensary	1 (2)
Private hospital	1 (2)
Pharmacy	1 (2)
Medical specialty, n (%)	
General practice	21 (45)
Microbiology	13 (28)
Pharmacist	4 (9)
Anesthesiology and intensive care	3 (6)
Infectious diseases	2 (4)
Neurosurgery	2 (4)
Guidelines used for clinical practice, n (%)	
French	20 (43)
World Health Organization	20 (43)
National ^b	12 (26)
Hospital	4 (9)
American	2 (4)
European	2 (4)
Portuguese	1 (2)

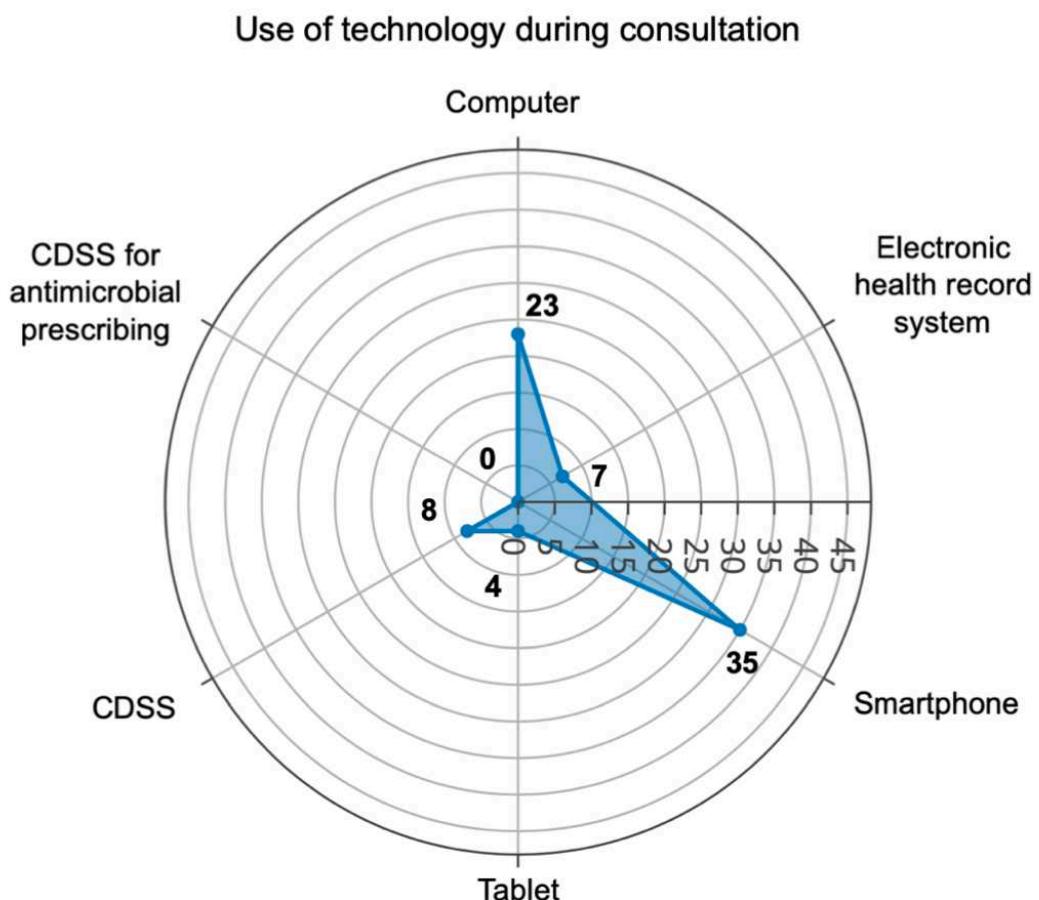
^aCentral Africa.^bThe 12 participants were from Burkina Faso.

Current Use of Technology and Clinical Decision Support Systems

Most of the participants (35/47, 74%) had a smartphone with internet access during their clinical consultations, but less than half (23/47, 49%) of the participants had access to a computer, and 15% (7/47) of the participants had no access to any electronic tools during their consultations. Most of the clinicians

did not use an electronic health record system (39/47, 83%) or CDSS (36/47, 77%) for any clinical decision making during their clinical consultations. The only CDSS mentioned by the participants was a tool for basic medical calculations and a tool that displays medical cards. No CDSS for antibiotic prescribing (nor for any antimicrobial drug) was used by the participants (Figure 1).

Figure 1. Current use of technology during consultation among participants. CDSS: clinical decision support systems.

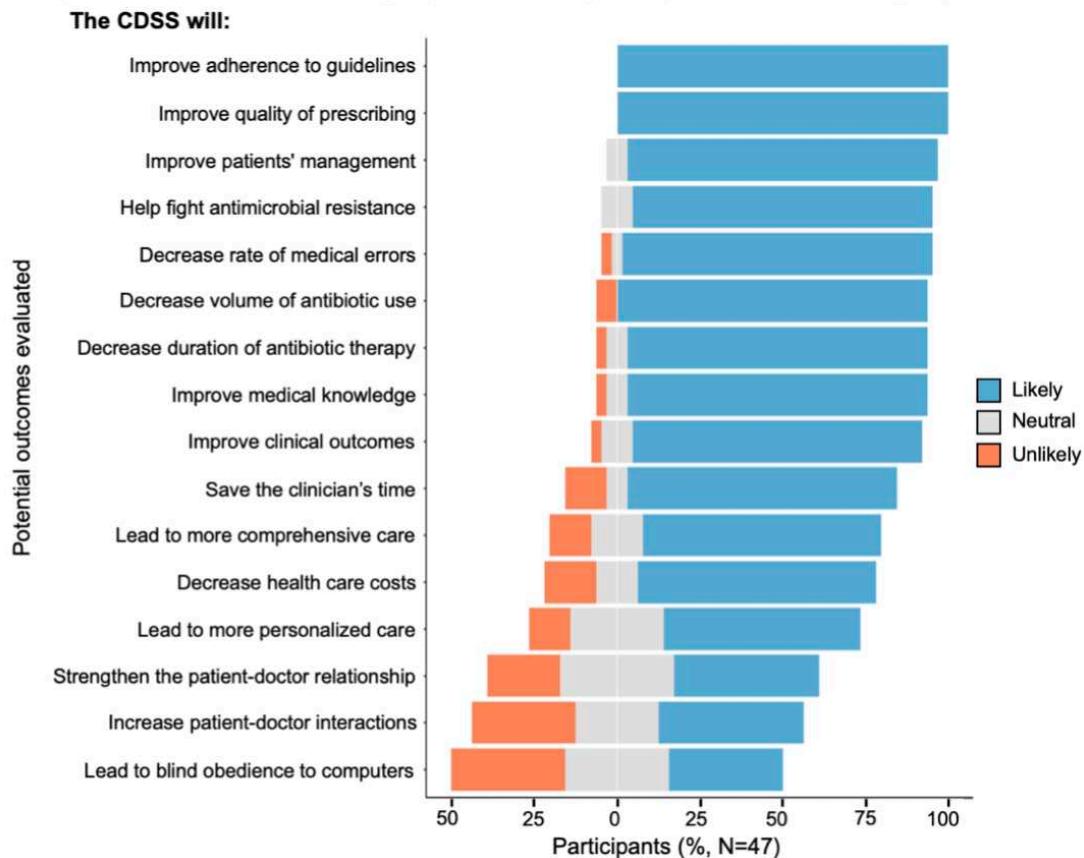


Potential of a Clinical Decision Support Systems for Antibiotic Prescribing

Most of the participants expected favorable outcomes from the implementation of a CDSS for antibiotic prescribing in primary care in their countries (Figure 2). They thought a CDSS was likely to improve the quality of antibiotic prescribing (47/47, 100%), improve adherence to guidelines (47/47, 100%), improve the management and care of patients (44/47, 94%), decrease the number of medical errors (44/47, 94%), improve the volume

of antibiotic use (44/47, 94%), improve the duration of antibiotic therapy (43/47, 91%), fight against AMR (43/47, 91%), increase the medical knowledge of users (43/47, 91%), and save time during consultation (38/47, 81%). Participants disagreed on the fact that such a tool could strengthen the physician-patient relationship (20/47, 43% judged it likely; 11/47, 23% unlikely; and 16/47, 34% were neutral) or could lead to blind obedience to electronic tools from prescribers (16/47, 34% judged it likely; 16/47, 34% unlikely; and 15/47, 32% were neutral).



Figure 2. Expected outcomes of a clinical decision support system for antibiotic prescribing. CDSS: clinical decision support systems.

During the roundtable discussion and through the open-ended questions, the participants identified a number of consequences of a CDSS on a wider scale. Participants underlined the lack of antimicrobial stewardship teams in West Africa. They hypothesized that a CDSS could help many isolated structures to have access to antibiotic prescribing recommendations and could relieve existing antimicrobial stewardship teams of simple antibiotic prescribing advice and let them focus on complex cases. One participant noted that a CDSS could be used to increase surveillance capability in primary care. Indeed, its use could be monitored and lead to reports on the incidence of infectious diseases and the rate of antibiotic prescriptions. The participants agreed that this is particularly important in West African countries where epidemiological data are scarce. The use of French guidelines was not seen as a barrier to a CDSS. Indeed, most of the participants declared that they did not have national guidelines to prescribe antibiotics in their country. However, the participants pointed out that a successful CDSS could have a positive impact in encouraging national societies to develop guidelines that could then be integrated into the CDSS. More broadly, they agreed that this CDSS could help to increase the awareness of health professionals on the importance of appropriate prescribing and the risks of AMR. The

participants also agreed that a CDSS could be used in the initial training and continuous medical education of health professionals by updating antibiotic prescribing knowledge:

If you use it continually, you certainly update your knowledge. [General practitioner in Burkina Faso]

Regarding the scope of a CDSS for antibiotic prescribing, the participants stated that it could have a positive impact on the management of urinary tract infections (84%); skin and soft tissue infections (84%); gastrointestinal tract infections (83%); genital infections (80%); pneumonia (77%); meningitis (70%); ear, nose, and throat infections (70%); dental infections (67%); and surgical site infections (61%). The participants identified a wide diversity of potential users of a CDSS for antibiotic prescribing in West Africa, including general practitioners, infectious diseases specialists, physicians in other specialties, pharmacists, nurses, clinical microbiologists, and midwives.

Challenges

The participants identified a number of challenges and proposed a number of solutions for the adaptation of a CDSS for antibiotic prescribing in a West African setting (Table 2), and these are grouped by system level.



Table 2. Challenges and potential solutions for the development and implementation of a clinical decision support system in the West African context.

Level	Challenges to CDSS ^a development	Challenges to CDSS implementation	Potential solutions
Country level	<ul style="list-style-type: none"> Scarce epidemiological data on the prevalence and incidence of infectious diseases and the level of antimicrobial resistance Lack of national guidelines Limited availability of diagnostic tests and antibiotics 	<ul style="list-style-type: none"> N/A^b N/A N/A 	<ul style="list-style-type: none"> Encouraging studies to better analyze the local and regional epidemiology Developing and updating the CDSS according to local and regional epidemiology regarding infectious diseases, microbiology, and antimicrobial resistance Including tuberculosis and common parasitic diseases The CDSS should follow local, regional, and national guidelines where they exist. If they do not, the CDSS could follow French or WHO^c guidelines as they are used by most participants The CDSS should be developed for the sub-continent of West Africa and then could be further adapted to each country To easily adapt the CDSS to local and national guidelines, the programming and code of the CDSS should be in open access Adapting the suggestions to locally available diagnostic tests and antibiotics by working with national scientific societies
Health care structure level	<ul style="list-style-type: none"> N/A N/A 	<ul style="list-style-type: none"> Lack of internet access and information technology infrastructure Independently operating and geographically isolated health structures such as dispensaries 	<ul style="list-style-type: none"> Development of an offline mode of the CDSS Development of a mobile version on iOS and Android Increasing the availability of computers and internet access in West Africa Pilot testing of the CDSS in a primary care structure linked to an academic hospital before disseminating the tool to other health structures Field communication with primary care prescribers Using the network of the Ministry of Health
Individual level: clinicians and patients	<ul style="list-style-type: none"> Diversity of training needs for primary care prescribers N/A N/A N/A N/A 	<ul style="list-style-type: none"> N/A Lack of awareness and training about CDSS Risk of increasing self-treatment with antibiotics as they are available without prescription in most West African countries Risk of deskilling and dependency of prescribers 	<ul style="list-style-type: none"> Co-designing the CDSS with general practitioners, nurses, midwives, microbiologists, dentists, and pharmacists Allowing for different modules of access for health professionals to meet the different information needs Dedicated training for primary care prescribers Communicating through scientific and professional societies, using traditional and social media Involving all the stakeholders, including health authorities, the Ministry of Health, and the media Limiting access to registered health professionals (disagreement between participants) Regulating access to antibiotics without prescription Improving the training of prescribers about antibiotic prescribing



Level	Challenges to CDSS ^a development	Challenges to CDSS implementation	Potential solutions
	• N/A	• Risk to lose patients' confidence by following the advice of an electronic tool	• Education of patients about the need to use reference books or electronic sources to provide the best care • Ensuring the independence of the tool from pharmaceutical companies

^aCDSS: clinical decisions support system.

^bN/A: not applicable.

^cWHO: World Health Organization.

Country Level

At the country level, the participants pointed out the scarcity of epidemiological data in West African countries, the difference between epidemiology of diseases in HICs and LMICs, the lack of national guidelines, and the limited availability of diagnostic tests and antibiotics. To produce computer-interpretable clinical guidelines, CDSS developers need to have access to clinical practice guidelines. For countries where national guidelines for infectious diseases management do not exist, the participants first suggested the development of a CDSS based on French or WHO guidelines to encourage the establishment of national guidelines. To address the specific needs of primary care prescribers in West Africa, the CDSS should not only target the management of common bacterial diseases but also the management of parasitic diseases and tuberculosis. Participants stressed the importance of tailoring the CDSS to local capacity and infrastructure, such as resource availability and antibiotics, with the help of national scientific societies.

Health Care Structure Level

The first challenge at the organization level was the lack of internet access and information technology (IT) infrastructure. Taking into account the wide availability of smartphones with internet access, the participants highlighted major opportunities through the development of mobile phone versions of CDSS (on iOS and Android) with an offline mode. The second challenge was the important number of independently operating and geographically isolated health structures, such as dispensaries, in the West African health system. To reach these structures, participants suggested the involvement of relevant stakeholders, including health authorities, the Ministry of Health, scientific societies, the media, and opinion leaders, using traditional and social media:

It is important to use the traditional networks of the Ministry of Health where information goes down hierarchically but also social media that are more and more used. [Physician in a university hospital, Burkina Faso]

The organization of a phased approach was suggested by initiating and evaluating CDSS in a pilot primary care structure linked to an academic hospital followed by dissemination to other health structures:

You have to show people that it's used by people like them starting with a pilot test site. [Physician in a general hospital, Burkina Faso]

Individual Level: Clinicians and Patients

The diversity of primary care prescribers who have different levels of decision support needs was identified as a challenge to developing effective CDSS. A physician working in a general hospital stated that in West Africa "nurses see a lot of patients, certainly more than physicians" highlighting the need to codevelop the CDSS with primary care health care professionals who frequently prescribe antibiotics, such as general practitioners, nurses, midwives, microbiologists, dentists, and pharmacists. The implementation of a CDSS in West Africa should take into account the lack of widespread knowledge on the use of CDSS by organizing training sessions with primary care prescribers. One participant said that some health care professionals or patients could be refractory to new technologies, but this was not considered a major barrier by the other participants. The participants identified a number of facilitators for the adaptation of a CDSS by primary care prescribers and patients, including the independence of the tool from pharmaceutical companies, codevelopment with users, free access to the CDSS, and good usability.

The most discussed unexpected consequence was that an open access CDSS such as Antibiotic could amplify self-medication of antibiotics due to availability without prescription:

My point of view is really mixed. This represents an undeniable progress for antibiotic prescribing but in the context of our country, there is a non-negligible risk of self-medication by non-healthcare professionals. [General practitioner, Burkina Faso]

A very good tool for the treatment of infections but which could be dangerous in the southern countries because of self-medication and the accessibility of antibiotics without prescription. [Physician in a university hospital, Burkina Faso]

In this context, the CDSS may be used as a substitute for expert health care opinion. However, some participants highlighted the fact that much information is already available on the web and that Antibiotic is already available, including in Burkina Faso, with no reported use by patients. In fact, there was uncertainty regarding if implementing a CDSS in West Africa would amplify the phenomenon of self-medication or would help by providing a reliable source to patients who would want to self-medicate anyway:

Some patients will buy antibiotics without prescription, with or without the tool. [General practitioner, Burkina Faso]

On the contrary, if patients have access to national recommendations, this reinforces and this even facilitates your message. [Professor in a university hospital, Burkina Faso]

A consensus emerged that the best solution is to increase efforts to limit access to antibiotics without prescription.

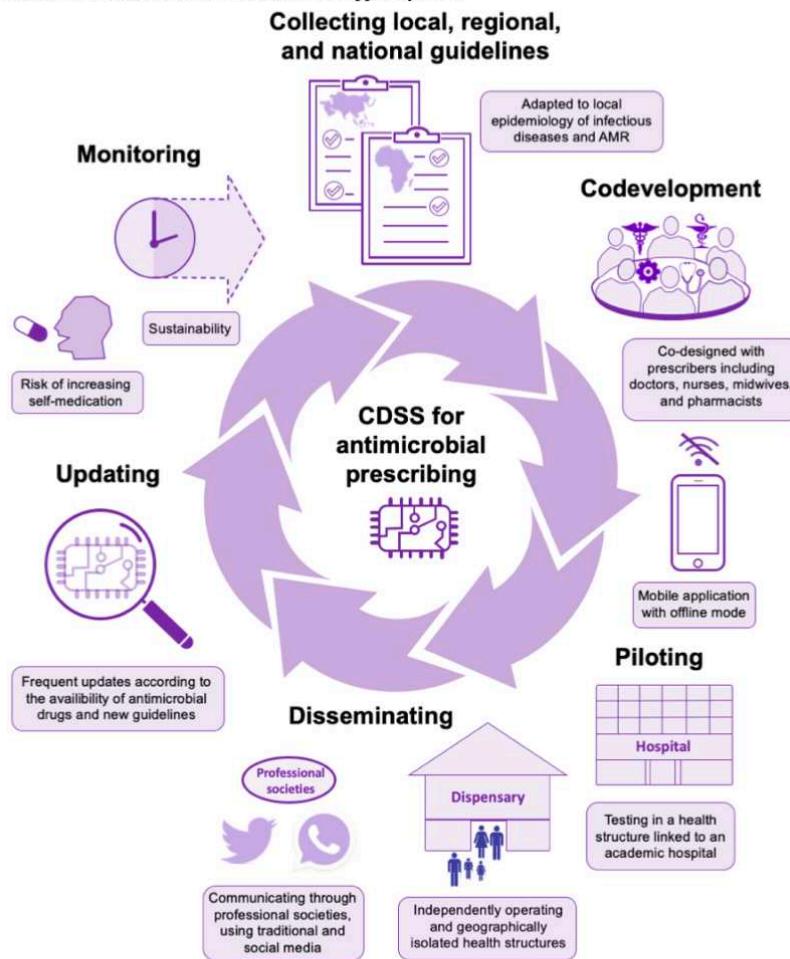
Discussion

Principal Findings

We conducted a preimplementation workshop with West African health professionals to examine the requirements for a CDSS adapted to the context of primary care in their countries. The use of CDSS for antibiotic prescribing (and other clinical decisions, in fact) is currently missing, but the importance and need for such tools to support antibiotic prescribing in primary care were stressed by all participants. Regarding the

implementation of a CDSS in primary care, the participants encouraged a procedure of co-designing the tool with health professionals and stakeholders involved in antibiotic prescribing and initiation via a primary care pilot site, which is linked to an academic hospital (Figure 3). The diffusion of the CDSS would be more successful if supported by networks of medical specialists and the Ministry of Health but should also take advantage of social media because of its high use among health care professionals. The lack of widespread internet access and computers during consultation was a barrier to the use of the CDSS, but it could be circumvented by the development of a mobile app with an offline mode. The CDSS should be tailored to the local epidemiology of infectious diseases and AMR, and the high prevalence of malaria, tuberculosis, and HIV in West Africa should be taken into account when developing the CDSS [28]. The availability of diagnostic tests and antibiotics may differ between West African countries and may vary over time, requiring frequent updates of the CDSS.

Figure 3. Key steps for the development and implementation of a clinical decision support systems for antibiotic prescription in low- and middle-income countries. AMR: antimicrobial resistance; CDSS: clinical decision support systems.



The participants pointed out the potential risk of self-medication in countries in which antibiotics can be bought with no

prescription. Such a risk should certainly be anticipated and monitored, but most of the participants did not think that the

CDSS should have restricted access. On the contrary, some participants thought that a CDSS could provide an opportunity to strengthen the education of the general public about antibiotic prescribing and AMR. Development and implementation of a CDSS was seen to be associated with a number of benefits related to improving clinical care and reducing AMR and also to strengthening and updating practitioners' knowledge of antibiotic prescribing recommendations, encouraging the development of national guidelines, and developing surveillance capabilities in primary care. Indeed, the implementation of a CDSS for antibiotic prescribing could be coupled with measures that allow an increase in the capability of surveillance of antibiotic use. Examples include real-time monitoring of requests expressed on the platform and extracting reports about antibiotic use [27,29]. Moreover, the implementation of a CDSS in the community could have implications beyond antibiotic prescribing in primary care. Indeed, primary care is the gateway to secondary and tertiary care, and AMR in primary care circulates in the whole health system [30].

Comparison With Prior Work

The lack of preimplementation and co-design work concerning the assessment of CDSS for antibiotic prescribing has been reported in recent reviews [10,31]. More broadly, research on the implementation strategies for CDSS in primary care is lacking [32]. A qualitative design involving 33 face-to-face interviews with general practitioners has been used to codevelop computer-delivered interventions to promote guidelines for antibiotic prescribing in the United Kingdom. The authors focused on the technical development of prompts and the determinants of their acceptability but did not study the implementation of the CDSS in clinical practice [33]. Postimplementation research found that the key factor for the use of this CDSS by general practitioners in primary care was their awareness of the implementation of the system within their practice [22]. The lack of end-user engagement with implementation and the rigidity of the guidelines incorporated in the prompts were barriers to the effective adaptation of the system, stressing the importance of a systematic and theoretically informed process of implementation for CDSS [34]. The nonadaptation, abandonment, scale-up, spread, and sustainability framework has been developed to support the implementation of technological innovations in health and social care [19]. It lists challenges in 7 domains: the condition or illness, the technology, the value proposition, the adopter system (comprising professional staff, patient, and lay caregivers), the organization(s), the wider (institutional and societal) context, and the interaction and mutual adaptation between all these domains over time.

Few studies have focused on CDSS for the management of infectious diseases in LMICs and in particular in West Africa. A recent review identified 6 CDSS for the management of febrile children in primary care in LMICs [35]. In a pilot cluster-randomized controlled study, the clinical algorithm for management of childhood illness available on smartphones (e-ALMANACH) increased the number of children screened for red flags and decreased antibiotic prescription in Tanzania [36]. This result was confirmed in another controlled study in which the use of e-ALMANACH to manage children improved

clinical outcomes and reduced antibiotic prescription by 80% [37]. Electronic point-of-care tool, an electronic algorithm using point-of-care testing results including C-reactive protein and procalcitonin, was shown to improve the clinical outcomes of children with febrile illnesses as compared with the e-ALMANACH CDSS [38,39]. Another study described a protocol for the implementation on a large scale in Burkina Faso of an electronic tool for integrated management of childhood illnesses [40]. The results of this trial have not been published yet. In general, few data are available on the adaptation and sustainability of such interventions. One team analyzed the implementation cost of a CDSS for antenatal and delivery care and found that most of the cost resulted from the recruitment and training of nurses and midwives using the CDSS and from buying laptops [41]. A CDSS that is easily used by health care professionals and is available as a free mobile app could lead to a decreased implementation cost. A study in Burkina Faso confirmed a positive attitude toward electronic decision support systems and the need for simplicity and good usability of the tool. They found similar barriers, such as the lack of infrastructure and IT systems and the limited availability of drugs and diagnostic tests [42]. The development of CDSS in LMICs could be facilitated by the development of mobile health [43] and by sharing open-source codes [44]; however, other challenges remain: countries often have to buy a back-office or another hosting solution and have to pay for the maintenance of the server [45,46]. These costs, if not anticipated, can limit the sustainability of CDSS.

Limitations

The participants stressed the diversity of prescribers and health structures in West Africa that must be taken into account when codeveloping the CDSS. However, most of the participants in our workshop were physicians specialized in general practice working in Burkina Faso university hospitals. This bias was related to our recruitment of participants via a university degree organized by French and Burkina Faso universities. We, thus, need to involve more primary care prescribers such as nurse prescribers, midwives, and physicians working in dispensaries to allow for a broader view of primary care antibiotic prescribing. Indeed, prescribing habits may vary between professional groups [47,48], and we would like to capture potential differences among prescribers concerning the use, needs, and expectations regarding CDSS for antibiotic prescribing.

To open the discussion, we decided to provide an example of a currently used CDSS. Indeed, as we anticipated that most of the participants had no experience using electronic decision support systems for antibiotic prescribing, we wanted to show them an existing CDSS and collect opinions. This approach was likely to influence the answers of participants and the discussion during the roundtable discussions. However, we think that the barriers and facilitators identified in the study are not limited to Antibioclic. Indeed, the contextual barriers that have been found have been described in other studies. Nonprescription dispensing of antibiotics in the community has been widely described both in LMICs [49,50] and in HICs [51]. In a recent review, the authors did not find any clinical practice guideline applicable to prehospital care in LMICs among 276 guidelines

[15]. For countries where national guidelines for the management of infectious diseases do not exist, the participants suggested the development of a CDSS first based on French or WHO guidelines to encourage the establishment of national guidelines.

The governance system and public health priorities could be important additional factors that need to be studied in West Africa before the implementation of a CDSS. Work has been done in European countries about governance to address AMR [52], and relevant frameworks for assessing this important factor exist [20,53]. However, the analysis and governance frameworks for antibiotic prescribing often lack the assessment of technological innovation, such as electronic decision support. Including CDSS in the national action plan as in the United Kingdom's 2019-2024 national plan that targets to "be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool by 2024" is probably an

important step toward the development and implementation of support systems [54]. We are not aware of Western African national action plans mentioning the development and use of CDSS.

Conclusions

Preimplementation research is needed to ensure that CDSS are adapted to the context in which they are deployed. Our study provided valuable information to develop and implement a CDSS for antibiotic prescribing among primary care prescribers in LMICs. We plan to organize workshops to co-design a CDSS tailored to the context of primary care in West Africa. Optimizing the use of antibiotics in primary care may have beneficial consequences for the entire health system and can contribute to limiting the spread of AMR. Most of the barriers and facilitators that we identified may easily relate to a broad spectrum of CDSS, including systems for clinical decisions other than antibiotic prescribing.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

How to use Antibioclic (slides).

[\[PPTX File , 31628 KB-Multimedia Appendix 1\]](#)

Multimedia Appendix 2

How to use Antibioclic (video).

[\[MOV File , 201584 KB-Multimedia Appendix 2\]](#)

Multimedia Appendix 3

Antibioclic users.

[\[PPTX File , 282 KB-Multimedia Appendix 3\]](#)

Multimedia Appendix 4

Electronic questionnaire.

[\[DOCX File , 75 KB-Multimedia Appendix 4\]](#)

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Abbreviations

- AMR:** antimicrobial resistance
CDSS: clinical decisions support system
HIC: high-income countries
LMIC: low- and middle-income countries
SPILF: French Infectious Diseases Society
WHO: World Health Organization

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VI. Preventing and managing urinary tract infections: use of a leaflet to enhance the role of community pharmacists

1. Summary

Surveillance has indicated a continuous rise in rates of *E. coli* bacteraemia in the United Kingdom.(131) Half of the cases of *E. coli* bacteraemia arise in the community, suggesting that community-based interventions are needed to control them. The key source of *E. coli* bacteraemia are urinary tract infections (UTIs), which are the most commonly seen bacterial infection in General Practice. Up to 50% of women will have a UTI in their lifetime and 30% among them will have recurring episodes.(132,133) It has been estimated that bacteraemia occurs in approximately 15% of the patients evaluated in the emergency department for UTI.(134) Appropriate antibiotic use in patients with a complicated UTI reduced length of hospital stay improved patient outcomes and healthcare costs.(135) Antibiotics are usually prescribed for most women presenting urinary symptoms. However, in a recent study,(136) 95% of women consulted a health professional for their most recent UTI: 74% reported being prescribed an antibiotic, yet only 63% reported taking them.(137) The UK multicentre POETIC study found that only 25% of urine samples sent to the laboratory for suspected UTIs were actually positive for pathogens, suggesting less than optimal antibiotic prescribing behaviour for this diagnosis.(138) Recent qualitative research by Public Health England, exploring both clinicians and patient experiences of consultations about suspected UTIs, confirms antibiotic prescribing is suboptimal.(139) The role pharmacists can and do play in the treatment of UTIs has emerged in recent years, for example a study showed that 13% of women used pharmacies for advice on their UTI. Since then, national and local campaigns around seeking your pharmacist's advice have been promoted.

We thus aimed to implement a UTI leaflet in community pharmacies in order to improve antibiotic prescribing for UTI by facilitating communication between service users and pharmacists, improving the diagnosis and management of UTI and educating service users on self-management, prevention measures and antibiotic resistance. The specific objectives of this study were to explore the views of pharmacy staff on giving advice to service users with UTIs,

to evaluate the feasibility and acceptability of a decision support tool in the pharmacy setting and to collect the opinions of service users who seek advice from pharmacy staff who use the information tools when giving advice about UTIs.

We included community pharmacies in one London borough (Newham), purposively sampled because of low socio-economic status, which would enable views from patients of different socio-economic status. Data collection was through a service user survey ($n=51$) and pharmacist surveys and semi-structured interviews before (16 interviews, 22 questionnaires) and after (15 interviews, 16 questionnaires) trialling UTI leaflets designed to be shared with patients. Data were analysed inductively using thematic analysis and descriptive tabulation of quantitative data.

Results from health service users and pharmacists independently showed that approximately 25-30% of health service users first visit a pharmacy for symptoms suggestive of a urinary tract infection. Pharmacists felt comfortable giving self-care advice for urinary tract infections and referring patients to general practitioners. They considered that going to community pharmacies offered advantages for service users, namely their extended opening hours, their local roots, and frequent mastery of the different languages spoken in their neighbourhood. The majority of health service users ($n = 33$, 65%) were also in favour of discussing their urinary symptoms with pharmacists. Community pharmacists insisted on their important role in the management of community infections and in the prescription of antibiotics, controlled by local prescription protocols. Patient group directions (PGD) allow healthcare professionals to supply and administer specified medicines to pre-defined groups of patients, without a prescription.(140) Whilst PGD for patients with uncomplicated UTIs fulfilling specific criteria allow pharmacists to provide nitrofurantoin thus improving patient access to early treatment,(54) few guidelines have been developed to guide pharmacists in the community management of suspected or confirmed UTI. All the pharmacists stressed the importance of the use of a decision support tool, e.g., the UTI leaflet, for service users coming first to the pharmacy and for service users coming to get antibiotics prescribed. The majority of pharmacists ($n=13$, 81%) considered that a CDSS could enable them to share significantly more information and more accurate information regarding prevention, red flags for consulting a GP and antimicrobial resistance. Among suggestions, pharmacists asked for a digital version of the tool and a more personalized approach for each patient. They also asked for a QR code on the paper leaflet that could be

linked to an electronic based decision support tool or information webpage. They encouraged the use of the leaflet or another CDSS as a guide to structure the discussion with service users, as a way to provide a take-away information for patients and to be used as a referral notice between healthcare professionals (unpublished data). Although obstacles to the involvement of pharmacists have been identified such as the lack of access to the medical file, the lack of staff or training, these results reinforce the importance of prescribing support tools as well as an integrated management of infections between pharmacists and doctors. The participants strongly encouraged the co-development of the decision support tool with all stakeholders, including nurses, GPs and pharmacists, who are frequently involved in prescribing antimicrobials in primary care.

In order to strengthen these results, semi-structured qualitative interviews were also conducted with community pharmacists in France (work submitted for publication). Participants were recruited through a professional organization of community pharmacists combined with a snowballing technique. Interviews were audio recorded, transcribed and analysed using thematic analysis. The Consolidated Framework for Implementation Research was used while developing the interview guide and carrying out thematic analysis. Sixteen community pharmacists participated. All the respondents had good awareness about antimicrobial resistance and believed community pharmacists had an important role in tackling AMR. Some barriers to community pharmacists' participation in AMS were identified such as difficult interactions with prescribers, lack of time, lack of access to patients' medical records and absent diagnosis on antibiotic prescriptions. Increased patient education, audits and feedback of antibiotic prescribing, increased point-of-care testing and delayed prescribing were interventions suggested by the pharmacists to improve antibiotic use in primary care. Strategies cited by participants to facilitate the implementation of such interventions were increased pharmacist-general practitioner collaboration, specialized training, and the use of clinical decision support systems.

2. Article



antibiotics



Article

Preventing and Managing Urinary Tract Infections: Enhancing the Role of Community Pharmacists—A Mixed Methods Study

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Abstract: Background: Community pharmacists are involved in antimicrobial stewardship through self-care advice and delivering medications for uncomplicated infections. Objectives: This mixed methods study aimed to identify opportunities to enhance the role of community pharmacists in the management of service users with suspected or confirmed urinary tract infection (UTI). Methods: Data collection was through a service user survey ($n = 51$) and pharmacist surveys and semi-structured interviews before (16 interviews, 22 questionnaires) and after (15 interviews, 16 questionnaires) trialing UTI leaflets designed to be shared with service users. Data were analysed inductively using thematic analysis and descriptive tabulation of quantitative data. Results: Twenty-five percent ($n = 13/51$) of service users with urinary symptoms sought help from a pharmacist first and 65% ($n = 33/51$) were comfortable discussing their urinary symptoms with a pharmacist in a private space. Community pharmacists were confident as the first professional contact for service users with uncomplicated UTI ($n = 13/16$, 81%), but indicated the lack of a specific patient referral pathway ($n = 16/16$, 100%), the need for additional funding and staff ($n = 10/16$, 62%), and the importance of developing prescription options for pharmacists (5/16, 31%). All community pharmacists reported playing a daily role in controlling antimicrobial resistance by educating service users about viral and bacterial infections and promoting a healthy lifestyle. Enhancing their role will need greater integrated working with general practices and more prescribers based in community pharmacy. Conclusion: This study suggests that community pharmacists could play a greater role in the management of uncomplicated UTI. The current reconfiguration of primary care in England with primary care networks and integrated care systems could provide a real opportunity for this collaborative working with potential learning for international initiatives.

Keywords: pharmacist; community; urinary tract infections; leaflet; self-care; general public

1. Introduction

Urinary tract infections (UTIs) are one of the most commonly seen bacterial infection in general practice. Up to 50% of women will have a UTI in their lifetime and 30% among them will have recurring episodes [1,2]. Outcomes are usually very good as most cases resolve in 3–4 days without complications with empiric antibiotics [3]. Of all the antibiotics prescribed in primary care, 15–20% are prescribed for UTIs [4]. However, as many as 60% of women with suspected UTIs have a urine culture negative for bacteria and may not need antibiotics [5]. The prevalence of inappropriate antibiotic prescribing for UTI in primary care may be over 70% [6]. However, UTIs account for around 20% of community-acquired bacteraemia in patients admitted to an English National Health Service (NHS) Trust in 2007–08 and studies suggest that up to 50% of *Escherichia coli* bloodstream infections in England could be owing to urinary tract infections [7,8]. Furthermore, increases in the incidence of *Escherichia coli* bloodstream infections in England were mostly driven by community cases [8].

In a recent study, 95% of women consulted a health professional for their most recent UTI: 74% reported being prescribed an antibiotic, yet only 63% of these reported taking them, highlighting the need for better advice about antibiotics in the community [9]. Community pharmacists are involved daily in antimicrobial stewardship (AMS) by providing patients with self-care advice, delivering medications, and recommending over-the-counter (OTC) treatments for common infections. The U.K. 2019 5-year antimicrobial resistance (AMR) action plan states that primary care pharmacists have a critical role in reviewing prescriptions for antimicrobials and challenging those that may be inappropriate [10]. National and local campaigns advise the general public to first contact their pharmacist for healthcare advice [9]. Community-based interventions by pharmacists have the potential to control the rise of bacteraemia and to improve antimicrobial use for UTIs by increasing patient knowledge and self-care skills. Measures such as enhanced self-care, preventative care, and referral to general practitioners (GPs) when appropriate could improve the health and wellbeing of the general public. This is particularly relevant as virtually all service users with suspected or confirmed UTI visit a community pharmacy either before their GP or after to collect a prescription. Patient group directions (PGDs) allow healthcare professionals to supply and administer specified medicines to pre-defined groups of patients, without a prescription [11]. While PGD for patients with uncomplicated UTIs fulfilling specific criteria allow pharmacists to provide nitrofurantoin, thus improving patient access to early treatment [12], few guidelines have been developed to guide pharmacists in the community management of suspected or confirmed UTI. The International Pharmaceutical Federation issued in 2015 a report on the contribution of pharmacists to fight antimicrobial resistance [13]. While most interventions are targeting hospital pharmacists, some countries have issued policies for community pharmacists, such as New Zealand or Canada, where community pharmacists can prescribe first-line antibiotics for uncomplicated UTIs [14,15].

The U.K. national action plan (NAP) for AMR indicates a need to strengthen the links between primary care pharmacists and GP practices [10], but further research is required to investigate the best measures to empower pharmacists in AMS roles.

The objective of this study was to explore the views of pharmacy staff and service users on providing or receiving advice for suspected or confirmed UTIs in the community pharmacy setting. More specifically, this study aimed to identify opportunities to enhance the role of community pharmacists in the management of UTI by exploring the journey of service users with urinary symptoms.

2. Methods

2.1. Study Design

This study is part of a trial to implement Public Health England's (PHE) UTI TARGET leaflets [16] in community pharmacies (Figure 1). The TARGET UTI leaflets are designed to be shared with service users to facilitate communication between healthcare professionals and service users and to increase their confidence on self-care [17]. The leaflets follow relevant National Institute for Health and Care

Excellence (NICE) guidelines. The study used mixed methods with questionnaires and interviews to explore the views of pharmacists and service users with suspected or confirmed UTI.

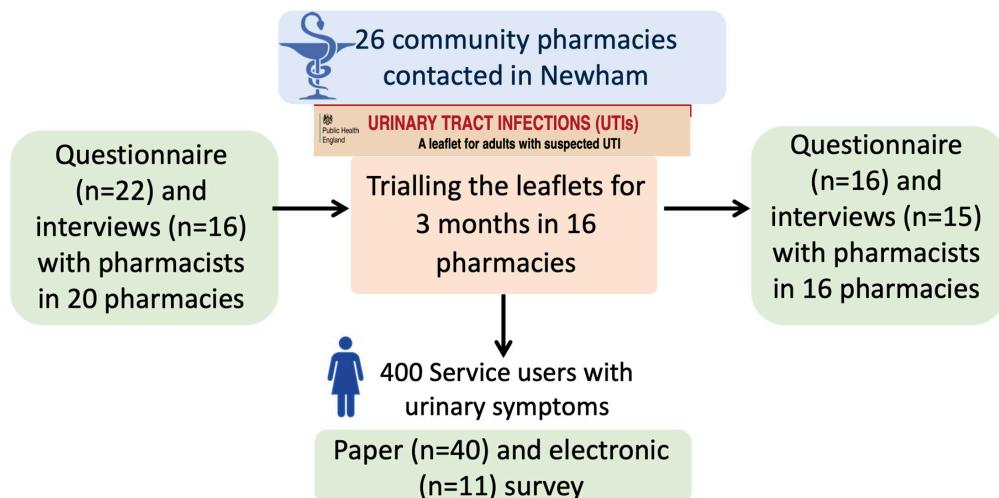


Figure 1. Design of the study.

2.2. Questionnaires and Interviews Schedules

Two semi-structured questionnaires and interview schedules to explore the role of pharmacists in the prevention and management of UTIs (before and after trialling the leaflets) and one semi-structured questionnaire to analyse the opinion of service users were developed by a multidisciplinary team of clinicians and researchers at Imperial College London and PHE (Supplementary Materials S1–S6). The team included doctors specialized in infectious diseases (N.P.S., A.H.), a community pharmacist (P.P.), a clinical microbiologist (C.M.), and researchers specialized in qualitative methodology and implementation science (R.A., L.J., D.L., R.Ah.).

The questionnaires were theoretically informed by the Consolidated Framework for Implementation Research to understand individual level and contextual influencing factors to the adoption of the leaflet [18]. The questionnaires were reviewed and tested by two community pharmacists and were refined according to comments. The pharmacist questionnaires collected information about demographics, characteristics of the pharmacies, particularities of giving advice in the pharmacy setting generally, and specifically about the UTI patient journey, using closed and open-ended questions. The questionnaire for service users collected information about demographics, literacy, the service user experience of their suspected UTI, its management, self-care, and resolution. This was piloted with a service user representative and subsequently revised based on feedback. Interviews were done by a doctor specialized in infectious diseases.

2.3. Study Setting: Community Pharmacies in Newham

Community pharmacies were included in one London borough (Newham), purposively sampled, which would enable views from service users of different socio-economic status. An invitation, including an information leaflet and consent form, was sent by the local pharmaceutical committee lead pharmacist to 26 pharmacies in April 2019. Researchers sent non-responders a reminder 2 weeks later.

2.4. Participant Enrolment

Pharmacists agreed to participate in a phone interview and complete an electronic questionnaire before trialling the TARGET UTI leaflets for 3 months in their pharmacy. At the end of the 3 months, the pharmacists participated in a second interview and completed a further questionnaire. These pharmacists were provided with a £30 voucher incentive after each interview. Service users who

received the TARGET UTI leaflet at the pharmacy were invited to participate in the study in person when they were given the leaflet to complete a paper or electronic survey at home. The paper survey with a written consent form was attached to the leaflet in a prepaid envelope and the electronic survey was accessible via the use of a QR code or a weblink both written on the paper survey. Service users were provided a £10 voucher incentive if they completed the survey electronically or sent it by mail.

2.5. Data Analysis

The interviews were recorded, anonymized, and transcribed verbatim by a professional company and checked against the interviews by a researcher. Interviews were analysed by a researcher using an inductive thematic analysis [19]. Two other authors independently and inductively coded three different transcripts. The three researchers collectively reviewed and reached a consensus about the application of themes through independent coding and group discussion, which were then reviewed and agreed by the research team. The interviews were then coded according to the themes using the NVivo 12 software. Data from the closed-ended questions of the surveys were imported into the R software (version 3.2.4). Numerical data were presented as absolute numbers, proportion, median \pm interquartile range (IQR). Pearson's chi-squared tests were used to compare the results among service users.

2.6. Ethics

The study received approval from Imperial College London and ethics committee [Imperial College Research Ethics Committee reference: 18IC4777]. Data management was compliant with the European General Data Protection Regulation.

3. Results

3.1. Participants: Pharmacists and Service Users

Among the 26 pharmacies contacted in Newham, 20 (77%) participated in the pre-intervention assessment. Among them, 16 pharmacies (62%) participated in the study including the pre-intervention questionnaire and interview, the 3-month trial of the leaflets, and the post-intervention questionnaire and interview. Sixteen interviews and 22 questionnaires were completed before and 15 interviews and 16 questionnaires after trialing the leaflet (Figure 1). The median duration of the interviews was 24 min (IQR, 19–27) and 16 min (IQR, 14–17) for the pre- and post-intervention interviews, respectively. The pharmacist participants comprised 8 women and 14 men, with a median of 15 years (IQR, 5–30) post qualification experience (Table 1). Fifty-one service users participated in the survey, the majority of whom were female; 43 (84%). Twenty-one participants (41%) had recurrent UTIs, 23 (45%) had previously experienced one or two UTIs, and 6 (12%) had a UTI for the first time.

Table 1. Characteristics of the participants. IQR, interquartile range; UTI, urinary tract infection.

Pharmacists	n (%) or Median (IQR) (n = 22)
Women	8 (36)
Job description	
Non-prescribing pharmacists	18 (82)
Prescribing pharmacists	3 (14)
Pharmacy technician*	1 (4)
Years since qualification	15 (5–30)
Years in the pharmacy	9.5 (5–17)
Pharmacy staff (full time equivalent) in the pharmacy	4 (3–5)
Service users per day	55 (40–100)
Estimated percentage of male service users seen in the pharmacy	61 (52–62)
Service users seen in the consultation room per day	8 (5–12)
Estimated number of service users given healthcare advice	20 (16–37)

Table 1. *Cont.*

Service Users	n (%) (n = 51)
Women	43 (84)
Age	
Children	1 (2) (completed by the mother)
18–24	8 (16)
25–34	10 (20)
35–44	4 (8)
45–54	11 (22)
55–64	7 (14)
65–74	4 (8)
>75	4 (8)
Ethnicity	
White	27 (53)
Asian	14 (27)
Black	4 (8)
Mixed	4 (8)
UTI history	
Recurrent UTIs	21 (41)
One or two prior episodes	23 (45)
No prior episode	6 (12)

* One pharmacy technician was asked by a pharmacist to complete the pre-assessment questionnaire for the pharmacy, but this participant did not participate in the interviews nor the trial of the leaflets.

3.2. Survey Results: The Patient UTI Journey in the Community

Before seeing a healthcare professional, 15/51 (29%) service users reported consulting their family and 9/51 (18%) reported consulting online sources (e.g., NHS choices) for information on urinary symptoms. Younger participants (aged 18–34 years versus those aged over 34 years) were more likely to access information about UTI on the internet (50% versus 18%) ($p = 0.01$). Two-thirds (n = 31, 62%) of the service users reported drinking more fluids before going to the pharmacy or visiting their GP, but 20 (39%) did not. Some service users reported taking paracetamol (n = 15, 29%), cranberry juice or capsules (n = 12, 24%), resting (n = 10, 20%), cystitis sachets (n = 8, 16%), nonsteroidal anti-inflammatory drugs (n = 7, 14%), or time off work (n = 2, 4%). Cystitis sachets are popular OTC medications in the United Kingdom that contain sodium citrate or potassium citrate and could reduce the acidity of urine. However, there is currently no evidence to support taking cystitis sachets or cranberry products to improve UTI symptoms. Thirty-seven service users (72%) went to a pharmacy following a GP visit after being prescribed an antibiotic and 13 (25%) went to a pharmacy before visiting a GP (Figure 2). The results from the pharmacists' questionnaires confirmed this finding stating that, on average, 71% of service users came to the pharmacy following a GP visit with an antibiotic prescription and 29% visited the pharmacy first for advice and OTC medication. Service users rarely reported (n = 2, 4%) going to the pharmacy following a GP visit when antibiotics had not been prescribed.

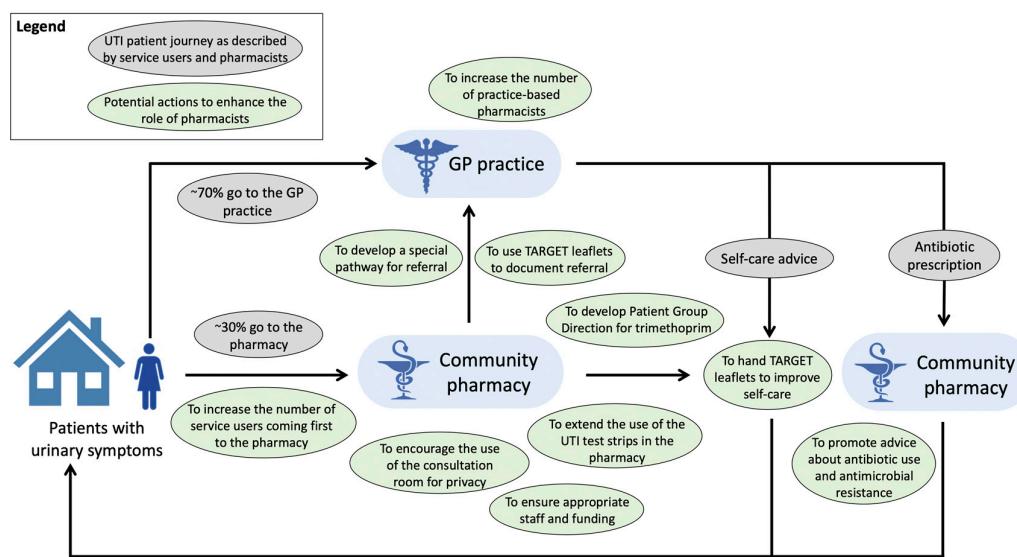


Figure 2. Potential actions to enhance the role of community pharmacists in the management of service users with suspected or confirmed urinary tract infection. GP, general practitioner.

3.3. Advice in the Pharmacy

During interviews, pharmacists identified barriers and facilitators to providing healthcare advice in the pharmacy setting compared with a GP practice (Table 2). The most cited barriers were lack of staff or time ($n = 17$, 77%), language barrier ($n = 13$, 59%), and absence of access to patient medical records ($n = 9$, 41%). On the contrary, facilitators were that pharmacists are trained and confident in giving advice ($n = 22$, 100%), that no appointment is needed ($n = 17$, 77%), and that pharmacies have long opening hours ($n = 14$, 64%). The language barrier was mitigated by the number of languages spoken by the pharmacists and their staff: we discussed this point with six pharmacists who all reported the fluent use of four to six Asian languages in their pharmacy in addition to English.

Table 2. Barriers and facilitators of giving advice in the pharmacy raised during interviews.

Pharmacists n = 22 (%)	
Barriers	
Lack of time or staff	17 (77)
Language barrier	13 (59)
No access to the medical record	9 (41)
Not recognised or funded by health authorities	5 (23)
No possibilities to prescribe medication	5 (23)
Outside the scope of expertise of pharmacists	3 (14)
Waiting time is unpredictable for service users	2 (9)
Some service users prefer information from doctors	2 (9)
Facilitators	
Pharmacists are confident and trained in giving advice	22 (100)
No appointment needed	17 (77)
Long opening hours	14 (64)
Ease of access	13 (59)
Multiple languages spoken by the staff	12 (55)
Financial incentive to give additional advice	10 (45)
Availability and use of a consultation room	9 (41)
Close contact with the service users	8 (36)
Flexible time for consultation (no time limit)	6 (27)
Counter assistants and sufficient staff	5 (23)
Local presence/community-based	2 (9)
Possibility to give advice on the phone	2 (9)

Service users were mostly ($n = 33$, 65%) comfortable discussing their urinary symptoms with a pharmacist, as long as it was confidential and in private. As expected, the majority of service users ($n = 36$, 70%) did not want to discuss urinary symptoms at the counter if they could be overheard by other customers.

When asked via questionnaires about the most important self-care advice given to service users with a suspected UTI, all the pharmacists ($n = 22$) recommended drinking plenty of fluids and taking OTC products (e.g., cystitis sachets, cranberry products), 64% ($n = 14$) recommended painkillers, 36% ($n = 8$) discussed red flags to visit the GP, and 27% ($n = 6$) gave advice regarding preventative care. All pharmacists who were interviewed agreed that it was difficult to give comprehensive self-care advice because of the lack of time. Overall, the pharmacists were confident in discussing UTIs with service users.

3.4. Communication with the GP

During pharmacist interviews, the reasons for referral to the GP were explored (Figure 2). The pharmacists referred all male patients, pregnant women, older adults (over 65 years old) or children (below 16 years old), patients with symptoms lasting for more than 48 h, lower abdominal pain or kidney pain, temperature, blood in the urine or severe comorbidities, and those presenting with recurrent UTIs to the GP. However, all pharmacist participants pointed out that they did not have a facilitated way to contact GPs and could only instruct patients to visit their GP:

"So, there's not much, much of a connection between the two settings. For example, if there was a patient that we were particularly concerned about, we can't call up the GP practice and say, oh, could you give them early appointment because I've seen them and I've noticed X, Y, Z. There's not that rapport yet or there's not that importance [placed in] a pharmacist's view, I feel, in community." P4.

As such, they stressed the need to develop a special referral pathway between pharmacies and GPs ($n = 16$, 100%) and also suggested that the TARGET UTI leaflets could be used as a referral notice between healthcare professionals.

3.5. The Role of Pharmacists

Table 3 presents the themes and sub-themes that were generated from the qualitative analysis of the interviews with the pharmacists regarding the management of service users with suspected or confirmed UTI. Most pharmacists interviewed ($n = 13$, 81%) suggested that pharmacists could act as a first-line triage for service users with UTIs:

"Well, I think they [the patients] should come first to the pharmacy (. . .) and then you could screen them and see whether they need to be actually seen by the GP." P13.

Table 3. Themes and sub-themes of the qualitative analysis of interviews on the role of pharmacists in the management of service users with suspected or confirmed urinary tract infection. PGD, patient group direction; NHS, National Health Service; AMR, antimicrobial resistance.

Management of Service Users with Suspected or Confirmed Urinary Tract Infection	n (%) (n = 16)
Pharmacists can act as a first-line triage	11 (69)
They need funding or additional staff to do so	10 (62)
They should have more possibilities to prescribe first line treatments (e.g., PGDs)	5 (31)
They can give dipstick tests and check the results	1 (6)
Strengthening the link between pharmacists and GPs	
Development of a special referral pathway between pharmacies and GPs	16 (100)

Table 3. *Cont.*

Management of Service Users with Suspected or Confirmed Urinary Tract Infection	n (%) (n = 16)
Self-care advice relieves pressure on the NHS and the GPs	6 (37)
Reducing the spread of AMR	
Education of service users about infections for which antibiotics are not always needed	16 (100)
Screening patients who need to go to the GP	10 (62)
Self-care advice for viral infections and benign bacterial infections	12 (75)
Promotion of a healthy lifestyle	5 (31)

The pharmacists reported that, if they were the first healthcare professional to give advice to service users with suspected or confirmed UTIs, this could relieve pressure on other NHS services, including GPs. However, they requested additional funding and staff to give advice for those with suspected UTI as pharmacies are not currently funded for this. Some also asked for reimbursement for this activity:

“Yeah, but you see having a role to play is one thing but you need to be remunerated for that role. You can’t expect pharmacists to do everything for nothing” P13.

Increasing the patient group directions (PGDs) to prescribe first-line treatments for uncomplicated UTIs could help enhance this role:

“[Having a UTI PGD] … could be something which might take a bit of work off the GPs. And in that service, we do get a consultation fee as well and we do that service for Pharmacy First or the Minor Ailment. So, I think that’s some revenue, it works for the GP and it works for the patient” P3.

All the pharmacists interviewed (n = 16, 100%) agreed that they had a major role in the control of AMR by educating service users about antibiotics and infections for which antibiotics are not needed. They reported giving daily self-care advice for viral infections and self-limiting UTIs, and triaging patients and advising when they should consult a GP. They also described having an important role in preventative measures in community care and participating in preventing bacterial infections by promoting a healthy lifestyle:

“That is where it should all start. We [pharmacy staff] should be highly focused on prevention, and providing advice for people to self-care and self-manage, and improve their health. And that will stop, forget the resistance [AMR], you will not even need to prescribe antibiotics if people are living a healthy lifestyle. (. . .) So, the biggest impact the pharmacist can make is in the prevention agenda” P10.

4. Discussion

4.1. Summary

We explored the UTI patient journey with both pharmacists and service users to identify opportunities to enhance the role of community pharmacists specifically in the management of UTIs. The self-care management of service users with suspected UTI can still be improved as 38% of service users did not report drinking plenty of fluids before seeing a healthcare professional. One-fourth of service users with suspected UTI sought help first from a pharmacy, but the majority visited the pharmacy to pick up their antibiotic prescription after a visit to the GP. Barriers to giving advice in the pharmacy were the lack of staff or time, the language barrier, and the absence of access to patient medical records. Pharmacists were trained and confident to give advice to patients with suspected UTIs, but they pointed out the lack of a specific pathway to refer patients who need an antibiotic

to GPs. Furthermore, they raised the need for additional funding and staff to enable an increased role of community pharmacists in the management of uncomplicated UTIs. Community pharmacists integrated their role to fight AMR into the wider context of healthcare education and promotion of a healthy lifestyle.

4.2. Comparison with Existing Literature

The proportion of service users with urinary symptoms coming first to a pharmacy (25%) is close to what has been found in another study, in which 36% of the patients presented directly to a pharmacy [12]. In a household survey conducted in 2014 in England, only 13% of females who had ever had a UTI reported going first to a pharmacy. The rate in this study may have been lower as it included a wide age range of participants [9]. As described in recent studies, this study found support from both patients and pharmacists for increased access to UTI management and advice through community pharmacies [12,20]. This confirms the need for interventions targeting community pharmacies to improve the UTI patient journey including self-care advice and appropriate referral. According to this study and the literature, the development of a PGD for uncomplicated UTIs is supported by pharmacists in order to extend their management options [12]. A recent study found that a community pharmacy-led UTI test-and-treat service for women aged 16–64 years with urinary symptoms helped to support the appropriate use of antibiotics and reduced demand on other NHS resources such as GP surgeries.²⁰ However, there is a need to carefully consider the advantages of PGDs, which should lead to more timely treatment of UTI with the potential drawback of increased use of antibiotics in UTIs, as has been found for chloramphenicol and eye infections [21]. The risk of overuse of antibiotics for suspected UTIs leading to increased AMR could be mitigated with an increased pharmacy access to clear protocols, accurate point-of-care testing [20], urine culture, and shared patients records [22]. Sixty-two percent of the service users in this study took extra fluids before consulting a healthcare professional, as compared with 35% in a study in 2014 in the United Kingdom [9]. This might reflect the effect of recent interventions including online campaigns to promote self-care of UTIs in the community [23,24].

The barriers to giving self-care advice about UTI in the community pharmacy setting confirm findings in a qualitative study with GPs, pharmacists, pharmacy staff, and representatives from pharmacy organisations in England and Wales [22]. Clinicians reported that lack of time or staff and lack of access to medical information were perceived as barriers to giving effective and thorough self-care advice. Overall, this study supports increasing the collaboration between GPs and community pharmacists as advocated in a joint statement by the Royal College of General Practitioners (RCGP) and the Royal Pharmaceutical Society (RPS) [25]. The proposals of this statement include many of the measures that have been asked for by pharmacists in this study such as a greater role for community pharmacy in managing minor conditions, access to health records, and better links between practice-based pharmacists (clinical pharmacists) and community pharmacy. This has also been highlighted in the community pharmacy 2019 to 2024 contractual framework that encourages the development of point-of-care testing in community pharmacies to support efforts to tackle AMR [26].

4.3. Strengths and Limitations

The acceptance rate by community pharmacies to participate was high, and we collected information from both pharmacists and service users' point of views, facilitating triangulation of data. Although patients from white ethnicity were over-represented in the user responses (53% in this sample versus 28% in the borough according to the 2019 Greater London Authority (GLA) housing-led projection), this sample of service users did have participants representing the diversity of Newham borough. Participants' age was similar to the local population as a whole. Service user questionnaire completion was quite low, as only 13% of 400 questionnaires were returned. However, this return rate is quite usual in any service evaluation by the public and the BAME (Black, Asian, and Minority Ethnic) populations in research are known to be hard to engage [27]. A large part of

the participants had recurrent UTIs (41%), which might be explained by an increased willingness of these patients to answer to questionnaires on UTIs. This population of patients could be more informed than the general population of patients with UTI, however, we still found in this study a large proportion of participants, including patients with recurrent UTIs, who did not report applying the standard self-care advice such as drinking plenty of fluids before seeing a healthcare professional. The small sample size, including 22 pharmacists and 51 patients, as well as the risk of recruitment bias when recruiting pharmacists or service users motivated to participate in a study, are recognised. However, qualitative research aims to attain a range of views rather than necessarily obtaining views representative of the general population. In order to strengthen the results of this study, we have planned with PHE to extend the trial of the leaflets in a rural area and to include interviews with service users. The answers obtained in this study may not easily translate to other countries that do not have a government-sponsored universal healthcare system. Indeed, patients in the United Kingdom have free access to the NHS, which may encourage them to visit their GP instead of going to a community pharmacy. Interviewing GPs may also have provided a more comprehensive scope and additional review regarding the role and value of community pharmacists in AMS for UTIs, but this has already been attained in other qualitative studies [17,22].

4.4. Implications for Practice

Prescription options for pharmacists, levels of funding, and incentives are areas to explore in policy and contractual developments. Developing a referral pathway is a way to strengthen the link between pharmacists and GPs and to give more importance to the place of pharmacists in the community setting. The referral of patients from pharmacy to GPs could be improved through the use of the TARGET UTI leaflets that highlight the management of patients with suspected UTI [28]. These results also provide evidence for the deployment of clinical pharmacists working in GP surgeries as they can represent a key link to community pharmacists [10] as part of the UK NHS long-term plan for better integration of care [29]. Primary care networks (PCNs) link the local community and community-based health and social care providers, including pharmacies, with constituent GP practices at its core [30]. PCNs intend to make greater use of community pharmacists' skills and opportunities to engage service users for integrated out-of-hospital care. Expanding the current test and treat programs for UTIs in community pharmacies by strengthening PGDs could be an interesting approach to increase the role of pharmacists. Indeed, in many countries, and particularly low- and middle-income countries, antibiotics are prescribed by community pharmacies without legal and regulatory framework, which could increase inappropriate prescriptions [31]. In some of these countries where access to a doctor is sometimes difficult, supporting and regulating these prescriptions by pharmacists could be a solution to consider. The results of this study, if confirmed, could inform the writing of guidelines for the management of service users with suspected or confirmed UTI in community pharmacies and inspire future strategies and interventions in the community.

5. Conclusions

We identified opportunities and potential interventions to improve the management of service users with suspected or confirmed UTI in community pharmacies. The current reconfiguration of primary care in England with primary care networks and integrated care systems could provide a real opportunity for this collaborative working with potential learning for international initiatives.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2079-6382/9/9/583/s1>. S1. Pre-intervention interview schedule with pharmacists; S2. Post-intervention interview schedule with pharmacists; S3. Post-intervention electronic questionnaire for pharmacists; S4. Pre-intervention electronic questionnaire for pharmacists; S5. Questionnaire for service users who used the leaflets; S6. Survey with service users—full results.

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Conflicts of Interest: Leah Jones, Rosie Allison, Donna Lecky, and Cliodna McNulty all work on Public Health England's TARGET Antibiotics Toolkit programme of work, developing and evaluating leaflets. All other authors declare no potential conflicts of interest.

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VII. Machine learning for clinical decision support in infectious diseases

1. Summary

Machine learning (ML) allows the analysis of complex and large data sets that are becoming more frequent in healthcare. Unlike expert systems which are based on the programming of a set of rules, ML algorithms are able to define their own rules directly from the data.

We conducted a narrative review in order to analyse the objectives, characteristics, development and measures of performance of ML systems to diagnose infectious diseases, predict severity, and guide antimicrobial therapy. References for this review were identified through searches of MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, ACM Digital Library, arXiV and IEEE Xplore Digital Library for articles by use of a combination of ML keywords. We included articles resulting from these searches and relevant references cited in those articles up to July 2019.

In total, 75 papers with 60 unique ML-CDSS addressing clinical ID decisions were included. Overall, 37 (62%) ML-CDSS focused on bacterial infections, 10 (17%) on viral infections, nine (15%) on tuberculosis and four (7%) on any kind of infection. Among them, 20 (33%) addressed the diagnosis of infection, 18 (30%) the prediction, early detection or stratification of sepsis, 13 (22%) the prediction of treatment response, four (7%) the prediction of antibiotic resistance, three (5%) the choice of antibiotic regimen and two (3%) the choice of a combination antiretroviral therapy. The vast majority of ML-CDSS ($n=58$, 97%) used supervised learning whereas two (3%) used reinforcement learning. Most ML-CDSS found in the literature were developed for secondary and tertiary care ($n=57$, 95%) whereas only three ML-CDSS (5%) targeted primary care. Moreover, only seven ML-CDSS (12%) were adapted to LMICs, six of them concerning HIV or TB. Data analysed in the ML-CDSS were often limited to a small set of variables and did not include many relevant clinical variables. The evaluation of ML-CDSS in clinical ID was still lacking with 57 ML-CDSS (95%) reporting measures of performance such as sensitivity and specificity and only three (5%) evaluated in clinical practice.

The development of ML-CDSS may be more difficult in primary care where available patient data for the clinician is limited and databases are scarce. The same statement can be made for LMICs where data extraction is difficult due to the frequent lack of clinical information system. Table 3 of the review describes some essential criteria for future ML-CDSS adapted for clinicians' use based on our review of the literature. Multiple challenges to the global development of ML-CDSS remain, ranging from the size and quality of databases in medicine to validation and commercialization processes, including risks to data security and confidentiality (Table 4 of the review).

The work of the review was extended to ML in the clinical microbiology laboratory.(141) Using a similar methodology, 103 articles with 97 unique ML systems for clinical microbiology were included in the review. Sixty-four articles were found in MEDLINE/PubMed, 14 in IEEE Xplore Digital Library, 14 in free repository of electronic preprints such as arXiv ($n = 7$) or bioRxiv ($n = 7$), eight in Google Scholar and three in ACM Digital Library. Overall, 82 (85%) ML systems targeted bacterial infections, 11 (11%) parasitic infections, nine (9%) viral infections and three (3%) fungal infections (some ML systems targeted more than one type of micro-organisms). More precisely, 40 (41%) ML systems focused on micro-organisms detection, identification and quantification, 36 (37%) evaluated antimicrobial susceptibility, 21 (22%) targeted diagnosis, disease classification and prediction of clinical outcomes. To achieve these aims, the ML systems used very diverse sources of data: 21 (22%) used WGS of micro-organisms, 19 (20%) microbiota data obtained by shotgun metagenomic sequencing, 19 (20%) analysed microscopic images, 17 (18%) spectroscopy data, eight (8%) targeted gene sequencing, six (6%) volatile organic compounds (the components of odour), four (4%) bacterial colonies photographs, four (4%) transcriptome data, three (3%) protein structure and three (3%) clinical data. The vast majority of ML systems used supervised learning ($n=96$, 99%) whereas 6 (6%) used unsupervised learning, all but one in association with supervised learning. No ML system used reinforcement learning. Overall, 34 different ML techniques were used with 40 (41%) systems using more than one ML technique (median 3, IQR 2-4). The most frequent ML techniques were Artificial Neural Network ($n=46$, 47%) including 15 Convolutional Neural Networks, Support Vector Machine ($n=34$, 35%), Random Forest ($n=28$, 29%), and Logistic Regression ($n=11$, 11%). In the same way as for infectious diseases, most articles were published using HICs data ($n=71$, 73%) but a significant number of ML systems were developed with LMICs data ($n=36$, 37%). Only one ML system was reported to be used in clinical practice in the UK.(142) This system aimed to screen urine samples in order to decide

which ones should be discarded because of a low probability of positivity. The authors analysed 212,554 urine reports including clinical data and described a potential relative workload reduction of 41%. However, the authors did not give any detail on the implementation of the system and its actual impact. The 96 other ML systems only reported performance measures such as sensitivity and specificity.

In infectious diseases as well as in clinical microbiology, the evaluation of ML systems was still incomplete from the clinical perspective with CDSS that always presented performance data but rarely use the system in clinical practice. Future ML-CDSS in ID should be developed in diverse health settings, including primary care and LMICs that are currently underrepresented, and should be embedded in a structured process of integration into clinical settings. Future studies involving ML-CDSS should aim to report clinical outcomes following integration and implementation in real-world settings and sustainable use in routine clinical care.

2. Article

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Narrative review

Machine learning for clinical decision support in infectious diseases: a narrative review of current applications

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ABSTRACT

Background: Machine learning (ML) is a growing field in medicine. This narrative review describes the current body of literature on ML for clinical decision support in infectious diseases (ID).

Objectives: We aim to inform clinicians about the use of ML for diagnosis, classification, outcome prediction and antimicrobial management in ID.

Sources: References for this review were identified through searches of MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, ACM Digital Library, arXiv and IEEE Xplore Digital Library up to July 2019.

Content: We found 60 unique ML-clinical decision support systems (ML-CDSS) aiming to assist ID clinicians. Overall, 37 (62%) focused on bacterial infections, 10 (17%) on viral infections, nine (15%) on tuberculosis and four (7%) on any kind of infection. Among them, 20 (33%) addressed the diagnosis of infection, 18 (30%) the prediction, early detection or stratification of sepsis, 13 (22%) the prediction of treatment response, four (7%) the prediction of antibiotic resistance, three (5%) the choice of antibiotic regimen and two (3%) the choice of a combination antiretroviral therapy. The ML-CDSS were developed for intensive care units ($n = 24$, 40%), ID consultation ($n = 15$, 25%), medical or surgical wards ($n = 13$, 20%), emergency department ($n = 4$, 7%), primary care ($n = 3$, 5%) and antimicrobial stewardship ($n = 1$, 2%). Fifty-three ML-CDSS (88%) were developed using data from high-income countries and seven (12%) with data from low- and middle-income countries (LMIC). The evaluation of ML-CDSS was limited to measures of performance (e.g. sensitivity, specificity) for 57 ML-CDSS (95%) and included data in clinical practice for three (5%).

Implications: Considering comprehensive patient data from socioeconomically diverse healthcare settings, including primary care and LMICs, may improve the ability of ML-CDSS to suggest decisions adapted to various clinical contexts. Current gaps identified in the evaluation of ML-CDSS must also be addressed in order to know the potential impact of such tools for clinicians and patients. **N. Peiffer-Smadja, Clin Microbiol Infect 2020;26:584**

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Introduction

Artificial intelligence (AI), initiated in 1956, is often defined as the study of 'intelligent agents', devices that perceive their

environment and take actions that maximize the likelihood of successfully achieving their goals [1]. AI in healthcare began with the development of expert systems, based on rules captured from interviews with medical experts, then translated and programmed [2]. With about 450 rules, MYCIN, the first expert system in medicine, was developed in 1976 and aimed to suggest antibiotic regimens for severe bacterial infections [3]. However, MYCIN was never actually used in practice because of the lack of system

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integration into clinical work. Another major limitation of expert systems is the large volume of rules needed to capture experts' knowledge in difficult clinical decisions.

Machine learning (ML) was developed to overcome the constraints of expert systems [2]. In ML, engineers programme algorithms able to define their own rules from data. Thus, human hand-coded rules are replaced by the artificial finding of rules from data. This allows ML systems to learn from data and interpret unknown situations. Among the panel of ML techniques developed, deep learning based on artificial neural networks is the most famous [4]. The performance and ability of the machine to learn is driven by the volume and quality of data provided, that is why ML systems are sometimes called data-intensive systems (Fig. 1).

The availability of healthcare data dramatically increased with electronic health record systems and the rise of connected devices [5]. The optimal analysis and interpretation of this important volume of data, called 'big data', needs the computing power of modern machines. In this context, ML tools integrating and making sense of huge amounts of complex data are becoming popular. Clinical decision support systems (CDSS) can be defined as software in which the characteristics of an individual patient are used to present patient-specific assessments or recommendations to the clinician towards a decision [6]. Most current CDSS or computer-aided diagnosis or therapy are expert systems [7], but Machine Learning-Clinical Decision Support Systems (ML-CDSS) are drawing increased interest (Fig. 2) [8–10].

ML systems have been developed in many fields of medicine, including radiology, with the interpretation of images from chest X-ray or magnetic resonance imaging for diagnostic purposes [11–15]. The first FDA approval for an autonomous AI system took place in 2018 with IDX, a ML system used to detect diabetic retinopathy in retinal fundus photographs [16]. In infectious diseases (IDs), most ML work focuses on research, drug development or clinical microbiology. Systems have been developed to analyse bacterial genome and improve the prediction of resistance [17,18], HIV genotype and predict susceptibility to antiretroviral drugs [19], patterns of epidemics for surveillance purpose [20,21] or to discover new antibacterial drugs or vaccines [22–24] (Table 1).

This article focuses on ML adapted to clinicians' decision (ML-CDSS) in ID. More precisely, we describe the objectives, characteristics, development and assessment of ML systems that may directly help clinicians with their work to diagnose infectious diseases, predict severity, decide whether they should use an antimicrobial and which antimicrobial to choose or what dosage.

Material and methods

Search strategy

References for this review were identified through searches of MEDLINE/PubMed, EMBASE, Google Scholar, biorXiv, ACM Digital Library, arXiv and IEEE Xplore Digital Library for articles by use of a combination of ML keywords ('deep learning', 'artificial intelligence', 'artificial learning', 'machine learning', 'machine intelligence', 'neural networks', 'probabilistic networks', 'knowledge representation', 'statistical learning', 'bayesian learning'), decision-making keywords ('medical decision', 'decision tool', 'support tool', 'clinical decision', 'physician decision', 'decision algorithm', 'CDSS', 'clinical management', 'decision making'), antimicrobial keywords ('antimicrobial', 'antibiotic', 'anti-infective', 'antifungal', 'antiparasitic', 'antiviral') or sepsis keywords ('sepsis', 'septic shock'). We included articles resulting from these searches and relevant references cited in those articles up to July 2019.

Study selection

Prospective and retrospective articles in English that reported original research on ML-CDSS for ID were included. We included development reports, implementation studies, clinical trials or qualitative studies in primary, secondary, tertiary care including intensive care and paediatrics. We excluded studies that describe expert system CDSS, as defined by the use of manually programmed rules, studies with ML systems that use data not currently available in routine clinical care (e.g. bacterial genome) or with outcomes irrelevant to clinicians' use for usual care (e.g. development of a new biomarker).

Definitions of learning methods

ML methods can be divided into supervised learning, unsupervised learning and reinforcement learning [2]. Supervised learning refers to algorithms using labelled data as a training dataset. Labelled data are data in which the outcome of interest is defined; for example, to train an algorithm for sepsis prediction, we use a dataset in which patients are already defined as having sepsis or not. The algorithm will then choose the best model to predict the outcome of interest. In unsupervised learning, data are used without a predefined outcome of interest. Algorithms are left to their own to find patterns and to extract hidden structure from data without any expert labelling. Unsupervised learning is mainly used in medicine to do clustering, aiming to discover inherent grouping in the data, such as similar groups of patients based on clinical data [25]. Reinforcement learning involves algorithms discovering actions that yield the greatest rewards through trial and error. In this category, the algorithm is programmed to consider survival or a reduced hospital length of stay as a reward. A training dataset is used by the algorithm to conduct multiple tests in order to develop the model that obtains the highest reward [2,26].

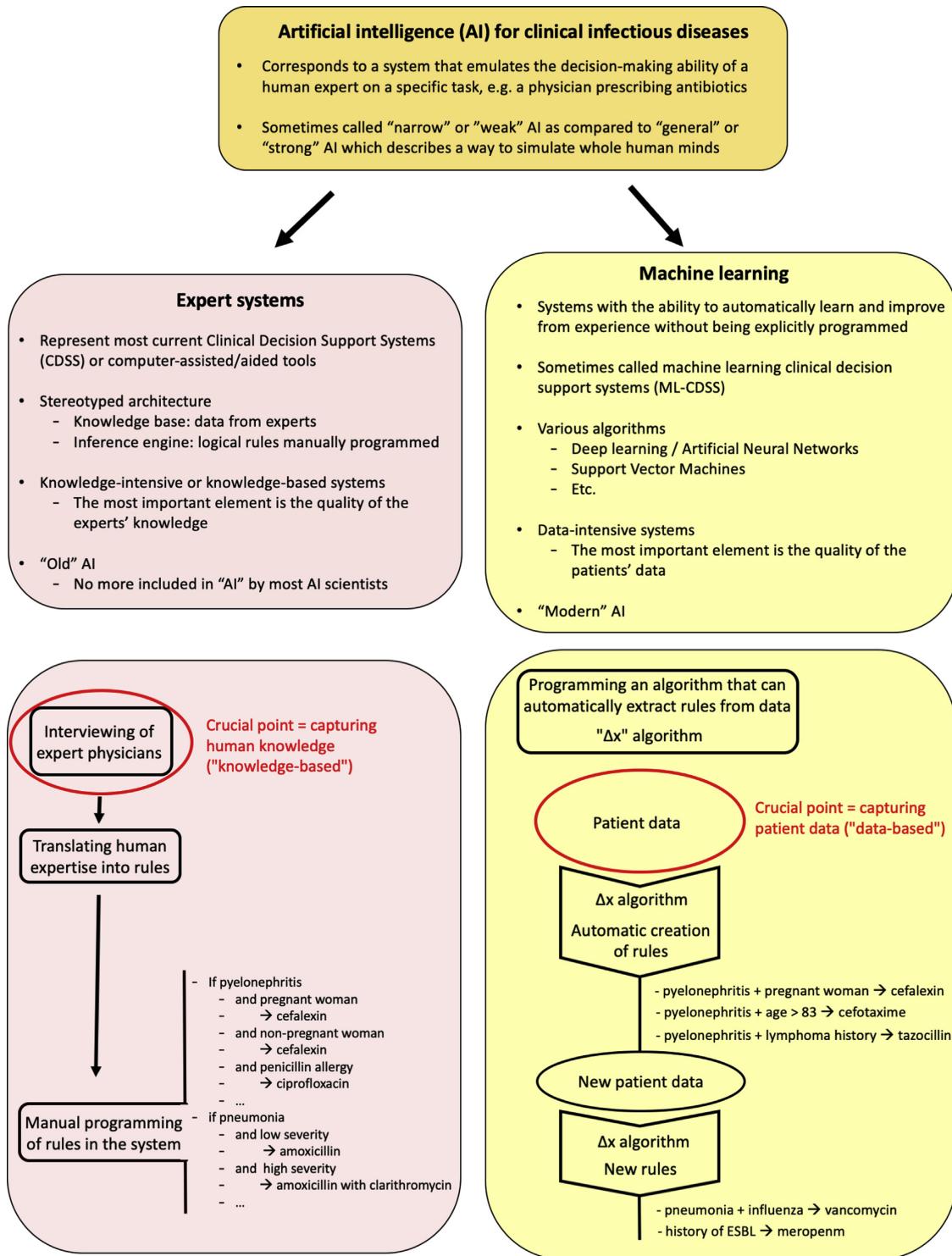
Analysis of data in the selected articles

In each article, we extracted the variables that were analysed by the ML-CDSS. We split these variables into structured and unstructured variables. Structured variables are variables in which the possible values are predefined, e.g. for wound aspect, 0 = no necrosis, 1 = non-viable tissue, etc. Unstructured variables refer to free text such as a description of the wound by a clinician. We further split structured variables into demographic data (e.g. age, ethnicity), medical or surgical history (e.g. comorbidities, date of admission), vitals (e.g. temperature), symptoms or physical examination findings (e.g. cough, lung auscultation), laboratory workup (e.g. creatinine), microbiology workup (e.g. antibiotic susceptibility testing), therapeutic history (e.g. type of surgery, administered drugs) or other workup (biopsy results, medical imaging). Medical imaging can be considered as a structured variable, for example 'presence of lung infiltrates' can be mapped a priori to a uniquely defined input value, or as an unstructured variable when the image itself is fed as input to the CDSS.

Results

General characteristics of ML-CDSS

Among the 126 abstracts identified and assessed for eligibility, 14 were excluded because the variables were not available in routine clinical practice (e.g. bacterial genome), 29 because the CDSS was an expert system and eight because the outcome of the CDSS was not clinical (e.g. development of a novel biomarker).

**Fig. 1.** Artificial intelligence for clinical infectious diseases.

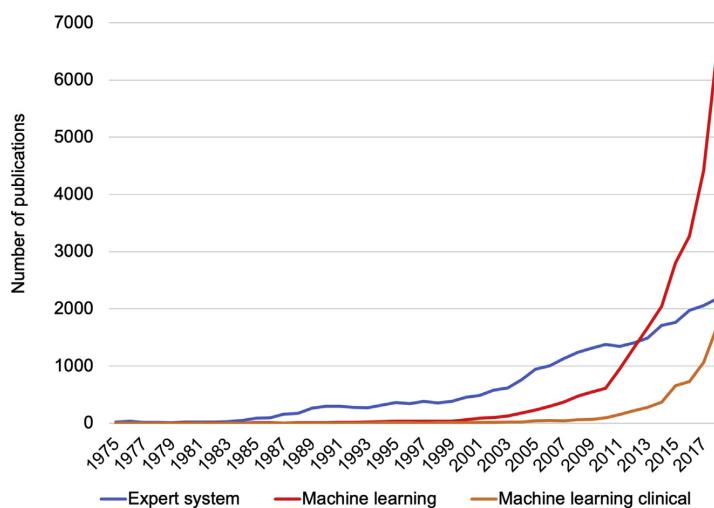


Fig. 2. Trends in the number of publications using selected search terms in PubMed in August 2019.

In total, 75 papers with 60 unique ML-CDSS addressing clinical ID decisions were included. Thirty-one articles were found in MEDLINE/PubMed, 12 in free repository of electronic preprints such as arXiv ($n = 8$) or bioRxiv ($n = 4$), ten in Google Scholar and ten in IEEE Xplore Digital Library. The main characteristics of the ML-CDSS are summarized in Table 2 and detailed in the Supplementary material.

Overall, 37 (62%) ML-CDSS focused on bacterial infections, 10 (17%) on viral infections, nine (15%) on tuberculosis and four (7%) on any kind of infection. Among them, 20 (33%) addressed the diagnosis of infection, 18 (30%) the prediction, early detection or stratification of sepsis, 13 (22%) the prediction of treatment response, four (7%) the prediction of antibiotic resistance, three (5%) the choice of antibiotic regimen and two (3%) the choice of a combination antiretroviral therapy (cART). Most of the ML-CDSS were developed with data from adult patients ($n = 54$, 90%) but some targeted paediatric patients ($n = 3$, 5%) [27–29] or neonates ($n = 3$, 5%) [30–32].

The vast majority of ML-CDSS ($n = 58$, 97%) used supervised learning whereas two (3%) used reinforcement learning [33,34].

Prediction, early detection or stratification of sepsis

Eighteen ML-CDSS (30%) addressed the prediction, early detection or stratification of sepsis in the Intensive Care Unit (ICU). Among these ML-CDSS, 16 exclusively analysed structured patient variables: vitals ($n = 15$), laboratory data ($n = 12$), basic demographic information ($n = 7$), medical history limited to main comorbidities and date of admission ($n = 7$), therapeutic data ($n = 5$) and electrocardiogram waveform ($n = 1$). Two ML-CDSS added unstructured clinical data to their model, one specifically looked for antibiotic prescription in nursing notes to predict sepsis [35], but the other did not give details [36]. No CDSS for sepsis prediction used symptoms, physical examination findings nor microbiology data.

All the 18 ML-CDSS were developed with data from high-income countries (HICs), with six ML-CDSS using the MIMIC (Multiparameter Intelligent Monitoring in Intensive Care) dataset. This dataset contains openly available data from ~50 000 critical care patients admitted to a Medical Center in Boston [37].

Seventeen ML-CDSS were evaluated with measures of performance such as sensitivity or specificity and one ML-CDSS was evaluated in the clinical setting. This ML-CDSS was developed by a company that published a set of papers describing its development, performance and impact in quasi-experimental studies [38]. They reported a relative reduction of in-hospital mortality between 30% and 60% after implementation of their ML-CDSS in ICUs [39–41] but do not use statistical methods adapted to quasi-experimental designs [42]. Indeed, they directly compare in-hospital mortality before and after the use of the ML-CDSS, a measure that is susceptible to biases such as the history bias, i.e. the possibility that the change in the outcome may be linked to other changes in the environment rather than to the addition of the ML-CDSS [43]. They also published a randomized clinical trial in which 67 patients were randomized to a group monitored by a machine learning algorithm and 75 patients to a control group [44]. The trial reported a relative reduction of 58% of mortality in the group monitored by the machine learning algorithm in which patients had blood cultures drawn and antibiotics administered approximately 2.8 hours before the control group.

Diagnosis of infection

Twenty ML-CDSS (33%) focused on the diagnosis of infection, to help clinicians decide if a patient has an infection, which infection (e.g. viral or bacterial) or an alternative non-infectious diagnosis. More precisely, six ML-CDSS address the diagnosis of tuberculosis (TB) in outpatient settings [45–50], five the diagnosis of bacterial infection in hospitalized patients [27,51–54], four the diagnosis of surgical site infection (SSI) [30,55–57], three the diagnosis of infection in emergency department [58–60] and two the distinction between bacterial and viral meningitis [61,62]. Among the five ML-CDSS to diagnose bacterial infection in hospitalized patients, two ML-CDSS included any kind of infection [27,51], two focused on the prediction of positive blood cultures [53,54] and one on MRSA infection [52]. The ML-CDSS for patients hospitalized in surgical wards aimed to diagnose SSIs following open abdominal surgery [55,57] surgery for head or neck cancer [56] or following any intervention on neonates [30].

Among the 20 ML-CDSS, 18 exclusively analysed structured patient variables: demographics ($n = 15$), medical history

Table 1

List of reviews with a focus on machine learning in the field of infectious diseases

Topic	Title	Year of publication	Review type	Detailed outcome	Settings	Including CDSS
Bacterial resistance	Genome-based prediction of bacterial antibiotic resistance [18]	2018	Narrative	Analysis of bacterial genome to predict resistance	Clinical microbiology lab	No
	Machine learning: novel bioinformatics approaches for combating antimicrobial resistance [17]	2017	Narrative	Analysis of bacterial genome to predict resistance	Clinical microbiology lab	No
Sepsis	Emerging technologies for molecular diagnosis of sepsis [99]	2018	Narrative	Microbiological diagnosis of sepsis Prediction of sepsis	Clinical microbiology lab ICU	No
HIV	A survey of machine learning applications in HIV clinical research and care [100]	2017	Systematic	HIV/AIDS clinical research and medical care studies that utilize machine learning methodology	Multiple settings	Yes
	Computer-aided optimization of combined anti-retroviral therapy for HIV: new drugs, new drug targets and drug resistance [101]	2016	Narrative	Analysis of HIV genotype to predict drug susceptibility in vitro or response to combination antiretroviral therapy in vivo	Virology lab	Yes
Infection control	Using online social networks to track a pandemic: A systematic review [102]	2016	Systematic	Analysis of online social network data to track pandemics	Health authorities	No
	Automated surveillance of healthcare-associated infections: state of the art [21]	2017	Narrative	Surveillance of healthcare-associated infections	Infection control unit	No
	Introduction to machine learning in digital healthcare epidemiology [20]	2018	Narrative	Prediction, detection of trends and patterns for surveillance purposes	Infection control unit	No
Molecular biology	Computational approaches for prediction of pathogen-host protein-protein interactions [103]	2015	Narrative	Prediction of pathogen-host protein-protein interaction	Research lab	No
	Progress in computational studies of host-pathogen interactions [104]	2013	Narrative	Prediction of pathogen-host protein-protein interaction	Research lab	No
Vaccine development	Identification of legionella effectors using bioinformatic approaches [105]	2012	Narrative	Identification of <i>L. pneumophila</i> effectors	Research lab	No
	Comparative pathogenesis and systems biology for biodefense virus vaccine development [24]	2010	Narrative	Analysis of Virus-Host Interactions	Research lab/Research and development	No
	Systems serology for evaluation of HIV vaccine trials [106]	2017	Narrative	Defining humoral signatures in response to vaccines	Research lab/Research and development	No
Drug discovery	Machine-learning techniques applied to antibacterial drug discovery [23]	2014	Narrative	Antibiotic drug discovery	Research lab/Research and development	No
Medical imaging	Computer-assisted detection of infectious lung diseases: a review [107]	2013	Narrative	Analysis of medical imaging of respiratory tract infections	Radiology department	No
Microscopy	Microscopy in infectious disease research-imaging across scales [108]	2018	Narrative	Analysis of microscopic images in ID research	Research lab	No

(n = 14), laboratory results (n = 13), vitals (n = 9), symptoms and physical examination findings (n = 8), therapeutic history (n = 7), chest X-ray for TB diagnosis (n = 2) and microbiology data (n = 2). Two ML-CDSS added free clinical text; nursing notes, clinical narrative or chief complaint [51,59]. Seventeen ML-CDSS were developed with data from HICs and three with data from low- and middle-income countries (LMICs), addressing the screening of TB in South Africa [48] or the diagnosis of TB in Turkey [49] or Iran [63].

Nineteen ML-CDSS were evaluated by measures of sensitivity, specificity and receiver ROC curves. One study described a ML-CDSS trained to diagnose bacterial infection using six routinely available blood parameters with data from 160 203 individuals and its use in a prospective observational cohort. Among 104 patients included, the ML-CDSS predicted a bacterial infection in three individuals who were not identified by clinicians as having an infection on admission but were diagnosed later with a bacterial infection [58]. No study assessed the clinical or microbiological impact of the use of ML-CDSS in clinical settings.

Determinants of treatment outcomes

Ten ML-CDSS (17%) addressed the prediction of treatment success for outpatients. Among them, five ML-CDSS predicted the virological response to HIV therapy [64–68] and three to HCV

therapy [69–71]. They all analysed therapeutic history but only four used viral genotype or medical history [65–67,71]. Therapeutic history was limited to previous HIV or HCV therapies but not to other drugs that the patient might have been taking. Two ML-CDSS predicted treatment outcome in TB using demographics data (e.g. education level, homelessness), TB history including constitutional symptoms, TB treatment and structured data from the chest radiograph (e.g. size of cavity) [72,73].

Three ML-CDSS (5%) addressed the prediction of *C. difficile* colitis complications [74] or recurrence [75,76] in hospital settings. We found four ML-CDSS (7%) for the prediction of drug resistance: one predicted the risk of developing multidrug-resistant TB in Chinese patients with TB [77] one combined demographic data and medical history for personalized prediction of baseline antibiotic resistance in urinary tract infection [78] one analysed demographic data, living conditions and treatment history of patients with positive blood cultures to predict baseline susceptibility to ampicillin, ceftriaxone and gentamicin [28] and one used ML to measure the impact of antibiotic exposure on the acquisition of colonization with extended-spectrum β-lactamase-producing Gram-negative bacteria [79].

Thirteen ML-CDSS in this category were developed with patient data from HICs and two with patient data from LMICs to predict TB outcomes, one in Pakistan [72] and the other in Eastern Europe [73]

Table 2
Summary of machine learning clinical decision support systems

ML-CDSS characteristics	n = 60 (%)
Medical settings ^a	
Intensive Care Unit	24 (40)
Infectious diseases consultation	15 (25)
Medical ward	9 (15)
Surgical ward	5 (8)
Emergency department	4 (7)
Primary care	3 (5)
Antimicrobial stewardship team	1 (2)
Geographical settings ^a	
High-income countries	54 (90)
Low- and middle-income countries	7 (12)
Population	
Adults	53 (88)
Neonates	3 (5)
Paediatric patients	3 (5)
Retirement-home	1 (2)
Types of decision support	
Diagnostic	
Diagnosis of infection	20 (33)
Prediction of sepsis	18 (30)
Prediction of antibiotic resistance	4 (7)
Therapeutic	
Prediction of treatment response	13 (22)
Antibiotic selection	3 (5)
HIV therapy selection	2 (3)
Type of infection	
Bacterial infection	37 (62)
Viral infection	10 (17)
Mycobacterial infection	9 (15)
Any kind of infection	4 (7)
Types of learning	
Supervised learning	58 (97)
Reinforcement learning	2 (3)
Data	
Clinical data (e.g. demographics, vitals)	52 (87)
Laboratory	38 (63)
Therapy	28 (47)
Microbiology	15 (25)
Other workup (e.g. ECG, imaging)	6 (10)
Unstructured clinical data (free text)	5 (8)
Evaluation ^b	
Performance	57 (95)
Use	3 (5)
Adoption	0

ML, machine learning; CDSS, clinical decision support systems; HIV, human immunodeficiency virus.

^a One article included patients in medical wards, surgical wards and intensive care units in high and middle-income countries.

^b We separated studies that describe the performance (e.g. receiver operating characteristic curves) of the ML-CDSS, studies that describe the use of the CDSS in real-life settings and studies that describe the adoption of the CDSS in routine clinical practice.

In addition, one ML-CDSS used data both from HICs and middle-income countries [79]. Another ML-CDSS was developed in HICs and then specifically adapted to the specificities of human immunodeficiency virus (HIV) care in LMICs such as limited access to genotype data, infrequent visits to clinics and restricted list of available drugs [67]. It used the HIV Drug Resistance Database that includes large datasets from patients around the world including sub-Saharan countries.

The 17 ML-CDSS predicting treatment outcomes or antibiotic susceptibilities were evaluated by measures of sensitivity, specificity and receiver operating characteristic (ROC) curves.

Treatment selection

Five ML-CDSS (8%) addressed the choice of antimicrobials: three ML-CDSS aimed to find the optimal antibiotic regimen [33,80,81]

and two the optimal cART for HIV [34,82]. All the CDSS focused on the choice of an agent but did not give individual advice on the dose or duration.

The two ML-CDSS to guide cART focused on outpatient settings: one analysed treatment history and treatment objectives but did not consider clinical or biological data [82], whereas the other used demographics, medical history, CD4+ cell count, viral load, genotypic data and treatment history [34]. Among the three ML-CDSS for antibiotic management, one was adapted to ICUs [33], another one to primary care [81] and the third one targeted antimicrobial stewardship teams [80]. Their use of patient data was heterogeneous; only one ML-CDSS took into account the identification of the pathogen in blood culture results but not the antimicrobial susceptibility testing [33], medical history was not used in two ML-CDSS [33,80] and limited to breastfeeding, pregnancy, allergy and kidney failure in the third [81]. They did not use the therapeutic history of patients, neither data from the physical examination nor local antibiotic resistance rates and were not adapted for a dynamic use over time.

All of these ML-CDSS concerned HICs, using data from North American or European patients and only one ML-CDSS was evaluated in a clinical setting. It was a ML-CDSS focusing on inappropriate prescriptions for review by antimicrobial stewardship pharmacists. The addition of a ML module to an expert system was shown to identify inappropriate prescriptions of piperacillintazobactam that were missed by the expert system [80]. However, this study does not report the clinical or microbiological outcomes of this intervention.

Discussion

Healthcare settings

Most ML-CDSS found in the literature were developed for secondary and tertiary care ($n = 57$, 95%) whereas only three ML-CDSS (5%) targeted primary care [48,78,81]. Four ML-CDSS were specifically tailored for emergency care [46,58–60], compared with more than 20 ML-CDSS for ICUs. Moreover, only seven ML-CDSS (12%) were adapted to LMICs [48,49,63,67,72,73,79], six of them concerning HIV or TB.

ML techniques usually need a large amount of data (e.g. more than 128 000 retinal images in a recent ophthalmologic ML system) [83]. Thus, it is no surprise that most ML-CDSS in ID currently should focus on domains generating high-quality databases including ICU and HIV patients from HICs. The MIMIC dataset was a recurrent data source for ML systems predicting sepsis [37]. In the same way, ML-CDSS targeting HIV therapy selection or the prediction of virological response were also based on large open-access databases [66]. The development of ML-CDSS is more difficult in primary care where available patient data for the clinician is limited and databases are scarce. The same statement can be made for LMICs where data extraction is difficult due to the frequent lack of clinical information system. The availability of data is also correlated with healthcare access: vulnerable populations tend to have a lower access to the healthcare system with a more fragmented care. This could undermine the ability of ML-CDSS to make adequate predictions for patients from vulnerable populations and lead to a potential increase in healthcare inequalities [84,85].

The unequal spreading of ML-CDSS across healthcare settings reflects the unequal availability of high-quality and large clinical databases. This is why a special effort should be made to target the development of such databases in underfunded settings such as primary care or LMICs and to include data from diverse settings and populations in training and validation datasets. Global open access

to these databases should be a requirement for future funding in order to increase the opportunities for ML-CDSS development everywhere in the world. Moreover, we have not found any study focusing on fungal or parasitic diseases in this review. These areas may represent interesting opportunities for developing CDSS using machine learning for diagnosis, prediction of resistance or choice of antifungal or antiparasitic therapy. The analysis of the outputs of ML-CDSS at the population level should also be encouraged as it may be useful for public health and research institutes to regularly monitor trends in diagnosis and prescribing and correct potential biases.

If these constraints and potential issues are considered, ML-CDSS appear as credible options for supporting infection management in countries where ID specialists and antimicrobial teams may not be readily available [86].

Choice of patient variables

In the present review, many ML-CDSS did not include some clinically relevant data. Medical history analysed in ML-CDSS was often limited to the presence of two or three predefined diseases (kidney failure, cirrhosis, etc.) [56,87]. No ML-CDSS for the diagnosis of infection considered patients exposed to infected individuals or high-risk environment (e.g. travel history). We did not find any ML-CDSS predicting sepsis and taking into account the results from blood cultures or from any other microbiology sample. Among the 60 ML-CDSS, chest X-Ray was the only medical imaging analysed [46,48,72]. No ML-CDSS to predict antibiotic resistance or to select an antibiotic regimen included data from local antibiotic resistance rates. Paradoxically, ML-CDSS often use less data than a human clinician would do. In some articles, the authors analysed the performance of ML-CDSS when using a reduced set of variables and they found that the sensitivity and specificity of ML-CDSS were systematically better when they used a larger panel of variables [60,87,48], especially when adding unstructured data [59,36]. Ensuring integration of physical examination or detailed medical history in these systems is of critical importance. Progress in Natural Language Processing (NLP, i.e. the ability of computers to analyse human language) may help the integration of free medical

text in future decision systems [88]. Nonetheless, the development of ML-CDSS using minimal variables may be of interest when data are not available across some areas or in resource limited settings. A particular attention should be paid to which variables are used by the ML-CDSS to predict their outcome: e.g. we found a ML-CDSS that used the prescription of antibiotics in ICU to predict sepsis [35], which could provide good performance but seems clinically irrelevant.

ML-CDSS are constrained by the quality and availability of the clinical data used for their development and validation. To ensure that future ML tools are useful for clinicians, efforts should be made to provide comprehensive databases that include relevant clinical data.

Evaluation and use of ML-CDSS

The evaluation of ML-CDSS in clinical ID is still lacking with 57 ML-CDSS (95%) reporting measures of performance such as sensitivity and specificity and only three (5%) evaluated in clinical practice. The validation of the performance in the original database should preferably be done in a prospective database collected for validation purpose in another location. Then, pilot studies testing the usability and usefulness of ML-CDSS in clinical settings should be conducted, followed by clinical trials, preferably randomized, evaluating patients' outcomes, process improvement or cost-effectiveness.

Special attention should be paid to the integration and implementation of systems into clinical practice, and their adoption and utilization by clinicians [89]. Co-design including clinicians, pharmacists engineers, data managers and service users may be key for success and may allow to study the interaction between CDSS and healthcare professionals [90]. The place of ML-CDSS in the workflow of clinicians has to be considered as different clinical tasks are likely to require different degrees of human involvement (Fig. 3) [10]. Data should be easily entered into the CDSS, ideally by automatic extraction from the EHR, and daily refreshed with new patient information. The CDSS need to fit into the complex medical decision-making pathway and support clinicians at different stages sometimes by presenting different

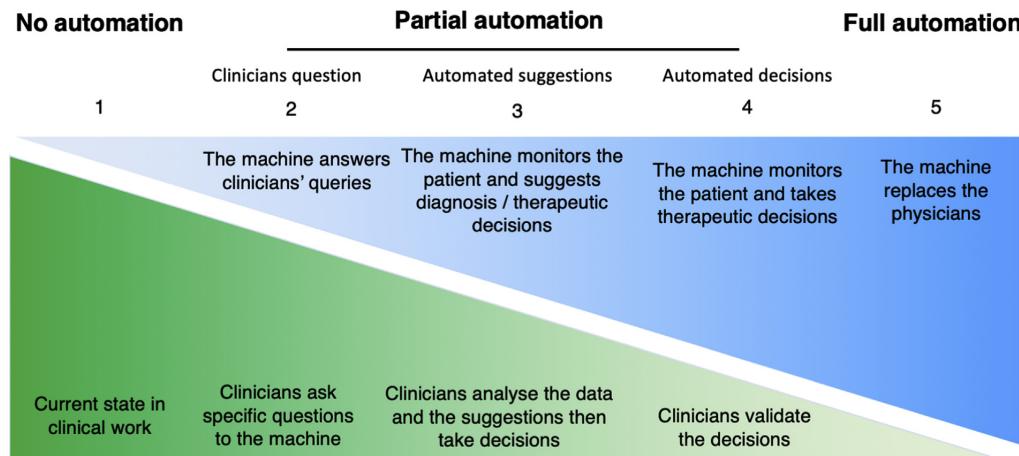


Fig. 3. Interaction between clinicians and machine-learning systems according to automation level.

aspects of data [91]. According to the numerous limits that we found concerning ML-CDSS in ID, the replacement of physicians by ML tools seems highly unlikely. AI is best suited to augmenting human intelligence, bringing big-data into focus to support human decision-making and developers should aim to emphasize the synergy and interaction between physicians and algorithms instead of reporting less interesting clinical-versus-algorithm comparison [8,92,93]. Clinicians' expectations are that ML-CDSS will relieve them of repetitive tasks that need to be performed without errors and allow them to focus on tasks that require human skills: analysis of the broader context, abstraction capability but also exercising empathy and building relationships. However, we have not found any in-depth describing of the interaction of physicians with ML-CDSS in real-world settings. Implementation research may help to take into account the global context in which ML-CDSS are used [7].

Unexpected consequences of the use of ML also have to be included in the research agenda. Consequences commonly cited are the risk of 'deskilling' clinicians who use ML-CDSS routinely, the risk of a blind obedience to the CDSS or the risk of decreased interaction between the clinician and the patient. Studies have shown that the development of the electronic health record (EHR) shifted clinicians' time from the patient to the computer and ML systems may represent an additional risk to do so [94,95]. By definition, unexpected consequences cannot be fully anticipated and research on ML-CDSS in real-world settings should aim to collect information on consequences both at the clinician and patient -levels.

Perspectives

In Table 3 we summarize some essential criteria for future ML-CDSS adapted for clinicians' use. Clinicians must know when and why errors by ML in clinical-decision predictions might occur and when they cannot rely on an automated system whose intrinsic mechanisms they do not understand (the so-called 'black box') [8]. Visualization tools highlighting the variable or combination of variables that determined the output ought to be available for the prescriber and are an important parameter in future ML-CDSS [28,96]. ML-CDSS should also detail the trade-off that they apply between risk-taking and caution and show the confidence interval of their decisions and suggestions [9]. The impact of under- and overdiagnosis or treatment is not the same when considering upper respiratory tract infection or sepsis therapy. Besides system improvement, we need to encourage and fund the education of clinicians about AI and ML in order to develop an AI-literate workforce in healthcare worldwide.

In addition, global challenges for the development of artificial intelligence and ML for clinical decisions are to be considered. Table 4 describes the main challenges for ML-CDSS that have been identified in the literature. For example, controls have to ensure that ML-CDSS are registered on public databases, thoroughly evaluated independently of economic interest and validated using standardized frameworks. The privacy protection of data [97], cost-effectiveness research at the organizational and global level [89,98], and ethics discussion about accountability and liability when using ML-CDSS are other potential challenges to deal with.

Table 3
Necessary requirements for clinical decision support systems using machine learning

Target	Type of decision	A clinically meaningful decision should be targeted, for example the diagnosis of a bacterial infection requiring antibiotics or the choice of an antibiotic regimen
	Justification of ML	The use of machine learning instead of expert systems should be justified, for example by the analysis of big data that could not be captured by expert systems.
	settings	ML-CDSS should not only be developed for secondary or tertiary care but should also target such primary care prescribers as GPs or nurse prescribers
	Patients	The ML-CDSS should offer a good performance in diverse settings including low- and middle-income countries
	Users	The ML-CDSS should be performant for different populations of patients like patients with diabetes, chronic kidney disease, cirrhosis, etc.
	Users	If some comorbidities prevent the use of the ML-CDSS, it should be clearly stated and explained Different practitioners may not need the same tools even for the same decision. For example, surgeons do not have the same need for ML-CDSS addressing antimicrobial management as antimicrobial stewardship specialists or nurse prescribers in primary care
Decision	Comprehensiveness	ML-CDSS should be able to analyse data from different sources such as structured clinical data, vitals, laboratory data, therapeutic history but also unstructured clinical data (e.g. free medical text, medical imaging)
	Availability	ML-CDSS should not require data that are not available for most patients
	Extraction	ML-CDSS should be able to automatically extract data from the electronic health record (EHR)
	Uncertainty	A way to present uncertainty should be found by the developers: e.g. it could give a confidence interval for the diagnosis of bacterial infection or a number of suggestions for antimicrobial therapy with associated probabilities of success according to its calculation
	Clarity	ML-CDSS should display what parameters were the most important for the suggested diagnosis or therapeutic decision
	Flexibility	Clinicians should be able to take out a specific clinical or laboratory element that they do not think reliable and thus have access to modified suggestions. They should also be able to add or emphasize elements that they find particularly important or reliable.
Interface	Memory	Clinicians need ML-CDSS that can keep track of patients and for whom the data can be updated to modify the suggestions of the system
	Limits	ML-CDSS should display very clearly what parameters have been used or not, e.g. medical history, medical imaging, etc. and other potential limits of its decision
	Integration	The ML-CDSS should ideally be integrated in the EHR used by the prescriber. A special attention should be paid to the interoperability of ML-CDSS across different EHR systems
	Speed	The ML-CDSS should be quick to use, should automatically extract pertinent data from the EHR and give its output immediately
	User-friendly	Clinicians should be able to use ML-CDSS without specific training
	Standardization	As multiple ML-CDSS may be available for different diseases and conditions, interfaces for ML-CDSS should be standardized to a common format to increase usability. We should avoid having a software for every decision, e.g. diagnosis, antimicrobial prescribing, dosing, prevention of venous thromboembolic disease, etc.

ML-CDSS, machine learning clinical decision support systems.

Table 4
Global challenges for machine learning clinical decision support systems

Challenges	Description	Potential solutions
Data quantity	There is a need for a huge quantity of clinical data to develop a machine learning (ML) system, especially for unsupervised ML	Shareable/open-source database such as MIMIC-III, a freely accessible critical care database that has helped to develop many ML-CDSS for sepsis in intensive care units
Data quality	ML-clinical decision support systems (CDSS) developers need to have access to high-quality data for training and validation dataset, especially for supervised ML	Electronic health record data standardization Pre-processing of data should be detailed in the description of ML-CDSS
Comprehensiveness	ML-CDSS must be able to analyse data from different sources such as structured clinical data, vitals, laboratory data but also unstructured free text (e.g. physical examination, medical history, etc.).	Developers should try to include all the sources of data that are used by clinicians to take clinical decision Clinicians should be included during development to make sure that unstructured data are not left out in ML-CDSS (co-design)
Availability	The data that are analysed by the system should be available for most patients (e.g. a CDSS analysing genetic data could not be used in usual care)	Importance of co-design with users, physicians, other prescribers and clinical managers to know what data is available for patients Possibility of adapting the ML-CDSS to different settings in which available data could be different
Interoperability	A multitude of technology platforms are involved in the generation, collection and mobilization of health data. ML-CDSS should be able to have good performance with different platforms and electronic health record systems.	Initiatives as FHIR (Fast Healthcare Interoperability Resources) that standardize healthcare data to common format
Equity	Most ML-CDSS are data-driven. As patients with low socioeconomic status usually have a limited access to healthcare, less data from these patients are available and ML systems could create new inequalities or increase health disparities. Patients with comorbidities should also be included in ML-CDSS.	Developing ML-CDSS with training and validation datasets from socioeconomically diverse health care systems Ensuring that patients with comorbidities (e.g. chronic kidney disease, cirrhosis) are included in the training dataset Ensuring that social determinants of health are being considered in the support system Test ML-CDSS for potential discriminatory behaviour
Adaptability	ML-CDSS should be usable in different clinical settings including primary, secondary and tertiary care. A special attention should be paid to low- and middle-income countries that should not be left out by progress in the development of AI.	Diverse datasets coming from different countries Specificities of LMICs should be considered early in the development of ML-CDSS Availability of antimicrobials in every healthcare setting should be considered
Interpretability	Clinicians should be able to understand the output of ML-CDSS and their determinants for an intelligent use and interpretation	Educating of an AI-literate clinician workforce (e.g. training in informatics and data science by the National Library of Medicine) Highlighting the variable or combination of variables that determined the output (e.g. 'saliency map') Reporting of confidence level in the prediction
Security	Alternatives should be developed to make sure that healthcare systems could function normally in case of an electronic problem. ML-CDSS should also be protected against hacking and other ill-willed practices	Systematic debugging Security software
Validation	ML-CDSS should be validated by an independent organization. Both the risk of under-regulation and over-regulation should be considered	Anticipation and preparedness Quality standards, precertification and certification Such regulatory framework as the Software as Medical Device (SaMD) framework developed by the International Medical Device Regulators Forum (IMDRF) working group chaired by the Food and Drug Administration (FDA)
Confidence	ML-CDSS developers should pay special attention to the confidence of clinicians and patients in artificial intelligence. Limited confidence or fear of the users would limit the use of ML and blind confidence also called automation bias could be dangerous	Behavioural science, sociological and anthropological research on artificial intelligence in medicine Training and education of clinicians about the benefits and limits of artificial intelligence and machine learning Studies on the interaction between machines and specifically human skills Co-design between engineers and clinicians
Evaluation	Evidence of the utility and benefits of ML-CDSS should not be limited to analysis of performance (e.g. ROC curves) but should consider clinical outcomes. Ideally, ML-CDSS should be evaluated in real-world settings from pilot study to clinical impact in real-world settings	Studies should not limit their outcomes to the evaluation of performance but should include clinical and microbiological outcomes Randomized controlled trial should try to determine the improvement of medical decision with the addition of ML-CDSS instead of comparing support systems with human clinicians
Accountability	The accountability of each actor (clinicians, ML-CDSS developers, certification organisms) should be defined beforehand	Research and forums on the accountability of AI and ML systems Inspiration from the work that has been done in other fields as driverless cars
Cost	Cost of ML-CDSS including development, data processing, implementation and impact on healthcare should be systematically studied, at the organizational and global level	Cost-effectiveness analysis and research
Privacy	ML-CDSS should respect the privacy of health data and ensure proper consent and patient governance in data collection	Global regulation as the European Union General Data Protection Regulation or United States Health Insurance Portability and Accountability Act Use of anonymized or pseudonymized data Privacy audits
Independence	Regulation agencies should make sure that ML-CDSS are independent from drug and diagnostic test companies and do not favour any treatments or tests for economic purposes	Regulatory frameworks should consider the need for independence Public funding for the development of AI and ML in healthcare
Unexpected consequences	ML-CDSS have the potential to deeply modify health systems and unexpected consequences should be systematically considered and studied	Systematic research on the limits of the ML-CDSS Studying potentially unexpected consequences on clinicians like 'deskilling' (loss of clinicians' skill due to the repeated use of ML-CDSS) or burn-out

Table 4 (continued)

Challenges	Description	Potential solutions
Implementation	The implementation of ML-CDSS should be thought of and organized as early as possible in the development	ML-CDSS developing teams should include specialists from implementation science Evaluation should include research on implementation, adoption, use and sustainability Specific task force committees to deal with AI implementation issues may be useful for developing a common vision at a specialty-wide level
Sustainability	ML-CDSS should be sustainable and updated according to new research, data or regulation	Specific and sustainable funding should be given to developers and adopters of ML-CDSS

Conclusion

Current ML tools cover a range of clinical outcomes such as the prediction of sepsis in ICUs, the diagnosis of TB or SSI, the prediction of virological success of cART or the selection of an antibiotic regimen. However, 57 ML-CDSS out of 60 only reported performance measures such as sensitivity or specificity and evidence is lacking regarding their use and impact in real-life clinical settings. Moreover, current ML-CDSS mainly use patient data from HICs, relying on large available open-access datasets and generally analyse a limited number of structured patient variables. Future ML-CDSS in ID should be developed in diverse health settings, including primary care and LMICs that are currently underrepresented, and be embedded in a structured process of integration into clinical settings. Future studies should aim to report clinical outcomes following sustainable use in routine clinical care.

Transparency Declaration

Dr Buchard reports that he is employed by Babylon Health. Dr Buchard has provided an expertise on machine learning methods exclusively on selected articles sent by the corresponding author. No tools developed by Babylon Health are discussed in the review.

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Appendix A. Supplementary data

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VIII. Discussion and perspectives

1. Discussion of principal results

In this thesis, two decision support tools for antimicrobial prescribing, one electronic decision support system and one leaflet were evaluated for implementation in specific health contexts.

First, we evaluated the interest of an electronic-based clinical decision support system for antimicrobial prescribing in West Africa. More specifically, we conducted a pre-implementation study in order to find the best pathway to adapt Antibioclic, an existing CDSS, to the local context of care. The study confirmed the relevance of a CDSS at primary care level, tailored to the local epidemiology of infectious diseases, available with a smartphone and including an offline mode. Co-design of the CDSS with diverse stakeholders was cited as one of the key strategies to ensure a sustainable adoption of the CDSS. Developing a CDSS dedicated to primary healthcare would require complementary advanced training modules in clinical diagnosis and antibiotic therapy. Participants also pointed out that the CDSS must include medicines that are available in the given country and the healthcare setting to reduce the risk of dropout.

A study reported that mobile health was more accepted and better adapted to existing infrastructure and local context due to the rising number of mobile subscriptions in Africa.(143) Similar initiatives regarding CDSS are ongoing: a protocol for the large-scale implementation of an electronic tool for the integrated management of childhood illnesses in Burkina Faso has been published but the results of this study are not yet available.(144) Pre-implementation studies and holistic evaluation to assess e-health readiness in LMICs are lacking and contribute to the limited uptake of effective clinical innovations.(145,146) Contextual factors are often underestimated in the implementation process and needs to be identified to optimise successful uptake. A recent multi-pronged evaluation carried out in Burkina Faso identified contextual factors that may have been underestimated thus limiting the implementation of CDSS.(144) A recent review focusing on behavioural interventions showed that multi-faceted interventions were more effective than educational interventions alone to improve antibiotic prescribing.(147) Multi-faceted interventions including bundle intervention, regulation enforcement, face-to-face education and peer influence have the potential to address behavioural factors cited by the participants. Another study identified partnerships with Health

Ministry, health managers, Non-governmental organizations and social entrepreneurs as being contributing factors to the upscaling of innovative digital tools.(148) Multi-sectoral coordination associated with incentives for stakeholders could also be a mean to enhance regulatory enforcement for antibiotic prescription.(149,150)

Second, we implemented a paper leaflet to help pharmacists guide and inform patients with UTIs. Analysis of the qualitative interviews showed that the pharmacists interviewed were willing to improve the management of infections and the proper use of antibiotics and that a leaflet could help them in this task. Several barriers to the use of the leaflets were raised by pharmacists such as the lack of access to medical diagnoses, the limited relations with GPs, or the lack of time and lack of specialised knowledge. We note that these barriers go beyond the individual characteristics of pharmacists and concern the overall organization of pharmacies and more generally of the primary care system. Regarding the relationship between pharmacists and GPs, we note that they could be described as a barrier as well as a facilitator when a framework for collaboration existed between professionals.

The barriers and facilitators identified in the interviews were similar to those found in qualitative surveys in the UK.(56) These two surveys also identified as barriers the inability to conduct clinical examinations in pharmacies, the lack of human resources and a language barrier between pharmacists and patients. Another limitation to the implementation of antimicrobial stewardship interventions in pharmacies, which was identified by the study by Jones *et al.* is the lack of understanding of the concept of antibiotic resistance by users and in particular of the link between the consumption of antibiotics and the development of antibiotic resistance.(56) Moreover, in the systematic review by Saha et al. on the knowledge, perceptions and practices of pharmacists regarding antimicrobial stewardship,(151), the authors found a favourable opinion of pharmacists on antimicrobial stewardship interventions in most of the studies. However, two studies included in this review found that this opinion varied according to the professional experiences and the qualifications of the pharmacists questioned and that the most qualified and experienced pharmacists were more favourable to interventions resulting in an optimal use of antibiotics in pharmacies. In addition, this review estimated the verification of compliance with antibiotic prescriptions usual for only 30% of pharmacists. Financial incentives and remuneration of pharmacists for antimicrobial stewardship activities were considered as an important lever for the implementation of this type of activities in pharmacies.(55) In the study conducted in the UK and in the follow-up work in France

(submitted for publication) pharmacists identified CDSS as an interesting implementation strategy to promote AMS in the community pharmacies.

Thirdly, we conducted a narrative review of the literature to provide an overview of the development of ML-CDSS in infectious diseases. As we have found, the development of clinical tools based on machine learning is still very largely limited to proof of concept. To date, we do not know of a tool using machine learning that is regularly used by infectious disease clinicians.(152) However, recent articles describe tools whose use could be close: Yelin et al have, for example, used data from over 700,000 community urinary tract infection episodes and over 5,000,000 antibiotic purchase records to develop an algorithm to analyse data from a patient with urinary tract infection, predict the likelihood of resistance to major antibiotics and advise appropriate antibiotic therapy. This algorithm could reduce inappropriate prescriptions of antibiotics by about 30%.(153) The development of CDSS based on machine learning will be more difficult in primary care where large patient databases available are scarce. The same observation is made for LMICs where the extraction and collection of data is difficult due to the frequent lack of a computerized medical file management system. The risk of these difficulties in accessing innovative tools is a potential increase in health inequalities.(154,155) However, if these potential limitations are taken into account, these new CDSS could appear as credible options for the management of infections in countries with few infectious disease specialists.(156)

These studies led us to common lessons applied to decision support systems for antimicrobial prescribing. First, tailoring CDSS to the context of care was considered paramount to the success of implementation. The use of a qualitative methodology and semi-structured interviews made it possible to define the needs and limits of the use of such tools directly with potential users. In West Africa, primary care prescribers face major challenges such as self-medication, limited availability of antibiotics and lack of national guidelines. In pharmacies, the absence of access to patients' medical record and to diagnosis, and the limits to antimicrobial prescribing are to be considered. In both contexts the lack of time and trained staff are barriers to the improvement of antimicrobial prescribing. These pre-implementation or early implementation studies in both cases allowed significant adaptations of the CDSS suggested by clinicians. Second, CDSS were seen by participants in both studies as ways to involve various prescribers in antimicrobial stewardship. Pharmacists are already involved in antimicrobial prescribing using local prescription protocols such as PGD. Patient facing leaflets

as well as more personalised decision support tools were considered useful to extend this activity by community pharmacists in the UK as well as in another study in France (work submitted for publication). In West Africa, the development and implementation of CDSS could encourage the development and updating of national recommendations in antibiotic therapy, increase the knowledge of practitioners about antibiotic therapy or facilitate the development of surveillance capacities for infectious diseases in primary care. Finally, future work aimed at preparing the implementation of CDSS for antibiotic prescription should make it possible to think about new types of user interface or to target new components of medical consultation such as patient information.

2. Perspectives

Figure 3 replaces some of the perspectives that stemmed from the thesis on a simplified diagram representing some of the main steps for a CDSS for antimicrobial prescribing.

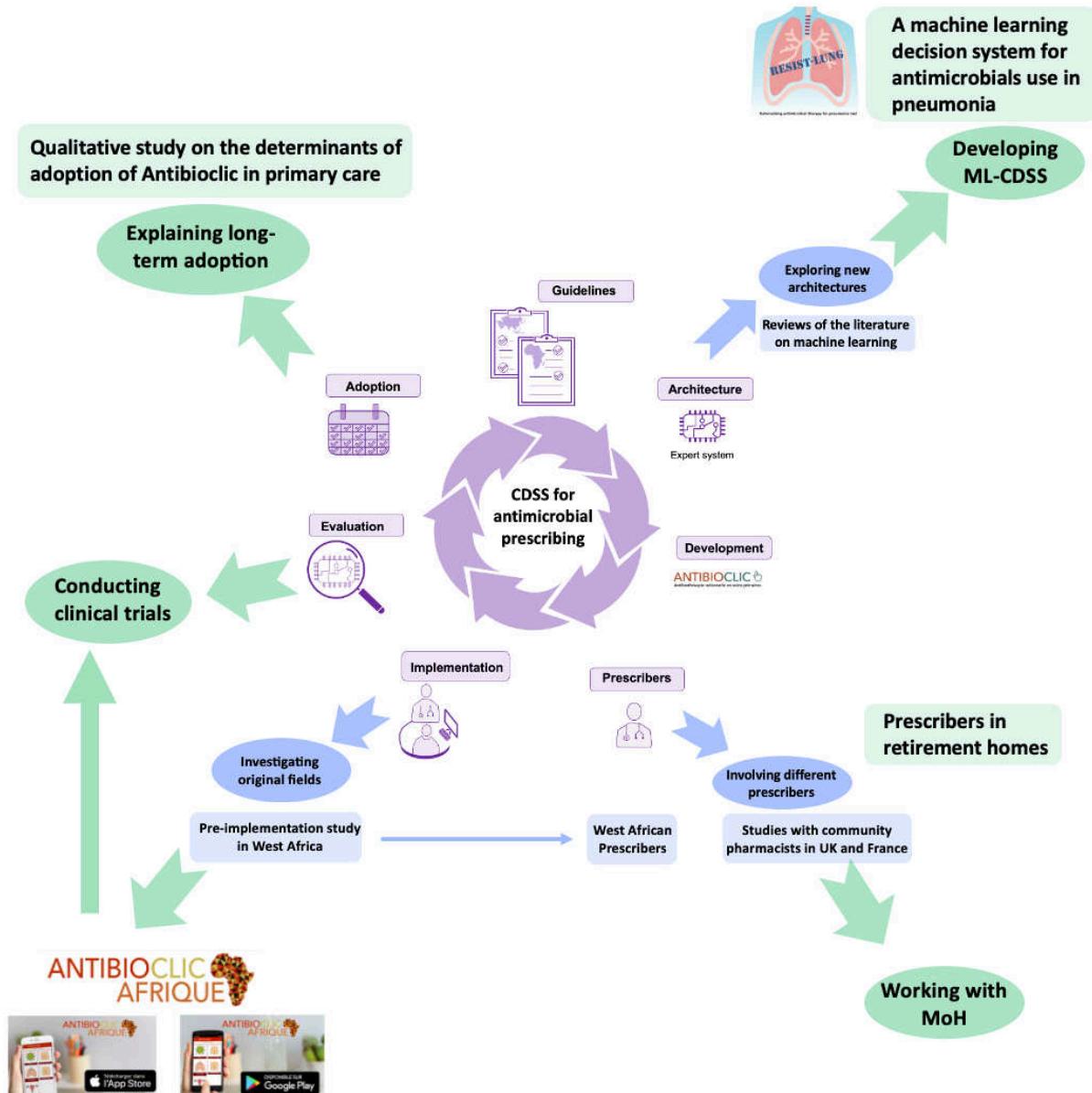


Figure 3. Perspectives following the thesis placed on a diagram representing some of the necessary steps for a CDSS for antimicrobial prescribing

ML: Machine Learning; CDSS; Clinical Decision Support System; MoH: Ministry of Health

a. *Determinants of the adoption of a decision support system for antimicrobial prescribing*

Another part of the pre-implementation work that we are conducting concerns the precise analysis of the determinants of the success of a CDSS. Indeed, certain specific characteristics of CDSS seem important for its sustained adoption. Studies have assessed the acceptance of IT

systems or CDSS in the hospital setting (157) but few have been conducted with GPs regarding AMS. Indeed, the characteristics and usefulness of decision support tools may be perceived differently according to professional groups and even to medical specialties and regarding CDSS, one size certainly does not fit all.(158)

In order to specify these characteristics with regard to antimicrobial prescribing in primary care, we carried out work including individual interviews with general practitioners. We interviewed 25 French GPs who regularly use AntibioClic about their use of this tool. The participants were recruited via the AntibioClic mailing list or in the course of a university degree in antimicrobial prescribing in primary care taking place at the University of Paris. The interviews were recorded, transcribed by a professional company and coded using NVivo 12. The data were then analysed using an inductive thematic analysis method and the analytical framework benefited from triangulation during a workshop including an individual questionnaire and round table with 9 other GPs.

AntibioClic was the most widely used CDSS across all medical disciplines for all the GPs interviewed. Although the precise analysis of this work is still ongoing, we have already identified a number of characteristics which seem to account for the success of AntibioClic. We have identified 7 key themes that explained the sustainable adoption of the CDSS: ergonomics, confidence, routinization, convenience, improvement of practices, contextualized learning and absence of negative consequences. GPs stressed the importance of co-design between users, primary care prescribers, and Information Technology (IT) developers for the creation of a CDSS. They also discussed the gap that sometimes exists between recommendations and daily clinical practice, the role a CDSS plays in continuing medical education, and the ongoing evolution of the doctor-patient relationship. Other initiatives have confirmed the potential training role of CDSS for antimicrobial prescribing, using AntibioHelp® a decision support system displaying both the recommended antibiotics and their justifications in the form of antibiotic properties.(159,160)

The existence of unexpected consequences associated with the use of a CDSS was discussed during the interviews. The majority of users seemed to rule out the various risks mentioned *a priori*, namely the unlearning of doctors, the loss of patient confidence or the replacement of referring infectious disease specialists. On the contrary, the interview physicians noted an important role of the CDSS for contextualized learning and updating knowledge during the

medical consultation. GPs considered that using Antibioclic saved time. These results confirm those of other qualitative studies which have looked at the use of CDSS on a regular basis and which did not find a negative impact on consultation time or deterioration of the relationship with the patient.(44,161) In addition, GPs stated that Antibioclic did not replace referring infectious disease specialists since it is mainly used for situations of simple to intermediate complexity for which an opinion would not have been requested. Complex infectious disease situations were the subject of a call to a referring infectious disease specialist or to a hospital department.

This study provided information on the determinants of long-term adoption of a CDSS for prescribing antibiotics in primary care. These elements complement those identified during the pre-implementation work in West Africa and reinforce the importance of co-design for the establishment of a CDSS. In addition, the themes that we have identified may be generalisable and could concern a wide range of CDSS.

b. Development and implementation of Antibioclic Afrique

Faced with the emergence of the COVID-19 pandemic and based on the pre-implementation work carried out, we co-designed with professionals in West Africa a CDSS to guide the management of COVID-19: Antibioclic Afrique. The objectives of Antibioclic Afrique were first to improve the management of COVID-19 patients and the prevention of SARS-CoV-2 transmission.

The ongoing project is divided into several stages : (i) development of an electronic tool to support the clinical management of patients based on the architecture of Antibioclic (ii) adaptation to the West African context in 5 different countries taking into account the data obtained in the pre-implementation study (162) (iii) implementation of the CDSS guided by the use of theoretical frameworks and implementation strategies in order to optimize the chances of success (iv) dissemination of the tool by relying on networks of project leaders, on the African Society of Infectious Diseases (SAPI) and on local research and health structures (v) monitoring and updating the tool so that it provides accurate clinical decision support.

This project was funded by the ANRS MIE (France Recherche Nord & Sud Sida-VIH Hépatites Emerging Infectious Diseases) and by a grant from the French Infectious Diseases Society

(SPILF). Preparatory meetings have been taking place since May 2020 with health professionals from West Africa via the network mobilised by the AphroCoV initiative. AphroCoV is an initiative piloted by the French National Institute for Health Research (Inserm), which aimed to improve health monitoring and the management of COVID-19 cases in 5 African countries: Burkina-Faso, Ivory Coast, Gabon, Mali, Senegal (Figure 4).

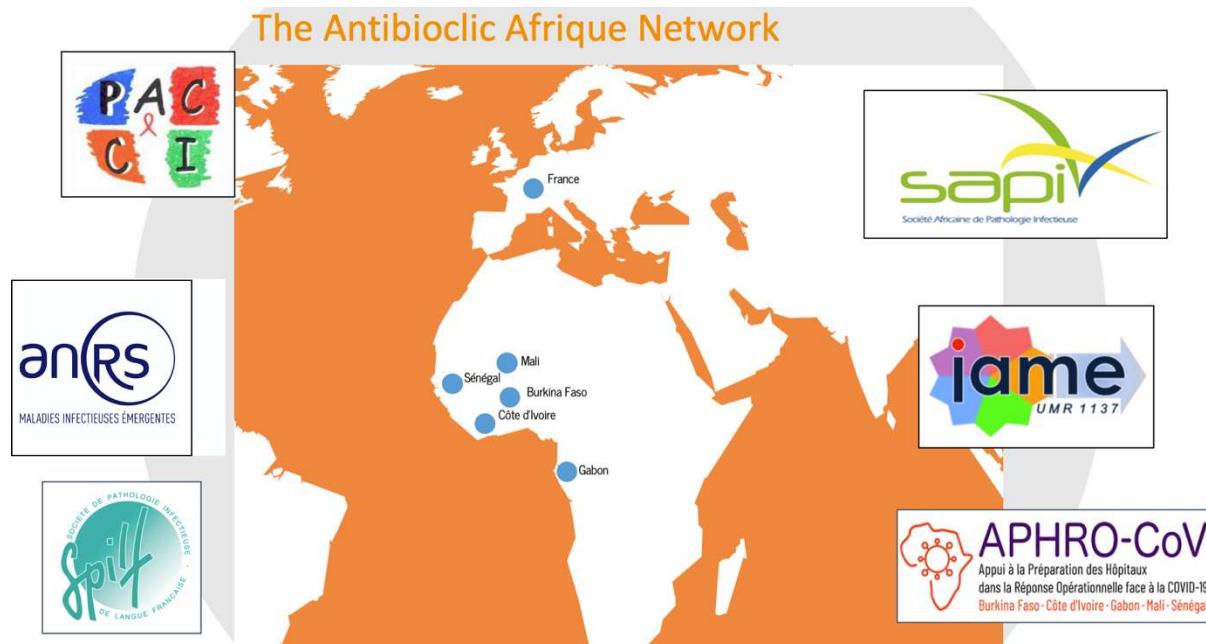


Figure 4. The network of the Antibioclic Afrique project (ANRS COV 003)

Antibioclic Afrique was co-developed by clinicians from the University Hospitals of Treichville (Côte d'Ivoire), Owendo (Gabon), Yalgado Ouedraogo, Bobo Dioulasso (Burkina Faso), Fann (Senegal) and Point G Hospital (Mali), and in partnership with the African Society of Infectious Diseases (SAPI), ANRS MIE, the AphroCoV network and the ANRS site in Ivory Coast. The regular steering committee meetings enabled consultative decision-making and adaptation to contextual factors for the 5 partner countries. The recommendations originated from national clinical practice guidelines from the partner countries and were transformed into decision trees in Antibioclic Afrique.

The Antibioclic Afrique CDSS is available as a website at the following address: <https://antibioclic-afrigue.com>, it is also available on iOS on the Apple Store: <https://apps.apple.com/fr/app/antibioclic-afrigue/id1575563381>) and on Google Play Store (Android):

https://play.google.com/store/apps/details?id=com.antibioclic.afrigue2&hl=en_US&gl=US).

(Figure 5). These applications can be used without an internet connection (offline mode) in

order to respond to connection difficulties in West Africa. Research work is underway involving a qualitative and quantitative assessment of the use of the CDSS and measurements of implementation markers as defined by Proctor *et al*. These implementation outcomes include acceptability, adaptation to the context and relevance, adoption, cost, feasibility, fidelity, penetration and sustainability of the tool.(163)



Figure 5. Website and smartphone versions of the free AntibioClic Afrique clinical decision support system

Work in progress conducted as part of the project with 21 healthcare professionals in West Africa using a multi-sectoral approach allowed the identification of wider political, social and

economic influences that facilitate or threatens or the implementation of the CDSS. Participants specialised in project engineering and e-health tools shared their best practices and the pitfalls in order to be able to the design and implement a CDSS. Other participants shared their global vision of the governance landscape in electronic health and AMR. Regarding the identification of implementation strategies, most of the participants stressed the importance of building a solid ecosystem involving diverse stakeholders from different backgrounds (hospital directors, policymakers, associations of health professionals, national clinical referees for epidemic management). Participants approved of implementation strategies such as promoting network weaving, creating a learning collaborative and identifying early adopters of the CDSS.

The medium and long-term objective is to extend the CDSS for COVID-19 that is already developed and used by clinicians in West Africa, to include recommendations for the management of bacterial, viral and parasitic infections. This would allow us to achieve one of the objectives of the first study of this thesis. Validations studies would then be conducted to evaluate the impact of Antibioclic Afrique. Protocols have been proposed to evaluate CDSS for AMS, such as a study protocol describing a stepped-wedge cluster randomised trial to evaluate the impact of a smartphone application for antimicrobial stewardship on the appropriateness of empiric antimicrobial prescribing.(164)

c. Development of a machine learning decision support system for the management of infections with antibiotic resistant micro-organisms

Empirical antibiotic therapy is the cornerstone of the treatment of severe bacterial infections. Any delay in the adequacy of treatment is linked to increased mortality and morbidity, prolonged hospital stays and higher hospital costs. The last decade has been characterized by the spread of resistant bacteria in the community, mainly multi-drug resistant gram-negative bacteria (MDRGNB), leading to an increase in inadequate empiric antibiotic therapy. Based on our experience and the literature, several factors are needed for the occurrence of MDR infections (carriage, prior antibiotic therapy and invasive procedures). Nevertheless, among previously colonized patients, less than 10% will develop an infection, with a different risk according to the population under study. Improving the choice of antimicrobial therapy at the initial phase of the infection therefore requires either immediate microbiological results or algorithms with an excellent performance to predict which patients are at high risk of infection

by MDR bacteria. As none of the current available methods satisfies these criteria, clinicians face increasingly difficult antibiotic choices. Consequently, early detection of patients at risk of being infected with MDRGNB is critical, in order to (1) initiate appropriate empiric therapy in case of suspected infection; (2) avoid overuse of broad-spectrum antimicrobials that are associated with an increase in antibiotic selection pressure; (3) appropriately prevent the spread of MDRGNB in the community and in hospitalized patients. Accumulated evidence, including from our group, suggests that microbiota-based data could be leveraged to improve the prediction of pneumonia, including those caused by MDRGNB. In addition, the identification of microorganisms in pneumonia has been accelerated by the development of rapid multiplex PCR and metagenomic sequencing.

Following the work on CDSS for antimicrobial prescribing and the analysis of the literature regarding ML-CDSS, we plan to develop a machine learning decision support system that can predict the individual risk of MDRGBN infection in a patient by combining previous medical history including past infections and antimicrobial prescriptions, local epidemiological data, laboratory and imaging work-up and immediately available microbiological data. This work will require the development of new predictive algorithms, technologies to access microbiota data and PK/PD models that will be combined into a bedside CDSS. Using existing databases such as OUTCOMEREA led by the IAME unit and the AP-HP data warehouse (30 hospitals, > 8 million admissions), we will develop novel algorithms aiming at identifying patients at-risk of MDRGNB infections. These algorithms will be generated using standard modelling and deep learning approaches taking advantage of ML high computing capabilities. Models and data generated with clinical and microbiota data will be integrated and combined to generate a CDSS usable by clinicians for the early detection of patients at risk of being infected with MDR bacteria, the early adequate therapy and the prevention of resistance spread. Qualitative interviews and workshops will be used to design a user-oriented CDSS and implementation strategies will be guided by results from a pre-implementation study using conceptual frameworks for implementation. In order to fill the gaps identified in the review of the literature, clinical trials will be conducted to assess implementation outcomes and the performance of the CDSS regarding clinical outcomes in real-life situations. Long-term adoption in clinical routine will be the overarching objective of this project.

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Appendices

Appendix 1. How to use Antibioclic (link to video and slides)

How to use Antibioclic (video):

https://jmir.org/api/download?alt_name=jmir_v22i7e17940_app2.mov&filename=1a6bab6734464330dab56256cf278c9d.mov

How to use Antibioclic (slides):

How to access Antibioclic - Web

- Type in your address bar
 - <https://antibioclic.com>
- OR
- Look for "Antibioclic" on your search engine



- Access the website "antibioclic.com"
 - antibioclic.com ▾
 - [Antibioclic : Antibiothérapie rationnelle en soins primaires](#)
 - Antibiothérapie pratique en soins primaires - Département de Médecine Générale, Université Paris DIDEROT-Paris 7.

How to access Antibioclic – iOs via Apple Store

The screenshot shows the 'Informations' section of the Antibioclic app page on the Apple App Store. It includes the following details:

- Distributeur: Les amis d'Antibioclic
- Taille: 6,3 Mo
- Catégorie: Médecine
- Compatibilité: iPhone
- Langues: Français
- Âge: 4+
- Rating: 5,0 ★★★★★ (20 notes)
- N°127 in Médecine
- 4+ Age rating

Below the information, there's a 'Nouveautés' (New features) section and a preview of the app interface.

Application (iOs and Android) is fully available offline (everything downloaded at installation) but needs internet to be updated

The screenshot shows the 'antibioclic' app page on the Google Play Store. It includes the following details:

- Play Store icon
- Name: antibioclic
- Icon: Antibioclic logo
- Developer: Les Amis d'Antibioclic
- Rating: 4,7 ★ (107 avis)
- Downloads: 10 k ou plus Téléchargements
- PEGI 3

Below the details, there are three screenshots of the app interface. To the right, there's a green 'Installer' button with a red arrow pointing to it, and below it is a red 'Download' button.

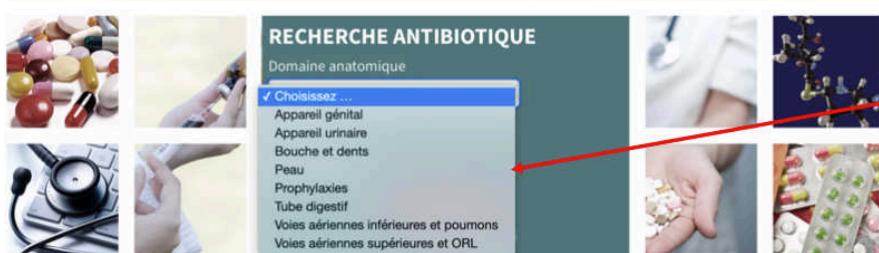
How to access Antibioclic – Android via Google Store

How to use Antibioclic

The website is exclusively in French but we have added translations in English for the following slides

RECHERCHE SOURCES ACTUALITÉ À PROPOS CONTACT

+ Antibioclic a créé un DU d'Antibiothérapie en Soins Primaires (DUASP, Paris 18e) pour aller + loin : cliquer pour en savoir ++

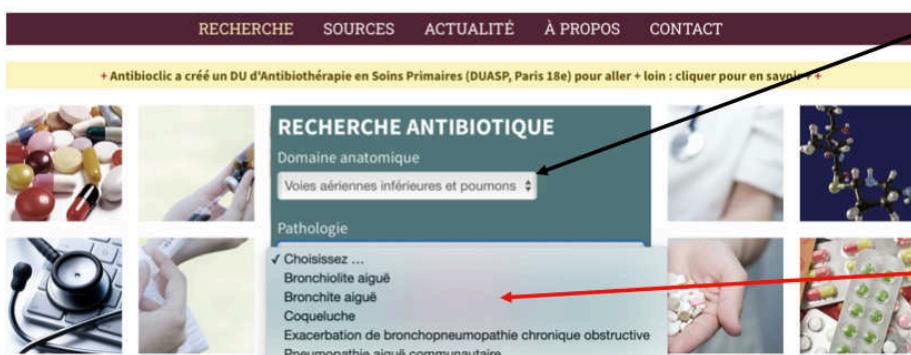


First, healthcare professionals have to choose the anatomical site

- Genital tract
- Urinary tract
- Mouth and teeth
- Skin
- Prophylaxis
- Digestive tract
- Lower respiratory tract
- Upper respiratory tract and ENT

RECHERCHE SOURCES ACTUALITÉ À PROPOS CONTACT

+ Antibioclic a créé un DU d'Antibiothérapie en Soins Primaires (DUASP, Paris 18e) pour aller + loin : cliquer pour en savoir ++



For this example we chose lower respiratory tract



The second step is to choose the infection

- Bronchiolitis
- Bronchitis
- Pertussis
- Chronic Obstructive Pulmonary Disease exacerbation
- Community-acquired pneumonia
- Tuberculosis (latent and prophylaxis)

We chose community-acquired pneumonia and then click on "Search"

Pneumopathie aiguë communautaire

- Les germes en cause le plus fréquemment sont : **pneumocoque** (*Streptococcus pneumoniae*), **bactéries dites atypiques** (notamment : *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*).
- Le diagnostic repose sur la clinique et sur la radiologie (indispensable).

Critères d'hospitalisation

- Signes de gravité : altération des fonctions supérieures ou héodynamique instable ou température > 35°C ou > 40°C ou néoplasie associée ou pneumonie d'inhaltung ou obstacle trachéo-bronchique.
- Situations particulières : pneumonie compliquée (abcédation ou épanchement pleural) ou précarité ou risque d'inobservance ou isolement.
- Spécificités pédiatriques : âge < 6 mois ou difficultés d'alimentation ou aggravation rapide.

Facteurs de risque de mortalité

- Âge > 65 ans
- Insuffisance cardiaque congestive
- Maladie cérébro-vasculaire (antécédents d'AVC)
- Insuffisance rénale chronique
- Hépatopathie chronique
- BPCO
- Immunodépression (traitement immunosupresseur dont corticothérapie par voie générale ou chimiothérapie dans les 6 mois, splénectomie, SIDA, cachexie ...)
- Dépancytose homozygote
- Antécédent de pneumonie bactérienne
- Hospitalisation dans l'année
- Vie en institution

The website displays a number of clinical reminders that are adapted to each infection

In this case, it displays:

- Most frequent micro-organisms
- The need to prescribe a chest X-Ray
- Hospitalization criteria
- Risk factors for increased mortality

Choisissez le groupe d'âge.

- Adulte
 Enfant

Choisissez le groupe d'âge.

- Adulte
 Enfant

As you click and depending on your answer, new questions appear (informed by the clinical practice guidelines)

Précisez l'âge.

- Adulte de 65 ans ou moins
 Adulte de plus de 65 ans

If we select adult, next question is more or less than 65-year old (risk factor)

Combien de facteur(s) de risque de mortalité présente votre patient(e) en plus de l'âge ?
Panneau la liste ci-dessus.

- Aucun facteur de risque (en plus de l'âge)
 Au moins un facteur de risque (en plus de l'âge)

If > 65 year-old: presence or absence of other risk factors than age

S'agit-il d'une pneumonie post-grippale ?

- Non
 Oui

If no, they ask if this is a post-influenza pneumonia (important for management recommendation according to guidelines)

Si besoin, choisissez la ou les situations particulières éventuelles auxquelles vous êtes confronté.
Vous pouvez ne rien cocher.

- Insuffisance rénale

At the end, existence of chronic kidney failure is always asked

SUIVANT

Then, click "Next"

The third step is to choose between adult and child (when adapted)

Depending on each answer, the new questions are different, ensuring a tailored recommendation, for example if we select child, you have to select between more and less than 3 years, then chronic kidney failure or not

Choisissez le groupe d'âge.

- Adulte
 Enfant

Précisez l'âge.

- Moins de 3 ans
 3 ans ou plus

Si besoin, choisissez la ou les situations particulières éventuelles auxquelles vous êtes confronté.
Vous pouvez ne rien cocher.

- Insuffisance rénale

SUIVANT

After clicking next, the tailored recommendation for your patient is displayed

The screenshot shows a web-based clinical decision support tool. At the top, there's a navigation bar with links to RECHERCHE, SOURCES, ACTUALITÉ, À PROPOS, and CONTACT. Below the navigation, a header says "Traitement conseillé". A red box on the left contains the following text:

- General management recommendation:** antibiotic therapy, clinical reassessment after 48 hours, etc.
- First choice antibiotic with dose and duration**
- Second choice if allergy or any contra-indication or clinical failure after 48 hours**
- Rationale for the choice and advice (preserving quinolones, risk of resistance, etc.)**

The main content area displays a "VOTRE SITUATION" section with patient details: Pathologie : pneumopathie aiguë communautaire; Groupe d'âge : adulte; Âge > 65 ans; FDR de mortalité (en plus de l'âge) : 0; Contexte grippal : non; Insuffisance rénale : non. To the right, a summary box lists selected clinical situations:

- Community-acquired pneumonia
- Adult
- More than 65-year old
- No other risk factor of increased mortality
- No chronic kidney disease

A "Last updated" box indicates the page was last modified on November 14, 2019. A note at the bottom states: "NB : Les choix soulignés sont ceux qui sont privilégiés par le groupe d'experts d'ANTIBIOCIC." A red box labeled "Links to the guidelines that are used" points to the sources section.

If at one point, a mistake is done, Antibioclic will point it and ask to correct it

Traitement conseillé

- L'insuffisance rénale est un facteur de risque de mortalité.
- Utiliser la touche "retour en arrière" de votre navigateur pour corriger les données.

SOURCES

- AFSSAPS. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte et de l'enfant. Recommandations. Octobre 2005.
- AFSSAPS. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte. Mise au point. Juillet 2010.
- Adaptation des recommandations à l'aide du dictionnaire Vidal.

Traitement conseillé

- Dans cette situation, l'hospitalisation est recommandée.
- La prise en charge ne relevant pas du soin primaire, ANTIBIOCIC ne donne pas d'indication sur le traitement antibiotique à utiliser.

SOURCES

- AFSSAPS. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte et de l'enfant. Recommandations. Octobre 2005.
- AFSSAPS. Antibiothérapie par voie générale dans les infections respiratoires basses de l'adulte. Mise au point. Juillet 2010.

In this example, always with community-acquired pneumonia, we selected "> 65 year-old" then "no other risk factor for mortality than age" then we "presence of chronic kidney failure" : Antibioclic is highlighting that chronic kidney failure is a risk factor for mortality and to modify accordingly

If we go back on modify it, selecting "presence of risk factors for increased mortality other than age", then Antibioclic is recommending hospitalization, as in the guidelines (mentioned just below)

Each infectious disease has a specific set of questions informed by the recommendations

Exacerbation de bronchopneumopathie chronique obstructive

- L'argument clinique pour une origine bactérienne est la présence d'une expectoration purulente verdâtre franche des crachats.
- Principales bactéries en cause : pneumocoque, *Haemophilus influenzae*, *Branhamella catarrhalis*, plus rarement *Pseudomonas aeruginosa*.
- Toujours rechercher d'autres causes à l'exacerbation qu'une infection bactérienne.

Critères d'hospitalisation

- Signes cliniques de gravité : altération des fonctions supérieures, hémodynamique instable, détresse respiratoire aiguë.
- Stade évolué de la BPCO : oxygénothérapie à domicile, corticothérapie orale prolongée.
- Situations particulières : comorbidités, précarité, isolement.
- Critère évolutif péjoratif : exacerbation récente avec hospitalisation, réponse insuffisante au traitement en ambulatoire.

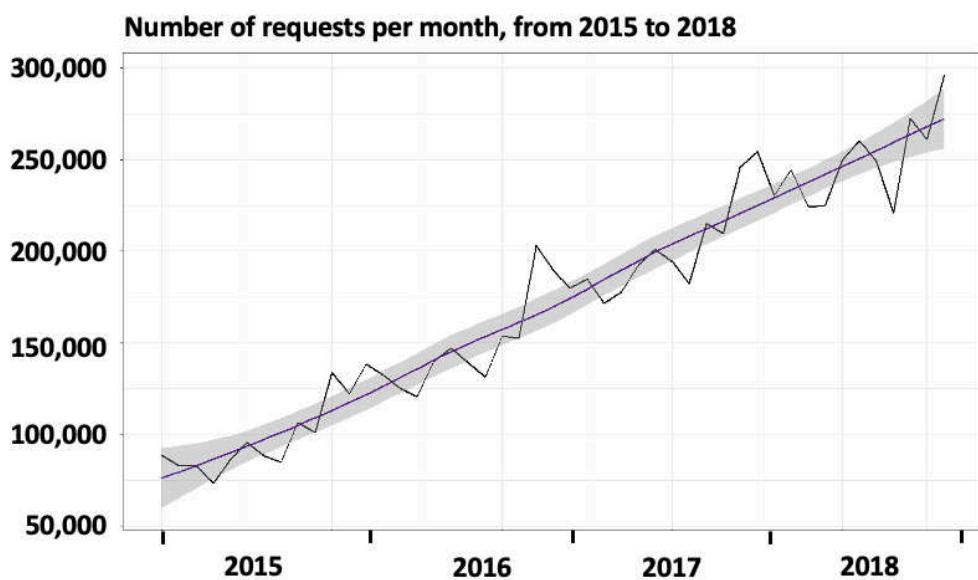
Indiquez l'état clinique de base de votre patient (en dehors de toute exacerbation).

- Absence de dyspnée (ou VEMS ≥ 80 % = stade I)
- Dyspnée d'effort inconstante (ou VEMS entre 50 et 80 % = stade II)
- Dyspnée d'effort (ou VEMS entre 30 et 50 % = stade III)
- Dyspnée au moindre effort ou de repos (ou VEMS < 30 % = stade IV)

If we select "COPD exacerbation", there is no question about adult/child (exclusively adult disease) and the first question is the GOLD classification using Forced Expiratory Volume first second as this is a major information to recommend or not an antibiotic treatment



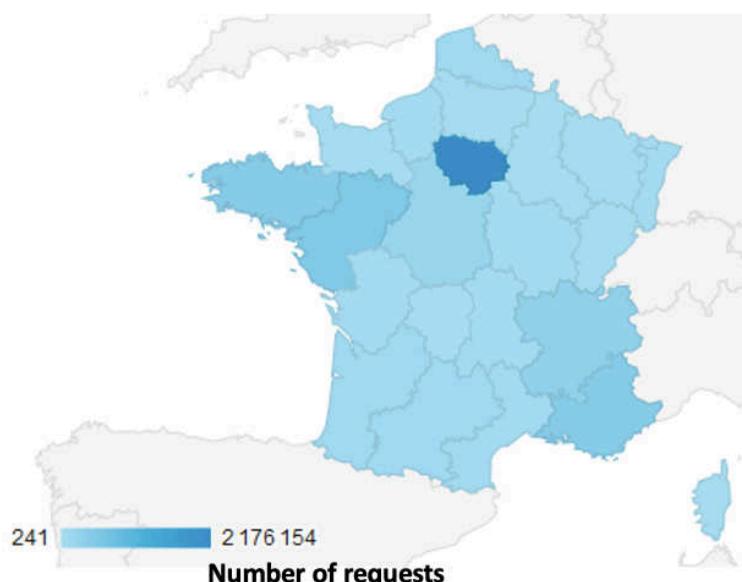
Appendix 2. Antibiotic users



	2012	2018
Total requests	369,317	3,549,488
Number of request per day	796 [578 – 989]	11,125 [5592 – 12 505]
Unique I.P. address / day	414 [245 – 394]	5365 [2891 – 5769]
Requests / 100 unique I.P. / day	196 [184 – 243]	212 [203 – 220]

1

Location of use in France



2

Appendix 3. Questionnaire for the pre-implementation of a CDSS in West Africa

You are being invited to complete this questionnaire to give your opinion on decision support systems for antimicrobial prescribing.

Please tick each box if you agree.

1. I confirm that I have read and understood the information given and have had the opportunity to ask questions
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected
3. I agree to take part in this study

Signature:

General question

What is your gender?

- Male
- Female
- Prefer to self-describe:

How old are you?

In which country do you work?

In which health structure do you work? (tick all that apply)

- Academic hospital
- Non-academic public hospital
- Private hospital
- Private surgery
- Dispensary
- Other:

What is medical specialty?

- Infectious diseases
- Intensive care
- Internal medicine
- Clinical microbiology
- Family medicine
- Other:

What is your status?

- Resident
- Doctor
- Associate professor
- Professor

Do you have national guidelines for antimicrobial prescribing?

- Yes
- No

If no, which guidelines do you usually use? (tick all that apply)

- European
- American
- French
- WHO
- Other:

Do you have access to the following devices for professional use during consultation? (tick all that apply)

- Computer
- Smartphone
- Tablet
- Other:

Do you use your phone for professional use during consultation?

- Yes
- No

Do you use a clinical information technology system during consultation?

Yes

No

Do you use any clinical decision support systems* in your practice?

*A clinical decision support system (CDSS) is an electronic tool that can provide users with assistance to take clinical decisions. Clinical decision support systems are sometimes called computer-based or computer-aided diagnosis or therapy. CDSS are electronic tools that help users in the diagnosis (e.g. suggesting list of diagnosis when you enter symptoms), in the work-up (e.g. suggesting a list of laboratory work-up for a patient) or in the therapy of a patient (e.g. suggesting drugs when you enter a diagnosis). Clinical decision support systems can be electronic guidelines, an alert system included in the electronic health record, a web-based platform or a stand-alone software.

Yes

No

If yes, which system(s)?

Do you use clinical decision support systems (CDSS) for infection management or antimicrobial prescribing?

Yes

No

If yes, which system(s)?

How did you know them?

What do you think of Antibioclic?

In your opinion, for which infectious diseases can a CDSS such as Antibioclic be useful?

	Useless	Neutral	Useful
Urinary tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Genital tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Meningitis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dental infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Upper respiratory tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lower respiratory tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Gastro-intestinal tract infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skin and soft tissue infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Surgical site infections	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Do you think that a CDSS such as Antibioclic could be used in your country?

Yes

No

In your opinion, what would be necessary to set up or modify for Antibioclic to be adapted to the practice of general medicine in your country?

What would be the benefits of using a CDSS such as Antibioclic in your country?

What would make it difficult to use a CDSS such as Antibioclic in your country?

What features or elements could facilitate the use and dissemination of a CDSS such as Antibioclic in your country?

Who are the health professionals who could use Antibioclic in your country? (Tick all that apply)

- General practitioners
- Infectious diseases specialists
- Intensivists
- Clinical microbiologists
- Other medical specialties
- Nurses
- Pharmacists
- Other:

For each of the following, can you tell us if you think this represents a barrier or facilitator for the use of AntibioClic in general practice in your country?

	Barrier	Neutral	Facilitator
Independence from the pharmaceutical industry	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Adapted to the guidelines of the French National Society of Infectious Diseases	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Written in French	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Developed in France	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Available on an electronic format (smartphone, computer)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Free	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Co-designed by general practitioners and engineers	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

It will:	Unlikely	Neutral	Likely
Improve my medical knowledge	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Increase the interaction with the patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lead to more personalized care	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lead to more comprehensive care	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Strengthen the doctor-patient relationship	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decrease the number of medical errors	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lead to blind obedience to electronical tools	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve clinical outcomes for patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve the quality of antimicrobial prescribing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Save you time	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decrease healthcare costs	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Help to fight against antimicrobial resistance	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve the adequacy of antimicrobial prescribing to guidelines	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Improve the care of patients with infectious diseases	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Decrease the duration of	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

antimicrobial
therapy

Decrease the global
volume of
antimicrobial use



Do you think that a CDSS such as Antibiotic will have the following consequences?

Do you have any comments on the study or regarding clinical decision support systems for antimicrobial prescribing?

Thank you for your participation

Appendix 4. Pre-intervention interview schedule with pharmacists

Generally, about healthcare advice

1. Tell me about how you give service users healthcare advice?

Probe: what are the difficulties that you encounter? what makes it easy?

2. You said that you [did not use leaflets / used leaflets for the following conditions:]:

Are leaflets helpful to give healthcare advice?

About UTI

3. Tell me about the most important advice that you usually give to women under 65 years with urinary symptoms or a suspected UTI?

4. How is it different for women over 65 years? For men under 65 years? For men over 65 years?

5. Is there anything else you would like to say about how you provide healthcare advice to service users with urinary symptoms or suspected UTI?

Let's talk about the leaflet for women under 65 years.

6. What are your first thoughts on this leaflet?

7. What is your general opinion about the following sections?

- Possible urinary signs and symptoms
- The outcome
- Recommended care
- Types of urinary tract infections (UTI)
- Self-care to help yourself get better more quickly
- When should you get help?
- Options to help prevent a UTI

- Antibiotic resistance

8. How are you going to use the leaflet?

Probe: shared and explained with the service user or given as a take-away? On line, hard copy, computer prompts (drug note)?

9. What is your opinion about the wording used in the leaflet.

Probe: is it simple enough?

10. Is there anything else that you think should be included in the leaflet?

11. What modifications would you suggest to make it more suitable to your needs?

12. Is there anything else you would like to say about this leaflet?

Let's talk about the leaflet for service users over 65 years

13. What are your first thoughts on this leaflet?

14. What is your general opinion about the following sections?

- Possible urinary signs and symptoms
- The outcome
- Recommended care
- Types of urinary tract infections (UTI)
- Self-care to help yourself get better more quickly
- When should you get help?
- Options to help prevent a UTI

15. How are you going to use the leaflet?

Probe: shared and explained with the service user or given as a take-away? On line, hard copy, computer prompts (drug note)?

16. What is your opinion about the wording used in the leaflet.

Probe: is it simple enough?

17. Is there anything else that you think should be included in the leaflet?
18. What modifications would you suggest to make it more suitable to your needs?
19. Is there anything else you would like to say about this leaflet?
20. In your opinion, what is the role of pharmacists in infection management and in the fight against antimicrobial resistance?

TO CLOSE

- Review the next steps with the pharmacist
 - Trial using the leaflets with service users for 3 months
 - Each leaflet given to a service user should be given with the envelope with the paper survey (name on the paper survey or online)
 - You can either directly give the leaflet and the envelope with the paper survey to service users
 - Or staple each leaflet to an envelope with the paper survey so that service users can take the leaflet themselves in the pharmacy
 - Please remind service users that they will have a £10 voucher if they complete the survey
 - If at one point you need more leaflets and envelopes with paper survey for service users, please contact us by email raheelah.ahmad@imperial.ac.uk or by phone: +44 (0)208 383 2072.
 - We will be in touch with you in 3 months for the post-trial interview (£30 voucher)
- Check the recording on the Dictaphone
- Upload to the shared drive – check that you can hear it

Appendix 3. Post-intervention interview schedule with pharmacists

The purpose of this interview is to discuss how you found trialling the UTI leaflets in your pharmacy.

21. Can you please give the number on the leaflets (upper corner) that you have?

22. How long did you trial the leaflets for? Probe: How many weeks, if they didn't trial for as long as expected ask them why?

23. Were you the only person trialing the leaflets or did others trial them? Who?

24. How did you find using the leaflets in the pharmacy?

25. If others trialed the leaflets, do you know what they thought about the leaflets?

26. Did you offer the leaflet to all the women and older adults with UTI symptoms? Probe: if not, why?

27. Can you take me through an example scenario of how you used the leaflet with a woman under 65? Was it different from using the leaflet with an older adult?

28. Did you use the leaflet differently between service users:

- coming first to the pharmacy and that you then referred to the GP**
- service users coming first to the pharmacy and not referred on**
- service users coming after a GP visit?**

29. How did the women younger than 65 adults respond to the leaflet? Probe:
did they comment on the leaflet, did they take them away, was there any negative feedback?

30. Were there any sections of the leaflet that were difficult to use/explain?

Leaflet > 65

31. How did the older adults respond to the leaflet? Probe: *did they comment on the leaflet, did they take them away, was there any negative feedback?*

32. Were there any sections of the leaflet that were difficult to use/explain?

Leaflets

33. Now that you have experience in using the leaflets, what would you change to make them more user friendly in the pharmacy setting?

34. Do you have any other comments about the leaflet or trialing the leaflet that you would like to add? Probe: *potential drawbacks?*

Taking into account your interviews before the intervention, PHE have modified the leaflets and have produced one combined leaflet.

35. What do you think of the new leaflet?

36. Do you think that this leaflet could be easier to use than the two leaflets separately in your pharmacy? Do you see any drawbacks to the new combined leaflet?

37. Would you recommend using the leaflet to your colleagues?

38. Do you think that photos should be replaced with graphics?

General questions

39. In your opinion, when should a service user with UTI symptoms seek advice?

40. In your opinion, from whom should a service user with symptoms seek advice? Probe: Pharmacy first? GP first? Someone else?

41. When and why do you refer service users with suspected or confirmed UTI to the GP?

Appendix 5. Pre-intervention electronic questionnaire for pharmacists

Q1 Pharmacy advice for service users with Urinary Tract Infection.

You are invited to take part in this study as described in the accompanying

The study includes the electronic survey and two interviews, one before using the leaflets in your pharmacy and one once you have trialled the leaflets for 3 months. All pharmacists will be offered £60 for participating in the study (£30 on completion of each interview).

Please read the following statements:

- I confirm that I have read and understood the information above and have had the opportunity to ask questions.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected.
- I understand that my consent form and anonymised data may be reviewed by the sponsor for audit purposes.
- I agree to be contacted for follow up interviews. These will be face to face or by telephone (according to my preferred method).
- I agree to receive by mail the leaflets developed by Public Health England and to use them with service users with urinary tract infection.
- I understand that the follow-up interviews will be audio recorded and transcribed.
- I agree to take part in this study.

Please click on Next if you consent to take part in the study.

End of Block: Consent

Start of Block: General questions

Q2 Thank you for taking part in this study about the role of Pharmacies in the prevention and management of urinary tract infections.

We would like to start by asking you a little about your broader role and then we will focus on urinary tract infections.

Q3 What is the name and address of your pharmacy?

Q4 What is your email address?

Q80 What is your name? (to send the vouchers)

Q81 What is your direct number or mobile number? (for the interviews)

Q5 What is your job title?

- Non-prescribing pharmacist (1)
 - Prescribing pharmacist (2)
 - Pharmacy technician (3)
 - Pharmacy assistant (4)
 - Other (5) _____
-
-

Q6 How long have you been qualified?

Q7 How long have you been working in this pharmacy?

Q8 How many pharmacy staff (full time equivalent) work in the pharmacy?

*

Q9 How many service users per day on average do you see in your pharmacy?

Q10 How many service users per day on average do you see in the consultation room?

Q11 What is the approximate gender representation of service users for this pharmacy?

Men

Women

0 10 20 30 40 50 60 70 80 90 100

Gender ()



Q12 Can you describe in a few words the ethnicity and socio-economic level of the service users coming to your pharmacy?

Q13 To how many service users per day do you usually give healthcare advice?

Q14 What are the most common conditions for which you give healthcare advice?

Q15 Please describe, if anything, that stops you giving healthcare advice?

Q16 What do you think are the advantages and disadvantages of giving healthcare advice in the pharmacy setting compared to in a GP practice?

- Advantages (1) _____
- Disadvantages (2) _____

Q17 How often do you use leaflets to give healthcare advice?

Q18 For which conditions do you use leaflets to give healthcare advice the most?

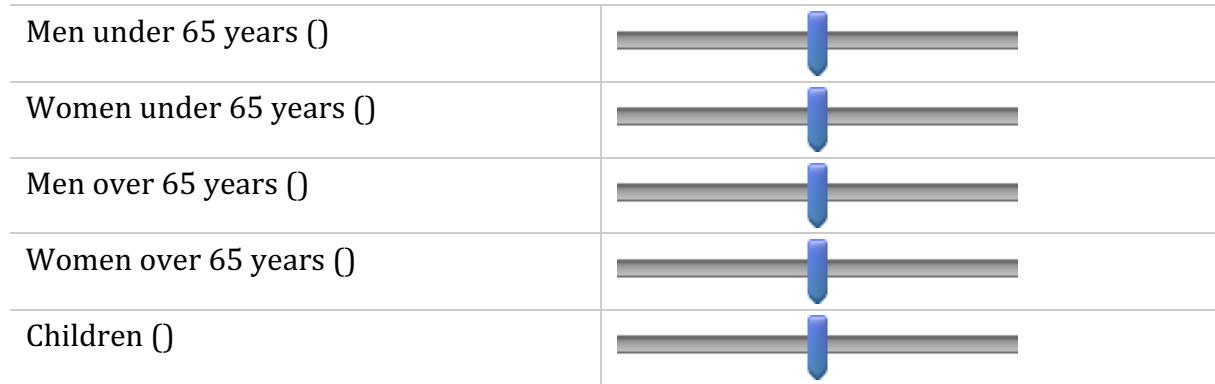
End of Block: General questions

Start of Block: Urinary Tract Infections

Q19 Now we would like to focus a little bit on service users with urinary symptoms or suspected urinary tract infections.

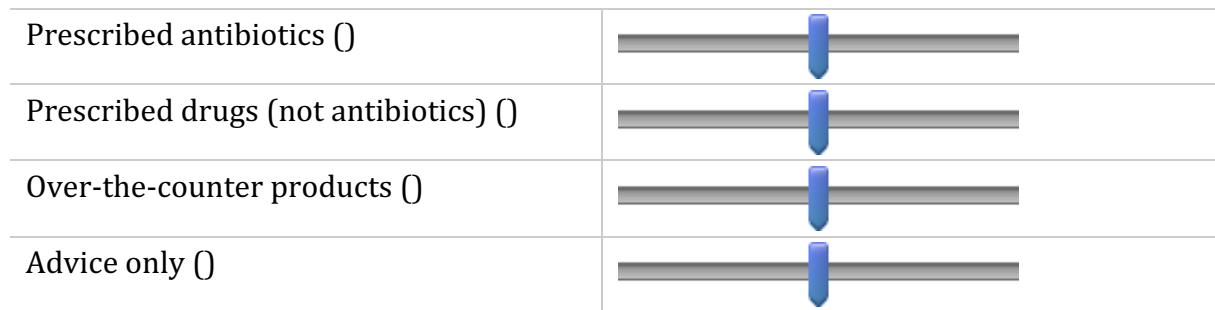
Q20 What is the average number of service users per week who visit for urinary tract infections?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



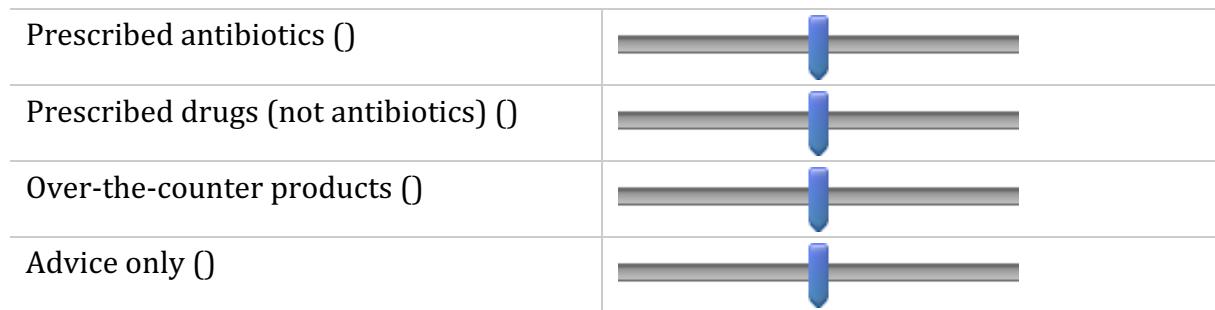
Q21 Among **men under 65 years**, what is the average number of service users per week who visit for urinary tract infections to get:

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



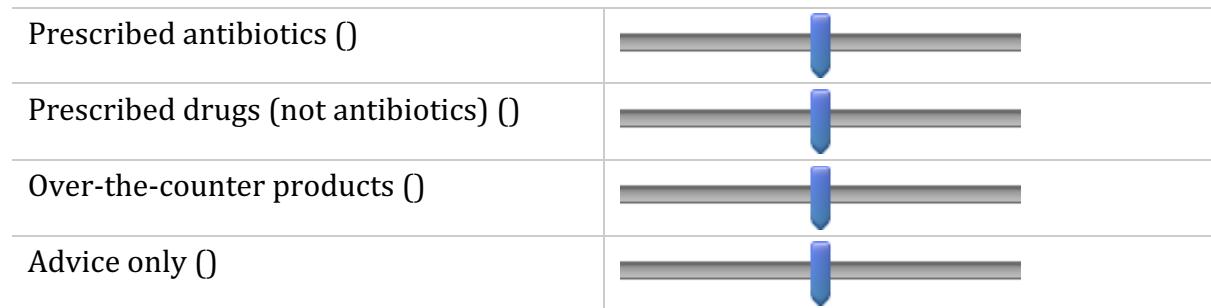
Q22 Among **women under 65 years**, what is the average number of service users per week who visit for urinary tract infections to get:

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



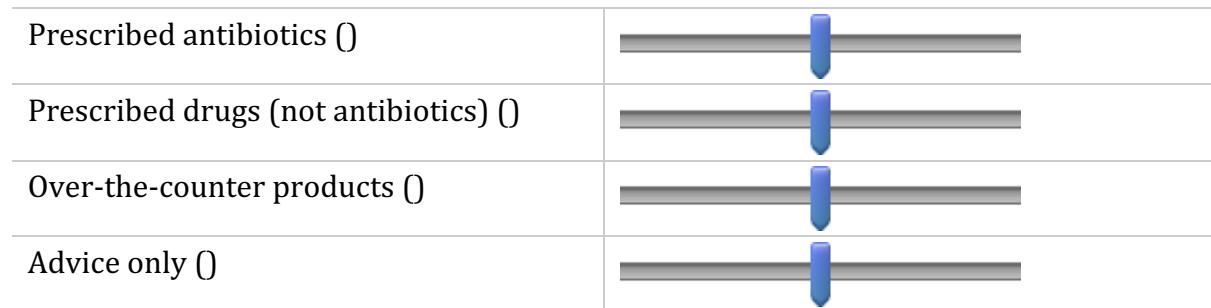
Q23 Among **men over 65 years**, what is the average number of service users per week who visit for urinary tract infections to get:

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



Q24 Among **women over 65 years**, what is the average number of service users per week who visit for urinary tract infections to get:

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20



Q25 At which point(s) do services users come to your pharmacy?

- Following a GP visit when they have been prescribed antibiotics (1)
 - Following a GP visit with no prescribed antibiotics (2)
 - Coming first to the pharmacy (no GP visit) (3)
 - Another stage (4) _____
-

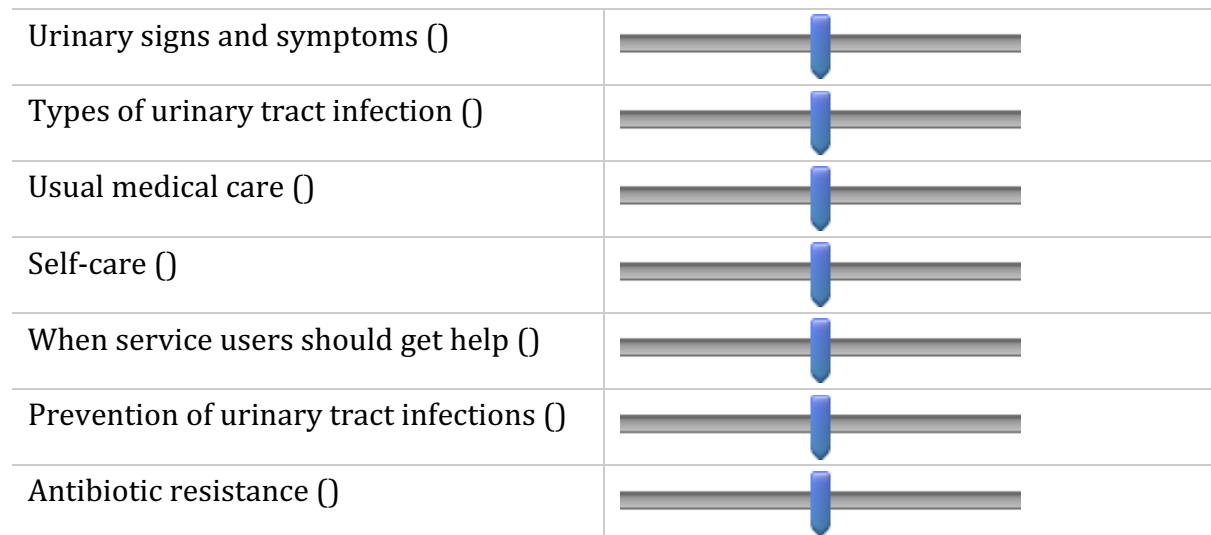
Q26 Which is the most frequent?

- Following a GP visit when they have been prescribed antibiotics (1)
 - Following a GP visit with no prescribed antibiotics (2)
 - Coming first to the pharmacy (no GP visit) (3)
 - Another stage (4) _____
-

Q27 How confident are you in discussing the following with service users?

Not at all confident Very confident

0 1 2 3 4 5 6 7 8 9 10



Q28 What, if any, self-care treatment options do you discuss with service users with suspected/proven urinary tract infection?

- Cystitis relief sachets (e.g. cranberry, sodium bicarbonate) (1)
 - Over-the-counter painkillers (e.g. nonsteroidal anti-inflammatory drugs, paracetamol) (2)
 - Adequate hydration (3)
 - Other over-the-counter products (4) _____
 - None (5)
-

Q29 Does your pharmacy use Patient Group Directives to dispense antibiotics to treat urinary tract infections?

- Yes (1)
 - No (2)
 - Do not know (3)
-

Q30 What sources of information do you use to give healthcare advice about urinary tract infections? Please say which.

- Leaflets (1) _____
- Websites (2) _____
- Other (3) _____

Q31 Please have a look at the two UTI information leaflets that have been developed by Public Health England in collaboration with various professional bodies. The leaflets aim to facilitate conversation between the service user and health care provider in their urinary symptoms and treatment plan. The leaflets also provide self-care and

preventative advice for the service user.

Q32 Leaflet for women under 65 years:

Please click once on the sections you like or twice on the sections you dislike.

	Dislike (1)	Neutral (2)	Like (3)
Possible signs (52)			
The outcome (53)			
Recommended care (54)			
Type of UTI (55)			
Self-care (56)			
Help (57)			
Options (58)			
Antibiotic resistance (59)			

Possible urinary signs & symptoms	The outcome	Recommended care	Types of urinary tract infection (UTI)
Key signs/symptoms: Dysuria: Burning pain when passing urine (wee) New nocturia: Needing to pass urine in the night Cloudy urine: Visible cloudy colour when passing urine Other severe signs/symptoms: Frequency: Passing urine more often than usual Urgency: Feeling the need to pass urine immediately Haematuria: Blood in your urine Suprapubic pain: Pain in your lower tummy Other things to consider: Recent sexual history <ul style="list-style-type: none"> • Inflammation due to sexual activity can feel similar to the symptoms of a UTI. • Some sexually transmitted infections (STIs) can have symptoms similar to those of a UTI. Changes during menopause <ul style="list-style-type: none"> • Some changes during the menopause can have symptoms similar to those of a UTI. 	All women: <input type="checkbox"/> If none or only one of: dysuria, new nocturia, cloudy urine; AND/OR vaginal discharge <ul style="list-style-type: none"> • Antibiotics less likely to help. • Usually lasts 5 to 7 days. • You may need a urine test to check for a UTI. Non-pregnant women: <input type="checkbox"/> If 2 or more of: dysuria, new nocturia, cloudy urine; OR bacteria detected in urine; AND NO vaginal discharge <ul style="list-style-type: none"> • Antibiotics are more likely to help. • You should start to improve within 48 hours. • Symptoms usually last 3 days. Pregnant women: Always request urine culture <input type="checkbox"/> If suspected UTI.	<input type="checkbox"/> Self-care and pain relief. <ul style="list-style-type: none"> • Symptoms may get better on their own. <input type="checkbox"/> Delayed or backup prescription with self-care and pain relief. Start antibiotics if symptoms: <ul style="list-style-type: none"> • Get worse. • Do not get a little better with self-care within 48 hours. <input type="checkbox"/> Immediate antibiotics prescription plus self-care. <input type="checkbox"/> If mild symptoms, delayed or back-up antibiotic prescription plus self-care. <input type="checkbox"/> Immediate antibiotic prescription.	<p>UTIs are caused by bacteria getting into your urethra or bladder, usually from your gut. Infections may occur in different parts of the urinary tract.</p>  <p>Kidneys (make urine) Infection in the upper urinary tract<ul style="list-style-type: none"> • Pyelonephritis (pie-lo-nef-right-is). • Not covered in this leaflet and always needs antibiotics. </p> <p>Bladder (stores urine) Infection in the lower urinary tract<ul style="list-style-type: none"> • Cystitis (sis-tight-is). </p> <p>Urethra (takes urine out of the body) Infection or inflammation in the urethra<ul style="list-style-type: none"> • Urethritis (you-ith-right-is). </p>
Self-care to help yourself get better more quickly	When should you get help? Contact your GP practice or NHS 111	Options to help prevent a UTI	Antibiotic resistance
<ul style="list-style-type: none"> • Drink enough fluids to stop you feeling thirsty. Aim to drink 6 to 8 glasses including water, decaffeinated and sugar-free drinks. • Take paracetamol or ibuprofen at regular intervals for pain relief, if you have had no previous side effects. • You could try taking cranberry capsules or cystitis sachets. These are effective for some women. There is currently no evidence to support their use. • Consider the risk factors in the "Options to help prevent UTI" column to reduce future UTIs. 	<p>The following symptoms are possible signs of serious infection and should be assessed urgently.</p> <p>Phone for advice if you are not sure how urgent the symptoms are.</p> <ol style="list-style-type: none"> 1. You have shivering, chills and muscle pain. 2. You feel confused, or are very drowsy. 3. You have not passed urine all day. 4. You are vomiting. 5. You see blood in your urine. 6. Your temperature is above 38°C or less than 36°C. 7. You have kidney pain in your back just under the ribs. 8. Your symptoms get worse. 9. Your symptoms are not starting to improve within 48 hours of taking antibiotics. 	<p><u>It may help you to consider these risk factors:</u></p> <p>Stop bacteria spreading from your bowel into your bladder. Wipe from front (vagina) to back (bottom) after using the toilet.</p> <p>Avoid waiting to pass urine. Pass urine as soon as you need a wee.</p> <p>Go for a wee after having sex to flush out any bacteria that may be near the opening to the urethra.</p> <p>Wash the external vagina area with water before and after sex to wash away any bacteria that may be near the opening to the urethra.</p> <p>Drink enough fluids to make sure you wee regularly throughout the day, especially during hot weather.</p> <p>If you have a recurrent UTI, also consider the following:</p> <ul style="list-style-type: none"> • Cranberry products and D-mannose: Some women find these effective, but there is currently poor evidence to support this. • After the menopause: You could consider topical hormonal treatment, for example, vaginal creams. 	<p>Antibiotics can be lifesaving. But antibiotics are not always needed for urinary symptoms.</p> <p>Antibiotics taken by mouth, for any reason, affect our gut bacteria making some resistant.</p> <p>Antibiotic resistance means that the antibiotics cannot kill that bacteria.</p> <p>Antibiotic resistant bacteria can remain in your gut for at least a year after taking an antibiotic.</p> <p>Common side effects to taking antibiotics include thrush, rashes, vomiting and diarrhoea. Seek medical advice if you are worried.</p> <p>Keep antibiotics working, only take them when advised by a health professional. This way they are more likely to work for a future UTI.</p>

Keep Antibiotics Working

Developed in collaboration with professional medical bodies. Version 20 October 2021. NAWI 16/07 © Crown copyright 2018.

Q34 Leaflet for service users over 65 years:

Please click once on the sections you like or twice on the sections you dislike.

	Dislike (1)	Neutral (2)	Like (3)
What is urine inf? (61)			
Prevent (62)			
Signs and symptoms (63)			
Confusion (64)			
To feel better (65)			
What might medics do (66)			
Advice about antibiotics (67)			
When help? (68)			

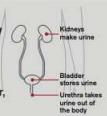
URINARY TRACT INFECTIONS

A leaflet for older adults and carers.

WHAT IS A URINE INFECTION?

A urine infection occurs when bacteria in any part of the urine system cause symptoms.

If a urine test finds bacteria but you are otherwise well, do not worry, this is common, and antibiotics are not usually needed. However, severe urine infections can be life threatening.



WHAT YOU CAN DO TO HELP PREVENT A URINE INFECTION?

Are you drinking enough? Look at the colour of your urine.



- Drink enough fluid (6-8 glasses) so that you pass pale coloured urine regularly during the day, and to avoid feeling thirsty, especially during hot weather
- Avoid drinking too many fizzy drinks or alcohol
- There is no proven benefit of cranberry products or cystitis sachets
- Prevent constipation. Ask for advice if needed
- Maintain good control of diabetes

Stop bacteria spreading from your bowel into your bladder:

- Wipe genitals from front to back after using the toilet
- Change pads and clean genitals if soiled
- Keep the genital area clean and dry; avoid scented soaps
- Wash with water before and after sex

Speak to your pharmacist about referral to a GP or other treatments.

WHAT SIGNS AND SYMPTOMS SHOULD YOU LOOK OUT FOR?

Consider these symptoms if you have a urinary catheter:

- Shivering or shaking
- High or low temperature
- Kidney pain in your back just under the ribs



New or worsening signs of urine infection in all people:

- Pain or burning when passing urine
- High or low temperature
- Shivering or shaking
- Urgency (feeling the need to urinate immediately)
- Pain in your lower tummy/above pubic area
- Inconvenience (wetting yourself more often than usual)
- Passing urine more often than usual
- Cloudy urine, or visible blood in your urine
- Confusion, change in behaviour, or unsteadiness on feet

ALTHOUGH CONFUSION IS CAUSED BY URINE INFECTION, CONSIDER OTHER THINGS THAT MAY ALSO CAUSE CONFUSION

- | | |
|---|--|
| <ul style="list-style-type: none"> • Pain • Constipation • Poor sleep • Low mood • Not drinking enough | <ul style="list-style-type: none"> • Side effects of medicine • Other infection • Change in your routine or home environment • Poor diet |
|---|--|

WHAT CAN YOU DO TO HELP FEEL BETTER?

- Drink enough fluid so that you pass urine regularly during the day, especially during hot weather
- Take paracetamol regularly, up to 4 times daily to relieve fever and pain
- There is no proven benefit of cranberry products or cystitis sachets
- If you're worried about wetting yourself, see your doctor or nurse for advice
- Ask for advice from your pharmacist/carer
- Drink enough fluids to avoid feeling thirsty and to keep your urine pale



WHAT MIGHT YOUR PHARMACIST / NURSE / DOCTOR DO?

- If your symptoms are likely to get better on their own you may receive self-care advice and pain relief
- Ask you to drink more fluid
- Ask you for a urine sample
- You may be given an antibiotic that you can use if your symptoms don't improve or you start to feel worse



ALWAYS TRUST YOUR PHARMACIST'S / NURSE'S / DOCTOR'S ADVICE ABOUT ANTIBIOTICS

- Antibiotics can be life saving for serious urine infections
- But antibiotics are not always needed for urinary symptoms
- Common side effects of taking antibiotics include thrush, rashes, vomiting and diarrhoea; ask for advice if you are worried
- Antibiotics affect the bacteria in your bowel, which may make them resistant to antibiotics for at least a year
- Keep antibiotics working, only take them when your doctor/nurse advises them

WHEN SHOULD YOU GET HELP?

The following symptoms are possible signs of serious infection and should be assessed urgently:

Contact your GP Practice or contact NHS 111 (England), NHS 24 (Scotland dial 111), NHS direct (Wales dial 0845 4647, or GP practice (NI)

Shivering, chills and muscle pain



Feeling very confused, drowsy or slurred speech



Not passing urine all day



Temperature is above 38°C or less than 36°C



Trouble breathing



Kidney pain in your back just under the ribs



Visible blood in your urine



Very cold skin



Symptoms are getting a lot worse, or not starting to improve within 2 days of starting antibiotics.

Trust your instincts, ask for advice if you are not sure how urgent the symptoms are.

Developed in collaboration with professional medical bodies. Version 1.2. Published: October 2018. Revision: June 2021

Appendix 6. Post-intervention electronic questionnaire for pharmacists

Q1 Thank you very much for taking part in this study about the use of urinary tract infection leaflets in pharmacies. A £30 voucher will be sent to you after you complete this short questionnaire and participate in the second phone interview.

Q2 What is the name and address of your pharmacy?

Q3 When did you use the UTI leaflets with service users? (multiple answers possible)

- Following a GP visit when they have been prescribed antibiotics (1)
 - Coming first to the pharmacy and that you then referred to the GP (3)
 - Coming first to the pharmacy and not referred on (6)
 - Another stage (4) _____
-

Q4 When did you use the UTI leaflets the most?

- Following a GP visit when they have been prescribed antibiotics (1)
 - Coming first to the pharmacy and that you then referred to the GP (2)
 - Coming first to the pharmacy and not referred on (3)
 - Another stage (4) _____
-

Q5 With approximately how many service users did you use the leaflet for women under 65 years?

Q6 With approximately how many service users did you use the leaflet for older adults?

Q7 Taking into account your interviews before the intervention, Public Health England have modified the leaflets and have produced a combined leaflet for all the service users.

Q8

Please click once on the sections you like or twice on the sections you dislike (zoom in to better see the leaflet).

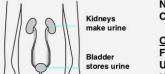
	Dislike (1)	Neutral (2)	Like (3)
what is a UTI (52)			
Possible signs and symptoms (55)			
Confusion (59)			
What can you do to prevent (60)			
Other causes of symptoms (61)			
Self-care (62)			
What might they do (63)			
Take advice (64)			
When should you get help? (65)			

URINARY TRACT INFECTIONS (UTIs)
A leaflet for adults with suspected UTI

WHAT IS A UTI?

A urinary tract infection (UTI) occurs when bacteria in any part of the urine system cause symptoms.

Diagnosis is made mainly on your symptoms. Urine dipstick tests are not usually used (unless pregnant).



POSSIBLE URINARY SIGNS & SYMPTOMS

Key signs/symptoms in ALL adults:

- Dysuria: Burning pain when passing urine
- New nocturia: Needing to pass urine in the night
- Cloudy urine: Visible cloudy colour when passing urine

Other severe signs/symptoms in ALL adults:

- Frequency: Passing urine more often than usual
- Urgency: Feeling the need to pass urine immediately
- Haematuria: Blood in your urine
- Suprapubic pain: Pain in your lower tummy

New or worsening signs of a UTI in OLDER, FRAIL adults:

- Incontinence: Wetting yourself more often than usual
- High or low temperature
- Shivering or寒颤
- Confusion, change in behaviour, or unsteadiness on feet

Consider these symptoms if you have a urinary catheter:

- Shivering or寒颤
- High or low temperature
- Kidney pain in your back just under the ribs

OTHER CAUSES OF URINARY SYMPTOMS TO CONSIDER

- Inflammation due to sexual activity
- Sexually transmitted infections (STIs)
- Vaginal changes during and after the menopause

ALTHOUGH CONFUSION CAN BE CAUSED BY UTIs IN OLDER, FRAIL ADULTS, CONSIDER OTHER THINGS THAT MAY ALSO CAUSE CONFUSION

- Pain
- Constipation
- Poor sleep
- Poor diet
- Low mood
- Not drinking enough
- Side effects of medicine
- Other infection
- Change in your routine or home environment

Speak to your pharmacist about referral to a GP or other treatments.

SELF-CARE
TO HELP YOURSELF GET BETTER MORE QUICKLY

- Drink enough fluids so that you pass pale urine regularly during the day, especially during hot weather!
- If you are worried about wetting yourself, see a healthcare professional for advice
- Take paracetamol regularly, up to 4 times daily to relieve fever and pain
- There is currently no evidence to support taking cranberry products or cystitis sachets to improve your symptoms
- Ask for advice from your pharmacist/carer

SHIVERING, CHILLS AND MUSCLE PAIN



NOT PASSING URINE ALL DAY



TROUBLE BREATHING



VISIBLY BLOODY URINE



WHEN SHOULD YOU GET HELP?

The following symptoms are possible signs of serious infection and should be assessed urgently:

Contact your GP Practice or contact NHS 111 (England), NHS 24 (Scotland dial 111), NHS direct (Wales dial 0845 4647), or GP practice (NI)

FEELING VERY CONFUSED, DROWSY OR SLURRED SPEECH



TEMPERATURE IS ABOVE 38°C OR LESS THAN 36°C



KIDNEY PAIN IN YOUR BACK JUST UNDER THE RIBS



VERY COLD SKIN



Symptoms are getting a lot worse, or not starting to improve within 2 days of starting antibiotics.

TRUST YOUR INSTINCTS, ASK FOR ADVICE IF YOU ARE NOT SURE HOW URGENT YOUR SYMPTOMS ARE

Developed in collaboration with: [publichealthengland.gov.uk](#), [target.org.uk](#), [version4.com](#), [unipharm.com](#), [rxbase.com](#)

Q9 What do you think of the new combined leaflet?

Q10 Do you think that the photos should be replaced with graphics / pictograms?

- Yes (1)
 - No (2)

Q11 Do you think that this leaflet will be easier to use than the two leaflets separately?

- Yes (1)
 - No (2)

Q12 Would you recommend using this combined leaflet or the two leaflets separately to your colleagues?

- The new combined leaflet (1)
- The two leaflets (2)

Appendix 7. Questionnaire for service users who used the leaflets

Options for completion:

1. Website - online via <https://surveys.phe.org.uk/UTIstudy>
 2. Website – online via QR code below



3. Return survey in prepaid envelope provided

Please read the Participant Information Sheet enclosed, or online, and complete the Informed Consent Form before completing the survey.

During your recent visit to the pharmacy for your urinary symptoms you were provided with a patient information leaflet. We would like to ask you a few questions about your experience at the pharmacy, the information the pharmacy staff gave you, and to get your thoughts on the use of the UTI leaflet in pharmacies.

Please contact utistudy@imperial.ac.uk if you have any questions.

You will be offered a £10 high street voucher on completion of the questionnaire

What is the number on the top right-hand side of your UTI leaflet?



For whose urinary symptoms did you recently visit the pharmacy?

Please tick one

- | | |
|--|--|
| <input type="checkbox"/> Mine | <input type="checkbox"/> A relative / friend over 65yrs |
| <input type="checkbox"/> My child | <input type="checkbox"/> A relative / friend under 65yrs |
| <input type="checkbox"/> Other, please specify | <input type="checkbox"/> Prefer not to say |

Even if you visited the pharmacy for someone else, please complete the rest of the questionnaire on behalf of that person.

Complete the following sentence about when you went to the pharmacy and got the UTI leaflet.

I went to the pharmacy...

Tick one

- with urinary symptoms before visiting another healthcare professional
- to pick up antibiotics I had been prescribed for a UTI
- to pick up antibiotics for someone else
- when the urinary symptoms came back or did not go away
- Don't know
- Other, please specify

Did you try to find information from anywhere else about your urinary symptoms before going to the pharmacy?

Tick all that apply

- No
- Yes, from family / friends / carer
- Yes, from another pharmacy
- Yes, from my GP / nurse
- Yes, online e.g. NHS choices
- Yes, other, please specify

Did you try anything to help your urinary symptoms before you went to the pharmacy?

Tick all that apply

- No
- Yes, I tried drinking fluids/more fluids
- Yes, I drank orange or lemon juice
- Yes, I took cranberry juice or capsules
- Yes, I took cystitis sachets

- Yes, I took painkillers e.g. paracetamol
- Yes, I took anti-inflammatory medicines e.g. ibuprofen
- Yes, I rested
- Yes, I took time off work
- Other, please specify

Where in the pharmacy were you given the UTI leaflet?

Tick one

- In a **private** consultation room
- Publicly** Over-the-counter / on the shop floor
- It was in / attached to my prescription bag
- Other, please specify

How often do you need to have someone help you when you read instructions, leaflets, or other written material from your doctor or pharmacy?

Never	Rarely	Sometimes	Often	Always
<input type="checkbox"/>				

Which best describes your experience in the pharmacy?

Tick one

- The pharmacy staff used the UTI leaflet to talk to me about my urinary symptoms / antibiotics
- The pharmacy staff spoke to me about my urinary symptoms / antibiotics and then gave me the UTI leaflet
- The pharmacy staff just gave me the UTI leaflet without any explanation
- I don't remember
- Other, please specify

Please tick how strongly you agree or disagree with the following statements. Please tick an option for each row

Pharmacy staff should discuss the UTI leaflet with patients / carers...

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
at the counter if they cannot be heard by other customers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
at the counter even if they can be heard by other customers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
anywhere in the pharmacy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
in a private consultation room	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tick how strongly you agree or disagree with the following statements about the UTI leaflet you were given.

The UTI leaflet...

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
has too much information	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
is colourful	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
has lots of useful information	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
is easy to understand	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
looks good	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tick how strongly you agree or disagree with the following statements about the information on the UTI leaflet you were given

Please tick an option for each row

The UTI leaflet improved my understanding of...

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
the signs and symptoms of urinary tract infections (UTIs)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
the different types of UTIs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
the ways I can use self-care to help my urinary symptoms get better quickly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
the signs and symptoms of serious infection that I should seek help for	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
how to help prevent a UTI	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
how antibiotic use can increase antibiotic resistance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please tick how strongly you agree or disagree with the following statements

Please tick an option for each row

The UTI leaflet made me more confident...

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
that I can help manage the symptoms of my UTI	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
that drinking more fluids will	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

help with my urinary symptoms					
that I can help prevent future UTIs	<input type="checkbox"/>				

Please give a reason for your answers

Looking back, when do you think the leaflet would be most helpful?

Tick one

- with urinary symptoms, before visiting another healthcare professional
- when picking up antibiotics prescribed for a UTI
- when the urinary symptoms came back or did not go away
- the UTI leaflet is not helpful
- Don't know
- Other, please specify

Who would you feel comfortable discussing your urinary symptoms and talking through the UTI leaflet with?

Tick all that apply

- Pharmacy staff
- GP/ Nurse
- Other, please specify

Please give a reason for your answer

[Redacted]

On the day you got the UTI leaflet, did you buy any products from the pharmacy to help your urinary symptoms?

- No
- Yes
- Do not know

[If yes] What did you buy?

Tick all that apply

- Cranberry juice
- Cranberry tablets / capsules
- Cystitis sachets
- Paracetamol
- Ibuprofen
- Other, please specify

[Redacted]

How do you plan to manage your urinary symptoms?

Tick all that apply

- Look out for signs of serious infection
- Take plenty of fluids to avoid feeling thirsty
- Take pain relief
- Take the antibiotics I have been prescribed
- Go to the GP, as advised by the pharmacist
- Go to the GP for a second opinion
- Go to another pharmacy for a second opinion
- Don't know
- Other, please specify

[Redacted]

What do you plan on doing with the UTI leaflet?

Tick all that apply

- Use the leaflet until my symptoms go away
- Keep it in case I need it in the future

- Show it to my friends / family to explain how to prevent urinary symptoms
- Show it to my friends / family if they have urinary symptoms in the future
- Throw it away
- Don't know
- Other, please specify

How useful is the UTI leaflet in managing the signs and symptoms of a UTI?

Tick one

Not at all useful	Not useful	Useful	Very useful
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please give a reason for your answer

How could the UTI leaflet be improved?

How would you rate your experience in the pharmacy?

Tick one

Poor	Fair	Good	Excellent
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please give a reason for your answer

[Large empty rectangular box]

How could your pharmacy experience be improved?

[Large empty rectangular box]

Please use the space below if you have any other comments about the leaflet or your pharmacy

[Large empty rectangular box]

Demographic Questions

The leaflet was completed for a person: Yes / No

Age

Tick one

- 18-24 years
- 25-34 years

- 35-44 years
- 45-54 years
- 55-64 years

- 65-74 years
- 75 years or older
- Prefer not to say

Gender

Tick one

- Male
- Female
- Other
- Prefer not to say
- Prefer to self-describe

Ethnicity

Tick one

- White
- Mixed / multiple ethnic groups
- Asian / Asian British
- Black / African / Caribbean / Black British
- Other ethnic group please specify.....

Marital status

Tick one

- Single (never married)
- Married, or in a domestic partnership
- Widowed
- Divorced
- Separated
- Prefer not to say

History of UTI

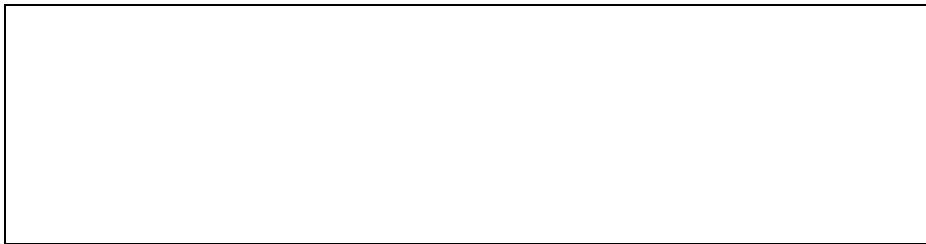
Tick one

- First time
- I've had one or two before
- I have recurrent UTIs (2 or more infections in six months or 3 or more infections in one year)
- Don't know
- Prefer not to say

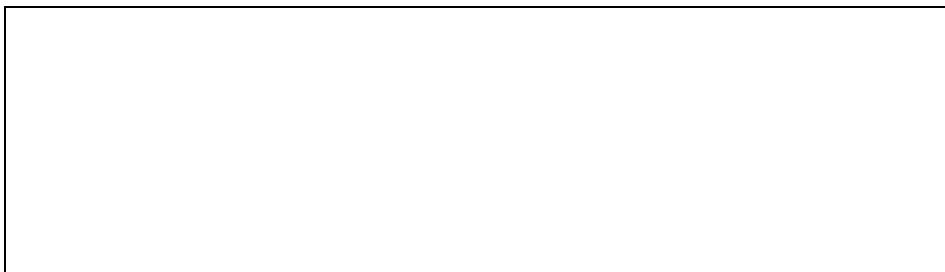
THANK YOU FOR COMPLETING THE SURVEY – Please return along with the signed Informed Consent Form.

Please fill in the details below to receive your £10 gift voucher.

Name



Address

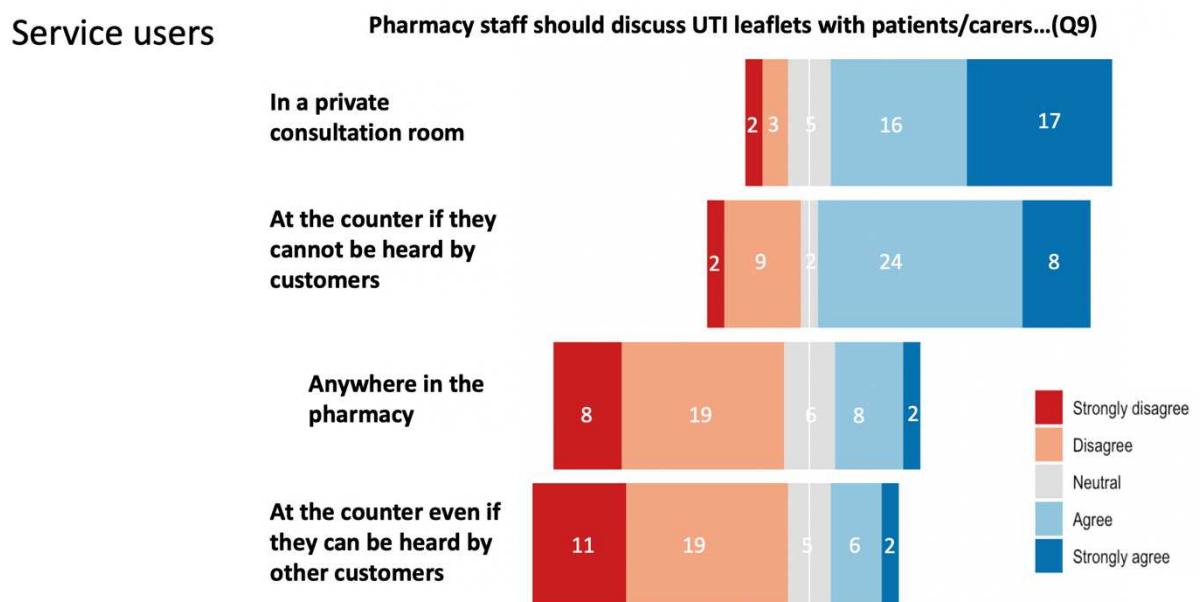


This sheet will be detached from your survey response so that the response remains anonymous.

Appendix 8. Survey with service users – full results

Service users		n (%) (n=51)
Women		43 (84)
Age		
	Children	1 (2) (completed by the mother)
	18-24	8 (16)
	25-34	10 (20)
	35-44	4 (8)
	45-54	11 (22)
	55-64	7 (14)
	65-74	4 (8)
	>75	4 (8)
Ethnicity		
	White	27 (53)
	Asian	14 (27)
	Black	4 (8)
	Mixed	4 (8)
Marital status		
	Married	22 (43)
	Single	16 (31)
	Widowed	9 (18)
	Divorced	4 (8)
UTI history		
	Recurrent UTIs	21 (41)
	One or two prior episodes	23 (45)
	No prior episode	6 (12)
Went to the pharmacy		
	to pick up antibiotics after GP/nurse visit	35 (67)
	before visiting another healthcare professional	12 (24)
	Because the symptoms came back or did not go away	2 (4)
Other sources of information (than GP/nurse or pharmacist)		
	Family	15 (29)
	Online e.g. NHS choices	9 (18)
	None	27 (53)
Selfcare before healthcare professional		
	Drink more fluids	31 (62)
	Cystitis sachets	15 (30)
	Cranberry juice	12 (24)
	Rest	10 (20)
	Painkillers	8 (16)
	Nothing	7 (14)
	Time off work	6 (12)
	NSAIDs	3 (6)

	Lemon / orange juice	2 (4)
	Did you buy OTC products in the pharmacy?	
	Yes	22 (43)
	NSAIDs	13 (25)
	Cystitis sachets	9 (18)
	Paracetamol	4 (8)
	Cranberry tablets	3 (6)
	No	29 (57)
	Who would you feel comfortable discussing your urinary symptoms with?	
	GP / nurse	18 (35)
	Pharmacy staff	7 (14)
	GP/nurse or pharmacy staff	26 (51)
	The leaflet is more useful	
	with urinary symptoms, before visiting another healthcare professional	28 (55)
	when picking up antibiotics prescribed for a UTI	12 (24)
	when the urinary symptoms came back or did not go away	7 (14)
	Experience in the pharmacy	
	Excellent	18 (35)
	Good	25 (49)
	Fair	8 (16)
	Poor	0





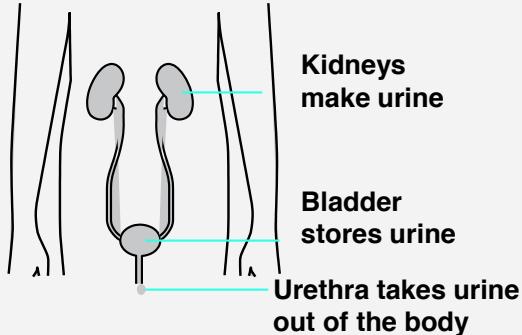
URINARY TRACT INFECTIONS (UTIs)

A leaflet for adults with suspected UTI

WHAT IS A UTI?

A urinary tract infection (UTI) occurs when bacteria in any part of the urine system cause symptoms.

Diagnosis is made mainly on your symptoms. Urine dipstick tests are not usually used (unless pregnant).



WHAT YOU CAN DO TO HELP PREVENT A UTI

Are you drinking enough? Look at the colour of your urine.



- Drink enough fluid (6-8 glasses) so that you pass pale coloured urine regularly during the day, and to avoid feeling thirsty, especially during hot weather
- Avoid drinking too many fizzy drinks or alcohol
- Prevent constipation. Ask for advice if needed
- Maintain good control of diabetes

Stop bacteria spreading from your bowel into your bladder:

- Keep the genital area clean and dry; avoid scented soaps
- Wipe genitals from front to back after using the toilet
- Pass urine after having sex
- Wash the external vagina area with water before and after sex
- Change pads and clean genitals if soiled

If you have recurrent UTIs, the following may help:

- Cranberry products and D-mannose: There is some evidence to say that these work to help prevent recurrent UTI in younger adults
- After the menopause: Topical hormonal treatment may help
- Antibiotics at night or after sex may be used if other measures do not work

Speak to your pharmacist about referral to a GP or other treatments.



POSSIBLE URINARY SIGNS & SYMPTOMS

Key signs/symptoms in ALL adults:

Dysuria: Burning pain when passing urine

New nocturia: Needing to pass urine in the night

Cloudy urine: Visible cloudy colour when passing urine



Other severe signs/symptoms in ALL adults:

Frequency: Passing urine more often than usual

Urgency: Feeling the need to pass urine immediately

Haematuria: Blood in your urine

Suprapubic pain: Pain in your lower tummy



New or worsening signs of a UTI in OLDER, FRAIL adults:

Incontinence: Wetting yourself more often than usual

High or low temperature

Shivering or shaking

Confusion, change in behaviour, or unsteadiness on feet



Consider these symptoms if you have a urinary catheter:

Shivering or shaking

High or low temperature

Kidney pain in your back just under the ribs

OTHER CAUSES OF URINARY SYMPTOMS TO CONSIDER

- Inflammation due to sexual activity
- Sexually transmitted infections (STIs)
- Vaginal changes during and after the menopause

ALTHOUGH CONFUSION CAN BE CAUSED BY UTIs IN OLDER, FRAIL ADULTS, CONSIDER OTHER THINGS THAT MAY ALSO CAUSE CONFUSION

- | | | |
|----------------|----------------------------|--|
| • Pain | • Low mood | • Change in your routine or home environment |
| • Constipation | • Not drinking enough | |
| • Poor sleep | • Side effects of medicine | |
| • Poor diet | • Other infection | |

Speak to your pharmacist about referral to a GP or other treatments.



SELF-CARE TO HELP YOURSELF GET BETTER MORE QUICKLY

- Drink enough fluids so that you pass pale urine regularly during the day, especially during hot weather
(If you are worried about wetting yourself, see a healthcare professional for advice)
- Take paracetamol regularly, up to 4 times daily to relieve fever and pain
- There is currently no evidence to support taking cranberry products or cystitis sachets to improve your symptoms
- Ask for advice from your pharmacist/carer



WHAT MIGHT YOUR PHARMACIST / NURSE / DOCTOR DO?

- Give self-care advice and advise pain relief (paracetamol)
- Ask you to drink more fluids
- Ask you for a urine sample
- You may be given an antibiotic immediately or to use if your symptoms don't improve or you start to feel worse (or referred to your GP)

TAKE YOUR PHARMACIST'S / NURSE'S / DOCTOR'S ADVICE WHEN IT COMES TO ANTIBIOTICS

- Antibiotics can be life saving for serious urine infections
- But antibiotics are not always needed for urinary symptoms
- Common side effects of taking antibiotics include thrush, rashes, vomiting and diarrhoea; ask for advice if you are worried
- Antibiotics affect the bacteria in your bowel, which may make them resistant to antibiotics for at least a year
- Keep antibiotics working, only take them when your doctor/nurse advises them

**Taking ANTIBIOTICS when you don't need them
puts you and your family at risk**



WHEN SHOULD YOU GET HELP?

The following symptoms are possible signs of serious infection and should be assessed urgently:

Contact your GP Practice or contact NHS 111 (England), NHS 24 (Scotland dial 111), NHS direct (Wales dial 0845 4647), or GP practice (NI)

Shivering,
chills and
muscle pain



Not passing
urine all day



Trouble
breathing



Visible blood
in your urine



Feeling very
confused,
drowsy or
slurred speech



Temperature is
above 38°C or
less than 36°C



Kidney pain in
your back just
under the ribs



Very cold skin



Symptoms are getting a
lot worse, or not starting
to improve within 2 days
of starting antibiotics.

**Trust your instincts, ask for advice if you are not
sure how urgent your symptoms are**



Developed in collaboration with professional medical bodies, Version x, unpublished, Revision:TBC

Appendix 9. List of the machine learning clinical decision support systems included in the review

Topic	Publication	Year	Output	Particular population / Settings	Data	ML algorithm	Evaluation*
Diagnosis of infection	Lamping et al. ¹	2018	Non-infectious SIRS or sepsis	Pediatric patients ICU	Structured clinical data Laboratory Therapy	Random Forest (RF)	Performance
	Hernandez et al. ²	2017	Diagnostic of culture-positive infection in hospitalized patients	Medical ward	Laboratory	Support Vector Machine (SVM) RF Decision tree Gaussian Naïve Bayes (GNB)	Performance
	Rawson et al. ³	2018	Diagnostic of bacterial infection on presentation to hospital	Emergency department	Laboratory	SVM	Performance Use
	Horng et al. ⁴	2017	Diagnostic of infection on presentation to hospital	Emergency department	Demographics Vitals Chief complaint Free text	SVM (Support vector machine)	Performance
	Taylor et al. ⁵	2018	Prediction of UTI infection	Emergency department	Demographics Vitals Medical history Physical findings Laboratory Outpatient medication	Random forest (RF) Extreme gradient boosting Adaptive boosting Support vector machine (SVM) Elastic net ANN LR	Performance

Revuelta-Zamorano et al. ⁶	2016	Prediction of HAI	ICU	Demographics Structured clinical data "Medical remarks"	Support Vector Machines (SVM) Decision Trees Random Forest (RF)	Performance
D'Angelo et al. ⁷	2019	Distinction between bacterial and viral meningitis	Medical ward	Demographics CSF characteristics	Naïve Bayes Classifier ANN (Artificial Neural Network) Decision tree Genetic programming and symbolic regression	Performance
Revett et al. ⁸	2006	Distinction between bacterial and viral meningitis	Medical ward	Age Laboratory	ANN	Performance
Hartvigsen et al. ⁹	2018	Prediction of MRSA infection	ICU	Demographics Vitals Laboratory Microbiology Antibiotics	Logistic Regression (LR) Support Vector Machine (SVM) Random Forest (RF)	Performance
Van Steenkiste et al. ¹⁰	2018	Predicting positive blood cultures	ICU	Vitals Laboratory	ANN SVM KNN LR	Performance
Sanger et al. ¹¹	2016	Prediction of surgical site infection	Surgical ward	Demographics Vitals Laboratory Intervention parameters Abdominal wound characteristics	Naïve Bayes classifier SVM	Performance
Kuo et al. ¹²	2018	Prediction of surgical site infection	Surgical ward	Demographics Structured clinical data Intervention parameters Laboratory	Artificial Neural Network (ANN)	Performance

	Bartz-Kurycki et al. ¹³	2018	Prediction of surgical site infection	Surgical ward Neonates	Demographics Comorbidities Laboratory Intervention parameters	Logistic regression (LR) Random Forest (RF)	Performance
	Ke et al. ^{14,14}	2016	Prediction of surgical site infection	Surgical ward	Demographics Risk factors Intervention parameters Abdominal wound characteristics Structured clinical data	Matrix regularization KNN Bayesian	
	Melendez et al. ¹⁵	2016	Screening of TB	Patients with a suspicion of TB presenting in primary care health centres	Vitals Medical history Physical examination (structured) Chest X-Ray (structured)	Random forests (RF) Extremely randomized trees (ERT)	Performance
	Saybani et al. ¹⁶ Shamshirband et al. ¹⁷	2015	Diagnosis of TB	Patients with a suspicion of TB (outpatient settings)	Demographics Physical examination (structured) Laboratory	SVM Unsupervised	Performance
	Ansari et al. ¹⁸	2012	Diagnosis of TB	Patients with a suspicion of TB (outpatient settings)	Demographics Medical history	ANN (Backpropagation rules-based)	Performance
	Er et al. ¹⁹	2010	Diagnosis of TB	Patients with a suspicion of TB	Medical history Vitals Physical examination (structured) Laboratory	ANN	Performance

			(outpatient settings)				
	El-Sohi et al. ²⁰	1999	Diagnosis of active TB	Patients with a suspicion of TB in the emergency department	Demographics Medical history Symptoms (structured) Structured X-Ray findings Laboratory	ANN	Performance
	Santos et al. ²¹		Diagnosis of smear-negative pulmonary TB	Patients with a suspicion of TB (outpatients and inpatients)	Demographics Medical history Symptoms	ANN	Performance
Sepsis	Culliton et al. ²²	2017	Prediction of sepsis	ICU	Structured clinical data (not detailed) Free text (not detailed)	Ridge regression (weight decay)	Performance
	Mani et al. ²³	2014	Prediction of sepsis	Neonates ICU	Structured clinical data Laboratory	SVM K-nearest neighbor (KNN) Decision tree Naïve Bayes RF Logistic regression (LR)	Performance
	Insight / Dascena algorithm Desautels et al. ²⁴ Calvert et al. ²⁵ Shimabukuro et al. ²⁶ McCoy et al. ²⁷ Calvert et al. ²⁸ Mao et al. ²⁹ Burdick et al. ³⁰ Burdick et al. ³¹	2016 - 2018	Prediction of sepsis	Pediatric patients ICU	Demographics Vitals Laboratory (MIMIC-II)	Gradient tree boosting	Performance Use

	Taneja et al. ³²	2017	Prediction of sepsis and stratification of sepsis	ICU	EMR data Biomarkers (e.g. IL-1 β , IL-6, etc.) in a single blood sample	Logistic regression (LR) SVM RF Adaboost Naïve Bayes (NB)	Performance
	Henry et al. ³³	2015	Prediction of patients at high risk of developing septic shock	ICU	Vitals Structured clinical data Laboratory Real-time data	Cox proportional hazards model with lasso regularization	Performance
	Nemati et al. ³⁴ Henry et al. ³⁵	2018	Prediction of sepsis	ICU	Demographics Vitals Laboratory	Modified Weibull-Cox proportional hazards model with gradient descent?	Performance
	Ghosh et al. ³⁶		Prediction of septic shock	ICU	Vitals (MIMIC-II)	SVM Hidden Markov Model (Bayes)	Performance
	Liu et al. ³⁷	2017	Diagnosis of sepsis	ICU	Demographics Laboratory	Artificial neural network (ANN) Support vector machine (SVM) Random forest (RF)	Performance
	Saqib et al. ³⁸	2018	Prediction of sepsis	ICU	Demographics Vitals Laboratory (MIMIC-III)	LR RF ANN	Performance
	Shashikumar et al. ⁶¹	2017	Prediction of sepsis	ICU	Demographics Vitals Structured clinical ECG	Elastic Net logistic	Performance
	Hu et al. ³⁹	2018	Prediction of sepsis	Neonates ICU	Vitals	LR SVM RF GBDT Gradient Boosting Decision Tree ANN	Performance
	Wang et al. ⁴⁰	2018	Prediction of sepsis	ICU	Demographics Vitals	Logistic regression (LR) Support vector machines	Performance

				Laboratory (MIMIC-III)	(SVM) Logistic model trees (LMT = LR + Decision Tree)		
	Khoshnevisan et al. ⁴¹	2018	Prediction and diagnosis of sepsis	ICU	Vitals Laboratory	ANN	Performance
	Van Wyk et al. ⁴²	2018	Prediction of sepsis	ICU	Vitals Laboratory	Random Forest (RF)	Performance
	Moor et al. ⁴³	2019	Prediction of sepsis	ICU	Vitals Laboratory	ANN	Performance
	Mitra et al. ⁴⁴	2018	Prediction of sepsis	ICU	Vitals (MIMIC-III)	Logistic Regression (LR) Random Forest (RF) XGBoost (XGB) ANN: feedforward neural network or Multilayer Perceptron (MLP)	Performance
	Apostolova et al. ⁴⁵	2018	Diagnosis of sepsis	ICU	Nursing notes (free text) (MIMIC-III)	SVM LR KNN	Performance
	Futoma et al. ^{46,47}	2017	Prediction of sepsis	ICU	Demographics Medical history Vitals Laboratory Partial treatment history	ANN	Performance
Antibiotic selection	Shen et al. ⁴⁸	2018	Infection inference and choice of first-line antibiotic therapy	Primary care	Patient-entered and patient-reported information	Unspecified (mix of knowledge representation, decision tree and fuzzy logic?)	Performance
	Beaudoin et al. ⁴⁹	2016	Identification of inappropriate prescriptions of piperacillin-tazobactam	Antimicrobial stewardship	Demographics Vitals Laboratory	Supervised learning rule induction algorithm	Use
	Tsoukalas et al. ⁵⁰ Spaan et al. ⁵¹	2015	Stratification of sepsis and optimal antimicrobial prescribing	ICU	Structured clinical data Laboratory Microbiology	Partially observable Markov Decision Process (POMDP) Model Value iteration (Reinforcement learning)	Performance

Prediction of resistance	Oonsivilai et al. ⁵²	2018	Prediction of antibiotic susceptibilities	Pediatric patients Medical ward or ICU	Demographics Medical history Partial treatment history	Logistic regression (LR) Random forests (RF) Boosted decision trees using adaptive boosting SVM KNN	Performance
	Yelin et al. ⁵³	2018	Prediction of antibiotic susceptibilities	Primary care (including retirement-home)	Demographics Urine sample history Antibiotic purchase history	Logistic Regression (LR) Gradient Boosting Decision Trees	Performance
	Li et al. ⁵⁴	2016	Prediction of the risk of TB patients converting to MDR-TB	TB outpatients	Demographics Laboratory Microbiology Treatment	Ensemble learning	Performance
HIV therapy selection	Ying et al. ⁵⁵	2007	HIV therapy selection (initial combination)	HIV outpatients	Regimen selection by experts Treatment parameters (e.g. potency, adverse, etc.)	Genetic algorithm coupled to fuzzy discrete event system (supervised)	Performance
	Parbhoo et al. ⁵⁶		HIV therapy selection	HIV outpatients	Demographics Structured clinical data Treatment history (EuResist)	Kernel-based (regression) approach (reinforcement learning) and bayesian POMDP	Performance
Prediction of treatment response	Hatzakis et al. ⁵⁷	2005	HIV: Prediction of virologic success/failure	HIV outpatients	Demographics Structured clinical data Treatment parameters	Artificial Neural Network (ANN)	Performance
	Zazzi et al. ⁵⁸ Rosen-Zvi et al. ⁵⁹ Zazzi et al. ⁶⁰ Prosperi et al. ⁶¹	2008 2012	HIV: Prediction of virologic success/failure and change in viral load	HIV outpatients	Demographics Structured clinical data Viral subtypes Treatment history Genotype	Generative-discriminative method, regression with derived evolutionary features	Performance
	Revell et al. ⁶² Revell et al. ⁶³	2007 2011	HIV: Prediction of virological response to	HIV outpatients	Treatment history Virologic data	Random forest (RF)	Performance

Larder et al. ⁶⁴	2018	a new therapy following failure		Genotype data	Artificial neural network (ANN)	
Petersen et al. ⁶⁵	2015	HIV: Prediction of virological failure	HIV outpatients	Pill container openings recorded (MEMS data) Laboratory Treatment history	LASSO	Performance
Beerenwinkel et al. ⁶⁶	2003	HIV: Prediction of viral response	HIV outpatients	Treatment history Virologic data Genotypes	SVM	Performance
Aval et al. ⁶⁷	2014	HCV: Prediction of response to Peg-IFN and RBV	HCV outpatients	Demographics Laboratory Biopsy results Genotype	Artificial neural network (ANN)	Performance
Maiellaro et al. ⁶⁸	2004	HCV: Prediction of response to Peg-IFN and RBV	HCV outpatients	Structured clinical Treatment parameters	Artificial neural network (ANN)	Performance
Takayama et al. ⁶⁹	2011	HCV: Prediction response to Peg-IFN and RBV	HCV outpatients	Demographics Laboratory Treatment parameters	Artificial neural network (ANN)	Performance
Hussain et al. ⁷⁰	2018	Prediction of completing treatment in drug-susceptible TB patients	TB outpatients	Demographics Structured clinical data Structured X-ray (0/1) Microbiology Baseline treatment	ANN SVM RF	Performance
Sauer et al. ⁷¹	2018	Prediction of treatment failure in TB patients	TB outpatients (TB portal database)	Demographics Medical history Structured imaging Microbiology Treatment	LASSO Stepwise regression Random forests (RF) SVM	Performance

*We separated studies that describe the performance (e.g. ROC curves) of the ML-CDSS, studies that describe the use of the CDSS in real-life settings and studies that describe the adoption of the CDSS in routine clinical practice.

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Appendix 10. Description of the patient variables analysed in each machine learning clinical decision support system included in the review

Publication	Data	Demographics	Medical history	Vitals	Symptoms / Physical examination	Other patient data (free text, ECG, imaging)	Laboratory	Microbiology	Therapeutic history
Lamping et al. ¹	Structured clinical data Laboratory Treatment	age sex weight at admission height at admission	PIM II at ICU admission PRISM score at ICU admission Length of ICU stay until onset of SIRS/ sepsis cumulative sepsis or SIRS episodes (n) total SIRS episovitedes (n) total sepsis episodes (n)	fraction of inspired oxygen (FiO2)*** respiratory frequency central venous pressure (CVP) systolic blood pressure (SBP) heart rate (HR) core temperature			pH (blood gas) partial pressure of carbon dioxide (pCO2) bicarbonate (HCO3-) oxygen saturation (SO2) central venous oxygen saturation (ScvO2) lactate aspartate transaminase (AST), serum alanine transaminase (ALT), serum glutamate dehydrogenase (GLDH) phosphate, serum (PO43-) creatinine, serum urea		surgery previous to ICU admission central venous catheter mechanical ventilation treatment with antibiotics***** yes/no treatment with steroids***** yes/no treatment with catecholamines yes/no number of peripheral IV cannulas
							urinary excretion C-reactive protein (CRP) procalcitonin, serum (PCT) interleukin 6 (IL-6) hemoglobin (Hb) leucocyte count platelet count fibrinogen D-dimer partial thromboplastin time (PTT) international normalized ratio (INR)		
Hernandez et al. ²	Laboratory						ALP ALT BIL CRE CRP WBC		
Rawson et al. ³	Laboratory						CRP white cell count (WCC) creatinine (Cr) ALT bilirubin (BIL) alkaline phosphatase (ALP)		
Horng et al. ⁴	Demographics Vitals Chief complaint Free text	Age Gender	Acuity (emergency)	Systolic blood pressure Diastolic blood pressure Heart rate		Free text chief complaint Free text nursing assessment			

				Pain scale Respiratory rate Oxygen saturation Temperature				
Taylor et al. ⁵	Demographics Vitals Medical history Physical findings Laboratory Outpatient medication	Demographic (5)	Arrival info (5) Past Medical/Surgical History (40)	Vitals (39)	Urinalysis (16) Physical Findings (28)	Labs (29)		Outpatient Medications (48: yes/no)
Revuelta-Zamorano et al. ⁶	Demographics Structured clinical data "Medical remarks"	Gender Age	Request microbiology Date request microbiology Sample ICU admission dates (start, end) Bed Length of stay Admission month			Clinical narrative free text which provides information about the patient's health status at the ICU admission or when a laboratory request was made.	Microbiology	
D'Angelo et al. ⁷	Demographics CSF characteristics	Age Race Sex				WBC Blood glucose CSF glucose CSF protein Total leukocytes in CSF		
Revett et al. ⁸	Age Laboratory	Age				Blood glucose CSF Glucose CSF protein CSF lymphocytes CSF leukocytes		
Hartvigsen et al. ⁹	Demographics Vitals	Age Gender	Admission type (emergency...)	Vitals (24)		Laboratory (20)	Microbiology (13)	Antibiotics

	Laboratory Microbiology Antibiotics	Ethnicity Marital status Religion	Admission location (transfer) Insurance Services (cardiac surgery)					High-risk antibiotics H2 antagonists PPIs
Van Steenkiste et al. ¹⁰	Vitals Laboratory			Temperature Mean systemic arterial pressure Heart rate Respiratory rate SOFA			Blood thrombocyte count Blood leukocyte count C-reactive protein concentration INR	
Sanger et al. ¹¹	Demographics Vitals Laboratory Intervention parameters Abdominal wound characteristics	Age Sex	Smoking Diabetes Chronic lung disease Ascites Infection (non SSI) at intake Alcohol use Alcohol quantity ASA score BMI Length of stay 30 day mortality In-hospital mortality	Heart rate Diastolic BP Systolic BP Tympanic temperature	Wound: induration, wound edge, slough/necro sis aspect, necrosis amount, granulation score, exudate type, exudate amount, wound edge color, wound malodor, hematoma, wound mass palpable, seroma, wound culture visual analog pain scale, wound length,	Hb Protein Albumin BUN Creatinine CRP Platelet WBC PT aPTT	Duration of surgery Ventilator Antibiotics (yes/no) Wound class (clean clean conta conta dirty) Type of operation (gastroduodenum. ..) emergency surgery Kidney / liver transplantation Ostomy Blood transfusion Systemic corticosteroids Chemotherapy Radiotherapy Reoperation Nasogastric tube	
Kuo et al. ¹²	Demographics Structured clinical data Intervention parameters Laboratory	Sex Age BMI	Tumor stage Tumor location Primary / Recurrent Betelnut hx Smoking hx Alcohol hx Diabetes Mellitus Hypertension Cerebral vascular accident Heart disease Liver disease Kidney disease		wound temperature		RBC WBC Hb Neutrophil Platelets INR Albumin Glucose K BUN Creatinine Na ASST ALT	Radiotherapy Chemotherapy Vein grafting Opposite recipient vessel Anastomosed vessels OP doctors Re-open Flap Flap length OP time OP experience Transfusion whole blood Transfusion packed RBC Transfusio plasma Transfusion platelets
Bartz-Kurycki et al. ¹³	Demographics Comorbidities Laboratory Intervention parameters	Gender Hispanic ethnicity Location of birth Race Weight at surgery (pounds) Age in days	Acute renal failure within 7 days prior to surgery ASA classification Asthma Biliary/liver/pan creatic disease Birth weight (<1500 g) Bronchopulmon ary dysplasia/Chroni c lung disease				Previous CPR within 7 days	Case status (elective/urgent/e mergent) Inotropic support at time of surgery Multiple procedures in same operation Open wound (with or without infection) Operative technique Ostomy Oxygen support

			Cardiac risk factors Cerebral palsy Congenital malformation (binary) Congenital malformation with birthweight Current pneumonia Cystic Fibrosis Developmental delay/impaired cognitive status Do Not Resuscitate (DNR) status Esophageal/Gastric/Intestinal disease Gestational age at birth Hematologic disorder Hospital status Interventricular hemorrhage Interventricular hemorrhage grade Mode of delivery Neonate type Neuromuscular Disorder Previous cardiac surgery Seizure Disorder					Preoperative dialysis Preoperative transfusion (within 48 h prior to surgery) Prior operation within 30 days Steroid use (within 30 d) Surgical Site (based on CPT code) Surgical specialty Surgical wound classification Tracheostomy Ventilator dependence Total operation time Nutritional support
			SIRS/sepsis/septic shock within 48 h prior to surgery Small for gestational age Structural pulmonary/Airway abnormalities Structural CNS Abnormality Weight loss or failure to thrive Admission year Transfer status Days from Hospital Admission to Operation					
Ke et al. ¹⁴	Demographics Risk factors Intervention parameters Abdominal wound characteristics Structured clinical data	Age Gender	Smoking Diabetes mellitus Chronic lung disease Ascites Infection (non SI) Alcohol use Alcohol quantity BMI	Heart rate Diastolic RR Systolic RR Tympanic temperature	Wound : induration, wound edge, slough/necrosis aspect, necrosis amount, granulation score, exudate type, exudate amount, wound edge color, wound malodor, hematoma, wound mass palpable, seroma, wound culture			Ventilator Antibiotics Type of operation Systemic corticosteroid Chemotherapy Radiotherapy Reoperation Nasogastric tube

					visual analog pain scale, wound length, wound temperature Cough Productive cough Vomiting Suspicion of ileus			
Melendez et al. ¹⁵	Vitals Medical history Physical examination (structured) Chest X-Ray (structured)	HIV status	Axillary temperature Heart Rate BMI	MUAC (mid-upper arm circumference) Anaemic conjunctivae Lung auscultation findings (1/0) Cough Haemoptysis Night sweats Dyspnoea Chest pain	Chest X-Ray as evaluated by a CAD score in a range 0-100			
Saybani et al. ¹⁶ Shamshirband et al. ¹⁷	Demographics Physical examination (structured) Laboratory	Sex		Chest pain Weight loss Coughs Night sweats Fever Shortness of breath Purified Protein Derivative (PPD)	CD4 counts HIV WBC Neutrophil count Platelet Hb ALT ESR Lymphocyte count ALK			

							LDH Albumin concentration		
Ansari et al. ¹⁸	Demographics Medical history	Age International connections Economic status	Weakened immune system (yes / no including HIV, diabetes, malnutrition...) Alcohol consumption						
Er et al. ¹⁹	Medical history Vitals Physical examination (structured) Laboratory		Smoking	Temperature	Complaint of cough Chest pain Weakness Dyspnea Rattle in chest Pressure on chest Sputum Sound on respiratory tract		WBC RBC PLT HCT Hb Albumin ALK ALT Amylase AST Bilirubin CK CK-MB Iron GGT Glucose HDL-cholesterol Calcium BUN Cl- Cholesterol Creatinin LDH K Na Protein Triglycerids Uric acid		
El-Sohl et al. ²⁰	Demographics Medical history Structured X-Ray findings Symptoms Laboratory	Age	Diabetes mellitus HIV		PPD (Mantoux) Chest pain Weight loss Cough Night sweats Fever Shortness of breath	Structured X-Ray findings: Upper lobe infiltrate Lower lobe infiltrate Upper lobe cavity Lower lobe cavity Unilateral pleural effusion Bilateral pleural effusion Pleural thickening Miliary Adenopathy	CD4 count		
Santos et al. ²¹	Demographics Medical history Symptoms	Age Inpatient	Diabetes Alcoholism HIV Extra pulmonary TB Smoker		Cough Sputum Sweat Fever Weight loss Chest pain Shudder Dyspnea Anorexia Hemoptysis				
Culliton et al. ²²	Free text		Structured data?			Unstructured clinical notes?			
Mani et al. ²³	Structured clinical data Laboratory		NICU variables for neonates (24)	Pulse rate Respiratory rate SpO2 Heart rate			Laboratory (59)		Resuscitation with oxygen / intubation / bag mask / epinephrine / cardiac comp. Transfusion
Insight / Dascena algorithm Desautels et al. ²⁴	Demographics Vitals Laboratory (MIMIC-II)	(Age)		Systolic Blood pressure Pulse pressure Heart rate			(pH) (WBC) (Glucose) (BUN)		

Calvert et al. ²⁵ Shimabukuro et al. ²⁶ McCoy et al. ²⁷ Calvert et al. ²⁸ Mao et al. ²⁹ Burdick et al. ³⁰ Burdick et al. ³¹				Respiration rate Temperature SpO2 (Glasgow coma score) (FiO2)			(Creatinine) (Lactate) (INR) (Platelets) (Bilirubin)		
Taneja et al. ³²	EMR data Biomarkers (e.g. IL-1 β , IL-6, etc.) in a single blood sample	Age Gender		Systolic Blood Pressure Diastolic blood pressure Pulse Temperature Respirations GCS			WBC Lactic acid PCO2 Bilirubin Creatinine Platelet TNF-alpha IL-1beta GCSF IL6 PCT sTREM1 IL18 MMP9 TNFR1 TNFR2 IL10 MCP1 IL1ra NGAL CD64		
Henry et al. ³³	Vitals Structured clinical data Laboratory Real-time data		Chronic liver disease and cirrhosis Cardiac surgery patient Immunocompromised Haematological malignancy Chronic heart failure	Heart rate Systolic Blood pressure GCS RR urine / 6hr FiO2 SIRS			BUN Creatinine Arterial pH PaO2 Bilirubin WBC Platelets		Time since first antibiotics

			Chronic organ insufficiency Diabetes Metastatic carcinoma					
Nemati et al. ³⁴ Henry et al. ³⁵	Demographics Vitals Laboratory	Age	Care unit Surgery past 12 hours Wound Class Surgical specialty Charleston comorbidity index	MAP HR SpO2 SBP DBP RR FiO2 Temperature GCS SD of RR and MAP Entropy of RR and MAP Multiscale conditional entropy of RR and MAP		PaO2 WBC Hb Hct Creatinine Bilirubin Platelets INR PTT AST ALT Lactate Glucose K+ Ca2+ Pho Mg, HCl BUN BNP Troponin Fibrinogen CRP Sedimentation Rate Ammonia pH PaCO2 HCO3- Base excess SaO2		Number of antibiotics in the past 12, 24 and 48 hours Mechanical ventilation
Ghosh et al. ³⁶	Vitals (MIMIC-II)			RR MAP Heart rate				
Liu et al. ³⁷	Demographics Laboratory	Age Gender				WBC Neutrophils Eosinophils Basophils Lymphocytes Monocytes		

						RBC Hb Hct Platelets Procalcitonin CRP		
Saqib et al. ³⁸	Demographics Vitals Laboratory (MIMIC-III)	Weight Height		HR DBP SBP MAP SpO2 Temperature Urine output			WBC Anion gap Bicarbonate pH BUN Glucose	
Shashikumar et al. ³⁹	Demographics Vitals Structured clinical ECG	Age Gender Weight Race	Charlson comorbidity index Unit information Surgical specialty Wound type	MAP HR SpO2 DBP SBP RR GCS Temperature SD HR SD MAP Multiscale entropy and conditional entropy MAP BP waveform		ECG waveform		Mechanical ventilation
Hu et al. ³⁹	Vitals			HR RR SpO2				
Wang et al. ⁴⁰	Demographics Vitals Laboratory (MIMIC-III)			Pulse SpO2 SBP			Hemoglobin Calcium Magnesium Platelet WBC ALK BUN INR Phosphorus	

Khosnevisan et al. ⁴¹	Vitals Laboratory		Location type (emergency...)	SBP DBP HR RR Temperature SpO2 MAP		"infection, inflammation and organ dysfunction identified by rules designed by two clinician experts"	BUN Procalcitonin WBC Bands Lactate Platelet Creatinine Bilirubin CRP Sedimentation rate		
Van Wyk et al. ⁴²	Vitals Laboratory			Temperature HR SBP RR			WBC		
Moor et al. ⁴³	Vitals Laboratory			SBP DBP MAP RR HR SpO2 Temperature Cardiac output Tidal volum set / observed / spontaneous Peak inspiratory pressure Total Peep level O2 flow FiO2			Albumin Bands Bicarbonate Bilirubin Creatinine Chloride Sodium Potassium Lactate Hematocrit Hemoglobin Platelet PTT INR PT BUN WBC CK CK MB Fibrinogen LDH Mg Ca PO2 pH		
							PcO2 So2 Glucose Troponin T		
Mitra et al. ⁴⁴	Vitals (MIMIC-III)			HR SpO2 RR SBP DBP Temperature					
Apostolova et al. ⁴⁵	Nursing notes (free text) (MIMIC-III)					Nursing notes indicating prescription of antibiotics: "The final infection-treating antibiotic list consists of 402 unambiguous expressions indicating antibiotics."			
Futoma et al. ^{46,47}	Demographics Medical history Vitals Laboratory Partial treatment history	Age Race Gender	Admission type (transfer...) Comorbidities	Temperature RR Pulse SpO2 BP			WBC Toponin Sodium Creatinine POtassium Platelets PH PCO2 Mg Lactate INR Hematocrit Glucose Fibrinogen CK BUN Bilirubin Bicarbonate AST		8 medication classes

							ALT Ammonia Bantemia CK-MB CRP D-Dimer Sedimentation Rate LDH pO2		
Shen et al. ⁴⁸	Patient-entered and patient-reported information	Age	Pregnancy Breastfeeding Reduced renal function Allergy	Temperature		Symptoms and signs as entered by the patient "Infection site" as determined by the patient Complications			Drugs in use
Beaudoin et al. ⁴⁹	Demographics Vitals Laboratory	Age BMI Gender	Patient location	SBP DBP Heart rate RR Temperature			Absolute neutrophil count WBC Creatinine clearance		
Tsoukalas et al. ⁵⁰ Spaan et al. ⁵¹	Structured clinical data Laboratory Microbiology			Temperature RR MAP SBP			WNC Lactate	Blood culture results	
Oonsivilai et al. ⁵²	Demographics Medical history Partial treatment history	Age Gender Location Weight Household size Domestic animals Livestock Owns refrigerator	ICU Transfer Hospitalization last year Outpatient Defecate in a toilet Family member hospitalized last 3 months Exposure environmental water		Diagnosis (sepsis, meningitis, LRI, URTI, gastroenteritis, cellulitis, abscess, URI)			Ventilation Treatment prior (pharmacy, nurse, traditional healer, IV fluids, medication) Taken antibiotic 3 in the last 3 weeks Taken antibiotics prior admission : penicillin / unknown	
			Drinks treated water HAI Days from admission to blood sample						
Yelin et al. ⁵³	Demographics Urine sample history Antibiotic purchase history	Gender Age Pregnancy Residence in retirement home City Season					Sample history: date bacterial species resistance (16 resistance)	Antibiotic purchase history (over 20 year, 34 drug groups): date, type of antibiotic	
Li et al. ⁵⁴	Demographics Laboratory Microbiology Treatment	Age Sex Job category				AST ALT	Sputum smear inspection result	Treatment Treatment adherence (dispensing records, medication records)	
Ying et al. ⁵⁵	Treatment							Prior treatment history Treatment objectives: potency, adherence, adverse events, future drugs options Regimen selection by experts	
Parbhoo et al. ⁵⁶	Demographics Structured clinical data Treatment history (EuResist)	Gender Age Ethnicity	"Risk group"			CD4+ count	Viral load Genotypic data	Prior treatment response Number of past treatments Length of treatment history	
Hatzakis et al. ⁵⁷	Demographics	Age	Year of HIV+			T cell subsets	Viral load	Prior ARV	

	Structured clinical data Treatment parameters	Gender Race	Mode of HIV acquisition AIDS defining illnesses				T cell activation	Nadir / Max HIV RNA	Number of treatments Number of drugs and drug classes Number of switches Adverse clinical events Grade 3-4 Rash, lipodystrophy, neuropathy Suppression Time to suppression Duration of suppression Treatment failure Time to failure
Zazzi et al. ⁵⁸ Rosen-Zvi et al. ⁵⁹ Zazzi et al. ⁶⁰ Prosperi et al. ⁶¹	Demographics Structured clinical data Viral subtypes Treatment history Genotype	Age Sex	Route of infection				CD4 cell count	HIV-1 genotype (list of mutations or whole sequence) Baseline viral load	Number of previous treatment lines Previous use of NRTIs NNRTIs and PIs (yes/no)
Revell et al. ⁶² Revell et al. ⁶³ Larder et al. ⁶⁴	Treatment history Virologic data Genotype data						Baseline viral load Baseline CD4 count Genotype (105 input variables) On treatment baseline plasma viral load and CD4 count Follow up viral load and	Baseline viral load Baseline CD4 count Genotype (105 input variables) On treatment baseline plasma viral load and CD4 count Follow up viral load and	Treatment history (22 binary variables) Time to follow-up Treatment change episodes
Petersen et al. ⁶⁵	Pill container openings recorded (MEMS data) Laboratory Treatment history						CD4+ count (baseline, nadir, recent) Time since most recent CD4	HIV RNA measurement (full history)	ART regimen class Change of regimen class MEMS: medication event monitoring system (percent doses taken, number interruptions, variance across days of percent doses, only weekday, only weekend)
Beerenwinkel et al. ⁶⁶	Treatment history Virologic data Genotypes						Genotypic resistance test Nearby mutants Viral load (before beginning and follow-up)	ART regimen	
Aval et al. ⁶⁷	Demographics Laboratory Biopsy results Genotype	Age Gender Weight Height BMI				Biopsy score (ISHAK)	CBC Blood glucose Lipid profile PT AST ALT	HCV RNA Genotype HCV Genotype IL-28B SNP	
Maiellaro et al. ⁶⁸	Unprecised								
Takayama et al. ⁶⁹	Demographics Laboratory Treatment parameters	Sex Age Height Weight	Diabetes mellitus				WBC RBC Hb Platelet AST ALT Creatinine	HCV RNA level 2 log decrease in HCV RNA 12 weeks after therapy	Previous treatment with interferon and interferon plus ribavirine Dose of PEGIFN and RBV

						Serum cholesterol		total amount PEGIF and RBV
Hussain et al. ⁷⁰	Demographics Structured clinical data Structured X-ray (0/1) Microbiology Baseline treatment	Age Ethnicity Weight Height GP name Health worker name Caretaker	Screening year Registration year Mode of diagnosis Disease category TB in family Contact diagnosis Past TB Delay in diagnosis Screening to X Ray delay XRay to baseline delay Screening to Gene Xpert delay	Symptoms at diagnosis Mantoux Screen to baseline weight Disease site Nightsweats	Structured X-Ray		Smear microscopy GeneXpert (resistance to rifampicin)	Baseline treatment Treatment phase (intensive continuation) Dose Last regimen Antibiotics
Sauer et al. ⁷¹	Demographics Medical history Structured imaging Microbiology Treatment history	Country Sex Education level Employment status Number of daily contacts BMI Ex-prisoner Homeless	Age of onset Number of X-Rays Number of CT scans Dissemination Social risk factors (smoking, alcoholism) Documented MDR contact Registered drug abuse	Localization in the lung Size of the lung cavity Pleural involvement Imaging pattern Pneumothorax Pleuritis Nodal calcinosis Process extension Decrease in lung capacity Lung caverna		Type of resistance Culture results Microscopy results	Drug regimen	

*We separated studies that describe the performance (e.g. ROC curves) of the algorithm (performance), studies that describe the use and the impact of the ML algorithm in real-life settings (impact) and studies that describe the implementation / adoption process of ML in clinical practice (adoption).

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Title: Evaluation and implementation of clinical decision support tools for antimicrobial stewardship

Abstract:

Inappropriate prescription of antimicrobials impacts clinical outcomes and increases antimicrobial resistance. Antimicrobial stewardship interventions have been developed to improve the quality of antimicrobial prescribing. Among the interventions studied, clinical decision supports tools or systems (CDSS), whether digital or in paper format, may help optimize antimicrobial prescribing.

The overarching objective of this work was to assess and extend the implementation and use of existing decision support tools for antimicrobial prescribing. More specifically, the first part of the thesis aimed to expand the use of a CDSS to a new context, from high-income countries (HIC) to low- and middle-income countries (LMIC), the second part aimed to expand the use of decision support tools to a wider set of healthcare professionals by working with community pharmacists, and the third part aimed to provide a state of the art of the use of machine learning (ML) in CDSS for antimicrobial prescribing.

The first part of the thesis work consisted of a qualitative study analysing the potential benefits and risks of the extension of Antibioclc in West Africa, as well as the obstacles and facilitators to its development, its adaptation and its implementation in this context. Antibioclc is a free clinical decision support system (CDSS) for antimicrobial prescribing, targeting 37 common infectious diseases and used daily in primary care by more than 5,000 doctors in France. To this end, we organized a workshop in Burkina Faso in June 2019 which brought together 47 doctors representing 9 West African countries and 6 medical specialties. The participants considered that Antibioclc could improve patient care, encourage the development and updating of national antibiotic therapy recommendations and help develop capacities for the surveillance of infectious diseases in primary care. Participants stressed the need to adapt the tool to the local epidemiology of infectious diseases and antimicrobial resistance, and to include tuberculosis, HIV and malaria. The CDSS should be tailored to the availability of diagnostic tools and antibiotics in West Africa, as well as to the diversity of primary care structures in this region. The most frequently cited contextual barrier was the potential risk of increasing self-medication in West Africa.

The second part of this thesis aimed to study the utility of a paper-based decision tool developed by Public Health England for primary care doctors, if expanded to the community pharmacy setting for the management of urinary tract infections (UTI). This UTI leaflet includes prevention and antibiotic prescribing guidance. This qualitative study included individual interviews with Pharmacists, before and after the implementation of the UTI leaflet in 16 pharmacies in London and data from 50 service users via a detailed self-completed questionnaire. Community pharmacists recognised their important role in the management of community infections and in the prescription of antibiotics by pharmacists through Patient Group Directions. Although obstacles to the involvement of pharmacists were identified such as lack of access to the patient medical records, and lack of staff and training, these results reinforced the importance of decision support tools for antimicrobial prescribing as well as the development of an integrated management of community infections between pharmacists and doctors. In order to optimize the chances of success of CDSS, participants in each of the two studies strongly encouraged co-development of the tools with all stakeholders, including nurses, midwives and pharmacists, who are frequently involved in prescribing antimicrobials in primary care.

In the third part of the thesis, we carried out a review of the literature which analysed the development of machine learning CDSS in infectious diseases and in particular the current obstacles and limits to their large-scale use. ML-CDSS were limited by a low number of clinical variables used to guide de decision, by a small number of healthcare settings considered, by an evaluation restricted to technical performance and by a lack of integration into clinical practice.

This thesis provides insights for the development and implementation of low and high-tech decision support systems for antimicrobial prescribing in a primary care setting, both in low- and middle-income countries and in high-income countries. These results were rapidly used in in the response to the pandemic emergency by co-development of a CDSS for the management of COVID-19 in West Africa, which will subsequently be adapted to other infectious and tropical diseases.

Keywords: Clinical decision support system; Antimicrobial prescribing; West Africa; Implementation science; Antimicrobial Resistance; Co-design; Primary care