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par Maïa SIMON

Évaluation d'interventions visant à améliorer les pratiques de prescription des antibiotiques en soins primaires

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Membres du jury

Rapporteurs :	**Professeur Pierre Tattevin** Président de jury	PU-PH, Inserm U 1230 BRM, Université de Rennes 1
	Professeur Bruno Giraudeau	PU-PH, Inserm UMR 1246 SPHERE, Université de Tours
Examinateurs :	**Professeur Nathalie Thilly** Directrice de thèse	PU-PH, UR 4360 APEMAC, Université de Lorraine
	Professeur Céline Pulcini Co-directrice de thèse	PU-PH, UR 4360 APEMAC, Université de Lorraine

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UR 4360 APEMAC « Maladies chroniques, santé perçue et processus d'adaptation. Approches épidémiologiques et psychologiques »

Université de Lorraine, Faculté de Médecine de Nancy, 9 avenue de la Forêt de Haye, 54505 Vandœuvre-Lès-Nancy

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Liste des abréviations

DRIVE-AB : *driving re-investment in R&D and responsible antibiotic use*

ECBU : examen cytobactériologique des urines

EHPAD : établissement d'hébergement pour personnes âgées dépendantes

SNDS : système national des données de santé

Chapitre 1 – Introduction

I – L'histoire des antibiotiques

1. Définition des antibiotiques

Les antibiotiques sont des substances capables de tuer des bactéries (effet bactéricide) ou d'inhiber leur multiplication (effet bactériostatique).(1) On distingue les antibiotiques naturels, qui sont produits par des bactéries ou des champignons (comme la pénicilline), des antibiotiques synthétiques qui sont des analogues ou des dérivés d'antibiotiques naturels.(2)

2. La découverte de la pénicilline

En 1929, le bactériologiste britannique Alexander Fleming constate qu'une de ses cultures de staphylocoques a été contaminée par une moisissure *Penicillium notatum*. La moisissure semble avoir bloqué le développement des bactéries. Ses tentatives d'extraction de la substance active de cette moisissure se soldent par des échecs.(2) Ce n'est qu'en 1940 qu'Howard Florey et Ernst Boris Chain parviennent à isoler cette substance en très faible quantité : la pénicilline.(3) L'efficacité de la pénicilline sur le pneumocoque est remarquable chez la souris. Les premiers essais réalisés chez l'Homme sont également concluants, mais l'utilisation de la pénicilline à large échelle est limitée car elle reste difficile à isoler et donc à produire.(3)

3. L'accélération de la recherche et du développement des antibiotiques

La seconde guerre mondiale a largement contribué à l'essor de l'industrie pharmaceutique. Sous l'impulsion d'Howard Florey, une nouvelle levure est isolée aux Etats-Unis : *Penicillium chrysogenum*, capable de produire 200 fois plus de pénicilline que celle identifiée par Alexander Fleming. La production à l'échelle industrielle est alors engagée par les laboratoires Pfizer en 1941, permettant de soigner des milliers de soldats et plaçant la pénicilline comme médicament majeur de cette période de guerre.(3) Les antibiotiques constituent ainsi une avancée considérable pour la médecine. Alexander Fleming, Howard

Florey et Ernst Boris Chain reçoivent en 1945 le prix Nobel de physiologie et médecine pour leurs travaux sur la pénicilline.(4)

De nombreuses autres molécules antibiotiques sont découvertes après la guerre. Ces progrès en termes de recherche et de développement de nouveaux antibiotiques et d'optimisation de leur production entraînent une explosion de leur utilisation dans les années après-guerre. Ainsi, plus de 200 substances antibiotiques différentes ont été mises sur le marché durant la seconde moitié du vingtième siècle.

4. Le ralentissement de l'innovation

Cette prospérité des antibiotiques est freinée dans les années 90. Les nouveaux antibiotiques sont dérivés de familles déjà connues, le développement et la production étant plus faciles et plus rentables.(5) La découverte de nouvelles familles d'antibiotiques est aujourd'hui quasiment au point mort, par le manque d'innovation et la diminution des investissements qui y sont dédiés.(6) Mais, considérés comme un remède miracle, les antibiotiques restent excessivement prescrits, dispensés et consommés.

II – La consommation des antibiotiques

1. La France dans l'Europe

La France est, en 2019, le quatrième pays européen en termes de consommation d'antibiotiques (25,1 doses définies journalières pour 1000 habitants par jour), derrière la Grèce (34,1), Chypre (30,1) et la Roumanie (25,8), avec une surconsommation existant surtout pour les antibiotiques dispensés en ville.(7) La dose définie journalière est une unité internationale définie par l'Organisation Mondiale de la Santé (OMS) permettant la comparaison de consommations de médicaments dans le temps et dans l'espace.(8)

2. La répartition de la consommation d'antibiotiques

En 2020 en France, 92% des antibiotiques à usage humain étaient dispensés en médecine de ville (8% en établissements de santé). Quatre-vingt-cinq pour cent des antibiotiques dispensés en pharmacie de ville avaient été prescrits en ville (15% prescrits à l'hôpital).(9) L'arrivée de l'épidémie de COVID-19 sur le territoire au début de l'année 2020 n'a pas impacté cette répartition, qui est similaire à celle de 2019.(10)

3. L'évolution de la consommation d'antibiotiques

L'épidémie de COVID-19 a eu un impact très important sur la consommation d'antibiotiques en médecine de ville. L'analyse des données du Système National des Données de Santé (SNDS) par Santé publique France montre une tendance à la baisse du nombre de prescriptions d'antibiotiques en secteur de ville depuis une dizaine d'années (**Figure 1**).(11) L'épidémie de COVID-19 a entraîné une diminution de 18% du nombre de prescriptions d'antibiotiques dispensés en ville en 2020 par rapport à ce qui était attendu (17% en doses définies journalières). En établissement de santé, la consommation d'antibiotiques a augmenté de 2,1% en doses définies journalières entre 2019 et 2020, malgré une baisse de l'activité. On enregistre un total de 44,4 millions de prescriptions d'antibiotiques en France en 2020.(9)

Cette diminution importante du nombre de prescriptions d'antibiotiques en médecine de ville en 2020 peut être expliquée, au moins en partie, par les gestes barrières (port du masque, distanciation physique, lavage des mains) appliqués pour lutter contre l'épidémie de COVID-19. La transmission des maladies infectieuses virales et bactériennes transmises par voie respiratoire et par les mains a ainsi été limitée et donc les antibiotiques moins consommés.(9)

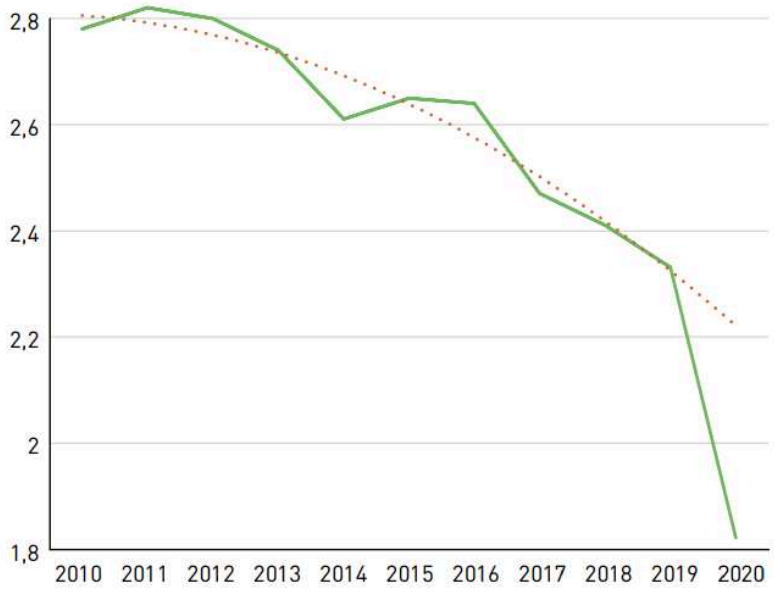

Figure 1. Nombre de prescriptions d'antibiotiques en secteur de ville pour 1000 habitants par jour, France, 2010-2020.(11)
La courbe tracée en pointillé montre la tendance 2010-2019 et indique le résultat attendu pour 2020.

4. Les principales molécules antibiotiques prescrites

Parmi les 665 prescriptions d'antibiotiques pour 1000 habitants par an en médecine de ville en 2020, les principales molécules étaient les suivantes : les pénicillines à large spectre (34% de l'ensemble des antibiotiques consommés en médecine de ville) représentées en quasi-totalité par l'amoxicilline, qui est l'antibiotique le plus consommé en médecine de ville ; les associations de pénicillines avec des inhibiteurs des béta-lactamases (16%) telles que l'amoxicilline-acide clavulanique ; les macrolides (15%) ; les associations et autres antibactériens (13%) et les autres béta-lactamines (8%) dont les céphalosporines.(12)

5. Des variations régionales

Des disparités régionales de consommation d'antibiotiques en secteur de ville sont observées (**Figure 2**).(11) Les régions enregistrant le plus de prescriptions d'antibiotiques sont les régions Hauts-de-France, Provence-Alpes-Côte d'Azur et Occitanie. Parmi les régions prescrivant le moins d'antibiotiques, on trouve certains départements et régions d'outre-mer, la Guyane, la Martinique et la Guadeloupe, et la région Pays de la Loire. On notera que la région Grand Est, objet de cette thèse, fait partie des régions pour lesquelles le nombre de prescriptions est supérieur à la moyenne nationale.

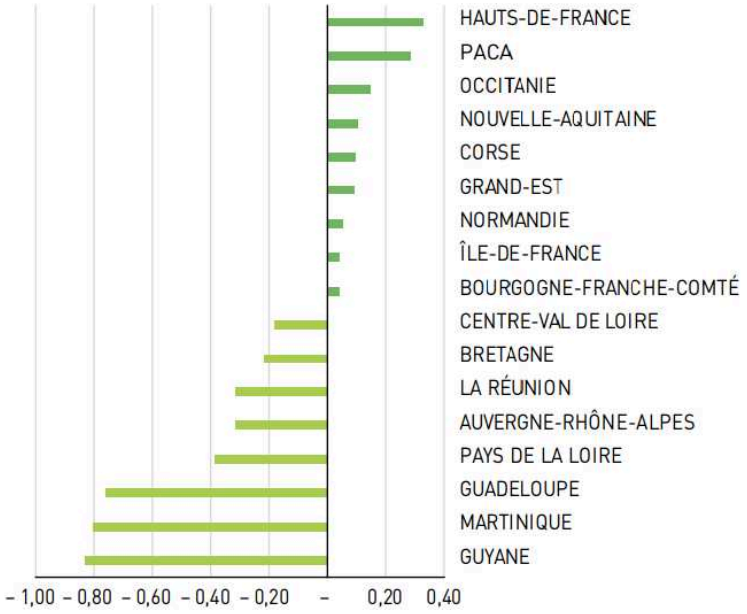

Figure 2. Différence des taux de nombre de prescriptions par région par rapport à la moyenne nationale sur les cinq dernières années (2016 - 2020).(11)
Les régions dont les taux sont supérieurs à la moyenne nationale sont représentées en sombre.

6. Les principaux prescripteurs d'antibiotiques

En France, les principaux prescripteurs d'antibiotiques de médecine de ville sont les médecins généralistes (72% des prescriptions en 2020), les médecins spécialistes (14%), les chirurgiens-dentistes (13%) et les sages-femmes (0,2%).(12) Nous allons aborder les prescriptions faites par les médecins généralistes et les chirurgiens-dentistes, qui font l'objet de cette thèse.

7. Les prescriptions d'antibiotiques par les médecins généralistes

Les médecins généralistes prescrivent en moyenne 486 prescriptions d'antibiotiques/1000 habitants/an.(12) La franche diminution du nombre de prescriptions faites en médecine de ville en 2020 est retrouvée pour les prescriptions faites par les médecins généralistes (**Figure 3**).(11) Les médecins généralistes prescrivent à des patients vivant à domicile, mais aussi à des résidents d'Etablissements d'Hébergement pour Personnes Agées Dépendantes (EHPAD).

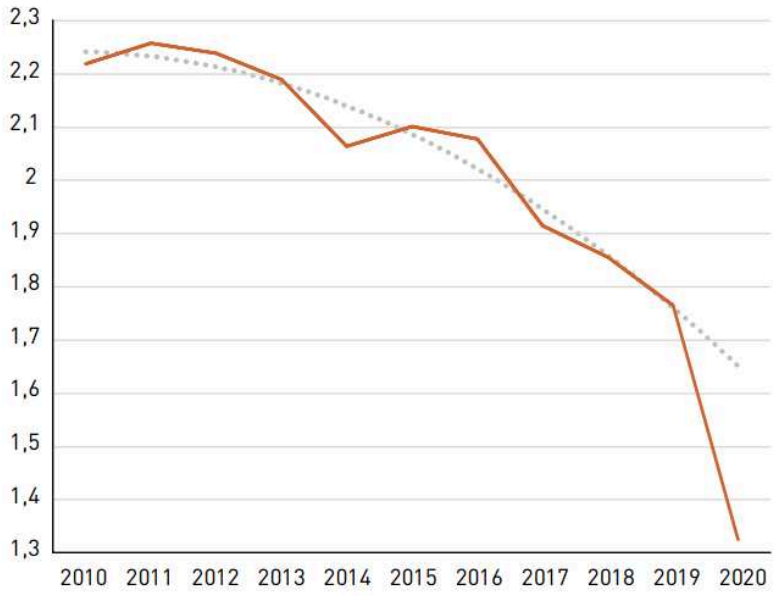

Figure 3. Nombre de prescriptions d'antibiotiques par des médecins généralistes pour 1000 habitants par jour, France, 2010-2020.(11)
La courbe tracée en pointillé montre la tendance 2010-2019 et indique le résultat attendu pour 2020.

8. Les prescriptions d'antibiotiques aux résidents d'établissements d'hébergement pour personnes âgées dépendantes

Les EHPAD accueillent des personnes âgées de 60 ans et plus, nécessitant de l'aide et des soins au quotidien.(13) Le vieillissement de la population augmente le risque de perte d'autonomie et le nombre de placements en EHPAD.

Les personnes âgées, dont les résidents d'EHPAD, présentent de nombreuses spécificités sanitaires parmi lesquelles : un système immunitaire moins efficace, des déficits fonctionnels limitant les déplacements et augmentant le risque de chutes, l'usage de dispositifs médicaux plus ou moins invasifs (sondes urinaires, cathéters, …), des déficits cognitifs, des polypathologies et des polymédications.(14,15) Les personnes âgées sont particulièrement vulnérables aux infections, qui sont plus sévères et plus fréquentes qu'en population générale. Le diagnostic d'infection peut s'avérer difficile à poser du fait des symptômes qui sont parfois atypiques (fièvre inconstante, confusion, fatigue), des comorbidités pouvant masquer les signes d'infection, des troubles cognitifs pouvant rendre l'expression de la demande et la description des symptômes difficiles, et d'un accès plus difficile aux tests diagnostiques (rarement disponibles sur site, avec la difficulté fréquente de déplacer le patient).(16–18)

En France, environ 80% des EHPAD sont indépendants (non rattachés à un établissement hospitalier). Les pharmacies, laboratoires d'analyses et centres d'imagerie sont ceux de ville. Le résident choisit son médecin traitant, qui exerce en libéral et n'est pas employé par l'EHPAD.(19) Ainsi, le médecin traitant n'est pas présent dans l'établissement et, ne pouvant pas toujours se déplacer rapidement, il peut parfois être amené à prescrire des antibiotiques sans réaliser d'examen clinique (à partir des informations transmises par le personnel soignant). Les molécules favorisées sont souvent celles à large spectre et pour des durées prolongées.(16)

En 2019, la consommation d'antibiotiques en EHPAD s'élevait à 37,0 doses définies journalières pour 1000 journées d'hébergement avec de larges variations entre les établissements (de 1,2 à 164,0 doses définies journalières).(20) Les antibiotiques les plus consommés étaient l'amoxicilline-acide clavulanique (34,0% de la consommation totale d'antibiotiques), l'amoxicilline (27,7%) et la ceftriaxone (6,2%).

9. Les prescriptions d'antibiotiques par les chirurgiens-dentistes

Les chirurgiens-dentistes sont responsables d'une part non négligeable des prescriptions d'antibiotiques (13% en 2020), avec 88 prescriptions d'antibiotiques/1000 habitants/an/. Alors que le nombre de prescriptions d'antibiotiques par les chirurgiens-dentistes a régulièrement

augmenté entre 2010 et 2019, il diminue pour la première fois en 2020 (**Figure 4**).(11) Cette soudaine diminution est liée à l'épidémie de COVID-19 qui a entraîné la fermeture des cabinets dentaires pendant environ deux mois en 2020.(21)

Parmi les trois principaux antibiotiques prescrits par les chirurgiens-dentistes en 2019, on trouve l'amoxicilline (55,7% en nombre de consommants), la spiramycine-métronidazole (21,4%) et l'amoxicilline-acide clavulanique (12,0%).(22)

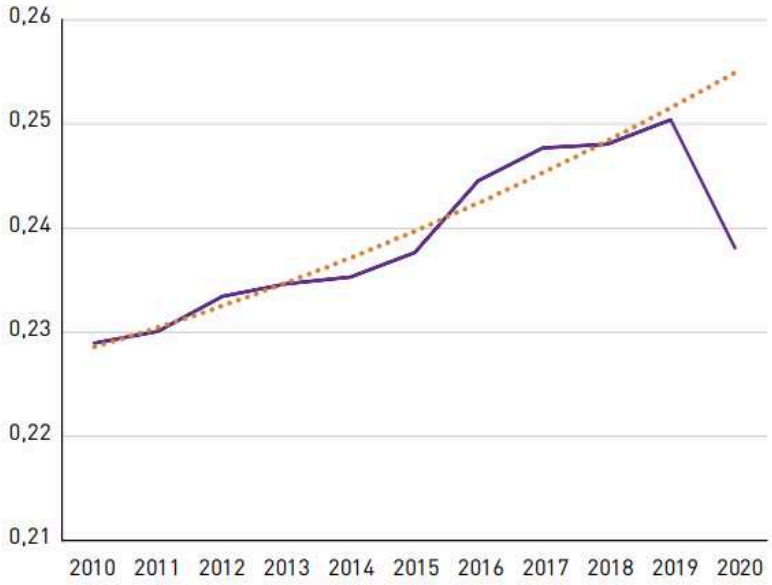

Figure 4. Nombre de prescriptions d'antibiotiques par des chirurgiens-dentistes pour 1000 habitants par jour, France, 2010-2020.(11)
La courbe tracée en pointillé montre la tendance 2010-2019 et indique le résultat attendu pour 2020.

III – L'antibiorésistance

1. L'alerte d'Alexander Fleming

Par son discours lors de la remise de prix Nobel en 1945, Alexander Fleming lance un premier signal d'alarme sur la capacité des bactéries à devenir résistantes aux antibiotiques et sur les risques engendrés par le mésusage des antibiotiques : "*It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant*."(23)

Cet avertissement s'est avéré précurseur, puisque depuis la découverte de la pénicilline, tout nouvel antibiotique découvert et mis sur le marché est suivi par l'apparition de mécanismes de résistance des bactéries à cet antibiotique (**Figure 5**).(24)

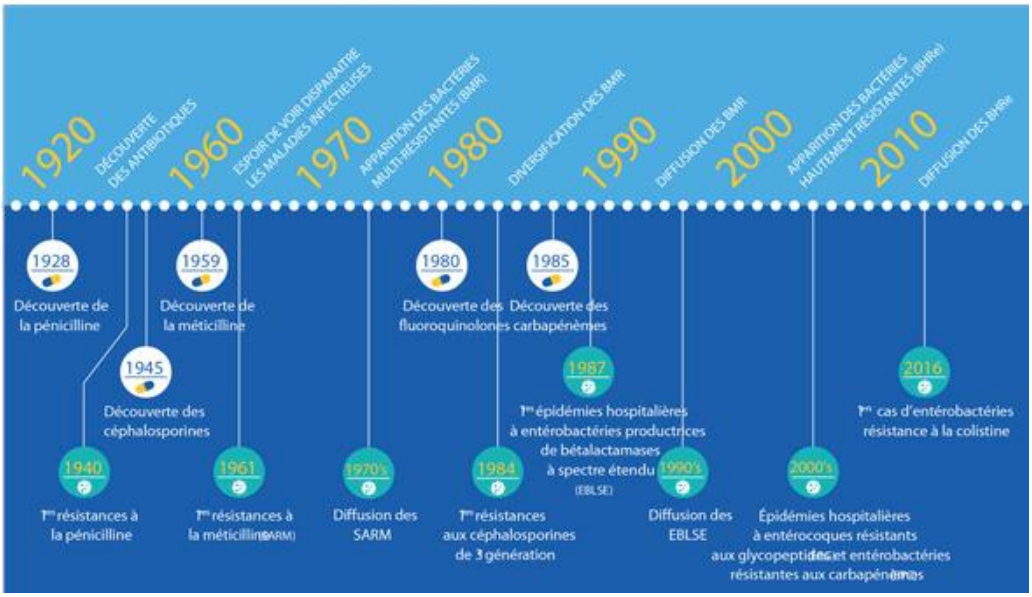

Figure 5. Engrenage : de la surconsommation d'antibiotiques à l'impasse thérapeutique.(24)

2. <u>Définition de l'antibiorésistance</u>

La résistance aux antimicrobiens désigne la capacité des bactéries, des virus, des champignons ou encore des parasites, à résister respectivement aux antibiotiques, aux antiviraux, aux antifongiques et aux antiparasitaires. Dans ce manuscrit, nous nous intéresserons plus particulièrement à l'antibiorésistance, c'est-à-dire la capacité des bactéries à résister aux antibiotiques.

Certaines bactéries sont naturellement résistantes à certaines familles d'antibiotiques. Les résistances acquises s'avèrent plus préoccupantes, elles représentent l'apparition de résistances à des antibiotiques auxquels la bactérie était jusqu'alors sensible. Ces résistances peuvent être causées par une mutation génétique au niveau du chromosome de la bactérie (spontanée ou favorisée par l'exposition aux antibiotiques), la bactérie pouvant ensuite transmettre cette résistance à sa descendance lors de sa multiplication.(25)

Dans 80% des cas, ces résistances peuvent être acquises par transmission d'une bactérie à une autre de matériel génétique, notamment des plasmides (et moins fréquemment des transposons et intégrons), porteurs de gènes de résistance.(26) Ce phénomène est

particulièrement préoccupant car la transmission de cette résistance plasmidique peut se faire non seulement à la descendance, mais également à des bactéries d'autres espèces.(27)

Toute prise d'antibiotique crée de l'antibiorésistance, notamment dans le microbiote.(28,29) L'exposition répétée des bactéries aux antibiotiques crée une pression de sélection favorisant les mutations et les échanges plasmidiques entre bactéries, qui vont acquérir des résistances aux antibiotiques.(24) Les bactéries sensibles aux antibiotiques seront alors éliminées et laisseront place aux bactéries ayant développé des résistances qui vont pouvoir se multiplier et se transmettre. La liste des antibiotiques dits « critiques » a été diffusée en 2013 puis révisée en 2015 par l'Agence Nationale de Sécurité du Médicament et des produis de santé (ANSM).(30) Elle a été actualisée en 2022 par la Société de Pathologie Infectieuse de Langue Française (SPILF).(31) Les antibiotiques critiques regroupent les molécules à indications restreintes, particulièrement génératrices de résistances (comme l'amoxicilline-acide clavulanique, les céphalosporines – en particulier de troisième et quatrième génération – et les fluoroquinolones) et les antibiotiques de dernier recours, à réserver pour préserver leur efficacité (comme les glycopeptides et les carbapénèmes).

3. L'impact de l'antibiorésistance

Les bactéries résistantes peuvent entraîner une inefficacité des traitements, les maladies infectieuses deviennent alors plus difficiles voire impossibles à traiter et le risque de transmission est augmenté.(32) Sans antibiotiques pour prévenir et traiter les infections, des interventions médicales telles que les transplantations d'organes, les chimiothérapies anticancéreuses ou les chirurgies complexes seront compromises car le risque infectieux serait alors trop élevé. L'inefficacité des antibiotiques entraîne une augmentation des décès causés par des infections bactériennes. Sans amélioration de nos pratiques, les maladies infectieuses pourraient redevenir l'une des premières causes de mortalité dans le monde d'ici 2050, causant jusqu'à dix millions de morts chaque année.(33)

L'antibiorésistance augmente également les coûts de santé, avec des durées d'hospitalisation prolongées, un besoin de soins accru, une multiplication des tests diagnostiques et l'utilisation de traitements coûteux.(28)

4. Les bactéries multirésistantes

Certaines bactéries résistent à plusieurs antibiotiques : ce sont les bactéries multirésistantes, allant même parfois jusqu'à la pan-résistance, c'est-à-dire la résistance à tous

les antibiotiques. Bien que les cas de pan-résistance soient aujourd'hui rares en France, ils sont en augmentation constante. Ce phénomène est alarmant car il conduit à des impasses thérapeutiques, plus aucune molécule ne permettant de lutter contre l'infection.(26) Parmi les bactéries multirésistantes surveillées actuellement, on trouve les *Staphylococcus aureus* résistants à la méticilline (SARM), les entérobactéries productrices de béta-lactamases à spectre étendu (comme *Escherichia coli* ou *Klebsiella spp*) et *Acinetobacter baumannii* multirésistant.

Les bactéries hautement résistantes aux antibiotiques émergentes sont des bactéries commensales du tube digestif résistantes à de nombreux antibiotiques. Leur mécanisme de résistance est plasmidique et donc transférable d'une bactérie à une autre. Deux groupes de bactéries hautement résistantes aux antibiotiques émergentes sont particulièrement alarmantes : les entérocoques résistants aux glycopeptides (comme *Enterococcus faecium* résistant à la vancomycine) et les entérobactéries productrices de carbapénémases (comme certaines souches de *Klebsiella spp*).(27)

5. Une menace majeure pour la santé publique mondiale

En accélération constante depuis les années 2000, l'antibiorésistance représente aujourd'hui une problématique majeure pour la santé de la population mondiale.(28) En effet, l'Organisation Mondiale de la Santé (OMS) a classé la résistance aux antimicrobiens parmi les dix menaces pour la Santé publique mondiale en 2019, au même titre que le changement climatique ou encore le virus de l'immunodéficience humaine (VIH).(34) Dans les problématiques à surveiller en 2021, on retrouve toujours la résistance aux médicaments, notamment aux antimicrobiens.(35)

6. L'épidémiologie de l'antibiorésistance

A l'échelle mondiale, 1,27 millions de décès seraient attribuables à des résistances microbiennes chaque année.(36) Les coûts financiers seraient de 100 000 milliards de dollars.(37)

Environ 670 000 personnes sont atteintes d'infections à bactéries multi-résistantes en Europe chaque année, causant 33 000 décès.(38) Les coûts engendrés par l'antibiorésistance sont estimés à 1,5 milliard d'euros chaque année en Europe.

En France chaque année, environ 125 000 personnes sont atteintes d'infections à des bactéries multi-résistantes et 5 500 personnes en décèdent.(24)

7. L'antibiorésistance en soins de ville et secteur médico-social

La mission nationale PRIMO, pilotée par Santé publique France, est responsable de la surveillance et de la prévention de la résistance bactérienne aux antibiotiques et des infections associées aux soins, en soins de ville et en secteur médico-social.(39) *Escherichia coli*, *Klebsiella pneumoniae* et *Staphylococcus aureus* font l'objet d'une surveillance accrue.

Les figures ci-dessous présentent l'évolution entre 2012 et 2020 des résistances d'*Escherichia coli* aux fluoroquinolones (**Figure 6**) et aux céphalosporines de troisième génération (**Figure 7**) et des souches d'*Escherichia coli* productrices de béta-lactamases à spectre étendu (**Figure 8**), chez les patients vivant à domicile et chez les résidents d'EHPAD sans pharmacie à usage intérieur. Alors que le pourcentage de souches d'*Escherichia coli* résistantes aux fluoroquinolones sont en diminution depuis 2013 pour les patients vivant en EHPAD, les souches résistantes aux céphalosporines de troisième génération et les souches productrices de béta-lactamases à spectre étendu sont en légère augmentation depuis 2012. Les pourcentages de résistances chez les patients vivant à domicile, quant à eux, restent relativement stables depuis 2012.

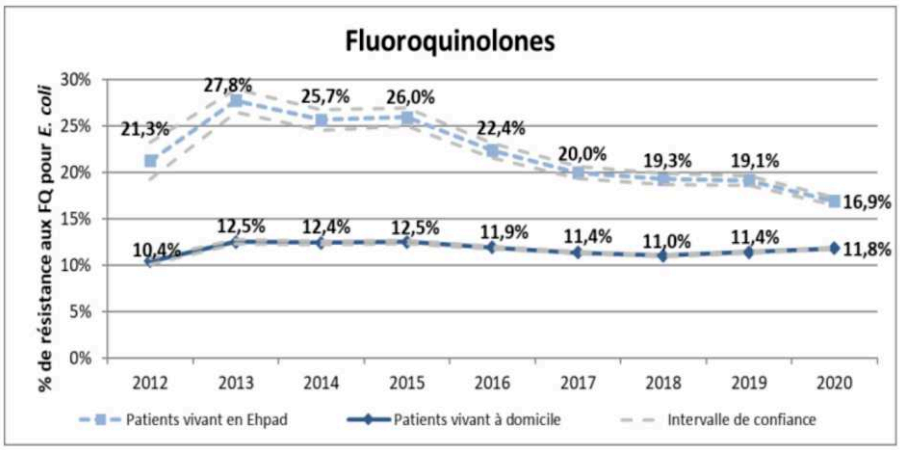

Figure 6. Evolution de la résistance bactérienne aux fluoroquinolones (FQ) de 2012 à 2020 chez les souches urinaires d'Escherichia coli selon le type d'hébergement. Mission PRIMO.(40)

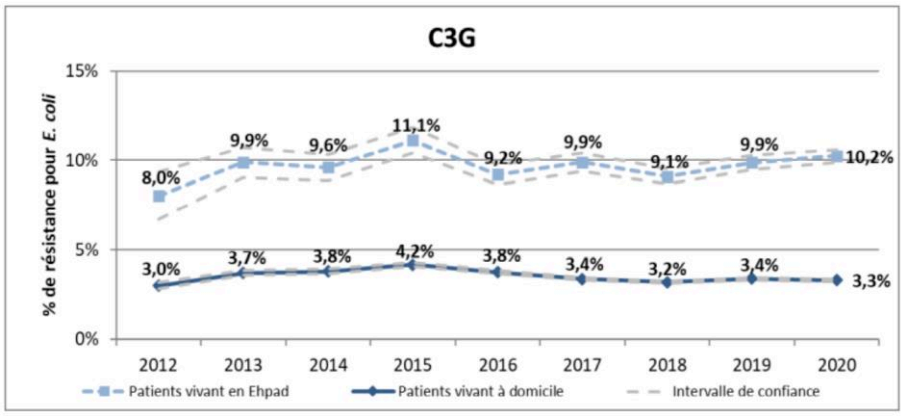

Figure 7. Evolution de la résistance bactérienne aux céphalosporines de troisième génération (C3G) de 2012 à 2020 chez les souches urinaires d'Escherichia coli selon le type d'hébergement. Mission PRIMO.(40)

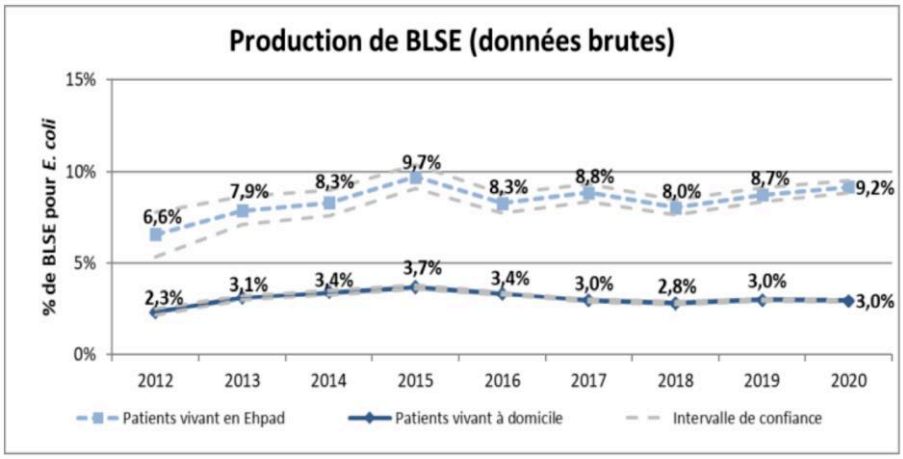

Figure 8. Evolution de la production de béta-lactamases à spectre étendu (BLSE) chez les souches urinaires d'Escherichia coli selon le type d'hébergement de 2012 à 2020. Mission PRIMO.(40)

Les figures ci-dessous présentent l'évolution entre 2018 et 2020 des résistances de *Klebsiella pneumoniae* aux fluoroquinolones (**Figure 9**) et aux céphalosporines de troisième génération (**Figure 10**) et des souches de *Klebsiella pneumoniae* productrices de béta-lactamases à spectre étendu (**Figure 11**), chez les patients vivant à domicile et chez les résidents d'EHPAD. On observe une diminution du pourcentage de souches de *Klebsiella pneumoniae* résistantes aux fluoroquinolones depuis 2018 chez les patients vivant en EHPAD. Après une diminution des pourcentages de souches résistantes aux céphalosporines de troisième génération et des souches productrices de béta-lactamases à spectre étendu entre 2018 et 2019, on observe un rebond de ces résistances en 2020. Les pourcentages de résistances sont en légère augmentation entre 2018 et 2020 pour les patients vivant à domicile.

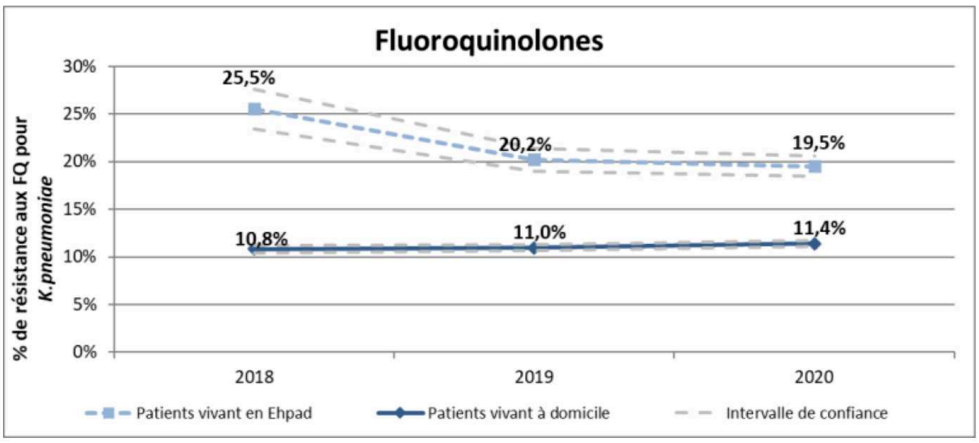

Figure 9. Evolution de la résistance bactérienne aux fluoroquinolones (FQ) de 2018 à 2020 chez les souches urinaires de Klebsiella pneumoniae selon le type d'hébergement. Mission PRIMO.(40)

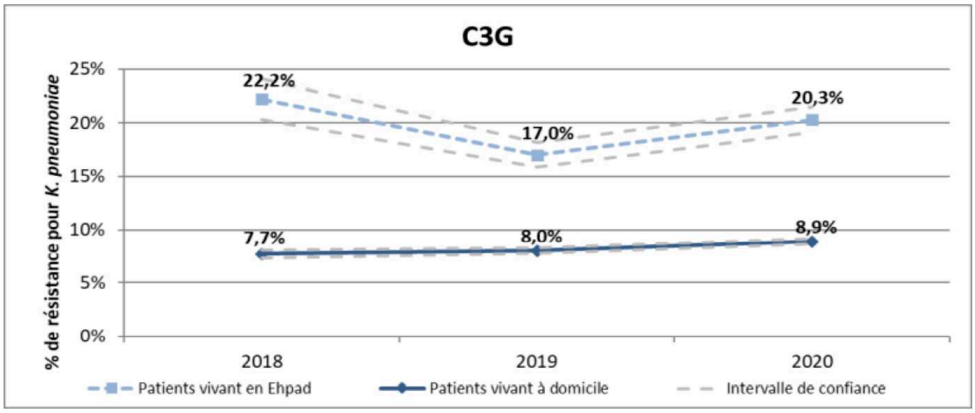

Figure 10. Evolution de la résistance bactérienne aux céphalosporines de troisième génération (C3G) de 2018 à 2020 chez les souches urinaires de Klebsiella pneumoniae selon le type d'hébergement. Mission PRIMO.(40)

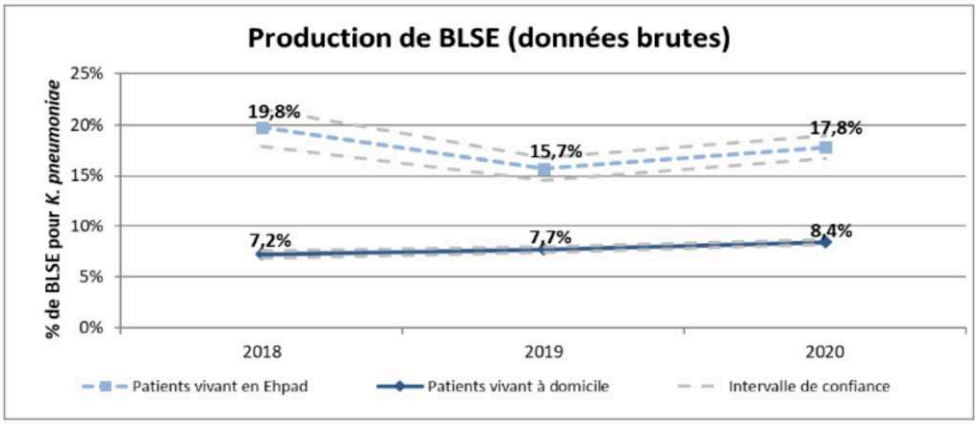

Figure 11. Evolution de la production de béta-lactamases à spectre étendu (BLSE) chez les souches urinaires de Klebsiella pneumoniae selon le type d'hébergement de 2018 à 2020. Mission PRIMO.(40)

La **Figure 12** présente l'évolution entre 2012 et 2020 des résistances de *Staphylococcus aureus* à la méticilline, chez les patients vivant à domicile et chez les résidents d'EHPAD. En EHPAD, les pourcentages de *Staphylococcus aureus* résistants à la méticilline diminuent depuis 2013. La résistance reste stable depuis 2012 chez les patients vivant à domicile.

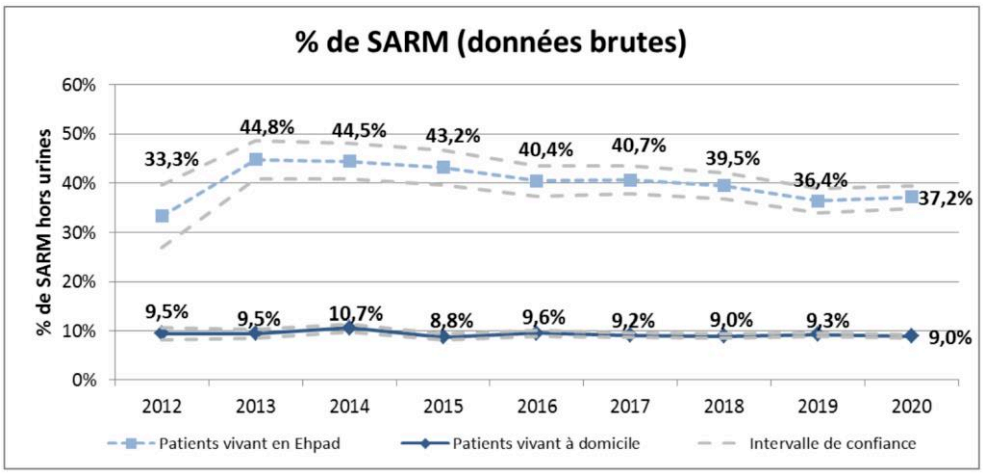

Figure 12. Evolution de la résistance à la méticilline de 2012 à 2020 chez les souches de Staphylococcus aureus isolées de tous types de prélèvements (hors urines) selon le type d'hébergement. Mission PRIMO.(40)

8. <u>L'antibiorésistance en établissements d'hébergement pour personnes âgées dépendantes</u>

Les différents graphiques présentés ci-dessus illustrent la problématique particulière des résistances bactériennes en EHPAD, qui sont systématiquement plus importantes par rapport aux patients vivant à domicile et atteignent des niveaux très élevés (jusqu'à environ 40% de *Staphylococcus aureus* résistants à la méticilline).

Les infections, déjà fréquentes chez la personne âgée, le sont encore plus chez les résidents d'EHPAD, à cause de leur perte d'autonomie et de la vie en collectivité qui favorise la transmission de pathogènes, notamment des bactéries résistantes.(16,17) Le transfert des résidents vers un milieu hospitalier dans les cas d'urgence, entraîne également un risque accru de transmission de bactéries résistantes (dans les deux sens).(41)

Environ la moitié des prescriptions d'antibiotiques faites en EHPAD sont inutiles (par exemple dans le cas des colonisations urinaires pour lesquelles les antibiotiques ne sont pas recommandés sauf en cas de procédure urologique invasive)(42,43) ou inappropriées (par exemple prescriptions de molécules à large spectre ou pour des durées prolongées).(14,18,44) Cette surconsommation et cet usage inapproprié augmentent le risque d'effets indésirables et

de développement de bactéries résistantes, qui seront ensuite aisément transmissibles au sein d'un établissement.(18,45)

9. Une seule santé

En plus de toucher l'ensemble de la population humaine mondiale, l'antibiorésistance représente une menace globale, impactant à la fois la santé humaine (en ville, en établissements de santé et en établissements médico-sociaux), la santé animale et l'environnement, qui sont interconnectés. Les antibiotiques sont utilisés à faibles doses comme facteurs de croissance pour les animaux d'élevage. Cette pratique est interdite en Europe depuis 2006, mais persiste dans de nombreux pays. Ainsi, plus de la moitié des antibiotiques produits dans le monde sont employés pour l'élevage. Les antibiotiques consommés sont ensuite rejetés, par les hommes et les animaux, dans l'environnement à travers les eaux usées et les nappes phréatiques.(26) Des initiatives conjointes *One Health* (« une seule santé ») sont ainsi indispensables pour maîtriser l'antibiorésistance.(9)

IV – La lutte contre l'antibiorésistance

1. La mobilisation internationale

En réponse à la menace croissante de l'antibiorésistance, les instances se sont mobilisées à travers le monde.(46) En 2015, l'Organisation Mondiale de la Santé (OMS) a diffusé un plan d'action global pour combattre la résistance aux antimicrobiens.(47) En 2016, l'Organisation des Nations Unies (ONU) a mis en place un groupe de coordination inter-agences sur la lutte contre l'antibiorésistance, en collaboration avec l'Organisation Mondiale de la Santé (OMS), l'Organisation des Nations Unies pour l'Alimentation et l'Agriculture (ONUAA) et l'Organisation Mondiale de la Santé Animale (OMSA).(48) Le Programme des Nations Unies pour l'Environnement a rejoint ce groupe de coordination en 2022.(49) Depuis 2016, les sommets économiques mondiaux du G7 et du G20 ont inscrit l'antibiorésistance à leur ordre du jour, à travers des communiqués et déclarations soulignant leur engagement et la nécessité d'un effort collectif dans la lutte contre l'antibiorésistance.(46)

2. La mobilisation européenne

En 2016, le Conseil Européen a publié ses conclusions sur les prochaines étapes de la lutte contre la résistance aux antimicrobiens selon une perspective *One Health*.(50) Suite à cette publication, un programme international d'initiative européenne *Joint Programming Initiative on Antimicrobial Resistance* (JPI-AMR) a été conçu pour renforcer la recherche pour lutter contre la résistance aux antimicrobiens.(51) En 2017, la Commission Européenne a adopté un nouveau plan d'action *One Health* pour lutter contre l'antibiorésistance.(52) De 2017 à 2021, une action conjointe européenne sur la résistance aux antimicrobiens et les infections associées aux soins *European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections* (EU-JAMRAI) a été pilotée par la France. Cette action avait pour objectif de mettre en application des politiques de maîtrise de l'antibiorésistance et des infections associées aux soins dans l'Union Européenne, en mobilisant notamment les Etats membres.(53) En 2019, le conseil de l'Union Européenne a souligné le besoin urgent de prendre des mesures pour développer de nouveaux antibiotiques, des alternatives à leur utilisation et des outils diagnostiques.(54) Une conférence ministérielle *One Health* sur la résistance aux antimicrobiens a eu lieu à Paris en mars 2022, dans le cadre de la présidence française du conseil de l'Union Européenne.(55) La nécessité d'un engagement et d'une coopération de l'ensemble de l'Union Européenne a été mise en avant pour lutter contre la résistance aux antimicrobiens.

3. La mobilisation en France

La France se mobilise dans la lutte contre l'antibiorésistance depuis les années 2000, à travers plusieurs plans d'actions ministériels : deux plans nationaux 2001-2005 puis 2007-2010 pour préserver l'efficacité des antibiotiques, puis un plan national 2011-2016 d'alerte sur les antibiotiques.(56) En 2016, une feuille de route interministérielle *One Health* a été adoptée pour maîtriser l'antibiorésistance.(56) La stratégie nationale de santé 2018-2022 comprenait un chapitre sur la préservation de l'efficacité des antibiotiques.(57) En 2021, le programme prioritaire de recherche antibiorésistance du gouvernement a financé un méta-réseau professionnel de lutte contre l'antibiorésistance à l'échelle nationale *Professional community network on antimicrobial resistance* (PROMISE), pour inciter à la collaboration et au partage d'expertise dans la recherche *One Health*.(58) En février 2022, le Ministère en charge de la Santé a présenté la stratégie nationale 2022-2025 pour la prévention des infections et de l'antibiorésistance en santé humaine.(59) Cette stratégie repose sur deux piliers fondamentaux de la lutte contre l'antibiorésistance : la prévention et le contrôle des infections et le bon usage des antibiotiques.

4. La prévention et le contrôle des infections

Il est nécessaire d'appliquer des mesures d'hygiène (notamment l'hygiène des mains) afin de limiter la transmission des infections et ainsi limiter le recours aux antibiotiques.(24) Dans le cadre de l'épidémie de COVID-19, la population a été encouragée à mettre en place des mesures pour prévenir la transmission des infections, telles que le port du masque, le respect de la distanciation physique, l'aération des espaces clos, le nettoyage des surfaces, ou encore l'isolement des personnes à risque. La vaccination est également une mesure phare de la lutte contre l'antibiorésistance, permettant de prévenir et d'éviter la propagation de maladies infectieuses.

Dans une perspective *One Health*, ces mesures de prévention et de contrôle des infections doivent également être appliquées en santé animale et dans l'environnement : améliorer l'hygiène et la biosécurité des élevages, vacciner les animaux (domestiques et d'élevage), isoler les animaux malades, éviter le contact avec les animaux sauvages, retourner les antibiotiques non utilisés en pharmacie afin d'éviter leur dissémination dans l'environnement et traiter les eaux usées pour limiter les contaminations *via* l'environnement.(24,60)

5. Le bon usage des antibiotiques

Nous l'avons vu, l'usage des antibiotiques créé une pression de sélection qui favorise la survie des bactéries résistantes.(24) Il est donc indispensable d'avoir une meilleure utilisation des antibiotiques afin de réduire cette pression de sélection et de maîtriser l'antibiorésistance. Le bon usage des antibiotiques repose sur une prescription à bon escient, uniquement quand c'est nécessaire, une utilisation de la bonne molécule, à la bonne dose, pour une bonne durée de traitement et avec la bonne voie d'administration.

- La bonne indication : les antibiotiques doivent être utilisés uniquement pour le traitement ou la prévention des infections bactériennes suffisamment sévères pour nécessiter un traitement. Ils sont inefficaces et ne doivent pas être prescrits dans le cadre des infections virales, comme la grippe. Des tests diagnostiques existent dans certaines situations pour différencier les infections bactériennes et virales.
- La bonne molécule : les bactéries ayant des résistances (naturelles ou acquises) à certains antibiotiques, il est important d'utiliser des antibiotiques auxquels elles sont sensibles pour que le traitement soit efficace. Un antibiogramme peut être parfois

réalisé, afin d'identifier à quels antibiotiques la bactérie est sensible et adapter le traitement. Le choix de l'antibiotique doit également se porter sur les molécules générant le moins de résistance (classées en première intention dans les recommandations) et diffusant dans le foyer infectieux.

- La bonne dose : la dose doit être adaptée au patient (ou à l'animal) et au type d'infection. Un surdosage peut augmenter le risque d'effets indésirables. Un sous-dosage peut entraîner une inefficacité du traitement et le développement de résistances bactériennes au niveau du foyer infectieux.
- La bonne durée : la durée de prescription doit être respectée, elle est définie de manière à optimiser l'efficacité du traitement tout en limitant le risque de développement des bactéries résistantes.
- La bonne voie d'administration : la voie d'administration doit être adaptée au patient et au foyer infectieux.

6. Des actions pour le bon usage des antibiotiques

Le terme anglophone « *antimicrobial stewardship* » est défini comme un ensemble cohérent d'actions visant à promouvoir un usage responsable des antimicrobiens.(61) Il s'agit d'interventions ayant pour objectif d'améliorer l'usage des antibiotiques, en réduisant les prescriptions inutiles et/ou les prescriptions inappropriées, afin de limiter les résistances bactériennes. Ces actions peuvent prendre des formes très diverses et toucher l'ensemble des acteurs (prescripteurs, pharmaciens, biologistes, autres professionnels de santé, patients, direction d'établissements, population générale). Des exemples d'actions visant à favoriser le bon usage des antibiotiques sont :

- La mise en place de politiques et de ressources dédiées au bon usage dans les établissements de santé ;
- Le déploiement de centres régionaux en antibiothérapie et d'équipes multidisciplinaires en antibiothérapie (composées de pharmaciens, infectiologues, biologistes, …) ;
- La sensibilisation du grand public à l'antibiorésistance et au bon usage des antibiotiques : sites internet e-Bug (62) et Antibio'Malin (63) ;
- La formation initiale et continue et l'information des professionnels de santé sur l'antibiorésistance et le bon usage des antibiotiques (64) ;

- Des outils d'aide à la prescription, comme des recommandations synthétiques et faciles d'accès : ANTIBIOCLIC (65), recommandations sur les durées d'antibiothérapie dans les infections courantes (66), AntibioDentaire (67) ;
- Le développement d'indicateurs décrivant la consommation des antibiotiques dans le temps et dans l'espace afin de surveiller les consommations, de guider les actions pour le bon usage et d'évaluer l'effet d'interventions : observatoire cartographique des indicateurs de santé GEODES (68) ;
- Des retours aux prescripteurs sur leurs prescriptions à l'aide de profils individuels de prescription et/ou d'audit, comme mis en place dans la région Grand Est pour les chirurgiens-dentistes (22) ;
- La modification du rendu des antibiogrammes (rendu ciblé) pour orienter les prescripteurs vers les molécules appropriées (69) ;
- Des outils d'aide à la non prescription : utilisation d'ordonnances de non prescription d'antibiotiques, permettant d'aider les prescripteurs à justifier à leurs patients la non utilisation d'antibiotiques.(70)

V – Thèse

1. Objectif

Dans ce contexte de menace de l'antibiorésistance et d'urgence à agir pour un meilleur usage des antibiotiques, cette thèse s'intéresse à l'évaluation d'interventions visant à améliorer les prescriptions d'antibiotiques en soins primaires de ville et comprend deux thématiques : (i) les antibiogrammes ciblés, intervention permettant de favoriser le bon usage des antibiotiques et (ii) les indicateurs de prescriptions d'antibiotiques, outils permettant notamment d'évaluer l'effet d'interventions de bon usage des antibiotiques. Les deux catégories de prescripteurs ciblés étaient les médecins généralistes et les chirurgiens-dentistes.

2. Source de données : le système national des données de santé

L'ensemble des projets de cette thèse a utilisé les données du Système National des Données de Santé (SNDS). Le SNDS est une base de données unique en Europe, plaçant la France parmi les *leaders* dans la promotion et la valorisation des données massives de santé.(71,72)

Le SNDS a été développé en 2017 suite à la loi de modernisation de notre système de santé, afin d'améliorer les connaissances sur la prise en charge médicale et de faciliter la recherche dans le domaine de la santé.(71) Il est aujourd'hui sous la responsabilité conjointe de la caisse nationale d'Assurance Maladie et de la plateforme des données de santé (*Health data hub*).(73)

Les finalités du SNDS sont de contribuer à l'information sur la santé, l'offre de soins, la prise en charge médico-sociale et leur qualité ; définir, mettre en œuvre et évaluer des politiques de santé et de protection sociale ; connaître les dépenses de santé, les dépenses de l'assurance maladie et les dépenses médico-sociales ; informer sur l'activité des professionnels, des structures et des établissements de santé ou médico-sociaux ; participer à la surveillance, à la veille et à la sécurité sanitaires ; et contribuer à la recherche, aux études, à l'évaluation et à l'innovation en matières de santé et de prise en charge médico-sociale.(74)

Le SNDS centralise des données provenant de différents organismes publics (72) :

- Données de l'assurance maladie : Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM). Créé en 1999, il couvre la quasi-totalité des régimes de l'Assurance Maladie, permettant d'obtenir des informations sur 99% de la population française.(75)
- Données de l'Agence Technique de l'Information sur l'Hospitalisation (ATIH) : données hospitalières du Programme de Médicalisation des Systèmes d'Information (PMSI) ;
- Données de l'Institut national de la santé et de la recherche médicale (Inserm) : causes médicales de décès du Centre d'épidémiologie sur les causes médicales de Décès (CépiDC) ;
- En cours de construction : données de la Caisse Nationale de Solidarité pour l'Autonomie (CNSA) : données relatives au handicap de la Maison Départementale des Personnes Handicapées (MDPH).

Chapitre 2 – Les antibiogrammes ciblés

I – Contexte

1. Les infections urinaires

Les infections urinaires font partie des infections les plus fréquemment rencontrées en médecine de ville.(76) Les femmes sont plus sujettes aux infections urinaires que les hommes, en raison de leur constitution anatomique. On distingue différents types d'infections urinaires : les cystites (infections localisées de la vessie) pouvant être aiguës simples, aiguës à risque de complication ou récidivantes ; les pyélonéphrites (infections touchant les reins) pouvant être aiguës simples ou aiguës à risque de complication ; et les infections urinaires masculines (incluant les prostatites).(65) La principale bactérie responsable d'infections urinaires communautaires est *Escherichia coli* (70 à 95% des cas).(77) D'autres entérobactéries peuvent également en être la cause, notamment *Proteus mirabilis*, *Klebsiella pneumoniae* et *Staphylococcus saprophyticus*.

Plus de la moitié des prescriptions antibiotiques pour les infections urinaires rencontrées en médecine de ville sont inutiles ou inappropriées.(78,79)

2. L'antibiogramme

L'antibiogramme est un test biologique effectué en laboratoire permettant d'évaluer la sensibilité d'une bactérie à certains antibiotiques. Dans le cadre des infections urinaires, un prélèvement urinaire est réalisé, puis un Examen Cytobactériologique des Urines (ECBU) permet d'identifier la bactérie pathogène. L'antibiogramme est ensuite effectué pour tester la sensibilité de cette bactérie pathogène à une série d'antibiotiques, afin de déterminer les molécules antibiotiques potentiellement efficaces sur cette bactérie et d'initier un traitement adapté, ou d'ajuster le traitement si un antibiotique avait été prescrit de manière probabiliste (c'est-à-dire avant les résultats de l'antibiogramme).(80)

3. Le principe de l'antibiogramme ciblé

L'antibiogramme ciblé consiste à modifier le rendu de l'antibiogramme, en ne rendant au prescripteur qu'un nombre limité (souvent entre quatre et six) des antibiotiques testés (souvent entre 16 et 18). Les antibiotiques rendus sont ceux recommandés en première intention d'après les recommandations.(65) Les autres antibiotiques sont quand même testés, mais ne sont rendus qu'en cas de résistance aux antibiotiques de première intention ou sur demande du prescripteur au laboratoire.(69) L'objectif est d'orienter le choix du prescripteur vers les molécules appropriées.

4. Les recommandations sur l'utilisation d'antibiogrammes ciblés et leur usage en France

L'antibiogramme ciblé est recommandé dans de nombreuses politiques de bon usage des antibiotiques.

Le plan d'action *One Health* adopté en 2017 par la Commission Européenne recommande l'utilisation des antibiogrammes ciblés, afin de s'assurer que les antibiogrammes et leur rendu soient en accord avec les recommandations d'antibiothérapie.(81)

La feuille de route interministérielle visant à maîtriser l'antibiorésistance, adoptée en 2016, incite à limiter le rendu du nombre d'antibiotiques sur les antibiogrammes dans les infections urinaires, pour restreindre les prescriptions d'antibiotiques critiques en santé humaine.(56) L'antibiogramme ciblé est également recommandé dans la nouvelle stratégie nationale 2022-2025 de prévention des infections et de l'antibiorésistance en santé humaine.(59)

Malgré ces recommandations nationales et européennes, les antibiogrammes ciblés sont très peu utilisés en pratique courante en France. Il est vraisemblable qu'il existe des freins à leur mise en place en termes de faisabilité pratique pour les laboratoires de biologie médicale ou d'acceptabilité par les prescripteurs et/ou par les professionnels de laboratoire. Notamment, lorsque nous avons entamé notre étude en 2017, peu de laboratoires étaient en capacité technique de mettre en place les antibiogrammes ciblés.

5. L'étude ANTIBIO-ciblés

Nous avons conduit une étude interventionnelle pragmatique, prospective, multicentrique, comparative (antibiogrammes ciblés *versus* antibiogrammes complets habituels) de type avant-après (la mise en place des antibiogrammes ciblés) en région Lorraine.(82) L'objectif principal était d'évaluer l'impact des antibiogrammes ciblés dans les

ECBU positifs à *Escherichia coli*, sur les prescriptions d'antibiotiques critiques, en ambulatoire et en EHPAD. Les objectifs secondaires étaient d'évaluer (i) les conséquences négatives potentielles des antibiogrammes ciblés, (ii) la faisabilité de leur mise en place par les laboratoires de biologique médicale et (iii) l'acceptabilité par les prescripteurs et par les professionnels de laboratoires. Cette étude a obtenu un financement du Programme de Recherche sur la Performance du Système des soins (PREPS) suite à l'appel à projet national de la Direction Générale de l'Offre de Soins (DGOS) en 2017.

II – Article ANTIBIO-ciblés : évaluation de l'impact et des conséquences négatives potentielles des antibiogrammes ciblés

1. Contexte et objectifs

Malgré l'existence de recommandations de la mise en place des antibiogrammes ciblés en France et en Europe, on constate un manque d'études à haut niveau de preuve pour évaluer leur impact.(69) L'objectif principal de l'étude ANTIBIO-ciblés était d'évaluer l'impact des antibiogrammes ciblés dans les ECBU positifs à *Escherichia coli* des patients adultes en soins de ville, sur la prescription des antibiotiques critiques, en comparaison des antibiogrammes complets habituels. L'objectif secondaire présenté dans cet article était l'évaluation des conséquences négatives potentielles de l'antibiogramme ciblé.

2. Méthodes

L'étude ANTIBIO-ciblés est une étude pragmatique, prospective, multicentrique, comparative (antibiogrammes ciblés *versus* antibiogrammes complets habituels), non randomisée de type avant-après, conduite en région Lorraine. Les laboratoires du groupe ATOUTBIO (21 laboratoires en 2018) ont mis en place les antibiogrammes ciblés en septembre 2018 pour tous les patients adultes ayant eu un ECBU positif à *Escherichia coli* (groupe intervention). Les laboratoires du groupe BIOGROUP (20 laboratoires en 2018) ont continué à rendre les antibiogrammes complets habituels (groupe témoin). Un appariement probabiliste a été réalisé entre les données recueillies par les deux groupes de laboratoires et le SNDS. Cette étude a été conduite sur la période avant (2017) et la période après (2019) la mise en place de l'intervention. Le critère d'évaluation de l'impact était le taux de prescription d'amoxicilline-acide clavulanique, des céphalosporines de troisième génération, des quinolones et de ces trois antibiotiques critiques réunis, dans les 15 jours ayant suivi la prescription de l'ECBU. Le taux de prescription était défini comme suit : (nombre de prescriptions de l'antibiotique X dans les 15 jours suivant un ECBU positif à *Escherichia coli* avec antibiogramme sur l'année N) / (nombre de prescriptions de l'ensemble des antibiotiques dans les 15 jours suivant un ECBU positif à *Escherichia coli* avec antibiogramme sur l'année N). Les conséquences négatives potentielles étaient évaluées par la prévalence des consultations et hospitalisations survenues dans les 30 jours après la prescription de l'ECBU. Le protocole détaillé de l'étude ANTIBIO-ciblés a été publié en 2018 dans la revue *BMJ Open*.(82)

3. Principaux résultats et conclusions

Nous avons obtenu un taux d'appariement de 87,4%, permettant d'inclure 42 956 ECBU dans les analyses. Les résultats ont montré un impact positif des antibiogrammes ciblés sur les prescriptions d'antibiotiques critiques, attribuable à une réduction absolue de 9,4% du taux de prescription de céphalosporines de troisième génération (20,8% de réduction relative). Nous n'avons pas montré d'impact sur les prescriptions de quinolones, le taux de prescription ayant diminué d'environ 8% entre 2017 et 2019 dans les deux groupes, possiblement grâce à l'actualisation des recommandations de l'antibiothérapie dans les infections urinaires en 2017.(43) Nous n'avons pas montré d'impact sur les prescriptions d'amoxicilline-acide clavulanique, les taux de prescription étant faibles (moins de 3%) et ayant diminué d'environ 1% (en valeur absolue) entre 2017 et 2019 dans les deux groupes. L'impact de l'antibiogramme ciblé était très marqué sur les prescriptions documentées, alors qu'il y avait peu d'impact sur les prescriptions probabilistes. L'impact était très important pour les prescriptions faites à des femmes, pour qui les antibiotiques critiques ne sont pas recommandés dans la majorité des cas et n'étaient donc pas rendus sur l'antibiogramme ciblé. Le détail des prescriptions a montré un report des prescriptions de céfixime vers l'amoxicilline en documenté pour les femmes. A l'inverse, nous n'avons pas montré d'impact de l'intervention sur les prescriptions d'antibiotiques critiques chez les hommes, étant donné que la plupart des antibiotiques recommandés en première intention dans les infections urinaires masculines sont des antibiotiques critiques (céphalosporines de troisième génération et fluoroquinolones). Nous avons néanmoins noté une importante amélioration de la conformité aux recommandations pour les infections urinaires masculines (25% d'amélioration pour les antibiotiques prescrits en documenté). Nous n'avons pas mis en évidence de conséquences négatives de l'antibiogramme ciblé en termes de consultations ou d'hospitalisations, comparativement aux antibiogrammes complets habituels. Ces résultats très positifs et innovants pourront permettre de guider la mise en place des antibiogrammes ciblés à l'échelle nationale, voire internationale.

4. Mon implication

Pour cet article, j'ai assuré depuis le début de ma thèse en octobre 2019 la gestion et coordination du projet, le recueil de données dans les laboratoires de biologie médicale, le data management, les analyses statistiques, l'interprétation des résultats, la rédaction et la valorisation, sous la supervision de mes encadrantes.

5. Valorisation

Cet article sera soumis dans la revue *Clinical Microbiology and Infection* (rang A, *impact factor* 2021 : 13,310) en novembre 2022.

Un résumé étendu sur l'étude ANTIBIO-ciblés (évaluation de l'impact, des conséquences négatives potentielles, de la faisabilité et de l'acceptabilité) a été soumis à la Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI) qui a lieu à Paris en décembre 2022, en vue du concours pour le prix RICAI Junior 2022.

Original research

Impact of selective reporting of antibiotic susceptibility testing results for urinary tract infections in the outpatient setting: A prospective controlled before-after intervention study

Maïa Simon[1,2], PharmD; Sébastien Fougnot[3], MD; Patrice De Monchy[4], PharmD; Alain Duda[3], PharmD; Nathalie Thilly[1,2], Prof., PhD; Céline Pulcini[1,5], Prof., PhD; on behalf of the ANTIBIO-ciblés Scientific Committee: Christian Rabaud, Alain Lozniewski, Violaine Mauffrey, Emmanuelle Varon, Anne Fagot-Campagna, Joëlle Kivits, Gaëlle Le Dref, Aurélie Bocquier, Virginie Chopard, Alexandre Charmillon, Marion Delpuech, Amandine Luc

Author affiliations and full addresses:

[1] Université de Lorraine, Laboratoire APEMAC, 9 Avenue de la Forêt de Haye, F-54500 Vandoeuvre-lès-Nancy, France

[2] Université de Lorraine, CHRU-Nancy, Département Méthodologie, Promotion, Investigation, Hôpitaux de Brabois, Allée du Morvan, F-54500 Vandoeuvre-lès-Nancy, France

[3] Laboratoire ATOUTBIO, 1170 Avenue Raymond Pinchard, F-54000 Nancy, France

[4] Laboratoire BIOGROUP, Plateau Technique de Microbiologie, 3 Rue des Verriers, F-57000 Metz, France

[5] Université de Lorraine, CHRU-Nancy, Service de Maladies Infectieuses et Tropicales, Hôpitaux de Brabois, Allée du Morvan, F-54500 Vandoeuvre-lès-Nancy, France

Corresponding author: Dr. Maïa Simon, PharmD. Université de Lorraine, Laboratoire APEMAC, 9 Avenue de la Forêt de Haye, F-54500 Vandoeuvre-lès-Nancy, France. Tel.: + 33 (0) 3 83 15 72 71. E-mail: maia.simon@univ-lorraine.fr

Registration at Clinical Trials: NCT03612297

ABSTRACT

Background – The use of selective reporting of antibiotic susceptibility testing (AST) results is a recommended antimicrobial stewardship strategy to improve the appropriateness of antibiotic prescriptions. We conducted a large, pragmatic, prospective, multicentre, controlled before-after intervention study to assess the impact of selective reporting of AST results for *Escherichia coli*-positive urine cultures on the prescription of 'critical' antibiotics (i.e., amoxicillin-clavulanate, third-generation cephalosporins, and quinolones) in the outpatient setting. We also looked for possible unintended consequences of this intervention.

Methods – We compared two groups of laboratories located in a French region. We collected data from the health insurance databases before (2017) and after the implementation of the intervention (2019). The primary outcome was the prescription rates of critical antibiotics.

Findings – We showed an overall 9·4% absolute reduction (20·8% relative reduction) in the prescription rate of critical antibiotics, attributable to a decrease in the prescription of third-generation cephalosporins. This reduction was more marked for targeted therapy and female patients. Compliance with national guidelines was improved, particularly among male patients. Requests from clinicians for the complete reporting of AST results were infrequent (1·2% of all the selective AST results reported in 2019). No unintended consequences were observed.

Interpretation – The results showed a positive impact of the selective reporting of AST results, but room for improvement is still important.

Funding – This study is supported by a grant from the French Ministry of Health.

Keywords – microbiology; urinary tract infections; outpatient setting; antimicrobial stewardship; antibiotic prescriptions

INTRODUCTION

Antimicrobial resistance has been identified as one of the ten most pressing global health issues by the World Health Organisation.[1] There were an estimated 4·95 million deaths associated with antibiotic resistance in 2019 globally, including 1·27 million attributable deaths.[2] In France, it is estimated that 125,000 persons are infected by multidrug-resistant bacteria each year, of whom 5,500 die.[3]

Antimicrobial resistance is increased by unnecessary and inappropriate use of antibiotics. Antimicrobial stewardship (AMS), along with infection prevention and control, is thus one of the two pillar strategies to tackle antimicrobial resistance. AMS is defined as a coherent set of actions that promote the appropriate use of antimicrobials.[4] In France, almost 80% of antibiotics are prescribed in the outpatient setting, with approximately 70% being prescribed by general practitioners (GPs).[5] Urinary tract infections (UTIs) are among the leading causes for antibiotic prescriptions in general practice,[6] with *Escherichia coli* (*E. coli*) being responsible for 70%-95% of community-acquired UTIs[7] and the ratio of cystitis/pyelonephritis in French general practice being approximately 10/1 for female patients.[8] Half of antibiotic prescriptions for UTIs in the French outpatient setting seem to be either unnecessary or inappropriate (e.g., overprescription of broad-spectrum antibiotics such as fluoroquinolones and third-generation cephalosporins when narrow-spectrum antibiotics are effective and recommended).[9] A summary of the French national and regional AMS strategy in the outpatient setting is presented in Supplementary Table S1.

The use of selective reporting of antibiotic susceptibility testing (AST) results is a recommended AMS strategy in French, European, and international guidelines to reduce the number of inappropriate prescriptions.[10–12] Selective reporting of AST results consists of reporting to the prescriber only a limited number of antibiotics (i.e., first-line antibiotics

according to guidelines), while other antibiotics are still tested but reported only in cases of resistance to first-line agents or upon request from the clinician.[13] Two randomised controlled case vignette surveys were conducted among residents training in general practice and GPs[14,15] to assess the impact of the selective reporting of AST results on antibiotic prescriptions for UTIs. Both studies showed a significantly improved appropriateness of prescriptions and a decrease in the number of prescriptions of broad-spectrum antibiotics. However, to the best of our knowledge, no large-scale interventional study on this topic has been published worldwide. A recent review has indeed highlighted the need for high-quality studies to better assess the impact of selective reporting of AST results, including unintended consequences, the feasibility of its implementation, and its acceptability, which are poorly studied.[13]

The primary objective of this large pragmatic interventional study was to assess the impact of selective reporting of AST results for *E. coli*-positive urine cultures from adult outpatients on the prescription of 'critical' antibiotics that carry a higher risk of selection of resistance compared to standard reporting of AST results. Critical antibiotics (as defined by the French national drug agency) are amoxicillin-clavulanate, third-generation cephalosporins, and quinolones.[16] The secondary objective was to look for possible unintended clinical consequences for patients of selective reporting of AST results.

The feasibility of the implementation of selective reporting of AST results by French laboratories and the acceptability of selective reporting of AST results by GPs and laboratory professionals (microbiologists, technicians and secretaries) were also assessed as secondary objectives but will be described in an upcoming manuscript.[17]

METHODS

As the protocol of this study has already been published[17] and registered at Clinical Trials (NCT03612297), this section presents only a brief overview. This study complies with the TREND (Transparent Reporting of Evaluations with Nonrandomised Designs) reporting guidelines (see Table S2 available in the Supplementary Materials).[18]

Study design

This study was a pragmatic (in a real-life setting), prospective, multicentre, controlled (selective reporting *versus* usual complete reporting of AST results) before-after (the intervention) study. The 'before period' was the year preceding the implementation of selective reporting of AST results in the intervention group (i.e., 2017), and the 'after period' was the year following this implementation (i.e., 2019). We deliberately did not collect data during the first four months following the implementation of the intervention (September to December 2018) to let the different professionals adjust their practices.

Study setting

The interventional group was made up of the ATOUTBIO group of 21 laboratories, which implemented the selective reporting of AST results on 1st September 2018, for all *E. coli*-positive urine cultures from adults. The control group was made up of the BIOGROUP group of 33 laboratories, which continued to perform the usual complete reporting of AST results (20 laboratories from the EVOLAB group merged with 13 additional ones in 2018 to form the BIOGROUP group). ATOUTBIO and BIOGROUP are the two main laboratory groups of the Lorraine region located in northeastern France (2,306,000 inhabitants in Lorraine in 2021,[19] i.e., 3.4% of the French population). We chose these two laboratory groups because of their comparability in terms of activity.

The target population was defined by community physicians (GPs or other specialties) located in the geographic areas served by all 54 included laboratories. The indirect beneficiaries were all adult outpatients (living at home or nursing home residents) with an *E. coli*-positive urine culture for which AST was realised who were prescribed an antibiotic.

Description of the intervention

As previously mentioned, selective reporting of AST results consists of reporting to the prescriber only a limited number of antibiotics (i.e., first-line antibiotics according to guidelines). French UTI guidelines (presented in Supplementary Table S3) differ by sex, so two algorithms were developed. For each sex, four scenarios were defined according to the resistance of the isolate to first-line antibiotics. At least two different antibiotic classes were reported for each possible situation to facilitate antibiotic prescribing in cases of allergy or contraindication and to have options available for both cystitis and pyelonephritis in women. Antibiotics that should not be used for pyelonephritis or male UTIs were specifically flagged in the report. Supplementary Table S4 presents the selective reporting of AST results (antibiotics reported and associated comments). Prescribers were informed by the ATOUTBIO laboratory regarding the change in reporting (such information was included in AST reports in September-December 2018). The complete reporting of AST results was easily available upon request from the clinicians.

In the control group, approximately 16 different antibiotics were reported, with associated comments (see Supplementary Table S5).

Outcomes of interest

Impact evaluation: The primary outcome was the prescription rates of amoxicillin-clavulanate (J01CR02 in the Anatomical Therapeutic Chemical (ATC) classification system[20]), third-

generation cephalosporins (J01DD), quinolones (J01M), and all these critical antibiotics together in the 15 days following the prescription of the urine culture.

Unintended clinical consequence evaluation: The outcomes of interest were the prevalence of all-cause medical consultations and hospitalisations in the month following the prescription of the urine culture.

Data collection

In France, all antibiotics are prescribed and reimbursed. Data were collected from the French health insurance reimbursement databases, the Health Data National System (Système National des Données de Santé), which contains anonymous and linkable data at the patient and prescriber levels. Clinical indication is not available in these databases.

The two laboratory groups collected data on each *E. coli*-positive urine culture with AST performed in 2017 and 2019 (e.g., patient sex, age, type of residence, date of prescription, and date of collection of the urine culture). A probabilistic data linkage method was then applied within the anonymised health insurance reimbursement databases to identify patients and the antibiotics they received.

Impact evaluation: For each AST performed on *E. coli*-positive urine cultures during the 'before period' (2017) and the 'after period' (2019) in all laboratories of the two groups, we collected information on the patient's sex, age, and type of residence (community or nursing home), antibiotic(s) prescribed during the 15 days following the urine culture and dispensed by a community pharmacy, and the prescriber's specialty. Antibiotics prescribed less than three days after the prescription of the urine cultures were categorised as empirical therapy, whereas antibiotics prescribed three days or more after the prescription of the urine cultures were

categorised as targeted therapy. If more than three antibiotics were prescribed to an individual patient during the 15 days following urine culture prescription, we kept the first three antibiotics prescribed (chronologically) in the analyses, considering that the other antibiotics might be prescribed for another indication.

In 2019, biologists in the intervention group recorded all prescribers' requests for the complete reporting of AST results.

Unintended consequence evaluation: During the 'after period', we also collected the number of all-cause medical consultations and hospitalisations during the 30 days following urine culture prescription in each group to look for possible unintended clinical consequences. The presence of a health insurance-declared chronic disease for each patient was also collected to adjust for in case of imbalance between groups.

Statistical analyses

Our sample of laboratories was sufficient to detect a 10% difference in the prescription rate of critical antibiotics between groups after intervention, as more than 9,000 occurrences of AST on *E. coli*-positive urine cultures are usually performed each year by both groups.[17]

Impact evaluation

We first compared between groups (intervention *versus* control) in 2017 and 2019, the urine culture activity (number of urine cultures, number of AST occurrences for urine cultures, *E. coli* prevalence in urine cultures with AST), the antibiotic susceptibility profiles of *E. coli* isolated from urine cultures, the characteristics of patients with *E. coli*-positive urine cultures, and some prescription practices (% of antibiotics prescribed by GPs, number of *E. coli*-positive urine cultures with AST followed by a prescription of at least one antibiotic, and mean number

of antibiotics per *E. coli*-positive urine culture with AST) to assess the comparability of the two groups. The prescription rates of amoxicillin-clavulanate, third-generation cephalosporins, quinolones, and all these critical antibiotics together were calculated for each laboratory group in 2017 and in 2019 as follows: (number of prescriptions of antibiotic/class for *E. coli*-positive urine cultures with AST during year n)/(number of prescriptions of all antibiotics for *E. coli*-positive urine cultures with AST during year n) x 100. The prescription rates for the abovementioned antibiotics/classes were compared between the two groups in 2017 and in 2019 using a χ^2 test. The after-before (2019-2017) difference in the abovementioned antibiotics/classes was described for the two groups. Subgroup analyses (per patients' sex and per therapy category, i.e., empirical or targeted) were conducted to explore how prescribing practices were modified in 2019. The prescription rates of each type of antibiotic prescribed for *E. coli*-positive urine cultures with AST were described in 2017 and in 2019 per sex and per therapy category for each group to explore the evolution of prescriptions in the two groups. The percentage of compliance with guidelines was calculated as follows: (number of prescriptions of recommended antibiotics for *E. coli*-positive urine cultures with AST during year n)/(number of prescriptions of all antibiotics for *E. coli*-positive urine cultures with AST during year n) x 100.

The numbers and percentages of requests from clinicians for the complete reporting of AST results were described.

For the impact evaluation, the unit of analysis was the *E. coli*-positive urine culture for which AST was performed.

Evaluation of unintended clinical consequences

The prevalence of all-cause medical consultations and hospitalisations in the 30 days following the urine cultures was calculated in 2019 for the patients for whom selective reporting of AST

results was performed and for those for whom complete reporting of AST results was performed and compared using a χ^2 test.

A p value < 0·05 for two-sided tests was considered significant. All analyses were performed with SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

Ethics

This protocol was approved by French national ethics committees (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (TPS 29064) and Commission Nationale de l'Informatique et des Libertés (Décision DR-2018–141)).

Role of the funding source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the paper for publication.

RESULTS

Impact evaluation

Group characteristics

We included 21,123 E. coli-positive urine cultures with AST in 2017 (9,253 in the intervention group and 11,870 in the control group) and 21,833 in 2019 (10,530 in the intervention group and 11,303 in the control group). The matching rate following the data linkage method was 88·4% in 2017 and 86·5% in 2019 (see Supplementary Table S6 for details). Table 1 presents the characteristics of the two groups of laboratories in 2017 and 2019. The two groups were quite comparable, with the only exceptions being the prevalence of *E. coli* in urine cultures and susceptibility of *E. coli* to cotrimoxazole and amoxicillin-clavulanate.

Impact of selective reporting of AST results on critical antibiotics

Table 2 presents the comparison of the prescription rates of the critical antibiotics between the two groups. The 2017 prescription practices of critical antibiotics did not differ between the two groups, except for the prescription rate of amoxicillin-clavulanate, which was lower in the intervention group (3·6% *versus* 4·1%, p = 0·023). The prescription rates of amoxicillin-clavulanate remained lower in the intervention group in 2019 (2·5% *versus* 3·1%, p = 0·004). In 2019, the prescription rate of third-generation cephalosporins was significantly lower in the intervention group (12·4% *versus* 20·6%, p < 0·0001), resulting in an absolute reduction of 8·2% (relative reduction of 39·8%) in the intervention group compared to the control group. The prescription rates of quinolones did not differ between the two groups in 2019. Decreases in the prescription rates of amoxicillin-clavulanate and quinolones between 2017 and 2019 were observed, which were similar in the two groups (- 1·1% *versus* -1·0% for amoxicillin-clavulanate, and -7·9% in both groups for quinolones). Overall, the rate of critical antibiotic

prescriptions was significantly lower in the intervention group in 2019 (35·7% *versus* 45·1%, p < 0·0001, absolute reduction of 9·4%, relative reduction of 20·8%). The subgroup analyses showed that the abovementioned impact was mostly observed for female patients (Supplementary Table S7) and for targeted therapy (Supplementary Table S8).

Detailed description of the impact of selective reporting of AST results

Table 3 presents a detailed description of the antibiotics prescribed to male patients. We noticed a decrease in the prescription rates of cefixime, nitrofurantoin, amoxicillin and amoxicillin-clavulanate, whereas there was an increase in the prescription rates of ceftriaxone, ciprofloxacin and levofloxacin as targeted therapy in the intervention group. The percentage of compliance with guidelines was improved in both groups between 2017 and 2019, but improvement was more marked in the intervention group (+ 25·4% *versus* + 4·2% for targeted therapy; + 15·3% *versus* + 3·4% for empirical therapy).

Table 4 presents a detailed description of the antibiotics prescribed to female patients. We noticed a decrease in the prescription rates of cefixime and ofloxacin as targeted therapy, whereas there was an increase in the prescription rates of amoxicillin. The percentage of compliance with guidelines for cystitis was improved in both groups, but improvement was more marked in the intervention group for targeted therapy (+ 18·0% *versus* + 5·8%).

Requests for the complete reporting of AST results

Of the 11566 selective AST results reported in 2019 in the intervention group, 134 (1·2%) were followed by a prescriber's request to obtain the complete reporting of AST results.

Evaluation of unintended clinical consequences

The number of patients who had at least one consultation during the 30 days following urine culture prescription in 2019 did not differ between the two groups: 1,939 (23·7% of the patients for whom selective reporting of AST results was performed) in the intervention group *versus* 2,133 (23·9% of the patients for whom complete reporting of AST results was performed) in the control group (p value = 0·727). The same result was found for hospitalisations, with 1,595 (19·5%) patients hospitalised during the 30 days following urine culture prescription in the intervention group *versus* 1,708 (19·2%) in the control group (p value = 0·580).

DISCUSSION

Main results

Overall, this study resulted in a positive impact of the selective reporting of AST results. We showed a 9·4% absolute reduction (20·8% relative reduction) in the prescription rate of critical antibiotics, attributable to a decrease in third-generation cephalosporin use among female patients (i.e., approximately 85% of patients who had urine cultures prescribed). There was marked improvement in compliance with the national UTI guidelines, mostly among male patients. Requests for the complete reporting of AST results were infrequent (1·2% of all the selective AST results reported in 2019). No unintended consequences were observed.

Selective reporting of AST results mainly impacted targeted therapy (approximately 17% difference in the prescription rate of critical antibiotics between the two groups in 2019), with almost no impact on empirical therapy (approximately 4% difference), which makes sense as the reporting of AST results, by definition, allows review and adaptation of the treatment to bacterial isolate susceptibility.

The impact of selective reporting of AST results on the prescription rates of third-generation cephalosporins and all critical antibiotics was important among female patients. For most UTIs in women, guidelines do not recommend those critical antibiotics, and these antibiotics were therefore not reported in the intervention group, except when first-line antibiotics were resistant. In contrast, there was no impact on prescriptions among male patients, as most of the recommended and reported antibiotics for male UTIs are critical antibiotics. It should be noted that the prescription rates of quinolones decreased between 2017 and 2019, similarly in the two groups (approximately 8% absolute reduction). This may be the consequence of the release of updated national recommendations on community-acquired UTIs in 2017. Prior to this date, quinolones were recommended both as empirical and targeted therapy for cystitis. The lack of

an impact of selective reporting of AST results on the prescription rates of quinolones we observed in our study might be due to several factors that deserve further investigation: most quinolones are prescribed to male patients (fluoroquinolones being first-line treatment in national guidelines); and physicians might have prescribed quinolones as empirical therapy and did not want to change the antibiotic despite the AST results (e.g., due to physician preference or because treatment with fluoroquinolones is shorter than treatment with other antibiotics in uncomplicated pyelonephritis). The prescription rates of amoxicillin-clavulanate decreased in the same proportions in both groups (approximately 1% absolute reduction), and we therefore did not find an impact of the selective reporting of AST results on amoxicillin-clavulanate prescribing, possibly because the prescription rates were initially very low (approximately 3%). Among female patients, the impact of selective reporting of AST results was mostly driven by a shift from cefixime to amoxicillin as targeted therapy. The impact of selective reporting on other antibiotics was minimal. We noticed an important improvement in compliance with guidelines among both men and women, and it was particularly high among male patients (approximately 25% improvement for targeted therapy). Guidelines for female UTIs are more complex, and thus compliance with guidelines was more challenging to estimate given the absence of information on clinical indication.

Comparison with the literature

As highlighted in two recent reviews, no interventional study has evaluated the impact of selective reporting of AST results in the outpatient setting.[13,21,22] The present study confirmed the findings of the two case vignette randomised controlled studies that assessed the impact of selective reporting of AST results on the appropriateness of antibiotic prescriptions by trainees[14] and general practitioners in a real-life setting:[15] selective reporting in these two studies resulted

in a higher rate of appropriate prescriptions (i.e., compliant with guidelines) and a lower proportion of critical antibiotics, notably third-generation cephalosporins.

Strengths and limitations

To the best of our knowledge, this is the first large-scale comparative study evaluating the impact of selective reporting of AST results for UTIs in the outpatient setting. Our sample was large (more than 21,000 *E. coli*-positive urine cultures with AST per year), as data were collected from the health insurance databases, which cover 99% of the population living in France. We obtained a high matching rate (87·4%) due to the quality of data collected by laboratories and the number of variables we selected for the probabilistic data linkage method. Among the secondary objectives, we intended to evaluate the potential unintended clinical consequences, as data are scarce in the literature on this topic. However, even if our findings were reassuring, no causal relationship could be established between antibiotic prescriptions and medical consultations or hospitalisations. Moreover, we used a quasi-experimental design that combined a before-after comparison with a comparison to a control group and thus provided a high level of evidence. Finally, this study was pragmatic (i.e., conducted under real practice conditions), and prescribers were free to choose the antibiotic they prescribed as they could obtain the complete reporting of AST results upon request. Therefore, our results have good external validity.

We acknowledge that our study also has several limitations. First, patients or laboratories could not be randomised between the intervention and control groups due to feasibility issues. However, we selected two groups of laboratories that were initially comparable in terms of activity. Indeed, despite the absence of randomisation, we showed that the two groups were overall comparable during the two study periods. The characteristics that differed between the two groups were the following: *E. coli* prevalence in urine cultures, which should have no

consequence on antibiotic prescriptions, as we only included *E. coli*-positive urine cultures with AST; susceptibility of *E. coli* to amoxicillin-clavulanate in 2019, which might have no impact on our results, as amoxicillin-clavulanate prescription rates were very low (approximately 3%); and susceptibility of *E. coli* to cotrimoxazole, which was higher in 2019 in the control group. There might therefore have been a greater tendency to prescribe this antibiotic in the control group (and therefore fewer critical antibiotics); however, if such a bias exists, it results in an underestimation of the impact of the selective reporting of AST results on critical antibiotics. Second, information on clinical indications is not available in the health insurance databases. We used dispensation as a proxy for prescription, which could underestimate the number of prescriptions if patients did not collect their antibiotic at the community pharmacy. The absence of clinical indication information prevented us from identifying which indication the antibiotic was prescribed for (e.g., cystitis, pyelonephritis, indication other than UTI) and precisely measuring compliance with guidelines. The guidelines apply indiscriminately to all male patients but are different for female patients' cystitis and pyelonephritis. Thus, we estimated compliance with guidelines by sex, and for female patients, we estimated compliance by differentiating between cystitis and pyelonephritis, the exact proportion of urine cultures prescribed for each situation being impossible to evaluate.

Implications

Our study presents innovative results that will inform French AMS policy. We believe our study could also provide evidence supporting the implementation of selective reporting of AST results in other countries based on national guidelines.

Even though selective reporting of AST results led to substantial improvements in antibiotic prescription, there is still room for improvement. We voluntarily did not combine an educational component with the selective reporting intervention to isolate its specific effect.

However, it might be useful in routine practice to actively implement additional AMS interventions, such as the promotion of easily available educational resources on UTIs for prescribers, to enhance the impact of selective reporting. Moreover, such selective reporting of AST results aims to reduce the number of inappropriate prescriptions, but it does not target unnecessary prescriptions that should be addressed by other AMS interventions.

Conclusion

Our results confirm with a high level of evidence the positive impact of selective reporting of AST results in the outpatient setting.

NOTES

Data sharing

The data that support the present findings are available from the National Health Insurance but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Contributors

CP, NT, SF and PDM designed the study. MS performed the literature search, analysed the data, and wrote the original draft. All authors contributed to data interpretation and to the review and editing of the manuscript. All authors had final responsibility for the decision to submit for publication.

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Declaration of interests

MS: None

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Table 1. Description of the two groups of laboratories before (2017) and after the implementation of selective reporting of AST results (2019).

	2017		2019	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Laboratory activity regarding urine cultures				
Number of urine cultures	84236	87826	92820	88754
Number of AST occurrences for urine cultures (%)	17835 (21·2%)	18901 (21·5%)	20579 (22·2%)	19114 (21·5%)
E. coli prevalence in urine cultures with AST (number and %)	12024 (67·4%)	14998 (79·4%)	13641 (66·3%)	14714 (77·0%)
Number of *E. coli*-positive urine cultures with AST included in the analyses	9253	11870	10530	11303
Number of patients who had at least one *E. coli*-positive urine culture with AST during the year	7210	9376	8184	8917
Characteristics of patients				
Age in years (m ±SD)	59·2 ± 21·4	59·5 ± 20·0	60·2 ± 20·9	60·0 ± 20·1
Number (%) of male patients	1154 (16·0%)	1464 (15·6%)	1285 (15·7%)	1353 (15·2%)
Number (%) of patients living in a nursing home	362 (5·0%)	529 (5·6%)	354 (4·3%)	322 (3·6%)
Number (%) of patients with chronic diseases	..	..	3381 (41·3%)	3597 (40·3%)
Number (%) of patients who had more than one *E. coli*-positive urine culture with AST during the year	1319 (18·3%)	1660 (17·7%)	1544 (18·9%)	1588 (17·8%)
Antibiotic susceptibility of *E. coli* isolated from urine cultures				
Number (%) of *E. coli* isolates susceptible to fosfomycin	..	..	13433 (98·5%)	14568 (99·0%)
Number (%) of *E. coli* isolates susceptible to pivmecillinam	..	..	12737 (93·4%)	14074 (95·7%)
Number (%) of *E. coli* isolates susceptible to nitrofurantoin	..	..	13530 (99·2%)	14551 (98·9%)
Number (%) of *E. coli* isolates susceptible to cotrimoxazole	9403 (78·2%)	11887 (79·3%)	9762 (71·6%)	11867 (80·7%)
Number (%) of *E. coli* isolates susceptible to ofloxacin	10006 (83·2%)	12778 (85·2%)	..	..

Number (%) of *E. coli* isolates susceptible to amoxicillin	..	..	7560 (55·4%)	7926 (53·9%)
Number (%) of *E. coli* isolates susceptible to amoxicillin-clavulanate	10067 (83·7%)	12417 (82·8%)	8870 (65·0%)	11859 (79·1%)
Number (%) of *E. coli* isolates susceptible to ceftriaxone	11442 (95·2%)	14343 (95·6%)	..	..
Number (%) of *E. coli* isolates with extended-spectrum beta-lactamases	477 (4·0%)	558 (3·7%)	478 (3·5%)	574 (3·9%)
Prescription practices				
Number of antibiotics prescribed in the 15 days following urine culture prescription testing	10099	12502	11146	11805
Number (%) of AST occurrences associated with a urine culture prescribed by GPs	9564 (94·7%)	11809 (94·5%)	10494 (94·2%)	11142 (94·4%)
Number (%) of *E. coli*-positive urine cultures with AST followed by a prescription of at least 1 antibiotic	7609 (82·2%)	9684 (81·6%)	8434 (80·1%)	9165 (81·1%)
Mean number of antibiotics per *E. coli*-positive urine culture with AST	1·09	1·05	1·06	1·04

AST: antibiotic susceptibility testing; *E. coli*: *Escherichia coli*; m: mean; SD: standard deviation; GPs: general practitioners.

Table 2. Comparison of the prescription rates of critical antibiotics between the two groups.
The prescription rates of dispensed antibiotics are presented in parentheses. Prescription rate = (number of antibiotics/classes prescribed for *Escherichia coli*-positive urine cultures with AST during year n)/(number of all antibiotics prescribed for *Escherichia coli*-positive urine cultures with AST during year n). Antibiotic molecules/classes are followed by their ATC classification.[20] Bolded text indicates a p value < 0·05.

	2017			**2019**			**% 2019 - % 2017**	
	Intervention group	**Control group**	p value	**Intervention group**	**Control group**	p value	**Intervention group**	**Control group**
Total number of antibiotics prescribed J01	10099	12502	..	11146	11805	..	..	..
Number (%) of prescriptions of amoxicillin-clavulanate J01CR02	359 (3·6%)	518 (4·1%)	**0·023**	279 (2·5%)	370 (3·1%)	**0·004**	- 1·1%	- 1·0%
Number (%) of prescriptions of third-generation cephalosporins J01DD	2114 (20·9%)	2582 (20·7%)	0·606	1379 (12·4%)	2426 (20·6%)	**< 0·0001**	- 8·5%	- 0·1%
Number (%) of prescriptions of quinolones J01M	2909 (28·8%)	3659 (29·3%)	0·447	2325 (20·9%)	2528 (21·4%)	0·303	- 7·9%	- 7·9%
Number (%) of prescriptions of critical antibiotics J01CR02 + J01DD + J01M	5382 (53·3%)	6759 (54·1%)	0·248	3983 (35·7%)	5324 (45·1%)	**< 0·0001**	- 17·6%	- 9·0%

Table 3. Description of the antibiotics prescribed for *Escherichia coli*-positive urine cultures with AST for male patients for the two groups of laboratories.

The prescription rates of dispensed antibiotics are presented in parentheses. Prescription rate = (number of antibiotics/class dispensed for *Escherichia coli*-positive urine cultures with AST during year n)/(number of all antibiotics dispensed for *Escherichia coli*-positive urine cultures with AST during year n). Antibiotic molecules/classes are followed by their ATC classification.[20] Green represents the molecules recommended as first-line treatment in the French guidelines for male urinary tract infections.[23]

	Empirical therapy				**Targeted therapy**			
	2017		**2019**		**2017**		**2019**	
	Intervention group	**Control group**	**Intervention group**	**Control group**	**Intervention group**	**Control group**	**Intervention group**	**Control group**
All antibiotics J01	1049	1239	1055	1078	751	818	664	800
Amoxicillin J01CA04	45 (4·3%)	50 (4·0%)	35 (3·3%)	47 (4·4%)	46 (6·1%)	36 (4·4%)	15 (2·3%)	29 (3·6%)
Pivmecillinam J01CA08	3 (0·3%)	2 (0·2%)	2 (0·2%)	10 (0·9%)	4 (0·5%)	13 (1·6%)	1 (0·2%)	15 (1·9%)
Amoxicillin-clavulanate J01CR02	53 (5·1%)	90 (7·3%)	48 (4·6%)	54 (5·0%)	56 (7·5%)	73 (8·9%)	19 (2·9%)	52 (6·5%)
Ceftriaxone J01DD04	62 (5·9%)	65 (5·3%)	104 (9·9%)	58 (5·4%)	39 (5·2%)	28 (3·4%)	89 (13·4%)	50 (6·3%)
Cefixime J01DD08	114 (10·9%)	148 (12·0%)	86 (8·2%)	120 (11·1%)	119 (15·9%)	141 (17·2%)	39 (5·9%)	147 (18·4%)
Cotrimoxazole J01EE01	61 (5·8%)	66 (5·3%)	89 (8·4%)	92 (8·5%)	95 (12·7%)	79 (9·7%)	122 (18·4%)	99 (12·4%)
Ofloxacin J01MA01	441 (42·0%)	417 (33·7%)	357 (33·8%)	383 (35·5%)	219 (29·2%)	236 (28·9%)	214 (32·2%)	282 (35·3%)

Ciprofloxacin J01MA02	152 (14·5%)	221 (17·8%)	210 (19·9%)	178 (16·5%)	90 (12·0%)	114 (13·9%)	103 (15·5%)	50 (6·3%)
Norfloxacin J01MA06	37 (3·5%)	59 (4·8%)	9 (0·9%)	12 (1·1%)	13 (1·7%)	14 (1·7%)	1 (0·2%)	5 (0·6%)
Levofloxacin J01MA12	32 (3·1%)	34 (2·7%)	95 (9·0%)	79 (7·3%)	8 (1·1%)	18 (2·2%)	40 (6·0%)	17 (2·1%)
Nitrofurantoin J01XE01	30 (2·9%)	21 (1·7%)	3 (0·3%)	17 (1·6%)	38 (5·1%)	33 (4·0%)	1 (0·2%)	32 (4·0%)
Fosfomycin J01XX01	6 (0·6%)	30 (2·4%)	4 (0·4%)	7 (0·7%)	14 (1·9%)	16 (2·0%)	5 (0·8%)	10 (1·3%)
Other antibiotics*	13 (1·2%)	36 (2·9%)	13 (1·2%)	21 (1·9%)	10 (1·3%)	17 (2·1%)	15 (2·3%)	12 (1·5%)
Estimated compliance with guidelines	**246 (23·5%)**	**320 (25·8%)**	**409 (38·8%)**	**315 (29·2%)**	**451 (60·1%)**	**475 (58·1%)**	**568 (85·5%)**	**498 (62·3%)**

* Antibiotics that represent < 1% of antibiotic prescriptions: doxycycline (J01AA02), lymecycline (J01AA04), phenoxymethylpenicillin (J01CE02), cloxacillin (J01CF02), piperacillin-tazobactam (J01CR05), cefuroxime (J01DC02), cefotiam (J01DC07), ceftazidime (J01DD02), cefpodoxime (J01DD13), meropenem (J01DH02), spiramycin (J01FA02), roxithromycin (J01FA06), josamycin (J01FA07), clarithromycin (J01FA09), azithromycin (J01FA10), pristinamycin (J01FG01), gentamicin (J01GB03), amikacin (J01GB06), lomefloxacin (J01MA07), moxifloxacin (J01MA14), flumequine (J01MB07), spiramycin-metronidazole (J01RA04).

Table 4. Description of the antibiotics prescribed for *Escherichia coli*-positive urine cultures with AST for female patients for the two groups of laboratories.

The prescription rates of dispensed antibiotics are presented in parentheses. Prescription rate = (number of antibiotics/class dispensed for *Escherichia coli*-positive urine cultures with AST during year n)/number of all antibiotics dispensed for *Escherichia coli*-positive urine cultures with AST during year n. Antibiotic molecules/classes are followed by their ATC classification.[20] Yellow represents the molecules recommended as first-line treatment in the French guidelines for cystitis. Blue represents the molecules recommended as first-line treatment in the French guidelines for pyelonephritis. Green represents the molecules recommended as first-line treatment in the French guidelines for both cystitis and pyelonephritis.[23]

	Empirical therapy				**Targeted therapy**			
	2017		**2019**		**2017**		**2019**	
	Intervention group	**Control group**	**Intervention group**	**Control group**	**Intervention group**	**Control group**	**Intervention group**	**Control group**
All antibiotics J01	4987	6232	5662	5870	3312	4213	3765	4057
Amoxicillin J01CA04	300 (6·0%)	267 (4·3%)	472 (8·3%)	261 (4·5%)	353 (10·7%)	304 (7·2%)	700 (18·6%)	302 (7·4%)
Pivmecillinam J01CA08	240 (4·8%)	278 (4·5%)	564 (10.0%)	531 (9·1%)	145 (4·4%)	278 (6·6%)	470 (12·5%)	451 (11·1%)
Amoxicillin-clavulanate J01CR02	114 (2·3%)	168 (2·7%)	110 (1·9%)	123 (2·1%)	136 (4·1%)	187 (4·4%)	102 (2·7%)	141 (3·5%)
Ceftriaxone J01DD04	149 (3·0%)	112 (1·8%)	145 (2·6%)	102 (1·7%)	67 (2·0%)	71 (1·7%)	62 (1·7%)	66 (1·6%)
Cefixime J01DD08	787 (15·8%)	1066 (17·1%)	582 (10·3%)	946 (16·1%)	751 (22·7%)	916 (21·7%)	261 (6·9%)	909 (22·4%)
Cotrimoxazole J01EE01	68 (1·4%)	155 (2·5%)	177 (3·1%)	184 (3·1%)	85 (2·6%)	104 (2·5%)	215 (5·7%)	156 (3·9%)
Ofloxacin J01MA01	691 (13·9%)	490 (7·9%)	479 (8·5%)	492 (8·4%)	317 (9·6%)	336 (8·0%)	131 (3·5%)	345 (8·5%)

Ciprofloxacin J01MA02	207 (4·2%)	349 (5·6%)	220 (3·9%)	216 (3·7%)	172 (5·2%)	278 (6·6%)	138 (3·7%)	63 (1·6%)
Norfloxacin J01MA06	229 (4·6%)	438 (7·0%)	57 (1·0%)	123 (2·1%)	86 (2·6%)	172 (4·1%)	16 (0·4%)	42 (1·0%)
Lomefloxacin J01MA07	145 (2·9%)	359 (5·8%)	68 (1·2%)	108 (1·8%)	41 (1·2%)	88 (2·1%)	18 (0·5%)	37 (0·9%)
Levofloxacin J01MA12	15 (0·3%)	15 (0·2%)	109 (1·9%)	75 (1·3%)	10 (0·3%)	10 (0·2%)	57 (1·5%)	18 (0·4%)
Nitrofurantoin J01XE01	468 (9·4%)	438 (7·0%)	616 (10·9%)	512 (8·7%)	452 (13·7%)	439 (10·4%)	590 (15·7%)	464 (11·4%)
Fosfomycin J01XX01	1510 (30·3%)	1964 (31·5%)	2004 (35·4%)	2091 (35·6%)	621 (18·8%)	860 (20·4%)	926 (24·6%)	968 (23·9%)
Other antibiotics*	64 (1·3%)	133 (2·1%)	59 (1·0%)	106 (1·8%)	76 (2·3%)	170 (4·0%)	79 (2·1%)	95 (2·3%)
Estimated compliance with guidelines assuming all cases represent cystitis	**2218 (44·5%)**	**2680 (43·0%)**	**3184 (56·2%)**	**3134 (53·4%)**	**950 (28·7%)**	**1021 (24·2%)**	**1760 (46·7%)**	**1217 (30·0%)**
Estimated compliance with guidelines assuming all cases represent pyelonephritis	**371 (7·4%)**	**476 (7·6%)**	**474 (8·4%)**	**393 (6·7%)**	**1891 (57·1%)**	**2206 (52·4%)**	**1666 (44·2%)**	**2000 (49·3%)**
Estimated compliance with guidelines for cystitis + pyelonephritis	**2589 (51·9%)**	**3156 (50·6%)**	**3658 (64·6%)**	**3527 (60·1%)**	**2488 (75·1%)**	**2923 (69·4%)**	**2726 (72·4%)**	**2915 (71·9%)**

* Antibiotics that represent < 1% of antibiotic prescriptions: doxycycline (J01AA02), lymecycline (J01AA04), phenoxymethylpenicillin (J01CE02), benzathine benzylpenicillin (J01CE10), cloxacillin (J01CF02), ampicillin-sulbactam (J01CR01), piperacillin-tazobactam (J01CR05), cefuroxime (J01DC02), cefaclor (J01DC04), cefotiam (J01DC07), ceftazidime (J01DD02), cefpodoxime (J01DD13), imipenem (J01DH51), trimethoprim (J01EA01), erythromycin (J01FA01), spiramycin (J01FA02), roxithromycin (J01FA06), josamycin (J01FA07), clarithromycin (J01FA09), azithromycin (J01FA10), telithromycin (J01FA15), clindamycin (J01FF01), pristinamycin (J01FG01), tobramycin (J01GB01), gentamicin (J01GB03), moxifloxacin (J01MA14), flumequine (J01MB07), spiramycin-metronidazole (J01RA04), fusidic acid (J01XC01).

Supplementary Table S1. Summary of the main national and regional AMS strategy in the outpatient setting.

	Strategy	Year	Reference
National strategy	AMR One Health national action plan	2016	[1]
	National UTI guidelines	2017	[2]
	Antibioclic: computerized decision support system freely available (including national UTI guidelines) used by 60% of French GPs	2011	[3,4]
	Continuing medical education	< 2017 and ongoing	
	Health Insurance delegates visits to GPs promoting guidelines and tools	< 2016 and ongoing	[5]
Additional measures at regional level	AntibioEst: regional antibiotic stewardship centre	2003	[6]
	Antibiotel: infectious diseases physicians freely available by phone for advice	2004	[7]

AMR: antimicrobial resistance; UTI: urinary tract infection; GP: general practitioner

Supplementary Table S2. TREND Statement Checklist.[8]

Paper Section/Topic	Item No.	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how units were allocated to interventions		2
		• Structured abstract recommended		2
		• Information on target population or study sample		1
Introduction				
Background	2	• Scientific background and explanation of rationale		5
		• Theories used in designing behavioral interventions		NA
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)		9-10
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented		9-10
		• Recruitment setting		9-10
		• Settings and locations where the data were collected		9-10
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		9-10
		○ Content: what was given?		10
		○ Delivery method: how was the content given?		10
		○ Unit of delivery: how were subjects grouped during delivery?		9-10
		○ Deliverer: who delivered the intervention?		10
		○ Setting: where was the intervention delivered?		9-10
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?		9-10

		○ Time span: how long was it intended to take to deliver the intervention to each unit?	NA
		○ Activities to increase compliance or adherence (e.g., incentives)	NA
Objectives	5	• Specific objectives and hypotheses	8
Outcomes	6	• Clearly defined primary and secondary outcome measures	10-11
		• Methods used to collect data and any methods used to enhance the quality of measurements	11
		• Information on validated instruments such as psychometric and biometric properties	NA
Sample size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	12
Assignment method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	12
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	9-10
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	9
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed	NA
Unit of Analysis	10	• Description of the smallest unit that is being analysed to assess intervention effects (e.g., individual, group, or community)	12
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	NA
Statistical methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods for correlated data	12-13
		• Statistical methods used for additional analyses, such as subgroup analyses and adjusted analysis	13
		• Methods for imputing missing data, if used	NA

		• Statistical software or programs used	13
Results			
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	15
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	15
		○ Assignment: the numbers of participants assigned to a study condition	15
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	15
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	NA
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	15
		• Description of protocol deviations from study as planned, along with reasons	NA
Recruitment	13	• Dates defining the periods of recruitment and follow-up	NA
Baseline data	14	• Baseline demographic and clinical characteristics of participants in each study condition	15
		• Baseline characteristics for each study condition relevant to specific disease prevention research	NA
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	NA
		• Comparison between study population at baseline and target population of interest	NA
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	Table 1
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	Table 2
		• Indication of whether the analysis strategy was “intention to treat” or, if not,	NA

		description of how non-compliers were treated in the analyses	
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	15-16
		• Inclusion of null and negative findings	15
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	NA
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	Table 3, 4, S6, S7
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	16
Discussion			
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	17-18
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	17-18
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	19-20
		• Discussion of research, programmatic, or policy implications	20-21
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	20-21
Overall evidence	22	• General interpretation of the results in the context of current evidence and current theory	18-20-21

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/
NA: not applicable

Supplementary Table S3. 2017 French guidelines for urinary tract infections.[a]

Gender	Clinical situation	1st-line antibiotics recommended as empirical therapy	1st-line antibiotics recommended as targeted therapy
Female	Uncomplicated cystitis[b]	1) Fosfomycin-trometamol 2) Pivmecillinam	..
	Cystitis at risk of complication[c]	1) Nitrofurantoin 2) Fosfomycin-trometamol	1) Amoxicillin 2) Pivmecillinam 3) Nitrofurantoin
	Pyelonephritis	Ciprofloxacin, Levofloxacin, Ceftriaxone	1) Amoxicillin 2) Cotrimoxazole 3) Amoxicillin-clavulanate 4) Ciprofloxacin, Levofloxacin, Ofloxacin 5) Cefixime 6) Ceftriaxone
Male	Male UTI	Ciprofloxacin, Levofloxacin, Ceftriaxone	1) Ciprofloxacin, Levofloxacin, Ofloxacin 2) Cotrimoxazole 3) Ceftriaxone

[a] As presented in the widely used Antibioclic computerised decision support system[3]
[b] Performing a urine culture is not recommended
[c] Targeted treatment should be preferred whenever possible

Supplementary Table S4. Selective reporting of AST results by gender in 2019 (intervention group).

Gender	**Male**				**Female**			
Susceptibility profiles	**FQ S TMP-SMX S 3GCs S**	**FQ R and/or TMP-SMX R and 3GCs S**	**FQ S TMP-SMX S 3GCs R**	**FQ R TMP-SMX R 3GCs R**	**AMX S**	**AMX I/R and (AMC S or TMP-SMX S)**	**AMX I/R and AMC I/R and TMP-SMX I/R and 3GCs S**	**3GCs R**
Antibiotics listed in the selective reporting of AST	TMP-SMX Ciprofloxacin Ofloxacin Levofloxacin	TMP-SMX Cefotaxime Ceftriaxone Ciprofloxacin Ofloxacin Levofloxacin	TMP-SMX Cefotaxime Ceftriaxone Ceftazidime Ciprofloxacin Ofloxacin Levofloxacin	AMX Ticarcillin Piperacillin + tazobactam Pivmecillinam Fosfomycin TMP-SMX Cefoxitine AMC Temocillin Cefixime Cefotaxime Ceftriaxone Ceftadizime Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX **<u>If I/R :</u>** Ciprofloxacin Levofloxacin Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX AMC **<u>If I/R :</u>** Ciprofloxacin Levofloxacin Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX AMC Cefixime Ciprofloxacin Ofloxacin	AMX Ticarcillin Piperacillin + tazobactam Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX Cefoxitine AMC Temocillin Cefixime Cefotaxime Ceftriaxone Ceftadizime Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin

Comments	- When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures. - AMC, nitrofurantoin, fosfomycin, pivmecillinam, and cefixime should not be used in male UTIs (lack of diffusion in prostate). - Complete AST is available at the prescriber's request. - For more information regarding national guidelines: https://antibioclic.com.	- When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures. - Nitrofurantoin, pivmecillinam, and fosfomycin should not be used for pyelonephritis (lack of diffusion in renal parenchyma). - Complete AST is available at the prescriber's request. - For more information regarding national guidelines: https://antibioclic.com.

AST: antibiotic susceptibility testing; FQ: fluoroquinolones; TMP-SMX: cotrimoxazole; 3GCs: third-generation cephalosporins; AMX: amoxicillin; AMC: amoxicillin-clavulanate; I: intermediate; R: resistant; UTIs: urinary tract infections

Supplementary Table S5. Complete reporting of AST results by gender in 2019 (control group).

Gender	Male	Female
Antibiotics reported in the complete reporting of AST	Pivmecillinam Ampicillin (AMX) AMC Ticarcillin Cefoxitine Cefixime Ceftazidime Ceftriaxone Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin Fosfomycin Nitrofurantoin TMP-SMX	Pivmecillinam Ampicillin (AMX) AMC Ticarcillin Cefoxitine Cefixime Ceftazidime Ceftriaxone Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin Fosfomycin Nitrofurantoin TMP-SMX
Comments	- Cefixime, AMC, fosfomycin, and nitrofurantoin should not be used in male UTIs (lack of diffusion in prostate). Preferred antibiotics (depending on AST results): quinolones (ofloxacin), cotrimoxazole. - Results need to be interpreted according to the clinical symptoms.	- Results need to be interpreted according to the clinical symptoms.

AST: antibiotic susceptibility testing; TMP-SMX: cotrimoxazole; AMX: amoxicillin; AMC: amoxicillin-clavulanate; UTIs: urinary tract infections

Supplementary Table S6. Results of the data linkage method.

	2017		2019	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Number of *E. coli*-positive urine cultures with AST transmitted to the Health Insurance for data linkage	10074	13828	11566	13689
Number of *E. coli*-positive urine cultures with AST included in the analyses	9253	11870	10530	11303
Matching rate (%)	91·9%	85·8%	91·0%	82·6%

Supplementary Table S7. Description of the prescription rates of critical antibiotics according to the patients' gender in 2019.
Prescription rate = (number of antibiotic/class prescribed for *Escherichia coli*-positive urine cultures with antibiotic susceptibility testing during the year n) / (number of all antibiotics prescribed for *Escherichia coli*-positive urine cultures with antibiotic susceptibility testing during the year n). Antibiotic molecules/classes are followed by their ATC classification.[9]

	Male patients		**Female patients**	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Total number of antibiotics prescribed J01	1719	1878	9427	9927
Number (%) of prescriptions of amoxicillin-clavulanate J01CR02	67 (3·9%)	106 (5·6%)	212 (2·3%)	264 (2·7%)
Number (%) of prescriptions of third-generation cephalosporins J01DD	319 (18·6%)	379 (20·2%)	1060 (11·2%)	2047 (20·6%)
Number (%) of prescriptions of quinolones J01M	1032 (60·0%)	1007 (53·6%)	1293 (13·7%)	1521 (15·3%)
Number (%) of prescriptions of critical antibiotics J01CR02 + J01DD + J01M	1418 (82·5%)	1492 (79·5%)	2565 (27·2%)	3832 (38·6%)

Supplementary Table S8. Description of the prescription rates of critical antibiotics according to the type of therapy in 2019.
Prescription rate = (number of antibiotic/class prescribed for *Escherichia coli*-positive urine cultures with antibiotic susceptibility testing during the year n) / (number of all antibiotics prescribed for *Escherichia coli*-positive urine cultures with antibiotic susceptibility testing during the year n). Antibiotic molecules/classes are followed by their ATC classification.[9]

	Empirical therapy		**Targeted therapy**	
	Intervention group	**Control group**	**Intervention group**	**Control group**
Total number of antibiotics prescribed J01	6717	6948	4429	4857
Number (%) of prescriptions of amoxicillin-clavulanate J01CR02	158 (2·4%)	177 (2·6%)	121 (2·7%)	193 (4·0%)
Number (%) of prescriptions of third-generation cephalosporins J01DD	925 (13·8%)	1244 (17·9%)	454 (10·3%)	1182 (24·3%)
Number (%) of prescriptions of quinolones J01M	1606 (23·9%)	1667 (24·0%)	719 (16·2%)	861 (17·7%)
Number (%) of prescriptions of critical antibiotics J01CR02 + J01DD + J01M	2689 (40·0%)	3088 (44·4%)	1294 (29·2%)	2236 (46·0%)

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III – Article ANTIBIO-ciblés : évaluation de la faisabilité et de l'acceptabilité des antibiogrammes ciblés

1. Contexte et objectifs

Une revue de la littérature récente a souligné la nécessité de compléter les évaluations d'impact des antibiogrammes ciblés par des évaluations de leurs conséquences négatives potentielles, de la faisabilité de leur mise en place et de leur acceptabilité par les professionnels de santé, qui représentent les principaux freins à leur mise en place en pratique courante.(69) Cet article présente deux des objectifs secondaires de l'étude ANTIBIO-ciblés : (i) l'évaluation de la faisabilité de la mise en place des antibiogrammes ciblés par les laboratoires de biologie médicales et (ii) l'évaluation de leur acceptabilité par les prescripteurs et par les professionnels de laboratoires.(82)

2. Méthodes

Pour l'évaluation de la faisabilité, les laboratoires du groupe ATOUTBIO ont recueilli toutes les ressources (humaines, matérielles, informatiques) dédiées à la mise en œuvre des antibiogrammes ciblés d'août 2018 à février 2019. Pour l'évaluation de l'acceptabilité, les laboratoires ont recueilli le nombre et les raisons des appels des prescripteurs pour obtenir l'antibiogramme complet en 2019. Nous avons également réalisé des entretiens individuels semi-dirigés de médecins généralistes et des entretiens individuels et *focus groups* semi-dirigés de professionnels de laboratoire, un an après la mise en place des antibiogrammes ciblés. Ces entretiens visaient à recueillir leur opinion sur l'antibiogramme ciblé, l'impact qu'ils percevaient sur leur pratique, les principales contraintes à son utilisation et leur avis et attentes en cas de déploiement au niveau national.

3. Principaux résultats et conclusions

Environ 23 000 euros et 80 heures de temps de travail supplémentaires ont été dédiés au développement et à l'ajustement de l'antibiogramme ciblé par les laboratoires ATOUTBIO. Tous les patients éligibles ont reçu l'antibiogramme ciblé. Nous avons réalisé 21 entretiens individuels de médecins généralistes et des *focus groups* et entretiens individuels de treize professionnels des laboratoires ATOUBIO. L'acceptabilité était élevée pour l'ensemble des professionnels interrogés. L'antibiogramme ciblé était décrit comme un outil simple, clair et utile pour améliorer la pertinence des prescriptions antibiotiques et réduire l'antibiorésistance.

La principale contrainte identifiée était la nécessité pour les prescripteurs d'appeler le laboratoire afin d'obtenir l'antibiogramme complet. Les principales raisons des appels des prescripteurs au laboratoire étaient (i) qu'ils pensaient que l'antibiogramme ciblé n'était pas adapté à toutes les situations cliniques, notamment aux pyélonéphrites pour lesquelles ils étaient réticents à arrêter de prescrire des fluoroquinolones ; et (ii) qu'ils avaient prescrit un antibiotique en probabiliste qui ne se trouvait pas sur l'antibiogramme ciblé et qu'ils ne souhaitaient pas modifier le traitement (par manque de temps pour faire revenir le patient). Cependant, le nombre de demandes d'antibiogrammes complets était faible (1,2% de tous les antibiogrammes ciblés rendus) et aisément gérable pour les professionnels de laboratoire. Les professionnels étaient favorables à l'extension de l'antibiogramme ciblé à d'autres bactéries responsables d'infections urinaires et à d'autres prélèvements. L'hypothèse d'un déploiement de l'antibiogramme ciblé au niveau national a fait l'unanimité. Plusieurs leviers ont été identifiés pour optimiser cette mise en place à plus large échelle, afin d'améliorer l'acceptabilité et l'impact des antibiogrammes ciblés : (i) une information large des prescripteurs en amont de la modification du rendu de l'antibiogramme ; (ii) l'association à des actions éducatives pour accompagner le rendu des antibiogrammes ciblés, comme une meilleure sensibilisation des prescripteurs à l'antibiorésistance ou des outils facilitant l'accès aux recommandations ; (iii) une formation des professionnels de laboratoires pour répondre aux demandes des prescripteurs ; et (iv) une adhésion de l'ensemble des laboratoires au plan national, la biologie médicale de ville étant un secteur concurrentiel.

4. Mon implication

Pour cet article, j'ai contribué au recueil de données quantitatives, au recueil de données qualitatives (participation à quatre entretiens de médecins généralistes et à l'ensemble des *focus groups* et entretiens de professionnels de laboratoire, conduits par Gaëlle Le Dref, épistémologiste), aux analyses, à l'interprétation des résultats, à la rédaction et à la valorisation.

5. Valorisation

Cet article a été soumis le 20 septembre 2022 à la revue *Journal of Antimicrobial Chemotherapy – Antimicrobial Resistance* (rang et *impact factor* à venir).

Un abstract sur les résultats préliminaires de cette étude avait été accepté pour présentation sous format poster au congrès européen *European Congress of Clinical Microbiology and Infectious Diseases* (ECCMID) qui devait avoir lieu à Paris en avril 2020.

Malheureusement, le congrès a été annulé à cause de la COVID-19. Un *abstract book* a été réalisé regroupant les abstracts de l'ensemble des présentations qui étaient prévues.(83)

Un résumé étendu sur l'étude ANTIBIO-ciblés (évaluation de l'impact, des conséquences négatives potentielles, de la faisabilité et de l'acceptabilité) a été soumis à la Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI) qui a lieu à Paris en décembre 2022, en vue du concours pour le prix RICAI Junior 2022.

Original article

Selective reporting of antibiotic susceptibility testing results for urine cultures: feasibility and acceptability by general practitioners and laboratory professionals in France

Gaëlle Le Dref[1] (1), Maïa Simon[1,2] (1), Aurélie Bocquier[1], Sébastien Fougnot[3], Joëlle Kivits[1], Alain Duda[3], Céline Pulcini[1,4], Nathalie Thilly[1,2], on behalf of the ANTIBIO-ciblés Scientific Committee: Alexandre Charmillon, Virginie Chopard, Patrice De Monchy, Marion Delpuech, Anne Fagot-Campagna, Alain Lozniewski, Amandine Luc, Violaine Mauffrey, Christian Rabaud, Emmanuelle Varon

[1] Université de Lorraine, UR 4360 APEMAC, F-54000 Nancy, France

[2] Université de Lorraine, CHRU-Nancy, Département Méthodologie, Promotion, Investigation, F-54000 Nancy, France

[3] Laboratoire ATOUTBIO, F-54000 Nancy, France

[4] Université de Lorraine, CHRU-Nancy, Service des maladies infectieuses et tropicales, F-54000 Nancy, France

(1) Both authors contributed equally to this work

Corresponding author: Professor Nathalie Thilly. Université de Lorraine, CHRU-Nancy, département Méthodologie, Promotion, Investigation, F-54000 Nancy, France. Tel : +33 (0)3 83 15 54 57, e-mail : n.thilly@chru-nancy.fr

Running title: Feasibility and acceptability of selective reporting of antibiotic susceptibility testing

Registration in Clinical Trials: NCT03612297

ABSTRACT

Background: Selective reporting of antibiotic susceptibility testing (AST) is a recommended antibiotic stewardship strategy, aiming at reducing inappropriate antibiotic prescriptions.

Objectives: Our objectives were to evaluate (i) the feasibility of the implementation of selective reporting of AST for urine cultures for laboratory professionals, and (ii) its acceptability by prescribers and laboratory professionals, to explore facilitators and barriers to its potential implementation on a national scale.

Methods: As part of the 'ANTIBIO-ciblés' interventional study (northeastern France, August 2018 – December 2019), we prospectively collected quantitative data on all resources dedicated by the laboratories of the intervention group to implement selective reporting of AST for *Escherichia coli*-positive urine cultures, and on the numbers and reasons of complete reporting of AST the prescribers requested to the laboratories. We also collected qualitative data using semi-structured interviews and focus groups of general practitioners and laboratory professionals.

Results: The implementation of selective reporting of AST required around 80 hours and costed 23,000 euros. All interviewed professionals were favourable to the principle of this tool. Most of them found it clear, simple and useful to improve the appropriateness of antibiotic prescriptions and reduce antibiotic resistance. Its major constraint was the necessity for general practitioners to call the laboratory to obtain the complete reporting of AST, but the number of requests was actually low (1.2% of all selective reporting of AST).

Conclusion: Selective reporting of AST resulted in reasonable human and financial costs, and was well accepted by both general practitioners and laboratory professionals.

Keywords: antimicrobial stewardship; outpatient setting; antibiotic susceptibility testing; feasibility; acceptability

INTRODUCTION

The World Health Organisation underlines that antimicrobial resistance is one of the ten most pressing threats to global public health.[1] In France, 125,000 persons are infected by multidrug-resistant bacteria each year, causing 5,500 deaths.[2] A situation of greatest concern is antibiotic-resistant *Escherichia coli* (*E. coli*), particularly to third-generation cephalosporins and fluoroquinolones.[3] *E. coli* is the major pathogen for urinary tract infections (UTIs), isolated in more than 70% of urine cultures in the outpatient setting.[4] Antibiotic resistance is mainly driven by unnecessary and inappropriate use of antibiotics,[5] notably by the use of antibiotics that carry a higher risk of selection of resistance), called 'critical' antibiotics in France.[6] France is one of the European countries with the highest antibiotic consumption, in particular in the outpatient setting.[7] Most (77%) antibiotics are prescribed in the outpatient setting in France, 70% by general practitioners (GPs).[8]

Antimicrobial stewardship programmes are defined as a coherent set of actions which promote using antimicrobials responsibly, notably by limiting unnecessary and inappropriate antimicrobial use.[9] Among the list of potential actions within an antibiotic stewardship programme, selective reporting of antibiotic susceptibility testing (AST) results aims at guiding prescriptions to the most appropriate antibiotics, i.e. first-line antibiotics recommended in national guidelines.[10] It consists in reporting only few antibiotics (e.g. 4 or 5) to the prescriber, while all the antibiotics are still tested but only reported in case of resistance to first-line antibiotics or on prescribers' request.[11] Based on encouraging results from observational retrospective studies, selective reporting of AST has been recommended in several national or international guidelines to limit inappropriate antibiotic prescribing.[12–14] However, it has never been evaluated using an experimental design and is not routinely used in France.

In this context, we conducted a large interventional, controlled, before-after study (the 'ANTIBIO-ciblés' study) to assess the impact of selective reporting of AST for *E. coli*-positive

urine cultures on the prescription of critical antibiotics in the French outpatient setting.[15] As part of the secondary objectives of this study, we present here the evaluation of (i) the feasibility of the implementation of selective reporting of AST for laboratories, and (ii) its acceptability by prescribers and laboratory professionals, as well as facilitators and barriers to inform implementation and scale-up.

METHODS

Study design

Details on the 'ANTIBIO-ciblés' protocol have been previously published.[15]

To evaluate the feasibility, we prospectively collected (i) quantitative data on all resources dedicated by the laboratories to implement selective reporting of AST, and (ii) the percentage of selective AST reported out of the total number of *E. coli*-positive urine cultures with AST performed in adult outpatients.

To evaluate prescribers' acceptability, we collected (i) quantitative data on the numbers and percentages of complete reporting of AST requests to the laboratories and their reasons; and (ii) qualitative data from semi-structured individual interviews among GPs. To evaluate laboratory professionals' acceptability, we performed semi-structured focus groups, supplemented by some individual interviews when laboratory professionals could not participate in the focus group. Qualitative investigations comply with the COREQ reporting guidelines (**Supplementary Table S1**).[16]

Study setting and participants

Selective reporting of AST implementation began on the 1st September 2018 in the ATOUTBIO group of 21 laboratories located in the Lorraine region (2,306,000 inhabitants according to the 2021 census)[17] of north-eastern France. The focus groups and individual interviews were conducted one year after the beginning of the implementation.

GPs eligible for the qualitative investigation were those who had received at least one selective reporting of AST from one ATOUTBIO laboratory during the previous year. We excluded those who have particular practice (e.g. homeopathy, gynaecology). GPs were then randomly selected and contacted by phone by a member of the research team (GLD) to explain

the present investigation and to ask them for an interview. The randomisation was stratified by practice location (rural, suburban, urban). The recruitment continued until data saturation was reached.

Laboratory professionals were recruited by laboratory managers in collaboration with the biologist co-investigator (SF). Laboratory managers who accepted to participate in the qualitative investigation were asked to recruit at least two of their staff members from various professions (i.e. biologists, technicians and secretaries) to participate in a focus group. If some laboratory professionals could not participate in the focus group, they were offered to be individually interviewed.

Selective reporting of AST

Selective reporting of AST was performed for all adult outpatients with an *E. coli*-positive urine culture. Selective reporting of AST was automatically executed by an algorithmic software. As French guidelines for UTIs' treatment differ by gender,[10] algorithms were developed according to gender and to resistance of the isolate to first-line antibiotics. Details on the antibiotics reported in the selective reporting of AST by gender and on the usual complete reporting of AST are available in respectively **Supplementary Table S2** and **Supplementary Table S3**.

The ATOUTBIO laboratories informed each prescriber of the change in reporting of AST and that the complete reporting of AST was easily available upon request to the laboratory (e.g. phone call) in a paragraph of information included in the two first selective AST reports they received. We voluntarily limited this information, because of the comparative effectiveness design of the 'ANTIBIO-ciblés' study.

Data collection

Feasibility

During the selective reporting of AST's development (August 2018) and adjustment (September 2018 - February 2019) periods, ATOUTBIO laboratories' biologists prospectively collected all material/informatics, financial and human laboratory resources dedicated to the implementation of the selective reporting of AST, using a standardised form provided by the research team. They also collected the number of selective AST reported and the total number of *E. coli*-positive urine cultures with AST performed in adult outpatients from January to December 2019.

Acceptability

From January to December 2019, laboratories' biologists recorded each prescriber's request for a complete reporting of AST and its motive. We voluntarily did not collect those data during the first four months of the intervention, to let the professionals adjust their practices.

For the qualitative investigation of acceptability, two interview guides (one for GPs and one for laboratory professionals) were developed by GLD (epistemologist, PhD) and reviewed by NT (public health pharmacist, PhD), CP (infectious diseases physician, PhD), and JK (sociologist, PhD). The interview guide for GPs explored five themes: (i) their perceptions about antibiotic resistance; (ii) their opinion on selective reporting of AST; (iii) its perceived impact on their practices; (iv) potential constraints regarding its use; and (v) their expectations (e.g. about information and communication, generalisation) (**Supplementary Table S4**). The interview guide for laboratory professionals explored four themes: (i) their perceptions about antibiotic resistance; (ii) their opinion on selective reporting of AST; (iii) perceived constraints regarding its implementation; and (iv) their expectations (e.g. about information and communication, generalisation) (**Supplementary Table S5**). Interviews were conducted in

September and October 2019 by GLD and MS (PhD student) at the professionals' workplace. After an oral consent, they were recorded (handwritten notes were recorded in case of refusal). All recorded interviews were then anonymised and transcribed by MS and GLD.

Analyses

Quantitative data were analysed using descriptive statistics (numbers and percentages).

Qualitative data (interview transcripts and handwritten notes) were analysed by GLD and MS through a thematic analysis using analysis grids. Each theme and subtheme (see the Results section for a detailed presentation of the subthemes) were discussed until consensus was found between GLD and MS. The analyses were conducted using the QSR International's N'Vivo 11 and the Excel softwares.

Ethics

This protocol was approved by French national ethics committees (Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (TPS 29064) and Commission Nationale de l'Informatique et des Libertés (Décision DR-2018–141)).

RESULTS

Feasibility

The development and adjustment of selective reporting of AST by the ATOUTBIO laboratory group resulted in a cost of 3,610 euros for human resources (i.e. 80 working hours of the co-investigator and technician to program, test, and adjust the parameters of the software). Besides, 17,760 euros were dedicated to the purchase of the software, and 1,335 euros to the annual maintenance, amounting in total to an overall cost of 19,095. In 2019, the ATOUTBIO laboratories reported selective AST for 100% of adult outpatients with an *E. coli*-positive urine culture.

Prescribers' acceptability (quantitative data)

The proportion of selective reporting of AST giving rise to a request for a complete reporting of AST in 2019 was 1.2% (134/11,624; see **Table 1** for details per month). The main reasons given by the prescribers for these requests were that (i) their patient had a pyelonephritis and they did not want to prescribe one of the antibiotics reported, and (ii) they initiated an empiric therapy which was not among the reported antibiotics (fluoroquinolones and third-generation cephalosporins mostly mentioned) and did not want to modify the treatment (**Table 2**).

GPs' acceptability (qualitative data)

Characteristics of the participants

Data saturation was reached after interviewing 21 GPs and we had to contact a total of 74 GPs to recruit these participants (participation rate: 28%); 42 refused to participate (main reason: lack of time) and 11 GPs could not be reached and did not contact us back. Half of the participants practiced in a rural area (**Table 3**). Interviews lasted on average 20 ± 7 minutes. **Table 4** presents a selection of the most illustrative verbatims from GPs' interviews.

Opinion about selective reporting of AST

Most GPs (15/21) had already understood the principle and objectives of selective reporting of AST before the interview, most frequently after explanations from the laboratory professionals during the implementation, or on their own, by deduction. Only two of them had understood it by reading the paragraph of information included in the first selective AST reports. The others (6/21) understood it through explanations provided at the beginning of the interview.

Once the principle and objectives of the intervention were understood, all GPs were very favourable to selective reporting of AST. Most of them described it as an adapted, efficient and time-saving tool to improve the appropriateness of antibiotic prescriptions, and tackle antibiotic resistance, that the majority (18/21) perceived as a major public health threat. Most GPs (15/21) highlighted the clarity and the simplicity of the selective report, which provided the list of appropriate antibiotics according to guidelines in a concise manner. Moreover, some GPs (7/21) highlighted that this tool was provided by biologists, professionals that they trusted and who advised them appropriately.

However, despite a favourable opinion towards the principle of this tool, a few GPs had some reservations about its usefulness and effectiveness, due to: a lack of conviction that antibiotic resistance is a major public health issue; the belief that GPs do not have a main role to play to tackle antibiotic resistance; or the feeling that selective reporting of AST was an obstacle to their freedom of prescription.

Perceived impacts on practices

GPs' perceptions about the impact of selective reporting of AST on their prescription practices were mixed.

Many GPs (13/21), especially those who understood the principle of the tool at the beginning of the interview only, did not feel impacted in their practices.

The others (8/21) felt that this tool led them to modify their prescription practices and to improve their compliance with guidelines. It often prompted them to abandon third-generation cephalosporins or quinolones, and sometimes gave them the opportunity to discover antibiotics they never prescribed before.

However, some GPs were convinced that certain colleagues (especially older ones) will never accept to change their prescription practices.

Perceived constraints regarding the use of selective reporting of AST

Most GPs found the use of selective reporting of AST not, or only moderately, constraining. The main constraint (perceived by 8/21 GPs) was the necessity to call the laboratory to obtain the complete reporting, and in rare cases to wait several days for it.

GPs requested the complete reporting of AST for several reasons consistent with results from quantitative data (**Table 2**) and provided in-depth explanations of their choice. First, for some GPs, selective reporting of AST was not adapted to their patient's case (often

pyelonephritis, recurrent UTIs, or allergies). For pyelonephritis, a few GPs were used to prescribe fluoroquinolones and did not accept changing for another antibiotic, being convinced that a fluoroquinolone was the most appropriate choice. Second, they did not want to change the treatment after receiving the selective reporting: they wanted to avoid scheduling another appointment with the patient to prescribe a narrower spectrum antibiotic, and preferred to continue the treatment initially prescribed if it was effective.

Expectations regarding information and generalisation

Most GPs (16/21) would have liked to be better informed of the implementation of the selective reporting of AST (e.g. by a dedicated letter from the laboratory).

Overall, GPs were in favour of the extension of the selective reporting of AST to other bacteria responsible for UTIs, to other samples than urinary ones, and to other prescribers and settings (e.g. hospitals). They were also all favourable to its scale-up at national level.

Laboratory professionals' acceptability (qualitative data)

Characteristics of the participants

Four laboratory managers were contacted, and three agreed to participate in the qualitative investigation. Overall, nine biologists, one biology student, one technician and two secretaries were interviewed (see characteristics in **Table 3**). The focus groups lasted on average 29 ± 2 minutes. **Table 5** presents a selection of the most illustrative verbatims from laboratory professionals' interviews.

Opinion about selective reporting of AST

All laboratory professionals were in favour of selective reporting. They found it interesting and useful to improve prescription practices and tackle antibiotic resistance, that all

perceived as a significant threat. They believed that its clear and concise presentation facilitated prescribers' choice of antibiotics and guided them to prescribe antibiotics in accordance with guidelines.

Moreover, selective reporting of AST was considered as a necessary tool to value their profession and support their essential role in the global effort against antibiotic resistance.

Perceived constraints regarding selective reporting implementation

The laboratory professionals perceived the additional workload of the implementation of selective reporting of AST as very low. It had mainly fallen on the biologist co-investigator.

The main constraint they perceived was calls from unsatisfied prescribers (mostly at the beginning of the implementation) who asked for the complete reporting of AST. Many calls were due to the paragraph of information about the modification of report of AST not seen by the prescribers, who then perceived selective reporting as an error or a low-cost AST.

However, as the number of phone calls from prescribers was very low and related mainly to a lack of information, laboratory professionals perceived this constraint as minimal and bearable. Moreover, several laboratory professionals believed that the tool was not completely adapted to some particular clinical cases (e.g. pyelonephritis and prostatitis), and thus were understanding towards GPs.

Expectations regarding information and generalisation

Laboratory professionals would have liked to be more informed and trained, notably on the purpose and the conception of the selective reporting of AST, to provide a more accurate support to prescribers. Moreover, they were convinced that prescribers should be better informed about the implementation of selective reporting to improve acceptability. They also believed that a better training of prescribers on antibiotic treatments and awareness on antibiotic

resistance would increase the impact of antibiotic stewardship tools, such as selective reporting of AST.

All laboratory professionals were in favour of the extension of selective reporting of AST to other bacteria responsible for UTIs and to other samples than the urinary ones (e.g. ears nasal throat or gynaecological). Some professionals also suggested to add some clinical information to the algorithmic software (e.g. fever, lumbar pain), to help differentiate clinical situations and adapt the antibiotics reported to the indication, if it did not add too much workload.

Finally, all laboratory professionals strongly supported the scaling-up of selective reporting of AST at national level. However, some of them highlighted that, in a competitive context, this would require global adherence of all laboratories to prevent selective reporting of AST from becoming a disadvantage for those that implement it.

DISCUSSION

Main results

Selective reporting of AST for *E. coli*-positive urine cultures, implemented as part of the 'ANTIBIO-ciblés' French interventional study, required about 80 working hours from laboratory staff and costed about 23,000 euros.

All GPs and laboratory professionals interviewed were favourable to the principle of selective reporting of AST. Most of them described it as a clear, simple and useful tool to improve the appropriateness of antibiotic prescriptions and reduce antibiotic resistance. Its major constraint was the necessity for GPs to call the laboratory to obtain the complete reporting of AST but the number of requests was actually low. All professionals supported the extension of this tool to other bacteria, samples and the scaling-up at national level, accompanied by information of prescribers.

Comparison with the literature

The acceptability of selective reporting of AST was poorly studied in the literature. Results from two French case-vignettes studies showed that 81% of GPs[18] and 71% of trainees in general medicine[19] who experimented selective reporting of AST felt that it made their therapeutic choices easier. In a qualitative study that explored perceptions regarding antibiotic stewardship interventions by different prescribers' specialties in the French outpatient setting, most participants had a positive opinion on selective reporting of AST.[20] However, another study exploring the acceptability of antibiotic stewardship interventions in primary care showed that French GPs were reluctant to measures that restrict their freedom of practice and we feared that selective reporting of AST would have been perceived as such.[21] To the best of our

knowledge, no previous study has evaluated the acceptability of selective reporting of AST by laboratory professionals.

After one year of implementation, results from the present quantitative and qualitative investigations highlighted a high acceptability of selective reporting of AST by both GPs and laboratory professionals. This revealed the will and readiness of GPs to the use of this type of guiding tool to help them improve their antibiotic prescriptions.[20] Moreover, GPs highlighted the important mission of laboratory professionals to advise them and help them prescribe antibiotics appropriately. Indeed, it has been shown that clinical microbiologists can have a key role in antibiotic stewardship programmes and a profound impact on prescribing habits.[22]

Main perceived constraint: requests for complete reporting

Despite infrequent requests for the complete reporting of AST (1.2% of cases), some GPs found the necessity to call the laboratory to obtain the complete reporting as constraining. These requests were motivated by two main reasons that were observed in both the quantitative and qualitative results.

First, some GPs believed that selective reporting of AST was not adapted to all clinical cases, such as pyelonephritis. While some molecules recommended as targeted therapy in pyelonephritis (i.e. cotrimoxazole) were always reported on the selective reporting of AST, GPs wanted to prescribe fluoroquinolones, which were reported only in cases of resistance to first-line agents. The determination of some GPs to prescribe fluoroquinolones might be related to prescription habits they were not ready to change. This attachment to fluoroquinolones might partly explain why we did not found an impact of selective reporting of AST on quinolones prescription rates in the 'ANTIBIO-ciblés' study (results presented in another paper that has been submitted). Some GPs also perceived that selective reporting of AST was not adapted for specific cases (i.e. recurrent UTIs, allergies), even though those cases had been taken into

account in the development of the selective report. Better training of GPs on antibiotic prescribing recommendations might help them better understand the relevance of the selective report and thus improve the appropriateness of their antibiotic prescriptions.

Second, some GPs had initiated an empiric therapy and did not want to modify this treatment for an antibiotic reported in the AST. They may be reluctant to make another appointment with their patient, which is constraining for them, in a context of heavy workload, as for their patients. Telemedicine consultations, that have become more frequent in France since the COVID-19 pandemic, may help increase re-evaluation opportunities.[23] Moreover, some GPs might wonder whether it is relevant to modify a seven-day fluoroquinolone antibiotic therapy for uncomplicated pyelonephritis that has already been initiated for few days.

Perspectives towards the scale-up of selective reporting of AST

Both GPs and laboratory professionals were favourable to a national implementation of selective reporting of AST, and to its extension to other bacteria responsible for UTIs and other samples. In addition to the high acceptability, our study showed the feasibility of implementation of selective reporting of AST for laboratories. The purchased algorithmic software was not only used for the reporting of selective AST but was also included in the daily practice of ATOUTBIO laboratories (e.g. to edit AST for other samples or to describe the activity of laboratories). The additional workload for the development and adjustment of selective reporting mostly concerned the biologist co-investigator and a technician, while other biologists' workload was not impacted. Moreover, the choice of limiting the information about the selective reporting of AST implementation could have led to misunderstandings of the principle and the aim of the selective reporting of AST, and impaired GPs' acceptability.

Several facilitators have been identified to optimise the implementation of selective reporting on a larger scale. First, a better information of GPs might further improve

acceptability, as well as the addition of educational interventions (e.g. training on antibiotic prescribing guidelines, awareness on antibiotic resistance). Second, laboratory professionals expressed their need to be better trained to answer prescribers' requests and enhance their role in the fight against antibiotic resistance. Finally, in case of a national scale-up of selective reporting of AST, all laboratories should be incentivised to participate, as community biology laboratories work in a competitive sector.

Limitations

To the best of our knowledge, this is the first study assessing the feasibility of selective reporting of AST, and its acceptability by both GPs and laboratory professionals. However, our study might present a selection bias, as twenty-eight percent of the contacted GPs accepted to participate in an interview. GPs who participated might be more interested than others in issues related to antibiotic use and resistance, and generalisation might thus be imperfect. However, the low proportion of requests for complete reporting of AST seems to confirm the high acceptability found in the interviews.

Conclusion

In summary, implementation of selective reporting of AST for *E. coli*-positive urine cultures resulted in reasonable human and financial costs and was well accepted by both prescribers and laboratory professionals. Facilitators identified to enhance the acceptability and the impact of selective reporting of AST included a better information of GPs prior to the implementation, and if possible the addition of complementary educational actions. A better training of laboratory professionals to answer GPs' requests, and an involvement of all laboratories were also highlighted.

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AUTHORS' CONTRIBUTION

Conceptualisation: CP, NT, SF

Methodology: CP, NT, SF, GLD, JK

Software: SF, AD

Formal analysis: GLD, MS

Writing – original draft: MS

Writing – review & editing: GLD, AB, NT, CP, SF, AD

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TRANSPARENCY DECLARATIONS

All authors have no conflict to declare.

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TABLES

Table 1. Monthly number and proportion of complete reporting of AST requested by prescribers in 2019.

Month	Monthly number of selective reporting of AST	Monthly number of complete reporting of AST requested	Proportion of complete reporting of AST requested
January 2019	1065	19	1.8%
February 2019	936	29	3.1%
March 2019	1040	14	1.4%
April 2019	969	5	0.5%
May 2019	979	14	1.4%
June 2019	788	4	0.5%
July 2019	892	2	0.2%
August 2019	932	6	0.6%
September 2019	989	3	0.3%
October 2019	1095	24	2.2%
November 2019	991	8	0.8%
December 2019	948	6	0.6%
Total	**11624**	**134**	**1.2%**

AST: antibiotic susceptibility testing.

Table 2. Reasons given by prescribers for requesting a complete reporting of AST from January to December 2019 (n = 134).

Reasons for the request	**Number (%)**
Pyelonephritis	45 (33.6%)
Initiated antibiotic therapy	39 (29.1%)
Reason not specified	26 (19.4%)
Particular clinical case[a]	12 (9.0%)
Prostatitis	4 (3.0%)
Resistant to all antibiotics	4 (3.0%)
Formulation issue[b]	4 (3.0%)

AST: antibiotic susceptibility testing

[a] Particular clinical cases mentioned were kidney failure, adverse effect, cancer, porphyria, prostatectomy, recurring infection, allergies.

[b] No non-injectable molecule reported, or no injectable molecule reported when patient needed one.

Table 3. Characteristics of the participants in the qualitative interviews.

	Number of participants	Profession	Practice setting[a]
General practitioners			
Individual interviews	21	General practitioners	Rural: 10 Suburban: 6 Urban: 5
Laboratory professionals			
Focus group #1	3	1 manager biologist 2 biologists	Urban Suburban Rural
Focus group #2	5	1 manager biologist 1 biologist 1 laboratory technician 1 biology student 1 secretary	Urban
Focus group #3	3	2 manager biologists 1 secretary	Urban
Individual interviews	2	Manager biologists (including the biologist co-investigator)	Rural Urban Suburban

[a] Rural: < 10,000 inhabitants; Suburban: 10,000–30,000 inhabitants; Urban: > 30,000 inhabitants. In France, laboratory biologists can work in multiple laboratories, located in various settings.

Table 4. Selection of the most illustrative verbatims from general practitioners' interviews.

Theme	Subtheme	Verbatim (interview number)
Opinion about selective reporting of AST	Favourable opinion	"This is a progress this method. A progress. This is a progress that makes us work better, be more efficient" (n°20) "I think this is useful, and I think that helps us… Adapt to new guidelines easily…" (n°10)
	Clarity/simplicity	"I think it was well thought/designed. It was clear and accurate" (n°2) "Something reduced is really better, clearly" (n°19)
	Reservations	"However, when we asked for a urine culture in case of pyelonephritis suspicion, that [the AST selective report] was much less relevant" (n°14) "The GP who is used to prescribe "wrong" […] Maybe he/she will keep his/her habits, will do it [prescribe "wrong"], and will not consider the AST results. Because he/she is used to it working like that" (n°15)
Perceived impacts on practices	No impact	"So it does not change my practice" (n°7) "I barely noticed [the change in AST report], it's only when I heard about it and I took a step back, and I said ah yes" (n°12)
	Positive impact	"So the selective reporting of AST doesn't impact your prescriptions? – It does, for example, last time, I prescribed Bactrim® [cotrimoxazole] that I had never prescribed before" (n°15)
Perceived constraints	Not or moderately constraining	"I was not bothered in my practice, in my patients' care, in the selection of the treatment to choose" (n°5) "It doesn't disturb me at all" (n°8)
	Asking for the complete reporting	"I need to know if Augmentin® [amoxicillin-clavulanate] works, if Oroken® [cefixime] works, if the main fluoroquinolones work" (n°6) "Because when I have an antibiotic that is not on the selective reported list, it means calling the laboratory. Usually, they make me talk to the biologist, after a while, and either I have the patient in front of me, or it is late at night, so I wait…" (n°7)
Expectations regarding information and generalisation	Better information	"It would have been interesting to have the information, because our reasoning…" (n°7) "A letter of explanation would have made it clearer" (n°14)
	Extension to other bacteria and/or other samples	"I think the best is what you did, target the most common [bacteria, i.e. *E. coli*]. And do that in other pathologies" (n°2) "Yes of course! It might be done for all germs" (n°14)

	Extension to other prescribers	“Why not do it for everyone? That’s better” (n°2)
	National implementation	“Do you think it might be implemented at a national scale? – Sure. Sure. For me, this is a good thing” (n°2)

AST: antibiotic susceptibility testing; GP: general practitioner; *E. coli: Escherichia coli*.

Table 5. Selection of the most illustrative verbatims from laboratory professionals' interviews.

Theme	Subtheme	Verbatim (focus group or interview number)
Opinion about selective reporting of AST	Favourable opinion	"So our laboratory, anyway, we adhered at 100%" (n°2) "Of course, it's a great strategy, that's for sure" (n°3)
	Clarity/simplicity	"It will guide them [prescribers], it will target antibiotics that should be used" (n°4) "I think we're heading for simplicity for the GP" (n°5)
	Useful tool to value their profession	"This is not an effort; we are ready to participate because this is interesting and it values our profession" (n°1) "No this is rewarding! But it is only the beginning" (n°3)
Perceived constraints	Minimal constraint	"And we did not really have barriers to the realisation of this project" (n°2) "We only have few requests from GPs who want complete AST results" (n°4)
	Complete reporting requests	"At the beginning, some GPs were unsatisfied" (n°4) "Maybe the first weeks, there were some GPs who were a little aggressive, telling "I give this or that antibiotic, I would like the complete report"" (n°2)
	Not adapted to all clinical cases	"For cases of pyelonephritis or prostatitis, it was trickier" (n°2) "They [the prescribers] are fed up, for each pyelonephritis, to have to request an appropriate molecule. We totally understand that" (n°5)
Expectations regarding information and generalisation	Better information/training	"My training on antibiotic therapy is outdated, so we really need to keep abreast, even for biologists younger than me. So we really need support" (n°2)
	Prescribers' information	"Technically, to sum up, it should be an information before starting" (n°1) "I think we have to deliver information before, yes, but not for too long" (n°2)
	Extension to other bacteria and/or other samples	"We could extend it to other samples. That's the point also, to try to target more and more things, not only urine cultures" (n°5)
	National implementation	"So we all agree that to extend it to a national scale and for long term is good? – Yes!" (n°3)
	Competitive sector	"Be sure that all biologists adhere. That we are not the only ones to annoy and pressure the medical profession. We must be united with our biologist colleagues. But this is not easy. […] We are a competitive sector so sometimes we disregard the antibiotic stewardship pressure, and we submit to the physician pressure to please him/her" (n°3)

AST: antibiotic susceptibility testing; GP: general practitioner.

Supplementary Table S1. Consolidated criteria for reporting qualitative studies (COREQ).[a]

No	Item	Guide questions/description	Page
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	6
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	5-6
3.	Occupation	What was their occupation at the time of the study?	5-6
4.	Gender	Was the researcher male or female?	5-6
5.	Experience and training	What experience or training did the researcher have?	5-6
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	NA
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	NA
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	NA
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	NA
Participant selection			
10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	4
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	4
12.	Sample size	How many participants were in the study?	8,10
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	8
Setting			
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	6
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	6
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	8,10
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	6
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	NA
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	6
20.	Field notes	Were field notes made during and/or after the interview or focus group?	6
21.	Duration	What was the duration of the interviews or focus group?	8,10
22.	Data saturation	Was data saturation discussed?	8
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	NA
Domain 3: analysis and findings			
Data analysis			

24.	Number of data coders	How many data coders coded the data?	6
25.	Description of the coding tree	Did authors provide a description of the coding tree?	NA
26.	Derivation of themes	Were themes identified in advance or derived from the data?	6
27.	Software	What software, if applicable, was used to manage the data?	6
28.	Participant checking	Did participants provide feedback on the findings?	NA
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Tables 4 and 5
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	7-16
31.	Clarity of major themes	Were major themes clearly presented in the findings?	8-12
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	8-12

[a] The EQUATOR Network. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Available at: https://www.equator-network.org/reporting-guidelines/coreq/.

Supplementary Table S2. Selective reporting of AST results by gender.

Gender	**Male**				**Female**			
Susceptibility profiles	**FQ S TMP-SMX S 3GCs S**	**FQ R and/or TMP-SMX R and 3GCs S**	**FQ S TMP-SMX S 3GCs R**	**FQ R TMP-SMX R 3GCs R**	**AMX S**	**AMX I/R and (AMC S or TMP-SMX S)**	**AMX I/R and AMC I/R and TMP-SMX I/R and 3GCs S**	**3GCs R**
Antibiotics listed in the selective reporting of AST	TMP-SMX Ciprofloxacin Ofloxacin Levofloxacin	TMP-SMX Cefotaxime Ceftriaxone Ciprofloxacin Ofloxacin Levofloxacin	TMP-SMX Cefotaxime Ceftriaxone Ceftazidime Ciprofloxacin Ofloxacin Levofloxacin	AMX Ticarcillin Piperacillin + tazobactam Pivmecillinam Fosfomycin TMP-SMX Cefoxitine AMC Temocillin Cefixime Cefotaxime Ceftriaxone Ceftadizime Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX AMC **<u>If I/R :</u>** Ciprofloxacin Levofloxacin Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX AMC **<u>If I/R :</u>** Ciprofloxacin Levofloxacin Ofloxacin	AMX Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX AMC Cefixime Ciprofloxacin Ofloxacin	AMX Ticarcillin Piperacillin + tazobactam Pivmecillinam Nitrofurantoin Fosfomycin TMP-SMX Cefoxitine AMC Temocillin Cefixime Cefotaxime Ceftriaxone Ceftadizime Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin
Comments	- When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures. - AMC, nitrofurantoin, fosfomycin, pivmecillinam, and cefixime should not be used in male UTIs (lack of diffusion in prostate). - Complete AST is available at the prescriber's request. - For more information regarding national guidelines: https://antibioclic.com.				- When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures. - Nitrofurantoin, pivmecillinam, and fosfomycin should not be used for pyelonephritis (lack of diffusion in renal parenchyma). - Complete AST is available at the prescriber's request. - For more information regarding national guidelines: https://antibioclic.com.		

AST: antibiotic susceptibility testing; FQ: fluoroquinolones; TMP-SMX: cotrimoxazole; 3GCs: third-generation cephalosporins; AMX: amoxicillin; AMC: amoxicillin-clavulanate; I: intermediate; R: resistant; UTIs: urinary tract infections

Supplementary Table S3. Complete reporting of AST results by gender.

Gender	Male	Female
Antibiotics reported in the complete reporting of AST	Pivmecillinam Ampicillin (AMX) AMC Ticarcillin Cefoxitine Cefixime Ceftazidime Ceftriaxone Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin Fosfomycin Nitrofurantoin TMP-SMX	Pivmecillinam Ampicillin (AMX) AMC Ticarcillin Cefoxitine Cefixime Ceftazidime Ceftriaxone Ertapenem Amikacin Gentamicin Nalidixic acid Ofloxacin Fosfomycin Nitrofurantoin TMP-SMX
Comments	- Cefixime, AMC, fosfomycin, and nitrofurantoin should not be used in male UTIs (lack of diffusion in prostate). Preferred antibiotics (depending on AST results): quinolones (ofloxacin), cotrimoxazole. - Results need to be interpreted according to the clinical symptoms.	- Results need to be interpreted according to the clinical symptoms.

AST: antibiotic susceptibility testing; FQ: fluoroquinolones; TMP-SMX: cotrimoxazole; 3GCs: third-generation cephalosporins; AMX: amoxicillin; AMC: amoxicillin-clavulanate; I: intermediate; R: resistant; UTIs: urinary tract infections

Supplementary Table S4. Interview guide for semi-structured interviews of GPs.

Adherence/opinion towards selective reporting of AST	What do you think of selective reporting of AST?
	Did you adhere directly?
	Do you think it is a useful tool to improve the appropriate use of antibiotics?
	Do you think it is a useful tool to tackle antimicrobial resistance?
	Was its implementation unpleasant?
	If yes, why? (No prior consent? Disrespectful of your freedom of practice? Reducing quality of care? Feeling of being controlled?)
Information and communication	Do you feel that you were sufficiently informed when you received your first selective reporting of AST?
	If no, would you have preferred to be informed before?
	Would you have wanted more explanations?
	Would you have wanted some information meetings?
	Would you have wanted a website or a telephone number for more information?
	If you called the laboratory to have explanations about selective reporting of AST, was the information clear and adequate?
	Was the person who informed you prepared enough to help you?
Antibiotic resistance	Do you feel concerned by the threat of antibiotic resistance, as part of your practice of GP?
	Do you think that, in general, GPs could improve their antibiotic prescription practices?
	How?
	Did you know the term 'critical antibiotics'?
	Did you know that the bigger concern was Enterobacterales resistance to antibiotics, particularly *Escherichia coli* in urinary tract infections?
	Has selective reporting of AST made you want to know more about antimicrobial resistance and 'critical antibiotics'?
Impacts on practices, quality of health care	Did selective reporting of AST have an impact on your antibiotic prescriptions?
	Do you think that you have prescribed less antibiotics?
	Do you think that you have prescribed more appropriate antibiotics? (More in line with recommendations?)
	For all patients? (Which ones? In which cases?)
	On the contrary, do you think that you have prescribed less appropriate antibiotics?
	In which cases?
	Did patients express their discontent about the change of AST reporting?
Constraints	Has selective reporting of AST been a constraint?
	Why?
	Has it been annoying not to have all the antibiotics reported?
	Have you perceived this tool as a barrier to your freedom of prescription?
	Has the relationship with your patients been altered?
	Did it make you lose time and/or energy?

	If you called the laboratory to obtain the complete reporting of AST, how did it happen? (Ease of access? Time spent? Quality of delivered information?)
Commitment/responsibility	Has selective reporting of AST triggered some awareness?
	Concerning your prescription habits?
	Concerning the global threat of antibiotic resistance?
Expectations/generalisation	Would you like selective reporting of AST to be maintained and integrated to your practice?
	Do you think that selective reporting of AST should be proposed to all prescribers, for all specialties?
	Do you think that selective reporting of AST should be extended at a national level?
	Do you think that selective reporting of AST should be extended to other samples? (Which ones?)

AST: antibiotic susceptibility testing; GPs: general practitioners

Supplementary Table S5. Interview guide for focus groups of laboratory professionals.

Adherence	What do you think of selective reporting of AST?
	Did you think that selective reporting of AST was a good thing?
	Why?
	Have you liked being part of the fight against antibiotic misuse?
	Have you liked being part of the fight against antimicrobial resistance?
	Have you seen an adherence from prescribers?
	If you had the choice, would you keep the selective reporting of AST?
Implementation	Was the implementation of selective reporting of AST easy or difficult?
	Why?
	What was the reaction of prescribers?
	Have you been requested a lot by prescribers to deliver complete reporting?
	During the implementation?
	Now? (a year after the implementation)
	How was the explanation to prescribers?
	Was the implementation difficult regarding materials and technologies?
	Was it time-consuming?
	Have you encountered organisational or managerial issues?
	Have you received reactions from patients? (Which ones?)
Information/communication	Do you feel that you were sufficiently informed of the implementation and the purpose of selective reporting of AST?
	If not, what do you think should have been done?
	Do you feel that you were sufficiently informed/trained to respond to prescribers' questions and/or criticism?
Commitment/responsibility	In general, do you feel engaged in the fight against antibiotic misuse?
	Has implementation of selective reporting of AST changed your perception of antimicrobial resistance?
	Has implementation of selective reporting of AST changed your opinion on the measures that must be taken to tackle antimicrobial resistance?
	Would you like to do more, or differently?
	How?
Expectations	What do you think should be done to improve the implementation of selective reporting of AST?
	Do you think that selective reporting of AST is relevant? Sufficient?
	For both genders?
	For women?
	Do you think that selective reporting of AST is relevant in all cases of *E. coli* – positive urine cultures?
	Do you see some cases where selective reporting of AST is not adapted?
	Would you like selective reporting of AST to be maintained and integrated to your practice? (Why?)
	Do you think that selective reporting of AST should be proposed to all French laboratories? Imposed? (Why?)

	Do you think that selective reporting of AST should be extended to other samples? (Which ones?)
	Do you think that selective reporting of AST should be extended to other bacteria? (Which ones?)

AST: antibiotic susceptibility testing; *E. coli: Escherichia coli*

Chapitre 3 – Les indicateurs de prescriptions d'antibiotiques

I – Contexte

1. Définition des indicateurs

Un indicateur est un paramètre mesurable permettant de décrire la réalité. D'après la norme ISO 8402, un indicateur est défini comme « une information choisie, associée à un phénomène, destinée à en observer périodiquement les évolutions au regard d'objectifs périodiquement définis ». Il existe différents types d'indicateurs dans le domaine de la santé : les indicateurs de résultats (indicateurs de mortalité, de morbidité, de qualité de vie) ; les indicateurs de structure ou de ressources (moyens humains, équipements, ressources financières) ; les indicateurs de processus et de pratiques professionnelles ; et les indicateurs d'activité.(84)

Les indicateurs de pratiques professionnelles sont indispensables pour évaluer l'usage des antibiotiques et guider des actions pour leur bon usage. Ils sont particulièrement intéressants pour évaluer l'impact d'interventions visant à améliorer l'usage des antibiotiques, comme par exemple les antibiogrammes ciblés. Il existe des indicateurs quantitatifs qui vont estimer le volume d'antibiotiques. Ces indicateurs peuvent être exprimés selon différentes unités : doses définies journalières pour 1000 habitants par jour, nombre de prescriptions d'antibiotiques pour 1000 habitants par an, … Les indicateurs de qualité permettent d'estimer précisément la qualité ou pertinence des prescriptions.(85) Pour être calculés, ils nécessitent des données sur l'indication clinique ou le diagnostic. En France et dans la plupart des pays d'Europe, il n'existe pas de bases de données nationales permettant de relier les prescriptions antibiotiques à l'indication clinique.(86) En pratique, pour calculer ces indicateurs de qualité, il faut recueillir les données dans le dossier médical de chaque patient ayant eu un traitement (comme c'est le cas lors d'audits cliniques). Ce travail est très chronophage et irréalisable à grande échelle.

2. Les indicateurs proxy

Pour pallier l'absence de données cliniques dans les bases de données disponibles, Thilly *et al.* ont développé des indicateurs dits « proxy » estimant indirectement la pertinence des prescriptions antibiotiques. Ces indicateurs proxy, calculables à partir des données du SNDS, permettent d'approcher la qualité des prescriptions à un niveau agrégé (prescripteur, établissement, …), sans nécessité de données cliniques.(85) Ils ont été sélectionnés à partir du projet européen *Driving re-investment in R&D and responsible antibiotic use* (DRIVE-AB) visant à développer des indicateurs quantitatifs et qualité standardisés de l'usage des antibiotiques (87–89), puis adaptés aux recommandations d'antibiothérapie nationales. Ces indicateurs proxy ont été conçus accompagnés d'une cible optimale reflétant des pratiques optimales de prescription (conformité de 100% avec les recommandations) et d'une cible acceptable moins restrictive prenant en compte les situations très particulières pour lesquelles les recommandations ne seraient pas applicables.

Ce travail a tout d'abord été réalisé par notre équipe, avant mon arrivée, pour estimer la pertinence des prescriptions faites par des médecins généralistes (85), puis par les pédiatres.(90) Dans le cadre de cette thèse, nous avons développé selon la même méthodologie des indicateurs permettant de calculer le volume et d'estimer la pertinence des prescriptions faites aux résidents d'EHPAD (91) et des indicateurs estimant la pertinence des prescriptions faites par les chirurgiens-dentistes.(92)

3. Les profils de prescripteurs

A côté de leur utilisation comme outil d'évaluation de l'impact d'intervention, les indicateurs peuvent également être utilisés pour identifier des groupes de prescripteurs selon la pertinence de leur pratique de prescription d'antibiotiques. Il est également intéressant d'étudier les profils des prescripteurs en identifiant les facteurs associés à la pertinence des prescriptions, parmi des facteurs liés au prescripteur, à sa patientèle ou à sa pratique. Identifier ces groupes et profils de prescripteurs devrait aider à guider et à cibler des interventions pour le bon usage des antibiotiques.

Dans le cadre de cette thèse, nous avons réalisé ce travail pour les prescriptions faites par les médecins généralistes (93) et celles faites par les chirurgiens-dentistes.

II – Article indicateurs quantitatifs et proxy des prescriptions en établissements d'hébergement pour personnes âgées dépendantes

1. Contexte et objectifs

La consommation d'antibiotiques et l'antibiorésistance sont particulièrement élevées en EHPAD.(94) Environ la moitié des prescriptions faites à des résidents d'EHPAD sont inutiles ou inappropriées.(17) Des indicateurs estimant le volume et la pertinence des prescriptions d'antibiotiques sont nécessaires pour décrire l'usage des antibiotiques et pour concevoir, cibler et évaluer des interventions visant à améliorer l'usage des antibiotiques dans ces établissements. Les objectifs de cette étude étaient de (i) sélectionner et adapter des indicateurs quantitatifs et des indicateurs proxy aux prescriptions faites en EHPAD, (ii) décrire les résultats de ces indicateurs pour les EHPAD de la région Lorraine en 2018, (iii) évaluer les propriétés clinimétriques des indicateurs proxy et (iv) identifier des profils d'EHPAD selon les résultats des indicateurs proxy.

2. Méthodes

Les indicateurs quantitatifs et les indicateurs proxy ont été sélectionnés à partir du projet européen DRIVE-AB et adaptés au contexte des EHPAD et aux recommandations françaises.(87–89) Les résultats de ces indicateurs et leurs propriétés clinimétriques (mesurabilité, applicabilité et marge d'amélioration) ont été évalués pour les EHPAD sans pharmacie à usage intérieur de la région Lorraine pour l'année 2018, en utilisant les données de remboursement du SNDS. Enfin, des groupes d'EHPAD ont été identifiés par la méthode Ward, selon le nombre d'indicateurs proxy pour lesquels la cible était atteinte. Une analyse bivariée a permis d'explorer l'association entre la quantité et la pertinence des prescriptions, c'est-à-dire d'étudier si des meilleures pratiques de prescription d'antibiotiques étaient associées à des consommations plus faibles d'antibiotiques.

3. Principaux résultats et conclusions

Quinze indicateurs quantitatifs et onze indicateurs proxy ont été développés, permettant d'estimer respectivement le volume et la pertinence des prescriptions antibiotiques à l'échelle de l'EHPAD. Ces indicateurs concernaient différentes situations cliniques rencontrées en EHPAD pouvant faire l'objet de prescriptions inutiles ou inappropriées d'antibiotiques. Deux cent neuf EHPAD sans pharmacie à usage intérieur ont été inclus, avec un total de 21 570

prescriptions d'antibiotiques. Les résultats ont montré d'importantes variations de pratiques de prescription entre les EHPAD et des performances peu élevées, soulignant une marge d'amélioration importante. Six indicateurs proxy sur les onze présentaient de bonnes propriétés clinimétriques et ont permis d'identifier trois groupes d'EHPAD selon la pertinence des prescriptions. Nous n'avons pas mis en évidence d'association significative entre le volume et la pertinence des prescriptions, les EHPAD avec de meilleures pratiques de prescription d'antibiotiques n'avaient pas un volume plus faible d'antibiotiques que les autres. Il est donc important d'utiliser conjointement les indicateurs quantitatifs et les indicateurs proxy pour décrire et évaluer les prescriptions antibiotiques faites en EHPAD. Cet ensemble d'indicateurs des prescriptions antibiotiques en EHPAD peut être utilisé pour aider à améliorer les pratiques de prescriptions dans ces établissements (par exemple par les EHPAD eux-mêmes, les autorités de santé ou les centres régionaux en antibiothérapie). Ces indicateurs sont utiles pour comparer les EHPAD entre eux, suivre l'évolution des prescriptions dans le temps et évaluer l'impact d'interventions de bon usage des antibiotiques. Les indicateurs proxy peuvent également servir à la conception de plans d'actions personnalisés selon les situations cliniques pour lesquelles l'EHPAD présente des performances insuffisantes, avec des objectifs concrets, des interventions ciblées et un retour d'information individualisé pour évaluer l'évolution des pratiques.

4. Mon implication

Pour cet article, j'ai contribué à l'interprétation des résultats, à la rédaction et à la valorisation. Les analyses statistiques ont été réalisées par Ouarda Pereira, responsable de missions statistiques à la Direction Régionale du Service Médical (DRSM) du Grand Est.

5. Valorisation

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Clinical Infectious Diseases

MAJOR ARTICLE

Quantity Metrics and Proxy Indicators to Estimate the Volume and Appropriateness of Antibiotics Prescribed in French Nursing Homes: A Cross-sectional Observational Study Based on 2018 Reimbursement Data

Maïa Simon,[1] Ouarda Pereira,[2] Marlies E. J. L. Hulscher,[3] Jeroen Schouten,[3] Nathalie Thilly,[1,4] and Céline Pulcini[1,5]

[1]Université de Lorraine, APEMAC, Nancy, France, [2]Direction Régionale du Service Médical Grand Est, Strasbourg, France, [3]Radboud University Medical Center, Radboud Institute for Health Sciences, Scientific Center for Quality of Healthcare (IQ Healthcare), Nijmegen, The Netherlands, [4]Département Méthodologie, Promotion, Investigation, Université de Lorraine, Centre Hospitalier Régional Universitaire de Nancy, Nancy, France, and [5]Département de Maladies Infectieuses, Université de Lorraine, Centre Hospitalier Régional Universitaire de Nancy, Nancy, France

Background. Antibiotic resistance is an increasing threat to public health globally. Indicators on antibiotic prescribing are required to guide antibiotic stewardship interventions in nursing homes. However, such indicators are not available in the literature. Our main objective was to provide a set of quantity metrics and proxy indicators to estimate the volume and appropriateness of antibiotic use in nursing homes.

Methods. Recently published articles were first used to select quantity metrics and proxy indicators, which were adapted to the French nursing home context. A cross-sectional observational study was then conducted based on reimbursement databases. We included all community-based nursing homes of the Lorraine region in northeastern France. We present descriptive statistics for quantity metrics and proxy indicators. For proxy indicators, we also assessed performance scores, clinimetric properties (measurability, applicability, and room for improvement), and conducted case-mix and cluster analyses.

Results. A total of 209 nursing homes were included. We selected 15 quantity metrics and 11 proxy indicators of antibiotic use. The volume of antibiotic use varied greatly between nursing homes. Proxy indicator performance scores were low, and variability between nursing homes was high for all indicators, highlighting important room for improvement. Six of the 11 proxy indicators had good clinimetric properties. Three distinct clusters were identified according to the number of proxy indicators for which the acceptable target was reached.

Conclusions. This set of 15 quantity metrics and 11 proxy indicators may be adapted to other contexts and could be used to guide antibiotic stewardship programs in nursing homes.

Keywords. antimicrobial stewardship; nursing homes; quantity metrics; proxy indicators.

In 2019, the World Health Organization identified antimicrobial resistance as 1 of the 10 threats to public health [1]. Antimicrobial stewardship (AMS) has been defined as a "coherent set of actions which promote a responsible use of antimicrobials" [2]. Antimicrobial stewardship has been mostly studied in hospital settings [3], with few studies performed in nursing homes (NHs) [4]. In France, approximately 1% of the population lives in NHs [5], and this proportion is increasing because of aging of the population. Many studies have suggested that the prevalence of antibiotic use and resistance is higher in NHs as compared with the community [6–8], with approximately half of antibiotic prescriptions being unnecessary or inappropriate [9], highlighting significant room for improvement.

Measures reflecting the volume and appropriateness of antibiotic prescriptions and their change over time are required to guide AMS actions, as assessment of these measures provides targets for improvements. However, to the best of our knowledge, no such measures are available for NHs in the literature. Quantity metrics (QMs) measure the volume of antibiotic use and quality indicators the appropriateness to the clinical context. When no medical data/diagnoses are routinely available for each prescription, which is usually the case in most countries [10], proxy indicators (PIs) can be used as surrogates for quality indicators to estimate the appropriateness of antibiotic prescriptions, as recently demonstrated by Thilly et al [11]. for antibiotics prescribed by general practitioners.

In the present study, our objectives were as follows: (1) to select and adapt QMs and PIs from overviews of metrics; (2) to provide descriptive data for these QMs and PIs in French NHs, using regional routine reimbursement data; (3) to evaluate the

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Correspondence: C. Pulcini, Centre Hospitalier Régional Universitaire de Nancy, Service de Maladies Infectieuses et Tropicales, Hôpitaux de Brabois, Allée du Morvan, 54511 Vandoeuvre-Lès-Nancy, France (celine.pulcini@univ-lorraine.fr).

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PIs' clinimetric properties, using the same database; and (4) to look for clusters of NHs according to PI results.

METHODS

Nursing Home Context in France

In France, NH residents are usually aged 65 or older and may stay temporarily, but more frequently permanently, in the NH. They need constant supervision and nursing care, but they are medically stable and do not need invasive medical procedures or constant medical care [12, 13]. Residents are free to choose their own general practitioner (GP), who is not an employee of the NH present on site and is frequently the same GP they had while living in the community. Thus, GPs can care for residents of different NHs. Some NHs are hospital-based NHs (18.8% in France) and then benefit from the hospital services such as an on-site pharmacy, laboratory, or imaging facility; in that case, their AMS activities are those of the hospital they are related to. However, most French NHs are community-based NHs and then do not have an on-site pharmacy or biology/imaging services; in these NHs, residents can also choose their community pharmacy, biology laboratory, or radiology provider. These NHs do not have any mandatory requirement to implement AMS programs.

Study Setting and Population

Our study focused on community-based NHs of the Lorraine region of northeastern France. According to the 2016 census (Institut national de la statistique et des études économiques [INSEE] [14]), there are 2 338 000 inhabitants in the Lorraine region (66 362 000 in France). We included all community-based NHs of the Lorraine region that were active in 2018.

For each eligible NH, residents considered in the calculation of QMs were those who (1) had been staying at least 1 day in the NH in 2018, (2) were aged 65 years or more, and (3) were covered by the National Health Insurance (NHI; which covers 99% of the French population).

For each eligible NH, residents considered in the calculation of PIs were those who (1) had been staying at least 1 day in the NH in 2018, (2) were aged 65 years or more, (3) were covered by the NHI, and (4) had been prescribed at least 1 antibiotic during the year, regardless of the prescriber's specialty (GPs, dentists, or others).

Data Source and Study Design

In France, all antibiotics must be prescribed by a healthcare professional and all antibiotics dispensed by community pharmacies are reimbursed. The NHI reimbursement database contains information on the prescriber's specialty and patients' characteristics (eg, age, gender, presence of chronic disease, residence) for each antibiotic dispensed in the outpatient setting. The clinical indication related to a specific prescription and the exact duration of treatment are not available; data on the number and type of dispensed packages are, however, collected. Information on the prescription was not available; dispensation was therefore used as a proxy for prescription.

This cross-sectional observational study focuses on antibiotics prescribed in eligible NHs and dispensed by a community pharmacy during the year 2018. Data were collected from the reimbursement database of the Regional Health Insurance Fund (DRSM Grand Est/National Health Data System).

Selection of Quantity Metrics and Proxy Indicators Based on the Literature

Quantity metrics were selected and adapted from the QMs identified by the European project Driving Re-InVEstment in R&D and responsible AntiBiotic use (DRIVE-AB), using a systematic literature review and a structured consensus procedure [15, 16]. Since the vast majority of antibiotics received by NH residents are prescribed by GPs (92% in the Lorraine region), the PIs we selected were similar to those developed by Thilly et al [11] for GP prescriptions, which also used the DRIVE-AB results as a starting point [17].

Volume of Nursing Home Antibiotic Use and Its Variability Using Quantity Metrics

Quantity metrics were calculated at the NH level (aggregating individual antibiotic prescriptions made to the eligible residents of the NH), using resident-days as a denominator, to assess the volume of antibiotic use in French NHs. Resident-days represent the number of days the resident has lived in the NH during the year (2018) by analogy with the concept of patient-days commonly used in hospitals. Prescriptions were estimated by the antibiotics dispensed on a given day in 2018 by a community pharmacy, following a prescription to an eligible resident. If 2 different antibiotics were prescribed and dispensed on the same day, they were counted separately. Some QMs are calculated using Defined daily doses, which is an international unit of measurement. Defined daily doses correspond to the average dose per day for an antibiotic used for its main indication in a 70-kg adult [18].

Appropriateness of Nursing Home Antibiotic Use and Its Variability Using Proxy Indicators

Proxy indicators were calculated at the NH level to estimate the appropriateness of antibiotic use in French NHs using the same methodology as in the Thilly et al study [11]. Targets were set to indicate high quality of care. The optimal target represented a 100% adherence to national guidelines. The acceptable target was less restrictive and represented acceptable practices (considering that some clinical situations are not covered by recommendations).

Subgroup analyses (case-mix stability) were conducted for the following variables: age (>85 years old), male gender, and presence of a long-term illness (as identified by the NHI).

Clinimetric Properties of the Proxy Indicators

Clinimetric properties of the PIs were as follows:

1. Measurability: A PI was considered measurable if data were available for at least 75% of NHs.
2. Applicability: A PI was considered applicable if its score was meaningful for a NH (ie, if it was applicable to at least 10 clinical situations). PI scores could not be calculated for a given NH if less than 10 prescriptions per NH were identified for the denominator for PIs focusing on suboptimal practices (ie, drugs that should not be prescribed) with an optimal target value close to zero (PIs 1, 3, 7, 8, 9, and 10). The PI scores could also not be calculated when less than 10 prescriptions were identified for either the numerator or the denominator for the other PIs describing both suboptimal and good practices (PIs 2, 4, 5, 6, and 11). Overall, a PI was considered applicable if it could be calculated for more than 75% of the NHs.
3. Potential room for improvement: This was calculated as 100% minus the performance score (ie, the percentage of NHs that reached the PI acceptable target). Potential room for improvement was considered insufficient when it was less than 15%.

Proxy indicators were considered having good clinimetric properties when all the 3 of the following criteria were met: measurability of 75% or greater, applicability of 75% or greater, and potential room for improvement of 15% or greater. These cutoffs were the same as in the Thilly et al study [11].

Cluster Analysis

We conducted a cluster analysis to group NHs according to the number of indicators for which the acceptable target was reached (which might reflect good prescribing practices), among the PIs with good clinimetric properties. The Ward method was applied, which links clusters based on the degree of similarity between observations in the same cluster.

We then performed a bivariate analysis to look at the association between the identified clusters and the mean number of antibiotic prescriptions per resident per year using the nonparametric Kruskal-Wallis test. Our hypothesis was that better performing NHs might have lower total antibiotic use.

Statistical Analysis

The QM and PI results were calculated for each NH, with median, range (minimum, maximum) and interquartile range (IQR; lower quartile, upper quartile), as these variables were not normally distributed. Performance scores were calculated from PIs and are presented here in percentages. Clinimetric properties were evaluated. Case-mix stability was assessed for the subgroups described above, and their specific improvement potential is presented. The cluster analysis was conducted with the SAS Proc Tree Procedure (SAS Institute, Inc, Cary, NC). The variance analysis was conducted using the SAS NPAR1WAY Procedure. All analyses were performed with SAS Enterprise Guide version 7.1.

Ethics Statement

This retrospective study did not modify the medical care of residents, and anonymity was preserved for both residents and prescribers. An ethical committee was therefore not required according to the French law.

RESULTS

Nursing Home and Residents' Characteristics

In 2018, there were 290 NHs in the Lorraine region, among which 210 were community based. One NH was not included because it was not active in 2018 (ie, all residents had an entry date in 2019). We then included 209 NHs meeting our inclusion criteria, with a total number of eligible residents of 19 128. The mean number (± SD) of residents per NH was 91.5 ± 36.2. With regard to the residents' characteristics, their mean age was 87.3 ± 7.3 years, and 75.2% were women. Resident-days among NHs were 266.1 ± 127.3 days, on average. In the 209 included NHs, a total of 21 570 antibiotics were prescribed and dispensed to 9110 residents, 92% of them being prescribed by GPs.

Selection of Quantity Metrics and Proxy Indicators Adapted to the Nursing Home Context

Fifteen QMs (6 being expressed in 2 different units of measure) and 11 PIs of antibiotic use or influencing antibiotic use in NHs were developed based on the literature and expert opinion. The evidence base is presented in Supplementary Table 1 for the 15 QMs and in Supplementary Table 2 for the 11 PIs.

A low fraction represented a high quality of care for all proxy indicators, except for PIs 2, 6, and 11, where a high quality of care was indicated by a high fraction.

Volume of Nursing Home Antibiotic Use and Its Variability Using Quantity Metrics

Quantity metric results are presented in Table 1. Large variations were noted between NHs for all QMs.

Appropriateness of Nursing Home Antibiotic Use and Its Variability Using Proxy Indicators

Proxy indicator results are presented in Table 2. Antibiotic-prescribing practices in NHs were far from optimal. The large IQR highlighted the substantial variation in prescribing.

The case-mix analysis is presented in Table 3. For most PIs, performance was higher for male residents, older residents (>85 years), and those with a long-term illness.

Clinimetric Properties of the Proxy Indicators

Clinimetric properties results are presented in Table 3 and summarized below:

1. Measurability: Data were collected from the reimbursement database of the Regional Health Insurance Fund, so there

Table 1. Results for the 15 Quantity Metrics, Calculated at the Nursing Home Level

Quantity Metric	Calculation Description	Median	Range (Minimum, Maximum)	IQR (Lower Quartile, Upper Quartile)
QM 1a—Total antibiotic use	Number of antibiotic prescriptions (J01)/100 resident-days	0.39	0.05, 4.37	0.30, 0.48
QM 1b—Total antibiotic use	DDDs of antibiotics (J01)/100 resident-days	4.02	0.59, 46.17	3.13, 4.87
QM 2—Proportion of residents receiving at least 1 antibiotic per year, %	Number of residents[a] receiving at least 1 antibiotic (J01) per year/total number of residents[a] per year	47.93	8.47, 71.01	40.63, 53.90
QM 3—Mean number of antibiotic prescriptions per resident per year	Number of antibiotic prescriptions (J01)/total number of residents[a] per year	1.03	0.15, 2.70	0.83, 1.26
QM 4a—Broad-spectrum antibiotics use (amoxicillin-clavulanate, cephalosporins, quinolones)	Number of prescriptions of amoxicillin-clavulanate (J01CR02) + quinolones (J01M) + cephalosporins (J01D)/100 resident-days	0.18	0.02, 1.91	0.13, 0.23
QM 4b—Broad-spectrum antibiotics use (amoxicillin-clavulanate, cephalosporins, quinolones)	DDDs of amoxicillin-clavulanate (J01CR02) + quinolones (J01M) + cephalosporins (J01D)/100 resident-days	1.62	0.15, 43.77	1.20, 2.10
QM 5a—Amoxicillin-clavulanate use	Number of prescriptions of amoxicillin-clavulanate (J01CR02)/100 resident-days	0.06	0.00, 0.96	0.04, 0.08
QM 5b—Amoxicillin-clavulanate use	DDDs of amoxicillin-clavulanate (J01CR02)/100 resident-days	0.85	0.00, 43.23	0.59, 1.17
QM 6a—Cephalosporins use	Number of prescriptions of cephalosporins (J01D)/100 resident-days	0.05	0.00, 0.79	0.06, 0.12
QM 6b—Cephalosporins use	DDDs of cephalosporins (J01D)/100 resident-days	0.36	0.00, 4.45	0.23, 0.56
QM 7a—Quinolones use	Number of prescriptions of quinolones (J01M)/100 resident-days	0.03	0.00, 0.27	0.02, 0.05
QM 7b—Quinolones use	DDDs of quinolones (J01M)/100 resident-days	0.32	0.00, 2.05	0.18, 0.49
QM 8a—Macrolides (and related) use	Number of prescriptions of MSLK (J01F)/100 resident-days	0.04	0.00, 0.41	0.03, 0.06
QM 8b—Macrolides (and related) use	DDDs of MSLK (J01F)/100 resident-days	0.39	0.00, 3.55	0.26, 0.56
QM 9—Prescriptions of topical (dermatological) antibiotics	Number of prescriptions of topical antibiotics (D06A and D07C)/100 resident-days	0.02	0.00, 0.15	0.01, 0.04
QM 10—Proportion of parenteral antibiotics, %	Number of prescriptions of parenteral antibiotic (J01 with intravenous, intramuscular, or subcutaneous route)/ number of prescriptions of oral + parenteral antibiotics (J01)	11.76	0.00, 36.62	8.00, 17.14
QM 11—Proportion of antibiotic combinations, %	Number of prescriptions of more than 1 antibiotic (J01) on the same day/number of antibiotic (J01) prescriptions	0.98	0.00, 7.55	0.00, 2.25
QM 12—Proportion of treatment modifications, %	Number of prescriptions of antibiotics (J01) with a different antibiotic (J01) prescribed the week after the first prescription/number of antibiotic (J01) prescriptions	8.05	0.00, 19.19	5.95, 10.77
QM 13—Prescriptions of urine cultures	Number of urine cultures/100 resident-days	0.13	0.00, 0.49	0.09, 0.19
QM 14—Proportion of residents having at least 1 urine culture per year, %	Number of residents (regardless of their duration of stay) having at least 1 urine culture per year/total number of residents[a] per year	19.80	1.41, 48.85	13.85, 26.92
QM 15—Mean number of urine cultures per resident per year	Number of urine cultures/total number of residents[a] per year	0.34	0.01, 1.40	0.23, 0.51

The drugs mentioned here are presented with their ATC (anatomical, therapeutic, chemical) denomination in parenthesis.

Abbreviations: DDDs, daily defined doses; IQR, interquartile range; MLSK, macrolides, lincosamides, streptogramins, and ketolides; QM, quantity metric.

[a]Regardless of their duration of stay.

were no missing data. All PIs were therefore measurable in 100% of the cases.

2. Applicability: It was poor (<75%) for PIs 2, 3, 5, and 7.
3. Potential room for improvement: It was insufficient (<15%) for PI 9.

Overall, 6 of the 11 PIs demonstrated good clinimetric properties: PIs 1, 4, 6, 8, 10, and 11.

Cluster Analysis

For the 6 PIs with good clinimetric properties (PIs 1, 4, 6, 8, 10, and 11), we identified 3 clusters. Table 4 presents the performance for the 6 PIs with good clinimetric properties for these 3 clusters. Cluster 3 corresponds to NHs with the best prescription practices.

The mean number of antibiotic prescriptions per resident per year (QM 3) was not significantly different between the 3 clusters (Kruskal-Wallis test P value = .616).

DISCUSSION

Based on the literature, we designed 15 QMs and 11 PIs adapted to the NH setting to estimate the volume and appropriateness of antibiotic prescriptions based on routine reimbursement data. To the best of our knowledge, this is

Table 2. Results for the 11 Proxy Indicators, Calculated at the Nursing Home Level

Proxy Indicator	Calculation Description	Median	Range (Minimum, Maximum)	IQR (Lower Quartile, Upper Quartile)	Target Value	Percentage of NHs That Reached the Target (Performance)
PI 1—Antibiotic prescriptions against UTI in men, ratio	Number of prescriptions of nitrofurantoin (J01XE01) + certain (fluoro)quinolones [norfloxacin (J01MA06) + enoxacin (J01MA04) + lomefloxacin (J01MA07) + other quinolones (J01MB)] + fosfomycin-trometamol (J01XX01)/number of prescriptions of antibiotics (J01) for the year for male residents	0.00	0.00, 33.33	0.00, 3.85	Optimal target: 0; acceptable target: <0.5	Optimal: 68.9%; acceptable: 68.9%
PI 2—Antibiotic prescriptions against UTI in women, ratio	Number of prescriptions of nitrofurantoin (J01XE01) + pivmecillinam (J01CA08) fosfomycin-trometamol (J01XX01)/number of prescriptions of quinolones (J01M) for the year for female residents	1.60	0.00, 24.00	0.77, 3.00	Target: >1	64.3%
PI 3—Repeated prescription of quinolones, %	Number of prescriptions of quinolones (J01M) among residents having been prescribed quinolones (J01M) in the preceding 6 months/total number of prescriptions of quinolones (J01M)	18.18	0.00, 87.50	0.00, 28.57	Optimal target: 0; acceptable target: <10%	Optimal: 29.6%; acceptable: 33.0%
PI 4—Seasonal variation in total antibiotic prescriptions, %	[Number of prescriptions of antibiotic (J01) during the cold-weather season (January–March and October–December)/number of prescriptions of antibiotic (J01) during the hot-weather season (April–September) − 1] × 100	52.17	−50.00, 800.00	22.22, 83.87	Target: <20%	23.9%
PI 5—Seasonal variation in quinolone prescriptions, %	[Number of prescriptions of quinolones (J01M) during the cold-weather season (January–March and October–December)/number of prescriptions of quinolones (J01M) during the hot-weather season (April–September) − 1] × 100	0.00	−100.00, 900.00	−22.50, 66.67	Optimal target: <5%; acceptable target: <10%	Optimal: 52.7%; acceptable: 53.3%
PI 6—First-line antibiotics/second-line antibiotics prescriptions, ratio	Number of prescriptions of amoxicillin (J01CA04) + amoxicillin-clavulanate (J01CR02)/number of prescriptions of quinolones (J01M) + cephalosporins (J01D) + MLSK (J01F)	0.93	0.13, 3.11	0.70, 1.24	Target: >1	39.9%
PI 7—Prescriptions of not indicated antibiotics, %	Number of prescriptions of lomefloxacin (J01MA07) + moxifloxacin (J01MA14) + certain (fluoro)quinolones [norfloxacin (J01MA06) + enoxacin (J01MA04) + lomefloxacin (J01MA07) + other quinolones (J01MB)] + telithromycin (J01FA15) + spiramycin-metronidazole (J01RA04) + cefaclor (J01DC04) + cefadroxil (J01DB05)/total number of antibiotic (J01) prescriptions	1.25	0.00, 20.00	0.00, 2.61	Optimal target: 0; acceptable target: <0.5	Optimal: 29.2%; acceptable: 29.2%
PI 8—Estimated duration of antibiotic prescriptions >8 days, %	Number of prescriptions >8 days for specific antibiotics[a]/total number of antibiotic prescriptions for these antibiotics[a]	12.31	0.00, 52.27	7.69, 18.75	Optimal target: <5%; acceptable target: <10%	Optimal: 13.9%; acceptable: 33.5%
PI 9—Co-prescription of antibiotic + systemic NSAIDs, %	Number of antibiotics (J01) + systemic NSAID(s) (M01A) co-prescribed on the same day/total number of antibiotic (J01) prescriptions	0.00	0.00, 16.67	0.00, 0.99	Optimal target: 0; acceptable target: <5%	Optimal: 63.6%; acceptable: 97.6%
PI 10—Co-prescription of antibiotic + systemic corticosteroids, %	Number of antibiotics (J01) + systemic corticosteroids (H02AB) co-prescribed on the same day/total number of antibiotic (J01) prescriptions	5.77	0.00, 44.44	3.85, 9.72	Optimal target: 0; acceptable target: <5%	Optimal: 4.6%; acceptable: 41.6%
PI 11—Estimated flu vaccine coverage, %	Number of flu vaccines dispensed during the second semester/number of residents staying in the NH between October and December	72.37	0.00, 94.94	60.94, 80.85	Target: ≥90%	3.9%

The drugs mentioned here are presented with their ATC (anatomical, therapeutic, chemical) denomination in parentheses.

Abbreviations: IQR, interquartile range; MLSK, macrolides, lincosamides, streptogramins, and ketolides; NH, nursing home; NSAID, nonsteroidal anti-inflammatory drug; PI, proxy indicator; UTI, urinary tract infection.

[a]Refer to Thilly et al [11] for more information on the PI 8 calculation.

Table 3. Clinimetric Properties of the 11 Proxy Indicators and Case-mix Stability

Proxy Indicator	Measurability: Missing Data, %	Applicability, n (%)	Improvement Potential (100-[Acceptable] Performance), %	Case-mix Stability: Improvement Potential for Specific Residents' Characteristics
PI 1—Antibiotic prescriptions against UTI in men, ratio	0	161 (77.0)	31.1	Age >85: 20.2% Long-term illness: 27.9%
PI 2—Antibiotic prescriptions against UTI in women, ratio	0	103 (49.3)	35.7	Age >85: 38.2% Long-term illness: 38.9%
PI 3—Repeated prescription of quinolones, %	0	75 (35.9)	67.0	Age >85: 52.5% Male gender: 45.3% Long-term illness: 64.9%
PI 4—Seasonal variation in total antibiotic prescriptions, %	0	205 (98.1)	76.1	Age >85: 74.6% Male gender: 64.4% Long-term illness: 73.2%
PI 5—Seasonal variation in quinolone prescriptions, %	0	37 (17.7)	46.7	Age >85: 47.2% Male gender: 23.6% Long-term illness: 44.7%
PI 6—First-line antibiotics/second-line antibiotics prescriptions, ratio	0	202 (96.7)	60.1	Age >85: 60.6% Male gender: 57.6% Long-term illness: 58.2%
PI 7—Prescriptions of not indicated antibiotics, %	0	148 (70.8)	70.8	Age >85: 51.7% Male gender: 23.8% Long-term illness: 62.2%
PI 8—Estimated duration of antibiotic prescriptions >8 days, %	0	206 (98.6)	66.5	Age >85: 62.7% Male gender: 52.7% Long-term illness: 67.0%
PI 9—Co-prescription of antibiotic + systemic NSAIDs, %	0	208 (99.5)	2.4	Age >85: 0.0% Male gender: 8.3% Long-term illness: 1.0%
PI 10—Co-prescription of antibiotic + systemic corticosteroids, %	0	200 (95.7)	58.4	Age >85: 58.9% Male gender: 44.2% Long-term illness: 60.3%
PI 11—Estimated flu vaccine coverage, %	0	201 (96.2)	96.1	Age >85: 95.2% Male gender: 88.3% Long-term illness: 87.9%

The drugs mentioned here are presented with their ATC (anatomical, therapeutic, chemical) denomination in parentheses.
Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PI, proxy indicator; UTI, urinary tract infection.

Table 4. Performance (ie, Percentage of Nursing Homes That Reached the Acceptable Target) for the 6 Proxy Indicators With Good Clinimetric Properties for the 3 Clusters

	Cluster 1: NHs That Reached the Applicable Target for 0 or 1 of the 6 PIs (n = 62; 29.7%), %	Cluster 2: NHs That Reached the Applicable Target for 2 of the 6 PIs (n = 70; 33.5%), %	Cluster 3: NHs That Reached the Applicable Target for 3 or 4 of the 6 PIs (n = 77; 36.8%), %
PI 1—Antibiotic prescriptions against UTI in men, ratio	37.1	72.1	92.1
PI 4—Seasonal variation in total antibiotic prescriptions, %	4.8	22.9	40.3
PI 6—First-line antibiotics/second-line antibiotics prescriptions, ratio	12.9	31.4	69.7
PI 8—Estimated duration of antibiotic prescriptions >8 days, %	8.1	28.6	58.4
PI 10—Co-prescription of antibiotic + systemic corticosteroids, %	19.4	44.3	57.1
PI 11—Estimated flu vaccine coverage, %	1.6	2.9	6.6

Abbreviations: NH, nursing home; PI, proxy indicator; UTI, urinary tract infection.

the first published set of antibiotic use indicators for this setting.

This set of QMs and PIs explores a vast range of common clinical situations in NH residents, encompassing both unnecessary and inappropriate antibiotic use. For example, 3 QMs (QMs 13, 14, and 15) were included because a significant number of urine cultures are unnecessarily performed in NH residents, with positive urine cultures usually representing asymptomatic bacteriuria (that is very common in NH residents) and leading to unnecessary antibiotic treatments [19]. Brown et al [20] found a correlation between the number of urine cultures and the prevalence of antibiotic prescribing in NHs. Proxy indicator 11 was a newly designed indicator, estimating influenza vaccination coverage in NHs. This PI was included because improving flu vaccination might reduce antibiotic use [21].

The variability between NHs was high for all QMs and PIs. Six out of the 11 PIs had good clinimetric properties based on regional data. The PIs' performance was low (except for PI 9), suggesting significant room for improvement. The case-mix analysis showed that male gender, in particular, but also older age and presence of a long-term illness, seemed to be associated with higher performance scores, even though the PIs are relevant for all patient populations.

For the 6 PIs with good clinimetric properties, we identified 3 distinct clusters. Cluster 3 grouped NHs with more appropriate prescription practices, being constituted of the NHs that reached the acceptable target for 3 or 4 of the 6 PIs. Total antibiotic use was not significantly different between the 3 clusters. This result suggests that the volume of prescriptions does not necessarily reflect their appropriateness, as already shown in the literature [22]. This highlights the need for a concomitant use of PIs and QMs to describe and assess antibiotic prescriptions in NHs.

It is difficult to compare our results with those in the literature in the absence of similar data. We use here as a best available comparator the results of point-prevalence surveys.

The point-prevalence survey of healthcare-associated infections and antimicrobial use in European long-term care facilities (LTCFs) was conducted in April and May 2013 (HALT-2 project) [23], and included 10 categories of LTCFs, including NHs. The mean age of residents receiving an antimicrobial was 81.8 years (87.3 years in our study), with 67.6% being women (75.2% in our study). 94.5% of these residents received an antimicrobial monotherapy (99.2% in our study), and 87.3% of antimicrobials were administered orally (88.2% in our study). Of all antibacterials for systemic use, 16.9% were penicillins with B-lactamase inhibitors (15.4% were amoxicillin-clavulanate in our study).

Our results are also in line with the 2016 French nationwide point-prevalence Prev'Ehpad study (Santé Publique France) [24], conducted in 719 randomly selected NHs, of which 28% were hospital-based NHs. They found a proportion of orally administered antibiotics of 85.1%, whereas we found a proportion of 88.2%. The proportions of the main antibiotics were comparable to ours, with 16.0% for amoxicillin-clavulanate (15.4% in our study), 12.3% for macrolides and related antibiotics (10.3% in our study), and 11.4% for fluoroquinolones (7.7% for quinolones in our study). The main difference was the proportion of cephalosporins, which was higher in the Prev'Ehpad study (20.9% for third-generation cephalosporins) than in our study (12.8% for all cephalosporins), probably reflecting regional differences in antibiotic prescribing.

Our large set of QMs and PIs could be useful to different stakeholders (eg, health authorities, NHs, AMS teams) to help improve prescribing practices in NHs. Quantity metrics could be used in the same way as QMs developed for the hospital setting: for benchmarking purposes and to monitor antibiotic use over time and evaluate the impact of AMS interventions. However, QMs describe the quantity/volume of antibiotic use and do not reflect the appropriateness of prescriptions.

As a complement to QMs, PIs can estimate the appropriateness of antibiotic use at an aggregated level [11], as they present targets that reflect the quality of care at the NH level. We identified 6 PIs with good clinimetric properties (ie, PIs that are measurable, applicable, and with an improvement potential), which in our opinion might be relevant for larger-scale use. They can be used to guide AMS interventions in the facility; they also provide an almost real-time personalized feedback and are useful to monitor the impact of interventions. Different stakeholders might use these data, at different scales. For example, the Regional and National Health Insurance, Regional Health Agencies, and regional antibiotic stewardship networks might use these data to help NHs develop personalized action plans, with concrete objectives and a monitoring plan. These indicators might also be integrated in a pay-for-performance mechanism, which does not currently exist in France for NHs.

Both QMs and PIs could be aggregated at a geographic level and publicly reported. As an example, Geodes is a database of health-related indicators, piloted by Public Health France [25].

Finally, these QMs and PIs may be used in other countries, by adapting them to the national NH context and to the national prescribing guidelines for elderly patients and following a validation process, as we did in this work.

Our study is original, but it has some limitations. First, the NHI database gives information on drugs dispensed by community pharmacies, not on prescriptions. It might therefore overestimate the real quantity of antibiotics used by the resident if compliance is suboptimal, or underestimate the volume of prescribing if the antibiotic is not dispensed. However, we considered that dispensation data represent a good proxy for prescriptions and use, especially in the NH setting where drugs are usually administered to residents by nurses. Second, we acknowledge that the targets we set are debatable since some

are based on expert opinion; a structured consensus procedure involving a large group of stakeholders might be useful to validate these targets.

In conclusion, AMS programs should be implemented in NHs, since residents are particularly vulnerable to infections and antibiotic use is excessive and often inappropriate, as confirmed by our results. We designed 15 QMs and 11 PIs (including 6 with good clinimetric properties) to estimate the volume and appropriateness of antibiotic prescriptions in NHs. Our set of indicators can be adapted to different countries and may be used in many ways to guide AMS interventions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Supplementary Table S1. Evidence base for the design of quantity metrics (QMs) assessing the volume of antibiotic use.

Quantity metric (QM)	**Based on the following inpatient quantity metrics (IQMs)[1] and outpatient quantity metrics (OQMs)[2], identified through a literature review and structured consensus procedure (DRIVE-AB project)**
QM 1 – Total antibiotic use	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 2 – Proportion of residents receiving at least one antibiotic per year (%)	IQM 10 - Patients exposed to antibiotics per all patients
QM 3 – Mean number of antibiotic prescriptions per resident per year	OQM 4 - Prescriptions per defined population
QM 4 – Broad-spectrum antibiotics use (amoxicillin-clavulanate, cephalosporins, quinolones)*	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 5 – Amoxicillin-clavulanate use	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 6 – Cephalosporins use	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 7 – Quinolones use	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 8 – Macrolides (and related) use	IQM 1 - Defined daily doses per 100(0) Patient-Days OQM 1 - Defined daily doses per defined population OQM 4 - Prescriptions per defined population
QM 9 – Prescriptions of topical (dermatological) antibiotics**	OQM 4 - Prescriptions per defined population
QM 10 – Proportion of parenteral antibiotics (%)	IQM 10 - Patients exposed to antibiotics per all patients
QM 11 – Proportion of antibiotic combinations (%)	IQM 10 - Patients exposed to antibiotics per all patients
QM 12 – Proportion of treatment modifications (%)	IQM 10 - Patients exposed to antibiotics per all patients
QM 13 – Prescriptions of urine cultures	OQM 4 - Prescriptions per defined population

QM 14 – Proportion of residents having at least one urine culture per year (%)	IQM 10 - Patients exposed to antibiotics per all patients
QM 15 – Mean number of urine cultures per resident per year	OQM 4 - Prescriptions per defined population

***** The national medicine agency (ANSM) published in 2013 (and updated in 2015) the list of "critical antibiotics" including amoxicillin-clavulanate, cephalosporins and quinolones.[3]
** The unnecessary use of topical antibiotics is a common cause of antibiotic misuse in these facilities.[4]

Supplementary Table S2. Evidence base for the design of proxy indicators (PIs) estimating the appropriateness of antibiotic use.

Proxy indicator (PI)[5]	**Based on the following outpatient quality indicators (OQIs)[6] and outpatient quantity metrics (OQMs)[2] identified through a literature review and a structured consensus procedure (DRIVE-AB project)**	**National guidelines / recommendations used to adapt the definition of the indicators to the French context**	**Guidelines / recommendations used to set the targets**
PI 1 - Antibiotic prescriptions against UTI* in men (ratio)	OQI 4 - Some antibiotics should be rarely prescribed	National guidelines on Urinary Tract Infections (UTIs)[7,8] Nitrofurantoin, first-generation quinolones, norfloxacin, enoxacin, lomefloxacin and fosfomycin-trometamol are not recommended in male UTIs.	We set the optimal target at 0, but we also set an acceptable target at <0.5, based on expert opinion (since guidelines are not applicable to all patients and some of these antibiotics might be used in complex patients, e.g. with chronic UTIs or UTIs due to multi-drug resistant bacteria).
PI 2 – Antibiotic prescriptions against UTI* in women (ratio)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	National guidelines on UTIs[7,8]	In female cystitis, which is much more frequent in NHs as compared to pyelonephritis, nitrofurantoin, pivmecillinam and fosfomycin-trometamol are recommended as first-line treatments. Moreover, these three molecules are exclusively recommended for UTIs. Fluoroquinolones can be indicated in very selected indications, but they are never first-line treatments of cystitis. The level of use of fluoroquinolones should be very limited in UTIs if guidelines are complied with.[9] We selected a ratio >1 based on expert opinion,

			even though the optimal ratio might be even higher.
PI 3 – Repeated prescriptions of quinolones (%)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	National guidelines on UTIs and lower respiratory tract infections[7,8] National recommendations on fluoroquinolone use Quinolones should not be used among patients having been prescribed a quinolone in the preceding six months.	We set the optimal target at 0, but we also set an acceptable target at <10%, based on expert opinion (since guidelines are not applicable for some complex cases).
PI 4 – Seasonal variation of total antibiotic prescriptions (%)	OQI 2 - Antibiotics should not be prescribed for (most) viral infections or self-limiting bacterial infections OQM 6 - Seasonal variation of total antibiotic use	Quality indicators for antibiotic consumption in the community from the European Centre for Disease prevention and Control (ECDC)[10] European Surveillance of Antimicrobial Consumption (ESAC) : quality indicators for outpatient antibiotic use in Europe[11]	We set a target <20%, based on expert opinion and the range of European data from ESAC-Net[10]
PI 5 – Seasonal variation of quinolone prescriptions (%)	OQI 2 - Antibiotics should not be prescribed for (most) viral infections or self-limiting bacterial infections OQM 6 - Seasonal variation of total antibiotic use	Quality indicators for antibiotic consumption in the community from the European Centre for Disease prevention and Control (ECDC)[10] European Surveillance of Antimicrobial Consumption (ESAC) : quality indicators for outpatient antibiotic use in Europe[11]	We set a target <5%, based on a national indicator from Scotland.[12] We also set an acceptable target <10%, based on expert opinion and the range of European data from ESAC-Net.[10]
PI 6 – First-line antibiotics / Second-line antibiotics prescriptions (ratio)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	National guidelines on the most common infections encountered in primary care[7,8] Different from the indicator for GPs prescriptions to global population[5], since amoxicillin-clavulanate is recommended in first-line treatment of many infections of the elderly, and not for global population	We set a ratio >1 based on expert opinion, even though the optimal ratio might be even higher.
PI 7 – Prescriptions of not indicated antibiotics (%)	OQI 4 - Some antibiotics should be rarely prescribed	National guidelines on the most common infections encountered in primary care[7,8] According to these guidelines, lomefloxacin, moxifloxacin, first-generation quinolones, norfloxacin, enoxacin, telithromycin, spiramycin-	We set the optimal target at 0, but we also set an acceptable target at <0.5%, based on expert opinion (since guidelines are not applicable for some complex cases and some

		metronidazole, cefaclor and cefadroxil are not indicated.	of these antibiotics might be used as last-resort treatments).
PI 8 – Estimated duration of antibiotic prescriptions > 8 days (%)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	National guidelines on the most common infections encountered in primary care[7,8] The maximum recommended duration of antibiotic treatment for almost all bacterial infections encountered in primary care is one week, and durations of less than one week are common. We selected here antibiotics that are almost exclusively recommended in respiratory tract infections, skin infections, or cystitis, for which recommended durations are less than eight days. Details on calculation are available in the Thilly *et al.* paper.[5]	We set the optimal target at <5% for durations of nine days or more, and we also set an acceptable target at <10%, based on expert opinion. In France, unit dispensing is not in place, so antibiotics are dispensed using packages, whose size is adapted to the most frequent durations advised in national recommendations.
PI 9 – Co-prescription of antibiotic + systemic non-steroidal anti-inflammatory drugs (NSAIDs) (%)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	NSAIDs are never indicated and should be avoided in bacterial infections encountered in primary care (except if NSAIDs are contra-indicated).[13] National guidelines on the most common infections encountered in primary care[7,8] Self-medication with NSAIDs is not considered for this PI.	We set the optimal target at 0, but we also set an acceptable target at <5%, based on expert opinion (since guidelines are not applicable to all cases, and some patients might be on NSAIDs for another reason).
PI 10 - Co-prescription of antibiotic + systemic corticosteroids (%)	OQI 3 - Outpatients should receive antibiotic therapy compliant with guidelines	National guidelines on the most common infections encountered in primary care[7,8] Corticosteroids are never indicated and should be avoided in bacterial infections encountered in primary care (except for blocked acute bacterial sinusitis).	We set the optimal target at 0, but we also set an acceptable target at <5%, based on expert opinion (since guidelines are not applicable to all cases, and some patients might be on corticosteroids for another reason).
PI 11 – Estimated flu	OQM 4 - Prescriptions per defined population	National recommendations on vaccination for the elderly[14]	The national and international objectives are to reach a vaccine coverage of 75% of the senior population.[15] Considering the

vaccine coverage (%)	Flu vaccine is recommended every year for all seniors (≥65 years old).	nursing homes setting, where the risk of flu is very high and flu-related complications common, we set a target ≥90%. We also set a relatively high target because we had data on dispensed vaccines, that probably overestimates the true vaccine coverage in patients.

* UTI : Urinary Tract Infection

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III – Article profils de prescription des médecins généralistes

1. Contexte et objectifs

L'identification de groupes de médecins généralistes selon la pertinence de leurs prescriptions antibiotiques et de facteurs associés à ces pratiques de prescription est utile pour identifier les prescripteurs à cibler prioritairement par des interventions de bon usage. Ainsi, les objectifs de cette étude étaient (i) d'identifier des groupes de médecins généralistes selon leurs résultats pour les indicateurs proxy et (ii) d'identifier des caractéristiques des médecins généralistes, de leur patientèle et de leur pratique, associées à la pertinence des prescriptions antibiotiques.

2. Méthodes

Un score de pertinence a été calculé pour chaque médecin généraliste de la région Grand Est inclus, basé sur ses résultats pour les indicateurs proxy développés par Thilly *et al.* (85), à partir des données du SNDS de 2019. Le score de pertinence est défini comme suit : ((nombre d'indicateurs proxy applicables pour le médecin généraliste et pour lesquels il a atteint la cible acceptable) / (nombre d'indicateurs applicables pour le médecin généraliste)) x 100. Des groupes de médecins généralistes ont été identifiés par la méthode Ward, selon leur score de pertinence. Les caractéristiques des médecins généralistes et de leur patientèle ont été comparées entre les groupes de médecins généralistes par une analyse bivariée, puis par une régression logistique polytomique multivariée. Les caractéristiques liées aux pratiques des médecins généralistes ont été comparées uniquement par une analyse bivariée.

3. Principaux résultats et conclusions

Au total, 4 819 médecins généralistes pratiquant en région Grand Est ont été inclus dans cette étude et ont prescrit un total de 2 950 425 antibiotiques ayant été dispensés en 2019. Trois groupes de médecins généralistes ont été identifiés selon la pertinence de leurs prescriptions antibiotiques : 15% des médecins généralistes avaient des pratiques de prescription meilleures que la moyenne, 33% des pratiques dans la moyenne et 52% des pratiques moins bonnes que la moyenne. La majorité des caractéristiques explorées étaient associées à la pertinence des prescriptions. Il y avait plus de probabilité de trouver dans le groupe avec des pratiques de prescription meilleures que la moyenne des médecins généralistes qui étaient des femmes, exerçant dans la Marne, ayant un mode d'exercice particulier, en pratique depuis moins de

temps, avec un nombre de patients et un nombre de consultations moins élevés et avec une patientèle plus jeune. Concernant les caractéristiques liées aux pratiques des médecins généralistes, les pratiques de prescription étaient meilleures lorsque le médecin généraliste prescrivait moins de médicaments en général, moins d'antibiotiques et moins d'antibiotiques à large spectre. De plus, les médecins généralistes avec des meilleures pratiques de prescription que la moyenne atteignaient davantage les cibles fixées dans le cadre des deux rémunérations sur objectifs de santé publique dédiées aux antibiotiques. Cette étude peut aider à la conception d'interventions pour le bon usage des antibiotiques. Des actions spécifiques pourraient cibler le groupe de médecins généralistes avec des pratiques moins bonnes que la moyenne et les situations cliniques pour lesquelles les indicateurs présentaient les moins bonnes performances. Il serait également possible de cibler les médecins généralistes ayant des caractéristiques associées à des pratiques moins bonnes que la moyenne (par exemple des hommes, en exercice depuis longtemps, n'ayant pas de mode d'exercice particulier et ayant un grand nombre de consultations).

4. Mon implication

Pour cet article, j'ai contribué à la conception méthodologique, à l'interprétation des résultats, à la rédaction et à la valorisation. Les analyses statistiques ont été réalisées par Ouarda Pereira, responsable de missions statistiques à la Direction Régionale du Service Médical (DRSM) du Grand Est.

5. Valorisation

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Original article

Factors associated with the appropriateness of antibiotics prescribed in French general practice: a cross-sectional study using reimbursement databases

Maïa Simon [1], Nathalie Thilly [1, 2], Ouarda Pereira [3], Céline Pulcini [1, 4, *]

[1)] Université de Lorraine, APEMAC, Nancy, France
[2)] Université de Lorraine, CHRU-Nancy, Département Méthodologie, Promotion, Investigation, Nancy, France
[3)] Direction Régionale du Service Médical (DRSM) Grand Est, Strasbourg, France
[4)] Université de Lorraine, CHRU-Nancy, Département de Maladies Infectieuses, Nancy, France

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ABSTRACT

Objectives: Identifying characteristics associated with the appropriateness of antibiotic prescriptions is useful to guide antibiotic stewardship interventions. Proxy indicators estimating the appropriateness of antibiotic prescriptions at the general practitioner (GP) level have recently been validated. Our objectives were to identify (a) clusters of GPs according to their appropriateness score based on these proxy indicator results, and (b) GPs', patients' and practices' characteristics associated with inappropriate prescriptions.

Methods: We conducted a cross-sectional observational study analysing antibiotics prescribed by GPs in one large French region in 2019, using the Health Insurance databases. We identified clusters of GPs according to their appropriateness score calculated from ten proxy indicators' results. We then analysed the association between the clusters with more inappropriate practices compared with the one with less inappropriate practices, and GPs', patients', and practices' characteristics. We performed bivariate and multivariable analyses using logistic polytomous regressions.

Results: We included 4819 GPs who were grouped into three clusters. GPs who belong to the clusters with more inappropriate practices were more likely to practice in certain geographical area, to be male, not to have a particular medical practice, to be practicing for longer, to have more patients and consultations, to have a higher proportion of elderly patients, and to prescribe more drugs, more antibiotics and a higher proportion of broad-spectrum antibiotics.

Conclusion: We identified clusters of practice as well as factors associated with the appropriateness of antibiotic prescriptions, using routinely collected data. This might help to guide antibiotic stewardship interventions. **Maïa Simon, Clin Microbiol Infect 2022;28:609.e1–609.e6**

Introduction

Antimicrobial resistance is a rising threat to global health, and is accelerated by the misuse and overuse of antibiotics in humans and animals [1]. In France, around 125 000 persons are infected by multidrug-resistant bacteria each year, causing 5500 deaths [2]. Seventy-eight per cent of antibiotics are prescribed in primary care in France, with 70% of those being prescribed by general practitioners (GPs) [3].

Antimicrobial stewardship (AMS) has been defined as a 'coherent set of actions which promote using antimicrobials responsibly' [4]. Metrics are important AMS tools to set targets for improvement and provide feedback to professionals and stakeholders. Indications/diagnoses are required to calculate quality indicators, but computerized national systems linking drug prescriptions to indications/diagnoses are rarely available [5]. In this context, we recently developed ten proxy indicators (PIs) calculable from routine databases, estimating the appropriateness

* Corresponding author. Céline Pulcini, Centre Hospitalier Régional Universitaire de Nancy, Service de Maladies Infectieuses et Tropicales, Hôpitaux de Brabois, allée du Morvan, 54511, Vandoeuvre-Lès-Nancy, France.
E-mail address: celine.pulcini@univ-lorraine.fr (C. Pulcini).

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of antibiotic prescriptions at GP level without requiring indications/diagnoses [6].

Identifying factors associated with the appropriateness of antibiotic prescriptions is useful to guide AMS interventions. However, in the literature, few studies aimed at identifying such factors in general practice [7–10]. Table S1 (see Supplementary material) summarizes the four identified studies, all conducted more than 5 years ago.

Our objectives were to identify, based on routinely collected data, (a) clusters of GPs according to their appropriateness score based on PI results, and (b) GPs', patients' and practices' characteristics associated with inappropriate prescriptions (by comparing clusters with more inappropriate practices with the one with less inappropriate practices).

Materials and methods

Study setting and population

GPs were selected from the Health Insurance databases. We included GPs practicing in the Grand Est region of France (66 524 000 inhabitants in France and 5 550 000 inhabitants in the Grand Est region, according to the 2017 census [11]), who took care of at least 100 different patients in 2019 and prescribed at least ten antibiotic treatments during the year. We excluded GPs who had an exclusive particular medical practice during the year (e.g. homeopathy, acupuncture).

Study design

We conducted a retrospective cross-sectional observational study analysing antibiotics prescribed by eligible GPs and dispensed by a community pharmacy in 2019.

Data source

In France, all antibiotics are prescribed and reimbursed. The Health Insurance databases link the prescriber and the patient identification numbers to the antibiotics dispensed by community pharmacies, the prescriber specialty and his/her main characteristics and the patients' characteristics (e.g. age, gender, chronic diseases, low income). Dispensing was used as a proxy for prescription as information on prescriptions is not available. The term 'antibiotic prescription' refers here to an antibiotic course, whatever the duration of treatment. When two different antibiotics were prescribed by a GP and dispensed on the same day, they were counted separately. As mentioned previously, indications/diagnoses related to a prescription are not available in these databases.

Proxy indicators

To overcome the absence of indications/diagnoses in the Health Insurance databases, Thilly et al. developed ten PIs estimating the appropriateness of antibiotic prescriptions at GP level, calculable from routine Health Insurance databases [6]. These PIs were based on a literature review and used national guidelines as a reference [12].

Each PI was associated with targets set to reflect the appropriateness of antibiotic prescriptions: the optimal target aims at 100% compliance with national guidelines, whereas the acceptable target is less restrictive and takes into account that guidelines are not applicable to all patients. These targets were used to calculate the performance for each PI, which is the percentage of GPs who reach the defined target. Table S2 (see Supplementary material) presents these 10 PIs, their definition and targets.

Cluster analysis

For each GP, an appropriateness score expressed as a percentage was calculated as follows: ((number of PIs applicable for the GP and for whom the acceptable target is reached)/(number of PIs applicable for the GP)) $\times$ 100. A PI was considered applicable if it was based on at least ten clinical situations per year for the GP. A cluster analysis was conducted to group GPs according to their appropriateness score, reflecting the appropriateness of their antibiotic prescribing practices. The Ward method was used, linking clusters according to the degree of similarity between observations in the same cluster.

Statistical analyses

GPs' and patients' characteristics, as well as GPs' practices, explored for their potential association with inappropriate practices are presented in the Supplementary material (Appendix S1).

The PIs' results were first calculated for each GP and presented as medians with the interquartile range (IQR). Performances were calculated for each PI and presented as percentages. The cluster analysis was then conducted using a hierarchical clustering method to identify clusters of GPs according to their practices' appropriateness, estimated from their appropriateness score. For each cluster, the median appropriateness score with the IQR and the performances for each PI were presented.

Comparisons of GPs' and patients' characteristics between the previously identified clusters were performed using χ^2 tests for categorical variables (expressed as percentages) and Kruskal–Wallis tests for continuous variables (expressed as medians and IQR). Characteristics identified with p value less than 0.10 in bivariate analyses were then introduced in a multivariable polytomous logistic regression model to identify characteristics significantly associated with the clusters having more inappropriate practices compared with the one with less inappropriate practices (used as the reference), taking into account other characteristics. When two identified characteristics were highly collinear, we excluded from the model the one with the higher p value in the bivariate analysis.

Comparisons of practices' characteristics between clusters was restricted to bivariate analyses (as described for GPs' and patients' characteristics), because of high collinearity between the six considered variables.

For all final analyses, a p value less than 0.05 for two-sided tests was considered significant. Analyses were performed with SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC, USA).

Ethical statement

This is a retrospective observational study which did not modify the medical care of patients. Anonymity was preserved for both patients and prescribers. According to the French law, ethical approval was therefore not required.

Results

Characteristics of GPs and their patients

Of the 6041 GPs practicing in the Grand Est region, 1187 GPs took care of fewer than 100 different patients in 2019 or prescribed fewer than ten antibiotics during the year, and 35 GPs had an exclusive particular medical practice. We therefore included in this study 4819 GPs who met the inclusion criteria. Their mean age was 53 $\pm$ 11.6 years and 63% were male. They took care, on average, of 1471 $\pm$ 736 different patients in 2019, with 4957 $\pm$ 2521

consultations. The 4819 included GPs prescribed in 2019 a total of 2 950 425 antibiotic treatments that were dispensed to 1 962 654 different patients. Regarding the characteristics of these patients, 45% were male, 20% were under 16 years and 19% were over 65 years of age, 0.8% lived in a nursing home, 14% had a chronic disease and 10% were in the low-income category.

Appropriateness of antibiotic prescriptions

Results about the ten PIs are presented in Table 1. The performance results were not optimal, varying between 15.3% (PI 4) and 88.5% (PI 2). Substantial variations in prescribing were noticed (large IQR).

Cluster analysis

Three clusters of GPs were identified. Table 2 presents the description of the three clusters and their performances for each PI.

GPs' and patients' characteristics

Table 3 presents the GPs' and patients' characteristics for each of the three clusters and their comparisons in bivariate analyses. All GPs' characteristics were significantly associated with the clusters, except for the practice setting. All patients' characteristics were significantly associated with the clusters, except for the percentage of patients with low income.

Table 4 presents results of the multivariable analysis evaluating the association between GPs' and patients' characteristics and inappropriate practices (cluster 2 and cluster 3 versus cluster 1). All GPs' characteristics included in the model were significantly associated with the clusters with a gradient in the associations (OR in cluster 3 > OR in cluster 2 > OR in cluster 1 (=1), except for gender).

GPs' practices

Table 5 describes GPs' practices for each of the three clusters and their comparisons in bivariate analyses. All the investigated characteristics were significantly associated with inappropriate practices, with a gradient in the associations except for the attainment of the target for the variable 'number of antibiotic prescriptions per 100 patients aged 16 to 65 years old without a chronic disease per year'.

Discussion

Summary of the main findings

We identified three clusters of GPs reflecting the appropriateness of their antibiotic prescriptions: 15% of GPs with better than average practices, 33% with average practices and 52% with worse than average practices. Almost all GPs' and patients' characteristics were associated with the appropriateness of practices. Several quantity metrics reflecting the volumes of drugs and antibiotics prescribed by GPs were also associated with these clusters.

We identified several GPs' characteristics strongly associated with the appropriateness of prescriptions. We showed significant differences of practices across the geographic areas, which might be explained by different factors to be investigated, for example different medical densities [13]. Female GPs were more likely to belong to the cluster with better than average practices. It has been shown that male GPs participate less in postgraduate training in France [14]. GPs with a particular medical practice were more likely to belong to the cluster with better practices. They may use more alternatives to drugs for self-limiting infections, and so prescribe fewer antibiotics.

GPs who had been in practice longer were more likely to prescribe inappropriately, as has been shown previously [7,15]. Physicians who had been in practice longer may be less likely to adhere to standards of appropriate therapy [16], whereas younger GPs may be more aware and educated on antimicrobial resistance and stewardship.

We also found an association between a higher number of consultations per month and a higher risk of inappropriateness of antibiotic prescriptions. As has been shown in the literature, a high number of consultations could reflect short consultation durations [7,17]. In this case, it might be too time-consuming for GPs to educate patients and to explain to them why they do not need an antibiotic [17,18]. Shorter consultation duration or higher workload could also lead to less exhaustive clinical examination and so contribute to diagnostic uncertainty, with GPs prescribing more antibiotics and notably more broad-spectrum agents to avoid risks [18].

Overall, patients' characteristics were associated with the appropriateness of practices, except for the percentage of patients with low income. The National Health Insurance usually reimburses 65% of the cost of antibiotics in France, with 100% of the costs covered in case of low income and almost all other patients having a complementary insurance covering the remaining costs.

Table 1
Results for the ten proxy indicators estimating the appropriateness of antibiotic prescriptions by GPs of the Grand Est region in northeastern France in 2019 ($n = 4819$ GPs)

Proxy indicator [6]	Median	Interquartile range	Acceptable target value	Performance (% of GPs who reached the target)
PI 1 Antibiotic prescriptions against urinary tract infections in men (ratio)	0	0.0–0.3	<0.5	82.5
PI 2 Antibiotic prescriptions against urinary tract infections in women (ratio)	3.8	2.0–7.0	>1	88.5
PI 3 Repeated prescription of quinolones (%)	13.0	5.0–21.1	<10%	38.5
PI 4 Seasonal variation of total antibiotic prescriptions (%)	45.0	29.2–62.5	<20%	15.3
PI 5 Seasonal variation of quinolone prescriptions (%)	28.6	−9.1–80.0	<10%	38.0
PI 6 Amoxicillin/second-line antibiotics prescriptions (ratio)	0.9	0.5–1.3	>1	40.0
PI 7 Prescriptions of not indicated antibiotics (%)	1.1	0.4–2.2	<0.5%	29.7
PI 8 Estimated duration of antibiotic prescriptions >8 days (%)	3.9	2.1–6.9	<10%	86.5
PI 9 Co-prescription of antibiotic and systemic non-steroidal anti-inflammatory drugs (%)	9.9	5.3–16.6	<5%	23.2
PI 10 Co-prescription of antibiotic and systemic corticosteroids (%)	12.3	6.8–20.3	<5%	15.9

Abbreviations: GP, general practitioner; PI, proxy indicator.

Table 2
Description of the three clusters reflecting the appropriateness of antibiotic practices and their performances for the ten proxy indicators ($n = 4819$ GPs)

		Cluster 1 'Better than average practices' $n = 709$ GPs (14.7%)	Cluster 2 'Average practices' $n = 1574$ GPs (32.7%)	Cluster 3 'Worse than average practices' $n = 2536$ GPs (52.6%)
Appropriateness score[a]		71.4 (70.0–80.0)	55.6 (50.0–60.0)	30.0 (30.0–40.0)
Proxy indicator [6]	**Target value**	**Performances (% of GPs who reached the target)**		
PI 1 Antibiotic prescriptions against urinary tract infections in men	<0.5	97.8	94.9	70.5
PI 2 Antibiotic prescriptions against urinary tract infections in women	>1	95.9	96.1	82.0
PI 3 Repeated prescription of quinolones	<10%	76.0	53.5	19.5
PI 4 Seasonal variation of total antibiotic prescriptions	<20%	43.2	18.3	6.0
PI 5 Seasonal variation of quinolone prescriptions	<10%	64.2	51.7	23.4
PI 6 Amoxicillin/second-line antibiotics prescriptions	>1	75.2	58.3	18.8
PI 7 Prescriptions of not indicated antibiotics	<0.5%	76.9	39.6	10.3
PI 8 Estimated duration of antibiotic prescriptions >8 days	<10%	91.3	91.4	82.2
PI 9 Co-prescription of antibiotic and systemic non-steroidal anti-inflammatory drugs	<5%	69.1	28.6	6.9
PI 10 Co-prescription of antibiotic and systemic corticosteroids	<5%	44.6	18.3	6.3

Abbreviations: GP, general practitioner; IQR, interquartile range; PI, proxy indicator.
[a] The appropriateness score is expressed as a percentage, displayed using medians (IQR) and calculated as [(number of PIs applicable for each GP and for whom the acceptable target is reached)/(number of PIs applicable for each GP)] × 100.

The percentage of patients under 16 years old and the percentage of patients older than 65 years were highly collinear ($r = -0.64$): the more patients under 16 years old GPs had, the fewer patients over 65 years old they had and vice versa. Both variables were significantly associated with the appropriateness of prescriptions when they were selected individually in the multivariable model. Results show a global effect of patients' age with a gradient: practices are more inappropriate for older patients.

The percentage of patients with chronic diseases and the percentage of patients older than 65 years were also highly collinear ($r = 0.79$): patients aged 65 and more are indeed more likely to have chronic diseases. When we removed the percentage of patients younger than 16 years and the percentage of patients older than 65 years variables from the multivariable model, the percentage of patients with chronic diseases was significantly associated with the appropriateness of prescriptions.

Older patients are more likely to have chronic diseases. Among other potential contributing factors, GPs might be more likely to prescribe antibiotics to prevent potential bacterial superinfections [19].

We also looked at the association between the appropriateness of antibiotic prescribing and quantity metrics commonly used in

Table 3
Description of GP and patient characteristics for the three identified clusters; bivariate analyses ($n = 4819$ GPs)

Characteristics		Cluster 1 'Better than average practices' n = 709 GPs (14.7%)	Cluster 2 'Average practices' n = 1574 GPs (32.7%)	Cluster 3 'Worse than average practices' n = 2536 GPs (52.6%)	p value
GPs' characteristics					
Geographic area (%)	08 Ardennes	13.3	37.8	48.9	<0.0001
	10 Aube	9.6	36.8	53.6	
	51 Marne	25.1	39.0	35.9	
	52 Haute-Marne	8.3	22.6	69.2	
	54 Meurthe-et-Moselle	20.3	35.5	44.2	
	55 Meuse	13.8	34.8	51.5	
	57 Moselle	12.6	28.7	58.7	
	67 Bas-Rhin	11.3	29.8	59.0	
	68 Haut-Rhin	13.3	32.2	54.5	
	88 Vosges	15.1	35.6	49.4	
GP's gender (%)	Male	11.7	28.6	59.7	<0.0001
	Female	19.9	39.3	40.9	
Particular medical practice (%)	Yes	32.2	32.6	35.3	<0.0001
	No	13.7	32.7	53.6	
Practice setting (%)	Rural (<5000 inhabitants)	14.5	32.3	53.3	0.108
	Suburban (5000–20 000 inhabitants)	14.0	31.2	54.8	
	Urban (>20 000 inhabitants)	15.8	34.5	49.8	
Number of years of practice (2019 − installation date), median (IQR)		8 (2–25)	15 (5–28)	24.5 (13–32)	<0.0001
Number of patients (in 2019), median (IQR)		1257 (871–1709)	1397 (1029–1815)	1399 (1039.5–1847.5)	<0.0001
Number of consultations per month, median (IQR)		310.3 (219.8–420.0)	376.2 (282.1–497.4)	427.6 (315.4–565.4)	<0.0001
Patients' characteristics					
% of patients with chronic diseases, median (IQR)		13.2 (10.6–16.0)	13.1 (10.9–15.8)	13.8 (11.5–16.8)	<0.0001
% of patients with low income, median (IQR)		6.5 (3.3–13.1)	6.5 (3.5–12.6)	6.6 (3.3–12.5)	0.815
% of patients <16 years old, median (IQR)		21.0 (16.1–25.4)	19.8 (15.4–23.9)	17.8 (13.8–21.6)	<0.0001
% of patients >65 years old, median (IQR)		18.5 (13.1–24.7)	18.7 (13.7–24.5)	19.8 (14.9–25.5)	<0.0001

Abbreviations: GP, general practitioner; IQR, interquartile range.

Table 4
Association between the GPs' and patients' characteristics and the identified clusters—multivariable polytomous logistic analysis ($n = 4819$ GPs)

Characteristics		Multivariable analysis			
		Cluster 2 'average practices' versus Cluster 1 'better than average practices'		Cluster 3 'worse than average practices' versus Cluster 1 'better than average practices'	
		Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Geographic area	08 Ardennes	1.58 (0.98–2.55)	0.063	1.92 (1.17–3.15)	0.010
	10 Aube	2.52 (1.45–4.38)	0.001	3.80 (2.17–6.66)	<0.0001
	51 Marne	1 (reference)	—	1 (reference)	—
	52 Haute-Marne	1.60 (0.76–3.35)	0.216	5.18 (2.58–10.40)	<0.0001
	54 Meurthe-et-Moselle	1.19 (0.87–1.64)	0.280	1.35 (0.97–1.89)	0.075
	55 Meuse	1.43 (0.79–2.57)	0.238	1.91 (1.05–3.45)	0.033
	57 Moselle	1.24 (0.89–1.73)	0.213	2.17 (1.55–3.05)	<0.0001
	67 Bas-Rhin	1.75 (1.28–2.38)	0.0004	3.45 (2.51–4.73)	<0.0001
	68 Haut-Rhin	1.74 (1.22–2.48)	0.002	2.99 (2.08–4.30)	<0.0001
	88 Vosges	1.54 (1.01–2.35)	0.043	2.02 (1.32–3.11)	0.001
GP's gender	Male	0.92 (0.76–1.12)	0.411	1.23 (1.01–1.49)	0.040
	Female	1 (reference)	—	1 (reference)	—
Particular medical practice	Yes	1 (reference)	—	1 (reference)	—
	No	2.20 (1.57–3.08)	<0.0001	4.30 (3.00–6.18)	<0.0001
Number of years of practice (2019 − installation date) [a]		1.03 (1.02–1.03)	<0.0001	1.05 (1.04–1.06)	<0.0001
Number of consultations per month [b]		1.003 (1.002–1.003)	<0.0001	1.004 (1.003–1.005)	<0.0001
% of patients <16 years old [c]		0.99 (0.98–1.00)	0.126	0.95 (0.94–0.97)	<0.0001

The following variables were not included because they were highly collinear with included variables: number of patients (collinear with the number of consultations per month, $r = 0.71$); and percentage of patients 65 years old (collinear with the percentage of patients with chronic diseases, $r = 0.79$). The variable percentage of patients with chronic diseases was removed from the model because of its non-significance (p 0.131). The reference class is Cluster 1 'better than average practices'. For example, cluster 3 ('worse than average practices') included 23% more men than cluster 1 ('better than average practices'). The variables percentage of patients <16 years old, percentage of patients >65 years old and percentage of patients with chronic disease were moderately to highly collinear (percentage of patients <16 years old and percentage of patients with chronic disease ($r = -0.53$); percentage of patients <16 years old and percentage of patients >65 years old ($r = -0.64$); and percentage of patients >65 years old and percentage of patients with chronic disease ($r = 0.79$)). However, when we selected only one of these three variables in the model at a time, they were all significantly associated with inappropriate practices.

[a] Increased risk of being in cluster 2 or 3 (compared with cluster 1) per additional year of practice.
[b] Increased risk of being in cluster 2 or 3 (compared with cluster 1) per additional consultation per month.
[c] Increased risk of being in cluster 2 or 3 (compared with cluster 1) per 1% more patients.

Table 5
Description of GPs' practices according to the identified clusters—bivariate analyses ($n = 4819$ GPs)

Variables		Cluster 1 'Better than average practices' $n = 709$ GPs (14.7%)	Cluster 2 'Average practices' $n = 1574$ GPs (32.7%)	Cluster 3 'Worse than average practices' $n = 2536$ GPs (52.6%)	p value
Number of units of all drugs per patient per month, median (IQR)		4.5 (3.9–5.3)	4.8 (4.2–5.6)	5.3 (4.6–6.1)	<0.0001
Number of antibiotic prescriptions per 1000 patients per year, median (IQR)		236.1 (156.7–334.7)	335.9 (242.7–447.6)	455.1 (322.8–618.2)	<0.0001
Number of antibiotic prescriptions per 100 patients aged 16–65 years without a chronic disease per year, median (IQR)		20.7 (14.3–31.9)	28.6 (19.5–39.2)	36.5 (25.5–52.6)	<0.0001
% of patients treated by broad-spectrum antibiotics (amoxicillin-clavulanate, third- and fourth-generation cephalosporins and fluoroquinolones) per year, median (IQR)		25.3 (19.0–31.5)	27.4 (21.5–34.4)	34.2 (26.2–44.8)	<0.0001
Target reached (≤20%) for the P4P indicator 'number of antibiotic prescriptions per 100 patients from 16 to 65 years old without a chronic disease', %	Yes	25.7	38.7	35.6	<0.0001
	No	8.4	30.5	61.1	
Target reached (≤32%) for the P4P indicator 'percentage of patients treated by broad-spectrum antibiotics (amoxicillin-clavulanate, third- and fourth-generation cephalosporins and fluoroquinolones)', %	Yes	16.4	40.1	43.5	<0.0001
	No	6.3	22.8	70.9	

Abbreviations: GP, general practitioner; IQR, interquartile range; P4P: pay-for-performance.

France to describe the volume of drugs and antibiotics prescribed by GPs. GPs were more likely to belong to the clusters with average or worse than average practices when they prescribed more drugs, more antibiotics and a higher proportion of broad-spectrum antibiotics. More appropriate antibiotic prescribing practices seem therefore associated with more prudent use of drugs in general. Our results also suggest that targeting GPs with high total antibiotic use, when other more refined screening methods are not available, seems acceptable. These results are in line with the literature [20].

Comparison with existing literature

The few published studies aiming at identifying factors associated with the appropriateness of antibiotic prescriptions in general practice are summarized in the Supplementary material (Table S1) [7–10]. In three of the four studies, clinical indications were needed to define the appropriateness of antibiotic prescriptions. Some of the characteristics we identified as associated with the appropriateness of antibiotic prescriptions were also identified in at least one of these studies: number of years of practice, number of patients, patients' age.

Strengths and limitations

This work brings innovative findings. We believe that the method we used to identify clusters and explore characteristics associated with the estimated appropriateness of antibiotic prescriptions might be replicated in other countries by adapting the PIs and their targets to the national prescribing guidelines. However, we acknowledge that our study has several limitations. First, the PIs cannot directly assess the appropriateness of each antibiotic prescription, i.e. the adherence to antibiotic prescribing guidelines per indication, as they are calculated without data on indications/diagnoses. Second, while content and clinimetric validities have been assessed [6], a structured consensus procedure is currently ongoing in France, piloted by health authorities, to confirm the face validity of our ten PIs by a large group of stakeholders. So, the relevance and the understanding of each PI (definition and target) are not yet definitively validated. Third, the present investigation allowed us to identify associations between GPs', patients' and practices' characteristics and the appropriateness of antibiotic prescriptions but we cannot exclude that the associations we found might be due to other unexplored factors. For example, the association between gender and appropriateness might be the consequence of a higher participation in postgraduate training among female GPs in France.

Implications

Such a cluster analysis may be used to guide AMS interventions. For example, the 'worse than average' cluster might benefit from high-intensity AMS interventions and the situations covered by the different proxy indicators might help design tailored messages as already suggested previously (e.g. reducing durations of antibiotic prescriptions according to national guidelines for PI 8) [6]. In addition, identifying the GPs' and practices' characteristics associated with the appropriateness of antibiotic prescriptions can help to select those GPs to target in priority for AMS interventions. For example, in our sample of GPs from the Grand Est region of France, GPs who need to improve their antibiotic prescriptions the most are male who have been in practice longer, in certain geographical areas, who do not have a particular medical practice and who had a higher number of consultations per month.

In conclusion, several characteristics related to GPs, their patients, and their practices were associated with the estimated appropriateness of their antibiotic prescriptions. Identifying such characteristics as well as clusters of GPs was easily done based on routine reimbursement data and might help to guide antibiotic stewardship interventions, with the overall objectives of improving the quality of care and reducing antibiotic resistance.

Transparency declaration

All authors have stated that they have no conflicts of interest to declare.

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Author contributions

CP conceptualized the study; CP, NT, OP and MS contributed to the methodology; OP performed the software and formal analysis; MS wrote the original draft; and CP, NT and OP reviewed and edited the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.08.026.

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Supplementary Table S1. Published studies describing the factors associated with the appropriateness of antibiotic prescriptions in general practice.

Author	Study period	Country	Design	Databases	Availability of clinical indications/diagnoses in the databases	Measure of the appropriateness of antibiotic prescriptions	Analyses	Factors associated with the inappropriateness of antibiotic prescriptions
Cadieux *et al*. Can Med Assoc J 2007 [1]	1990 - 1998	Canada	Historical cohort	Registrant database, physician billing claims database, prescriptions claims database and hospitalization database	Yes	Two measures: Prescription of an antibiotic for a likely viral infection Prescription of a second- or third-line antibiotic for a likely bacterial infection	Multivariable analyses	Longer time in practice Higher practice volumes (mean number of patients seen per physician workday)
Pulcini *et al*. Eur J Clin Microbiol Infect Dis 2013 [2]	2009	France	Cross-sectional study	Health Insurance reimbursement databases	No	Six indicators indirectly reflecting appropriateness: % moxifloxacin % repeated fluoroquinolones % 1st quinolones % fluoroquinolones combinations % antibiotic combinations	Bivariate and multivariable analyses	Older GPs Higher total pharmaceutical expenses per patient Lower total antibiotic use Higher co-amoxiclav use Higher quinolones use Higher seasonal variation of quinolone use

						% urinary antibiotics in men		
Nowakowska *et al*. J Antimicrob Chemother 2019 [3]	2010 - 2015	UK	Observational study	Clinical Practice Research Datalink (electronic health records)	Yes	Adherence to guidelines: defined by indication by three clinical experts for common infections in general practice	Multivariable analyses	Higher proportion of comorbidities Gender of the patient (depending on the indication) Age of the patient (depending on the indication) Prescription of an antibiotic in the 12 previous months
Degnan et al. Infect Control Hosp Epidemiol 2021 [4]	Data not available	USA	Retrospective cohort study	Medical records	Yes	Proportion prescribing for respiratory tract diagnoses (RTD) for which antibiotics are almost never required Proportion prescribing for any RTD	Data not available	Advanced practice provider Family medicine training Board certification 1997 or later Nonteaching practice Nonurban practice

Supplementary Table S2. Description of the 10 proxy indicators developed by Thilly *et al.*[5]

Proxy indicator (PI)	Definition	Target
PI 1 Antibiotic prescriptions against urinary tract infections in men (ratio)	Number of prescriptions of nitrofurantoin (J01XE01) + certain (fluoro)quinolones[a] (J01MB + J01MA06 + J01MA04 + J01MA07) + fosfomycin-trometamol (J01XX01) / 100 active[b] male patients ≥ 16 years old	Optimal: 0 Acceptable: < 0.5
PI 2 Antibiotic prescriptions against urinary tract infections in women (ratio)	Number of prescriptions of nitrofurantoin (J01XE01) + pivmecillinam (J01CA08) + fosfomycin-trometamol (J01XX01) / Number of prescriptions of quinolones (J01M)	> 1
PI 3 Repeated prescription of quinolones (%)	Number of prescriptions of quinolones (J01M) among patients having been prescribed a quinolone (J01M) in the preceding 6 months / Total number of prescriptions of quinolones (J01M)	Optimal: 0 Acceptable: < 10%
PI 4 Seasonal variation of total antibiotic prescriptions (%)	(Number of prescriptions of antibiotics (J01) during the cold-weather season (January–March and October–December) / Number of prescriptions of antibiotics (J01) during the hot-weather season (April–September) – 1) x 100	< 20%
PI 5 Seasonal variation of quinolone prescriptions (%)	(Number of prescriptions of quinolones (J01M) during the cold-weather season (January–March and October–December) / Number of prescriptions of quinolones (J01M) during the hot-weather season (April–September) – 1) x 100	Optimal: < 5% Acceptable: < 10%
PI 6 Amoxicillin / second-line antibiotics prescriptions (ratio)	Number of prescriptions of amoxicillin (J01CA04) / Number of prescriptions of: amoxicillin-clavulanic acid (J01CR02) + quinolones (J01M) + cephalosporins (J01D) + MLSK[c] (J01F)	> 1
PI 7 Prescriptions of not indicated antibiotics (%)	Number of prescriptions of: lomefloxacin (J01MA07), moxifloxacin (J01MA14), certain (fluoro)quinolones[a] (J01MB + J01MA06 + J01MA04 + J01MA07), telithromycin (J01FA15), spiramycin-metronidazole (J01RA04) and cefaclor (J01DC04) / Total number of antibiotic prescriptions	Optimal: 0 Acceptable: < 0.5%
PI 8 Estimated duration of antibiotic prescriptions > 8 days (%)	Number of prescriptions > 8 days for the following antibiotics: amoxicillin (J01CA04), co-amoxiclav (J01CR02), cefuroxime (J01DC02), cefpodoxime (J01DD13), roxithromycin (J01FA06), clarithromycin (J01FA09), pristinamycin (J01FG01) and nitrofurantoin (J01XE01)	Optimal: < 5% Acceptable: < 10%

	/ Total number of antibiotic prescriptions for these eight antibiotics	
PI 9 Co-prescription of antibiotic and systemic non-steroidal anti-inflammatory drugs (%)	Number of antibiotic(s) (J01) + systemic NSAID(s) (M01A) co-prescribed on the same day / Total number of antibiotic prescriptions	Optimal: 0 Acceptable: < 5%
PI 10 Co-prescription of antibiotic and systemic corticosteroids (%)	Number of antibiotic(s) (J01) + systemic corticosteroid(s) (H02AB) co-prescribed on the same day / Total number of antibiotic prescriptions	Optimal: 0 Acceptable: < 5%

[a] J01MB (rosoxacin, nalidixic acid, piromidic acid, pipemidic acid, oxolinic acid, cinoxacin, flumequine, nemonoxacin), J01MA06 (norfloxacin) + J01MA04 (enoxacin) + J01MA07 (lomefloxacin).
[b] An active patient is a patient seen at least once by the general practitioner during the year 2019.
[c] MLSK: macrolides, lincosamides, streptogramins and ketolides.

Supplementary File S3. GPs', patients' and practices' characteristics tested for their association with inappropriate practices.

GP's and patients' characteristics

The association between inappropriate practices and the following GPs' and patients' characteristics was explored:

- Geographic area (the Grand Est region is divided into 10 subregions);
- GP's gender;
- (Non-exclusive) particular medical practice;
- Practice setting: rural (< 5,000 inhabitants), suburban (5,000 – 20,000 inhabitants) or urban (> 20,000 inhabitants);
- Number of years of practice (calculated as 2019 minus the installation date);
- Number of different patients seen by the GP in 2019;
- Number of consultations per month;
- Percentage of patients with chronic diseases [6];
- Percentage of patients with low income [7];
- Percentage of patients aged less than 16 years old;
- Percentage of patients aged more than 65 years old.

GPs' practices

The association between inappropriate practices and the following GPs' practices characteristics was investigated:

- Number of units (e.g. packages) of all (prescribed and dispensed) drugs per patient per month;
- Number of antibiotic prescriptions per 1000 patients per year;
- Indicators used in the national pay-for-performance (P4P) system [8]:
    - (i) the number of antibiotic prescriptions per 100 patients aged 16 to 65 years old without a chronic disease;
    - (ii) the percentage of patients treated by broad-spectrum antibiotics (amoxicillin-clavulanate, 3rd and 4th generation cephalosporins and fluoroquinolones) per year;
- Attainment of the national target for these P4P indicators:
    - (i) ≤ 20%;
    - (ii) ≤ 32%.

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IV – Article indicateurs proxy des prescriptions par les chirurgiens-dentistes

1. Contexte et objectifs

Les chirurgiens-dentistes sont responsables de plus de 10% des prescriptions antibiotiques en France.(11) L'usage des antibiotiques est souvent inutile ou inapproprié en odontologie (95,96), il est donc nécessaire de mettre en œuvre des programmes de bon usage des antibiotiques. Des indicateurs estimant la pertinence des prescriptions antibiotiques en odontologie, accompagnés de leur cible reflétant la qualité des soins, peuvent aider à la conception, à la définition d'objectifs adaptés et à l'évaluation d'interventions de bon usage. Les objectifs de cette étude étaient (i) de développer des indicateurs proxy estimant la pertinence des antibiotiques prescrits par les chirurgiens-dentistes, (ii) d'évaluer les propriétés clinimétriques de ces indicateurs proxy et (iii) d'évaluer les résultats des chirurgiens-dentistes de la région Grand Est pour ces indicateurs en 2019.

2. Méthodes

Les indicateurs proxy ont été sélectionnés à partir de la littérature (projet DRIVE-AB)(87) et adaptés à l'odontologie par un groupe d'experts (chirurgiens-dentistes, pharmaciens, spécialistes de santé publique et spécialistes de maladies infectieuses). Des valeurs cibles ont été définies pour chaque indicateur, reflétant une bonne qualité des prescriptions. Les propriétés clinimétriques (mesurabilité, applicabilité et marge d'amélioration) et les résultats de ces indicateurs proxy ont été évalués pour les chirurgiens-dentistes de la région Grand Est en 2019, en utilisant les bases de données du SNDS.

3. Principaux résultats et conclusions

Au total, 3 014 chirurgiens-dentistes pratiquant en région Grand Est ont été inclus dans cette étude et ont prescrit un total de 373 975 antibiotiques dispensés en 2019. Quatre indicateurs proxy ont été développés, couvrant les principales situations de prescriptions inappropriées des antibiotiques en odontologie : la sur-prescription d'amoxicilline-acide clavulanique (alors que l'amoxicilline est recommandée en première intention dans la majorité des situations d'infection en odontologie), les durées de traitement excessives et la sur-prescription d'antibiotiques rarement ou non recommandés en odontologie. Les quatre indicateurs présentaient de bonnes propriétés clinimétriques. Les résultats des chirurgiens-dentistes de la région Grand Est n'étaient pas optimaux et présentaient des variations

importantes de performances, selon les chirurgiens-dentistes, selon le type de patients et selon les indicateurs. Nous avons développé un ensemble innovant d'indicateurs proxy, facilement calculables, permettant d'estimer la pertinence des prescriptions antibiotiques à l'échelle du chirurgien-dentiste. Ces indicateurs proxy peuvent être utilisés pour améliorer les pratiques de prescription des antibiotiques des chirurgiens-dentistes, par les autorités de santé, les organisations de professionnels, les équipes multidisciplinaires en antibiothérapie ou encore les centres régionaux en antibiothérapie. Ils sont utiles pour identifier les priorités d'amélioration et ainsi adapter les interventions de bon usage des antibiotiques. Ils peuvent également permettre de transmettre des profils individuels de prescription aux chirurgiens-dentistes. Enfin, ils peuvent être utilisés dans l'évaluation de l'efficacité d'interventions de bon usage des antibiotiques.

4. Mon implication

Pour cet article, j'ai contribué à la conception méthodologique, à l'interprétation des résultats, à la rédaction et à la valorisation. Les analyses statistiques ont été réalisées par Ouarda Pereira, responsable de missions statistiques à la Direction Régionale du Service Médical (DRSM) du Grand Est.

5. Valorisation

Cet article a été publié le 8 mars 2021 dans la revue *Antimicrobial Agents and Chemotherapy* (rang B, *impact factor* 2021 : 5,938).

Simon M, Pereira O, Guillet-Thibault J, Hulscher MEJL, Pulcini C, Thilly N. Design of proxy indicators estimating the appropriateness of antibiotics prescribed by French dentists: a cross-sectional study based on reimbursement data. Antimicrob Agents Chemother. 2021;8;65(5):e02630-20.

J'ai présenté cette étude par une communication orale (pré-enregistrée) à la Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI) qui a eu lieu en ligne en décembre 2020.

J'ai également présenté cette étude sous forme de poster commenté lors des rencontres scientifiques organisées par le Réseau doctoral en Santé publique animé par l'Ecole des Hautes Etudes en Santé Publique (EHESP) en juin 2021.

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EPIDEMIOLOGY AND SURVEILLANCE

Design of Proxy Indicators Estimating the Appropriateness of Antibiotics Prescribed by French Dentists: a Cross-Sectional Study Based on Reimbursement Data

Maïa Simon,[a] Ouarda Pereira,[b] Julie Guillet-Thibault,[c,d] Marlies E. J. L. Hulscher,[e] Céline Pulcini,[a,f] Nathalie Thilly[a,g]

[a]Université de Lorraine, APEMAC, Nancy, France
[b]Direction Régionale du Service Médical (DRSM) Grand Est, Strasbourg, France
[c]Faculté d'Odontologie de Lorraine, Université de Lorraine, Nancy, France
[d]CHRU-Nancy, Service d'Odontologie, Nancy, France
[e]Radboud University Medical Center, Radboud Institute for Health Sciences, Scientific Center for Quality of Healthcare (IQ Healthcare), Nijmegen, The Netherlands
[f]Université de Lorraine, CHRU-Nancy, Département de Maladies Infectieuses, Nancy, France
[g]Université de Lorraine, CHRU-Nancy, Département Méthodologie, Promotion, Investigation, Nancy, France

ABSTRACT The literature shows that the prescription of antibiotics in dental care is often unnecessary or inappropriate. Indicators estimating the appropriateness of antibiotics prescribed by dentists based on routine databases are, however, not available in the literature. Our objectives were to (i) design proxy indicators estimating the appropriateness of antibiotics prescribed by dentists, (ii) evaluate their clinimetric properties, and (iii) provide results for these proxy indicators for dentists located in a northeastern French region. We selected and adapted proxy indicators from the literature. Using 2019 Regional Health Insurance data, we evaluated the proxy indicators' clinimetric properties (measurability, applicability, and potential room for improvement), their results with performance scores (percentage of dentists who reached the target value), and the case-mix stability. We included 3,014 general dental practitioners, who prescribed a total of 373,975 antibiotics to 308,123 patients in 2019. We identified four proxy indicators estimating antibiotic prescribing appropriateness in dental care. All proxy indicators had good clinimetric properties. Performance scores were generally low (10.5 to 73.0%, depending on the indicator), suggesting important room for improvement. These results showed large variations between dentists (large interquartile ranges) and according to the patients' characteristics (case-mix stability). These four proxy indicators might be used to guide antibiotic stewardship interventions in dental care.

KEYWORDS antimicrobial stewardship, appropriateness, dentists, proxy indicators, quality of care

Antimicrobial resistance is considered one of the 10 threats to global public health (https://www.who.int/vietnam/news/feature-stories/detail/ten-threats-to-global-health-in-2019), and the misuse and overuse of antimicrobials is accelerating this process (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance). In France, around 125,000 persons were infected by multidrug-resistant bacteria in 2015, and more than 5,500 of them died because of it (https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-associees-aux-soins-et-resistance-aux-antibiotiques/resistance-aux-antibiotiques). Overall, 78% of antibiotics are prescribed in primary care in France (https://www.santepubliquefrance.fr/les-actualites/2019/consommation-d-antibiotiques-et-antibioresistance-en-france-en-2018), of which 10% are prescribed by dentists. In dental care, antibiotics are recommended in a few indications, either as a curative treatment,

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Address correspondence to Nathalie Thilly, n.thilly@chru-nancy.fr.

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ideally in association with a source control procedure, or as a prophylactic treatment for very specific situations (1–3). The literature shows that the use of antibiotics in dental care is often unnecessary or inappropriate (1, 4–7), highlighting the urgent need for antibiotic stewardship programs in dentistry (3, 5, 6). The FDI World Dental Federation recently published a White Paper advocating for this (https://www.fdiworlddental.org/resource/fdi-white-paper-essential-role-dental-team-reducing-antibiotic-resistance).

Antimicrobial stewardship (AMS) has been defined by Dyar et al. as a "coherent set of actions which promote a responsible use of antimicrobials" (8). A systematic review published in 2017 assessed the effectiveness of interventions aiming at optimizing the prescription of antibiotics in dental care (9). The most frequent interventions were audit and feedback, education, and guidelines. All interventions led to a decrease in antibiotic prescribing. Few studies, however, looked at the appropriateness of antibiotic prescriptions.

Evaluating the quality or appropriateness of antibiotic prescriptions is essential to guide AMS interventions. Calculating quality indicators requires information on the clinical indication/diagnosis, but computerized national systems linking drug prescriptions to clinical diagnosis are not available in most European countries (10). The evaluation of the appropriateness of antibiotic prescriptions can be done at the prescriber or facility level, but manual data collection is time-consuming. Therefore, it is usually not possible to monitor quality indicators on a large scale (regional or national) and for prolonged periods of time. To overcome this issue, Thilly et al. used routine databases from the National Health Insurance to design proxy indicators (PIs) estimating the appropriateness of antibiotic prescriptions by general practitioners (GPs) (11). PIs share characteristics of both quantity metrics and quality indicators. They are derived from quantity metrics and have the advantage of not requiring clinical data to be calculated. PIs are associated with a quantitative target that reflects the appropriateness of prescription practices: depending on whether the defined target is reached or not, the antibiotic use at the prescriber level is appropriate or not. To the best of our knowledge, indicators estimating the appropriateness of antibiotics prescribed by dentists based on routine databases are not available in the literature.

In the present study, we used a large regional routine reimbursement database to (i) design PIs estimating the appropriateness of antibiotics prescribed by dentists, (ii) evaluate PIs' clinimetric properties, and (iii) provide performance results of these PIs for dentists located in a northeastern French region to illustrate the potential practical use of these indicators.

RESULTS

Dentist and patient characteristics. Out of the 3,372 general dental practitioners practicing in the Grand Est region, we included 3,014 (89.4%) who met the inclusion criteria. Their mean age was 47.5 $\pm$ 12.6 years, 56.9% were men, and, on average, they were practicing for 17.7 $\pm$ 12.6 years. On average, they took care of 804 $\pm$ 391 different patients in 2019, with a mean number of 1,678 $\pm$ 802 consultations. The 3,014 included dentists prescribed a total of 373,975 antibiotics in 2019, dispensed to 308,123 patients. Regarding their patients' characteristics, 16.7% were aged $<$16 years, 17.3% were aged $>$65 years, 0.3% lived in a nursing home, 11.8% had a chronic disease, and 7% had a low income.

Selection and operationalization of proxy indicators. Four PIs were selected from the literature and adapted to the dental care context (11, 12). Table 1 presents the four PIs, with their numerator, denominator, and targets. PI 1 focuses on preferred prescribing of amoxicillin rather than amoxicillin-clavulanate, amoxicillin being the first-line antibiotic in most indications in dental care (2, 3). PI 2 refers to the antibiotic treatment duration, which should rarely exceed 1 week (3 days for azithromycin) (https://www.ansm.sante.fr/Dossiers/Antibiotiques/Odonto-Stomatologie/(offset)/5). PI 3 and 4 focus on antibiotics that should not be used in routine dental practice (PI 3) or should be reserved for very specific cases (PI 4), according to national guidelines (https://www.ansm.sante.fr/Dossiers/Antibiotiques/Odonto-Stomatologie/(offset)/5).

TABLE 1 Description of the four proxy indicators estimating the appropriateness of antibiotics prescribed by dentists[a]

PI	Numerator description	Denominator description	Target value
1, amoxicillin/amoxicillin-clavulanate (ratio)	No. of prescriptions of amoxicillin (J01CA04)	No. of prescriptions of amoxicillin-clavulanate (J01CR02)	>10
2, estimated duration of antibiotic prescriptions (%)	No. of prescriptions of >8 days for amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), clindamycin (J01FF01), and pristinamycin (J01FG01) and >4 days for azithromycin (J01FA10)	Total no. of prescriptions for these five antibiotics	Optimal, <5%; acceptable, <10%
3, prescriptions of not indicated antibiotics (%)	No. of prescriptions of lymecycline (J01AA04), minocycline (J01AA08), pivmecillinam (J01CA08), phenoxymethylpenicillin (J01CE02), cloxacillin (J01CF02), cefadroxil (J01DB05), cefuroxime (J01DC02), cefaclor (J01DC04), cefotiam (J01DC07), ceftriaxone (J01DD04), cefixime (J01DD08), cefpodoxime (J01DD13), trimethoprim-sulfamethoxazole (J01EE01), erythromycin (J01FA01), midecamycin (J01FA03), roxithromycin (J01FA06), josamycin (J01FA07), telithromycin (J01FA15), tobramycin (J01GB01), gentamicin (J01GB03), ofloxacin (J01MA01), ciprofloxacin (J01MA02), norfloxacin (J01MA06), lomefloxacin (J01MA07), levofloxacin (J01MA12), moxifloxacin (J01MA14), flumequine (J01MB07), fusidic acid (J01XC01), nitrofurantoin (J01XE01), and fosfomycin (J01XX01)	Total no. of antibiotic prescriptions	<1%
4, prescriptions of rarely indicated antibiotics (%)	No. of prescriptions of pristinamycin (J01FG01), spiramycin-metronidazole (J01RA04), and doxycycline (J01AA02)	Total no. of antibiotic prescriptions	<5%

[a]The ATC (anatomical, therapeutic, chemical) denomination of the drugs mentioned here is presented in parentheses (https://www.whocc.no/).

For PI 1, a high fraction indicates high quality of care, while for the other PIs, a low fraction indicates high quality of care.

The scientific evidence base for the four PIs is presented in Tables S1 and S2 in the supplemental material.

Clinimetric properties of the proxy indicators. The clinimetric properties are presented in Table 2.

(i) Measurability. As data required to calculate the PIs were collected from the outpatient reimbursement database of the Regional Health Insurance Fund and all antibiotics are reimbursed, we had no missing data and all the PIs were 100% measurable.

(ii) Applicability. All PIs were applicable, i.e., scores could be calculated from at least ten clinical situations for more than 75% of dentists.

(iii) Potential room for improvement. Improvement potential was greater than 15% for all PIs and varied between 27.0% (for PI 3) and 89.5% (for PI 4).

Overall, all four PIs had good clinimetric properties.

Appropriateness of dentists' antibiotic prescriptions and variability. Table 3 presents results for the four PIs. Antibiotic prescription practices were not optimal, and wide variations between dentists were observed. Performances ranged between 10.5% for antibiotics rarely indicated (PI 4) and 73.0% for antibiotics not indicated (PI 3).

TABLE 2 Clinimetric properties of the four proxy indicators and case-mix stability ($n = 3,014$)

PI	Measurability of missing data (%)	Applicability, *n* (%)	Improvement potential[a] (%)	Case-mix stability of improvement potential for specific populations (%)
1, amoxicillin/amoxicillin-clavulanate (ratio)	0	2,822 (93.6)	60.4	Chronic disease, 80.2; low income, 89.4; nursing home, 100.0; age >65 yr, 71.8
2, estimated duration of antibiotic prescriptions (%)	0	3,007 (99.8)	37.2	Chronic disease, 36.4; low income, 29.9; nursing home, 14.8; age >65 yr, 35.8
3, prescriptions of not indicated antibiotics (%)	0	3,014 (100.0)	27.0	Chronic disease, 7.4; low income, 5.3; nursing home, 0.8; age >65 yr, 8.4
4, prescriptions of rarely indicated antibiotics (%)	0	3,014 (100.0)	89.5	Chronic disease, 65.3; low income, 48.7; nursing home, 18.3; age >65 yr, 69.5

[a]Improvement potential is determined as 100 – acceptable performance.

TABLE 3 Results for the four proxy indicators, calculated at the dentist level ($n = 3,014$)

PI	Median	IQR (lower quartile; upper quartile)	Range (minimum; maximum)	Performance (% of dentists who reached the target)
1, amoxicillin/amoxicillin-clavulanate (ratio)	7.0	2.5; 17.6	0.0; 444.0	39.6
2, estimated duration of antibiotic prescriptions (%)	5.1	1.1; 19.5	0.0; 96.9	Optimal, 48.7; acceptable, 62.8
3, prescriptions of not indicated antibiotics (%)	0.0	0.0; 1.1	0.0; 88.2	73.0
4, prescriptions of rarely indicated antibiotics (%)	14.2	5.3; 37.3	0.0; 100.0	10.5

The results for the case-mix stability are presented in Table 2. The performance scores were influenced by the patient populations for all PIs. For PIs 2, 3, and 4, improvement potentials were lower in the specific populations (i.e., the elderly, patients with chronic diseases, patients with low income, and residents of nursing homes) compared to the general population, highlighting better prescription practices for these specific populations. In contrast, the improvement potential for PI 1 (amoxicillin/amoxicillin-clavulanate ratio) was higher for these specific populations, especially for nursing home residents.

DISCUSSION

Four proxy indicators were defined from the literature, estimating the appropriateness of antibiotics prescribed by dentists, using routine reimbursement databases, and based on national guidelines. These PIs encompass the most common clinical situations encountered in dental care and address the most frequent causes of inappropriate prescribing (6), i.e., the overuse of second-line antibiotics when guidelines recommend amoxicillin as the first-line treatment for most indications, the excessive durations of treatment, and the overuse of nonindicated or rarely indicated antibiotics, such as the spiramycin-metronidazole fixed-dose combination that is frequently prescribed in France but is not recommended in national or international guidelines (https://www.ansm.sante.fr/Dossiers/Antibiotiques/Odonto-Stomatologie/(offset)/5) (13). All four PIs showed good clinimetric properties.

We decided to focus on prescriptions by general dental practitioners. The clinical practice of oral surgeons and orthodontists and, therefore, the indications to prescribe antibiotics are very different from those of general dental practitioners. However, even when focusing on the homogeneous group of general dental practitioners, we noticed a huge variability between dentists in antibiotic prescription practices for the four PIs. The room for improvement was significant for all PIs, being particularly high for rarely indicated antibiotics (89.5%).

The evaluation of case-mix stability showed that performance scores were different depending on the characteristics of the patient population (elderly people, patients with chronic diseases, residents in nursing homes, and patients with low income), while recommendations used to define PIs and their targets are applicable for these specific populations. These results can help dentists identify, for each PI, the patient populations for whom they need most to improve their prescription practices.

To the best of our knowledge, there is only one published article dealing with quality indicators of antibiotic prescriptions in dental care. Hussein et al. designed three quality indicators of antibiotic prescriptions by German dentists in 2013, with the aim of reducing both unnecessary and inappropriate prescriptions (14). These quality indicators were developed through a literature review, an analysis of the claims data of the statutory health insurance, and a panel process with dental experts and patient representatives. The three final selected indicators were usage of systemic antibiotics in dental treatments without indication for antibiotics, the percentage of penicillin prescriptions (first-line treatment) in dental treatments, and the percentage of clindamycin prescriptions (second-line treatment) in dental treatments. The first indicator needs a specific diagnosis/clinical indication to be calculated. Moreover, a clear target is missing for all three indicators, making it difficult to truly assess the quality of care. As a

consequence, our proxy indicators are innovative, as, by providing targets, they allow for an estimation of the appropriateness of prescriptions at the prescriber level.

Our PIs may be useful tools for estimating the appropriateness of antibiotic prescriptions by dentists, as they present targets reflecting the appropriateness of prescription practices. They are easily calculable from routine databases and can be used by different stakeholders to help improve antibiotic prescribing practices of dentists (e.g., by health authorities, professional organizations, AMS teams, and regional antibiotic stewardship networks), as already described in detail previously (11). These PIs may also be used in different countries by adapting their definition and target to the national prescribing guidelines, following a validation process similar to the one we used.

Contrary to GPs, who have been the target of many government-led AMS interventions over the last 20 years in France, dentists have not been targeted by such national multifaceted AMS interventions so far. Based on our results, we suggest different priorities to guide future AMS interventions among dentists. First, the PIs are useful to prioritize improvement interventions. For example, in our sample of dentists, prescriptions of nonindicated antibiotics do not seem a priority compared to the other three PIs. Second, PIs can be included in personalized audit and feedback programs and can help monitor the impact of AMS interventions. The Grand Est region in northeastern France is currently implementing a multifaceted AMS intervention called DentibioResist. This stepwise intervention, led by the Regional Health Insurance and targeting all general dental practitioners in the region, includes an information website (http://dentibioresist.online.fr/), annual audit and feedback using personalized prescription profiles, including the PIs described in the manuscript, academic detailing targeting low-performing dentists, and an e-learning training program. The literature suggests that such multifaceted AMS interventions can have a significant impact both on unnecessary and inappropriate prescribing (9, 15).

Our study is innovative but has some limitations. First, dispensations were used as a proxy for prescriptions. This can underestimate the quantity of antibiotics really prescribed if some patients do not collect their treatment from the pharmacy. Second, while being set by a multidisciplinary group of experts, the target values we selected are debatable, and a consensus procedure with a large group of stakeholders and experts might be useful to further validate these targets before using these PIs on a large scale.

To conclude, AMS interventions should urgently be implemented in dental care. Our easily calculable four PIs, showing good clinimetric properties and estimating the appropriateness of antibiotic prescriptions by dentists, could be a useful AMS tool.

MATERIALS AND METHODS

Study setting and population. Our study focused on primary care dentists of the Grand Est region of northeastern France, with 5,550,000 inhabitants according to the 2017 census (https://www.insee.fr/fr/statistiques). In France, primary care dentists can belong to three groups: general dental practitioners (who represent 95% of dentists), oral surgeons, and orthodontists. We included in the present study the general dental practitioners who had at least 100 patients in 2019 and prescribed at least 10 antibiotics during the year.

Data source and study design. In France, all antibiotics are prescribed and reimbursed. The National and Regional Health Insurance databases identify antibiotics dispensed by community pharmacies, prescriber specialty, and patient characteristics (e.g., age, gender, certain costly chronic diseases, and place of residence) from the prescriber and the patient identification numbers. As information on the prescription is not available, dispensation was used as a proxy for prescription. Clinical indications or diagnoses related to a prescription are not available in these databases.

We conducted a cross-sectional observational study to analyze the antibiotics prescribed by eligible dentists and dispensed by a community pharmacy during the year 2019. Data were collected from the Regional Health Insurance Fund databases (DRSM Grand Est/National Health Data System), covering 95% of the population.

Selection of proxy indicators based on the literature. The European project DRIVE-AB used a systematic literature review and a structured international multidisciplinary consensus procedure to identify quality indicators and quantity metrics on antibiotic use. Based on the DRIVE-AB quality indicators in the outpatient setting (12) and the PIs developed previously by our team for GPs (11), a group of experts

(including dentists, pharmacists, and public health and infectious disease specialists) designed PIs adapted to the dental care context.

Proxy indicators estimating the appropriateness of antibiotic prescriptions by dentists and its variability. As detailed in our previous work (11), PIs calculated at the prescriber level could estimate the appropriateness of antibiotic prescriptions by French dentists and the variability (i.e., variation in PI scores between dentists). For each PI, target values were defined to indicate a high quality of care. The optimal target reflected 100% compliance with national guidelines, while the acceptable target reflected acceptable practices and was less restrictive, as it was considered that recommendations do not cover some specific cases. The unit of measurement at the patient level was the antibiotic treatment, i.e., the antibiotic prescribed by a dentist and dispensed by a community pharmacy on a given day in 2019. As exact days of therapy are not available in health insurance databases, the procedure for the calculation of an estimated treatment duration is presented in Tables S1 and S2 in the supplemental material and was detailed in our previous work (11).

The case-mix stability was assessed through a subgroup analysis to look at the PI scores across different patient populations. The following patient characteristics were studied: age of >65 years, presence of a chronic disease (https://www.ameli.fr/medecin/exercice-liberal/presciption-prise-charge/situation-patient-ald-affection-longue-duree/definition-ald), living in a nursing home, and presence of low income (https://www.ameli.fr/assure/droits-demarches/difficultes-acces-droits-soins/complementaire-sante/complementaire-sante-solidaire-qui-peut-en-beneficier-et-comment).

Clinimetric properties of the proxy indicators. Three clinimetric properties were evaluated for each PI (11): measurability, applicability, and potential room for improvement.

(i) Measurability. Measurability represents the availability of data required to calculate the PI. A PI was considered measurable if data necessary for its calculation were available for more than 75% of prescriptions.

(ii) Applicability. A PI was applicable if the score was meaningful for the dentists, i.e., calculated from at least ten clinical situations. A PI was considered applicable if this was the case for more than 75% of dentists.

(iii) Potential room for improvement. Potential room for improvement represents the sensitivity of a PI to detect variations in appropriateness of prescriptions between dentists and over time. It is calculated as 100% minus the performance score (i.e., the percentage of dentists who reached the PI target). A low room for improvement corresponds to a less sensitive indicator, which is less useful in routine practice. The improvement potential was considered low when it was less than 15%.

Overall, a PI with good clinimetric properties had to meet all three of the following criteria: measurability of >75%, applicability of >75%, and potential room for improvement of ≥15%.

Statistical analyses. PI results are presented using medians, interquartile ranges (IQRs), and performance scores, i.e., the percentage of dentists who reached the optimal or acceptable targets. Measurability, applicability, and improvement potential are presented as percentages and case-mix stability as potential room for improvement for the above-mentioned specific patient populations. All analyses were performed with SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC).

Ethics statement. The present study was observational (i.e., did not modify the medical care of patients), and complete anonymity was preserved for both patients and dentists. Therefore, an ethical committee was not required, in accordance with French law.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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Supplementary Table S1. Evidence base for the proxy indicators estimating the appropriateness of systemic antibiotic prescriptions by dentists.

Proxy indicator (PI)(1)	Based on the following outpatient quality indicators identified by the DRIVE-AB project(2)	National recommendations/guidelines used to adapt the definition of the indicators to the French context	Recommendations/guidelines used to set the targets
PI 1 – Amoxicillin / amoxicillin clavulanate (ratio)	**OQI 3 –** Outpatients should receive antibiotic therapy compliant with guidelines	2011 national recommendations for antibiotic prescribing in dental care.(3) Amoxicillin is the first-line antibiotic in most situations.	We set a target > 10 based on expert opinion.
PI 2 – Estimated duration of antibiotic prescriptions (%)	**OQI 3** – Outpatients should receive antibiotic therapy compliant with guidelines	2011 national recommendations for antibiotic prescribing in dental care.(3) The recommended duration of antibiotic treatment for almost all indications in primary care is one week or less, and three days or less for azithromycin. We selected here the five antibiotics most prescribed by the included dentists during the year 2019, i.e. amoxicillin, amoxicillin-clavulanate, clindamycin, pristinamycin and azithromycin. As detailed previously,(1) the duration of treatment was estimated based on dispensed packages and recommended daily dosing, since days-of-therapy are not available in reimbursement databases.	We set the optimal target at < 5% for durations of nine days or more (five days or more for azithromycin), and we also set an acceptable target at < 10%, based on expert opinion. In France, unit dispensing is not in place, so antibiotics are dispensed using packages.
PI 3 – Prescriptions of not indicated antibiotics (%)	**OQI 4** – Some antibiotics should be rarely prescribed	2011 national recommendations for antibiotic prescribing in dental care.(3)	We set a target < 1% based on expert opinion (since guidelines are not applicable for some complex cases and some of these antibiotics might be used as last-resort treatments).

PI 4 – Prescriptions of rarely indicated antibiotics (%)	**OQI 4** – Some antibiotics should be rarely prescribed	2011 national recommendations for antibiotic prescribing in dental care.(3)	We set a target < 5% based on expert opinion (since guidelines are not applicable for some complex cases and some of these antibiotics might be used as last-resort treatments).

Supplementary Table S2. Calculation of the estimated durations of antibiotic prescriptions (PI 2) for dentists and GPs.
The detailed procedure for the calculation of this PI is available in Thilly *et al.* paper.(1)
The quantity of dispensed antibiotics for each prescription was calculated, by multiplying the number of packages dispensed by the quantity of antibiotic (in grams) per package. Then we determined a "usually recommended total daily dose" for the most frequently prescribed antibiotics, which represented the most commonly prescribed daily dose according to national guidelines.(3)

Antibiotic	**Total cumulated "usually recommended daily dose" corresponding to a duration of treatment > 8 days (> 4 days for azithromycin)**
Amoxicillin (J01CA04)	> 16 grams
Amoxicillin-clavulanate (J01CR02)	> 24 grams
Azithromycin (J01FA10)	> 1.5 grams
Clindamycin (J01FF01)	> 9.6 grams
Pristinamycin (J01FG01)	> 8 grams

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(3) Odonto - Stomatologie - ANSM : Agence nationale de sécurité du médicament et des produits de santé. https://www.ansm.sante.fr/Dossiers/Antibiotiques/Odonto-Stomatologie/(offset)/5.

V – Article profils de prescription des chirurgiens-dentistes

1. Contexte et objectifs

La littérature a montré que l'usage des antibiotiques en odontologie est souvent inutile ou inapproprié.(95,96) Explorer des facteurs associés à la pertinence des prescriptions antibiotiques peut aider à identifier les chirurgiens-dentistes à cibler prioritairement par des interventions visant à améliorer l'usage des antibiotiques. Les objectifs de cette étude étaient (i) d'identifier des groupes de chirurgiens-dentistes selon leur score de pertinence (calculé à partir des résultats des indicateurs proxy) de prescriptions antibiotiques et (ii) d'identifier des caractéristiques liées aux chirurgiens-dentistes, à leur profil de prescription et à leur patientèle qui soient associées à la pertinence des prescriptions antibiotiques.

2. Méthodes

La méthodologie était similaire à celle utilisée pour les médecins généralistes. Un score de pertinence a été calculé pour chaque chirurgien-dentiste de la région Grand Est inclus, à partir de ses résultats pour les indicateurs proxy développés précédemment, en utilisant les données du SNDS de 2019. Le score de pertinence est défini comme suit : (nombre d'indicateurs proxy applicables pour le chirurgien-dentiste et pour lesquels la cible acceptable a été atteinte) / (nombre d'indicateurs applicables pour le chirurgien-dentiste). Des groupes de chirurgiens-dentistes ont été identifiés par la méthode Ward, à partir de ce score de pertinence. Les caractéristiques des chirurgiens-dentistes et de leur patientèle ont été comparées entre les groupes par une analyse bivariée, puis par une régression logistique polytomique multivariée. Les caractéristiques liées aux profils de prescriptions des chirurgiens-dentistes ont été comparées par une analyse bivariée.

3. Principaux résultats et conclusions

Au total, 3 014 chirurgiens-dentistes pratiquant en région Grand Est ont été inclus dans cette étude et ont prescrit un total de 373 975 antibiotiques dispensés en 2019. Trois groupes de chirurgiens-dentistes ont été identifiés selon la pertinence de leurs prescriptions antibiotiques : 23% des chirurgiens-dentistes avaient des pratiques de prescription meilleures que la moyenne, 41% des pratiques dans la moyenne et 36% des pratiques moins bonnes que la moyenne. Plusieurs caractéristiques explorées étaient associées à la pertinence des prescriptions des chirurgiens-dentistes. Il y avait plus de probabilité d'être dans le groupe avec des pratiques de

prescription meilleures que la moyenne lorsque le chirurgien-dentiste était un homme, exerçant en Lorraine, en pratique depuis moins longtemps, pratiquant une majorité d'actes de chirurgie, avec une patientèle moins âgée et avec moins d'affections de longue durée, et pratiquant moins d'actes par patient. Pour les caractéristiques liées aux profils de prescription, les pratiques de prescription étaient meilleures lorsque les chirurgiens-dentistes prescrivaient moins de médicaments en général, moins d'antibiotiques, moins d'anti-inflammatoires non stéroïdiens et généraient moins de dépenses pharmaceutiques par patient. Cette étude peut aider à guider des interventions pour le bon usage des antibiotiques, en ciblant les chirurgiens-dentistes appartenant au groupe avec des pratiques moins bonnes que la moyenne, les chirurgiens-dentistes présentant les caractéristiques qui sont associées à des pratiques moins bonnes que la moyenne et les situations concernées par les indicateurs proxy pour lesquels les performances sont les moins élevées.

4. Mon implication

Pour cet article, j'ai contribué à la conception méthodologique, à l'interprétation des résultats, à la rédaction et à la valorisation. Les analyses statistiques ont été réalisées par Ouarda Pereira, responsable de missions statistiques à la Direction Régionale du Service Médical (DRSM) du Grand Est.

5. Valorisation

Cet article a été soumis le 4 octobre 2022 à la revue *BMC Oral Health* (rang B, *impact factor* 2021 : 3,747).

Un résumé a été soumis à la Réunion Interdisciplinaire de Chimiothérapie Anti-Infectieuse (RICAI) qui a lieu à Paris en décembre 2022.

Characteristics of dentists and patients associated with appropriate antibiotic prescriptions by French dentists: a cross-sectional study using Health Insurance databases

Maïa Simon[1,2], Ouarda Pereira[3], Marie-Louise Constant[4], Julie Guillet-Thibault[4], Céline Pulcini[1,5], Nathalie Thilly[1,2]

[1] Université de Lorraine, APEMAC, Nancy, France

[2] CHRU-Nancy, Département Méthodologie, Promotion, Investigation, Nancy, France

[3] Direction Régionale du Service Médical (DRSM) Grand Est, Strasbourg, France

[4] CHRU-Nancy, Service d'Odontologie, Nancy, France

[5] CHRU-Nancy, Département de maladies infectieuses, Nancy, France

Corresponding author: Professor Nathalie Thilly, PharmD PhD. Centre Hospitalier Régional Universitaire de Nancy, Département Méthodologie, Promotion, Investigation, Bâtiment Recherche, Hôpitaux de Brabois, allée du Morvan, 54511 Vandoeuvre-Lès-Nancy, France. Tel: +33 (0)3 83 15 54 57, e-mail: n.thilly@chru-nancy.fr

ABSTRACT

Background – The use of antibiotics in dental care is often unnecessary or inappropriate. Our objectives were to identify (i) clusters of dentists grouped according to their appropriateness score based on proxy indicators' results; and (ii) dentists' and patients' characteristics associated with the appropriateness of antibiotic prescriptions.

Methods – We used data of the Health Insurance reimbursement databases on antibiotics prescribed in 2019 by general dental practitioners of the Grand Est region in France. The appropriateness of antibiotic prescriptions was estimated by the results of recently published proxy indicators. We conducted a cluster analysis according to an appropriateness score calculated for each dentist, using the Ward method. We then conducted bivariate and multivariable analyses to identify characteristics associated with these clusters.

Results – We included 3,014 dentists, which were grouped into three clusters. We identified several characteristics significantly associated with the appropriateness of antibiotic prescriptions. Overall, dentists had more appropriate prescription practices when they were male, having a predominant surgery practice in the Lorraine area for less years, when they had healthier patients (i.e. younger, with no chronic diseases, and who received less procedures), and when they had a more prudent use of drugs in general (i.e. less drug expenses, less prescriptions of all drugs, less prescriptions of antibiotics and less prescriptions of systemic non-steroidal anti-inflammatory drugs).

Conclusions – We identified clusters and characteristics associated with the appropriateness of antibiotic prescriptions made by dentists, which might help guiding antimicrobial stewardship interventions.

Keywords: associated factors; dentists; prescriptions; antibiotics; appropriateness

BACKGROUND

Antimicrobial resistance has been listed among the ten global health issues to track in 2021 by the World Health Organisation.[1] The misuse and the overuse of antibiotics are among the main drivers of resistance.[2] Around 125,000 persons are infected by multidrug-resistant bacteria and more than 5,500 persons die of these infections each year in France.[3] In 2019, 78% of antibiotics were prescribed in the outpatient setting in France [4], with around 12% being prescribed by dentists.[5]

Antimicrobial stewardship (AMS) has been defined by Dyar *et al*. as a "coherent set of actions which promote a responsible use of antimicrobials".[6] In 2020, the World Dental Federation (FDI) published a white paper to promote AMS in dental care. Its objective was to help dental teams to tackle antibiotic resistance by raising awareness, preventing and controlling infections, and optimising the use of antibiotics.[7] This was a welcome initiative, as several studies have shown worldwide that the use of antibiotics in dental care is often unnecessary or inappropriate [8–12], while antibiotics are only recommended in rare indications (prophylactic treatment for very specific situations or curative treatment in association with a source control procedure).[8,13,14]

Metrics are useful AMS tools to help optimising antibiotic use by defining targets and giving feedback to professionals and stakeholders. Quality indicators need information on the clinical diagnosis to be calculated, but in most European countries including France, no computerised national systems link community drug prescriptions to clinical diagnoses.[15] To overcome this issue, our team recently developed four proxy indicators (PIs) estimating the appropriateness of antibiotic prescriptions at the dentist level, calculable without requiring information on clinical diagnoses, and using routine reimbursement databases. A cross-sectional study, conducted in two north-eastern French regions in 2019 and using these four

PIs, showed that antibiotic prescriptions by primary care dentists were suboptimal and important variations between practitioners were highlighted.[16]

Exploring dentists and patients' characteristics associated with the appropriateness of antibiotic prescriptions can help guide AMS interventions by targeting specific populations. To the best of our knowledge, no study has investigated this topic yet. We previously used the same methodology to identify characteristics associated with the appropriateness of antibiotic prescriptions made by general practitioners.[17]

Our objectives were to identify (i) clusters of dentists grouped according to their appropriateness score, based on PIs results; and (ii) dentists' and patients' characteristics associated with the appropriateness of antibiotic prescriptions.

METHODS

Study setting and population

We considered in the present study all general dental practitioners of the Grand Est region (5,550,000 inhabitants [18]) in France (67,000,000 inhabitants), who had seen more than 100 different patients and who had prescribed more than ten antibiotics in 2019. We chose to use 2019 data because dental activity was impacted in 2020 because of the COVID-19 pandemic.

Data source and study design

We conducted a one-year (2019) retrospective cross-sectional study using the reimbursement databases of the French Health Insurance, that covers 99% of the population. In France, all antibiotics must be prescribed by health professionals and are then reimbursed by the Health Insurance. The Health Insurance reimbursement databases can link each antibiotic dispensed by community pharmacies to the prescribers' and patients' characteristics such as age, gender, and the presence of chronic disease. Information on the prescription is not available, so dispensation was used as a proxy for prescription.

Proxy indicators (PIs)

We previously developed and validated four PIs estimating the appropriateness of antibiotic prescriptions at the dentist level, calculable without information on clinical diagnoses and using routine reimbursement databases.[16] These PIs, selected from the literature and based on national guidelines [19], cover the most frequent situations of inappropriate prescribing in dental care. They were associated with a clear target reflecting a high quality of care. Performance was defined as the percentage of dentists who reached the target. **Additional**

Table 1 presents the definition (numerator/denominator) of the four PIs and their associated target.[16]

Cluster analysis

An appropriateness score was calculated for each dentist as follows [17]:

$$\frac{\text{number of PIs applicable for the dentist and for whom the target is reached}}{\text{number of PIs applicable for the dentist}}$$

A PI was considered applicable if it was based on at least ten situations per year for the dentist. A cluster analysis was then conducted to group dentists according to their appropriateness score, i.e., to the appropriateness of their antibiotic prescribing practices. The Ward method was used to identify clusters according to the degree of similarity between observations in a same cluster.

Dentists' and patients' characteristics

The association between the appropriateness of antibiotic prescribing practices and the following 2019 dentists' and patients' characteristics was investigated. For each included dentist, we considered: the geographic area of professional practice (Alsace, Champagne-Ardenne or Lorraine); the dentist's gender; the practice setting (rural (< 5,000 inhabitants), suburban (5,000 to 20,000 inhabitants) or urban (> 20,000 inhabitants)); the number of years of practice; the main type of procedure performed in daily practice (prosthetic, prevention, operative dentistry, implantology, parodontology, or surgery); the number of different patients seen during the year; the number of procedures per patient (in France, the unit of reimbursement is the procedure, which may consist in several acts and/or several visits); the percentage of patients with chronic diseases among patients seen during the year [20]; the percentage of patients with low income [21]; the percentage of patients < 16 years old; and the percentage of patients > 65 years old.

Dentists' drug prescribing profiles

The association between the appropriateness of antibiotic prescribing practices and the 2019 dentists' drug prescribing profiles was explored considering the following variables: the total drugs expenses per patient; the number of units of all drugs per patient; the number of antibiotic prescriptions per 1000 patients; the number of systemic non-steroidal anti-inflammatory drugs per 1000 patients; and the number of systemic corticosteroids per 1000 patients.

Statistical analyses

The PIs' results were calculated and presented as medians and interquartile ranges (IQR), and performance (i.e. the percentage of dentists who reached the target) as percentage.

A hierarchical clustering method was conducted to identify clusters of dentists according to their appropriateness score, i.e. the appropriateness of their antibiotic prescribing practices. For each identified cluster, the median appropriateness score, its IQR and the performance for each PI are presented.

The dentists' and patients' characteristics were compared between clusters using Chi-square tests for categorical variables (expressed as percentage) and Kruskal-Wallis tests for continuous variables (expressed as medians and IQR). Characteristics associated with appropriateness of practices with a p-value < 0.10 in these analyses were then included in a multivariable polytomous logistic regression model to identify characteristics independently associated with the clusters with less appropriate practices as compared with the one with the most appropriate practices. When two characteristics were highly collinear, the one with the lower p-value in bivariate analyses was considered in the multivariable model.

For dentists' drug prescribing profiles, only bivariate analyses (Chi-square or Kruskal-Wallis tests) were used to compare the clusters, because of the high collinearity between all considered variables. However, if appropriate practices were significantly associated with 'total drugs expenses per patient' and /or 'number of units of all drugs per patient', we planned to adjust analyses on the number of procedures per patient and the percentage of patients with chronic diseases (variables reflecting patients' health), in order to interpret these results (i.e., to identify if the volume of drug prescriptions was due to differences in patients' health or in dentists' practices).

A p-value < 0.05 for two-sided tests was considered significant. All analyses were performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, N.C., USA).

RESULTS

Characteristics of dentists and their patients

In 2019, 3,372 general dental practitioners practiced in the Grand Est region of France, and 3,014 (89.4%) met the eligibility criteria for the present study (> 100 patients and > 10 antibiotics prescribed in 2019). Their mean age was 47.5 ± 12.6 years, with a mean number of years of practice of 17.7 ± 12.6, and 56.9% were men. On average, they took care of 804 ± 391 different patients in 2019 for a mean number of 2,439 ± 1,212 procedures. The 3,014 dentists prescribed 373,975 antibiotics in 2019, that were dispensed to 308,123 different patients. Among these patients, 16.7% were aged < 16 years and 17.3% > 65 years, 11.8% had a chronic disease, and 7% had a low income.

Appropriateness of antibiotic prescriptions

Additional Table 2 presents the results for the four proxy indicators.(16) Important variations between dentists were noted, with large interquartile ranges. Performance (percentage of dentists who reached the target) is presented in **Table 1**. The performance results were not optimal, particularly for the PI 4 (10.5% of dentists prescribed less than 5% of antibiotics rarely indicated in dental care) and PI 1 (39.6% of dentists prescribed at least 10 times more amoxicillin than amoxicillin-clavulanate).

Cluster analysis

Three clusters of dentists were identified. Cluster 1 grouped 686 dentists (22.8%) having better than average practices, Cluster 2 grouped 1,241 dentists (41.2%) having average practices and Cluster 3 grouped 1,087 dentists (36.1%) having worse than average practices. **Table 1** presents the performances of the three dentists' clusters for each PI. Substantial differences in

performances were noted between Cluster 1 and Cluster 3 (from a 30.0% difference for PI 4 to a 70.6% difference for PI 1), highlighting a huge variability in dentists' practices.

Dentists' and patients' characteristics associated with the appropriateness of antibiotic prescriptions

Table 2 presents the results of the bivariate analyses. All dentists' characteristics were significantly associated with the appropriateness of their antibiotic prescriptions, except the practice setting. Regarding patients' characteristics, the percentages of patients with chronic diseases and > 65 years old were significantly associated with the appropriateness of dentists' antibiotic prescriptions.

Table 3 presents the results of the multivariable polytomous logistic analyses. The geographic area and the number of procedures per patient were significantly associated with the appropriateness of antibiotic prescriptions, as well as the dentist's gender and the number of years of practice (only for Cluster 3). The number of patients was associated with the appropriateness of antibiotic prescriptions but not linearly: better practices were associated with an intermediate number of patients.

Overall, dentists who had the most appropriate antibiotic prescriptions were male with less years of practice, practicing in the Lorraine region, having a predominant surgery practice, with a lower percentage of patients aged > 65 years old, a lower percentage of patients with chronic diseases, and fewer procedures per patient.

Dentists' drug prescribing profiles associated with the appropriateness of antibiotic prescriptions

All drug prescribing variables were significantly associated with the appropriateness of antibiotic prescriptions, except the number of systemic corticosteroids prescriptions per 1000

patients (**Table 4**). The associations between the appropriateness of antibiotic prescriptions and the two variables, the total drug expenses per patient and the number of units of all drugs per patient, were not modified when adjusted for patients' health (i.e., the number of procedures per patient and the percentage of patients with chronic diseases).

Overall, dentists who had the most appropriate antibiotic prescriptions prescribed less drugs, less antibiotics, less systemic non-steroidal anti-inflammatory per patient, and had less drug expenses per patient.

DISCUSSION

Summary of the principal findings

The present cross-sectional study allowed us to identify three clusters of dentists according to the appropriateness of their antibiotic prescription practices: 23% of our sample of 3,014 dentists belonged to the "better than average practices" cluster, 41% to the "average practices" cluster and 36% to the "worse than average practices" one. Performance results showed that dentists' practices were suboptimal and highly variable between dentists and between PIs.

We identified three types of characteristics that were associated with the appropriateness of antibiotic prescriptions. The first one was characteristics related to dentists. Male dentists in the Lorraine region, with less years of practice, and having a predominant surgery practice, had the best antibiotics' prescription practices. As it has been shown for general pratitioners [23], we can hypothesise that male dentists might have a better attendance to postgraduate training, which has a positive impact on knowledge [24,25], and thus on compliance with guidelines. But this hypothesis would need further investigation. The better practices observed for the Lorraine area might be due to the differences in the training provided between the local universities (one for each area : Alsace, Champagne-Ardenne and Lorraine), and/or to the presence of the regional antimicrobial stewardship network AntibioEst [26] which started in Lorraine in 2003, before being extended to the whole Grand Est region in 2018. This regional network coordinates a multifaceted AMS strategy, including for example postgraduate training, guidelines, or infectious diseases advice freely available by phone. Previous studies in dental care have already shown that a more recent year of graduation is associated with a better level of knowledge and practice in antibiotic prescribing.[24,27] Finally, dentists who have a predominant surgery practice could be more aware of guidelines because surgery might be at

higher risk of complications than other procedures, and/or because they have less emergency as these procedures are scheduled, so their antibiotic prescriptions might be more anticipated and protocolised.

The second type of characteristics was characteristics related to patients. Dentists with more complex patients, i.e. with older patients, more patients with chronic diseases, and patients who received more procedures, were more likely to have worse than average prescription practices. As shown elsewhere [28], dentists might be more likely to prescribe antibiotics inappropriately, in particular an increased use of broad-spectrum antibiotics, to prevent a perceived increased risk of bacterial complications in these patients.

Finally, characteristics related to dentists' drug prescribing profile were associated with antibiotics prescribing practices. Dentists with worse than average practices had higher drug expenses and prescribed more drugs, more antibiotics and more systemic non-steroidal anti-inflammatory drugs (non-steroidal anti-inflammatory drugs are usually not indicated in bacterial infections in dentistry [22]). We showed that this was not related to patients' health but to dentists' drug prescriptions habits. Overall, dentists who prescribed antibiotics more appropriately seemed to have an overall more prudent use of drugs, as already observed for general practitioners.[17]

Comparison with existing literature

Few published studies aimed at identifying characteristics associated with the appropriateness of antibiotic prescriptions made by dentists. Kerr *et al.* conducted in 2020 an online questionnaire-based survey to investigate potential factors that may impact the appropriateness of antibiotic prescriptions to treat adults with acute dental pain in the United Kingdom (UK). The inappropriate prescribing practice was defined as a prescription of antibiotic(s) in a clinical situation that does not require it. The authors identified that the

likelihood of inappropriate prescriptions was increased by the following factors: the qualification from a non-UK university, the low or no confidence in achieving adequate local anaesthesia, the duration of the appointment (< 20 minutes *versus* all other times), and the lack of a postgraduate qualification.[25]

A scoping review conducted in 2018 identified dentist-related factors influencing the use and the misuse of antibiotics in dentistry.[14] Some of the characteristics we identified in the present study were already reported in the literature: practice location, practice type, years in practice, and dentist's gender.

Strengths and limitations

This study brings innovative and useful findings, as data on the topic is scarce. However, our work has some limitations. First, we aimed to explore the association between characteristics related to dentists or their patients and the appropriateness of their antibiotic prescriptions, but we cannot prove a causal relationship. Second, the characteristics we investigated were limited to those available from the routine reimbursement databases. We acknowledge that they do not explain all the variability of practices, and that other characteristics – not explored here – could also influence this variability.

Implications/perspectives

The present study showed that performance results of dentists were far from optimal, especially in the clusters of dentists with average and worse than average practices, and presented a wide variability between clusters, highlighting the urgent need for AMS interventions in dentistry. Therefore, this study could be useful to help guiding AMS interventions. First, AMS interventions can target dentists belonging to the "worse than average" cluster and focus on the situations covered by PIs that showed the worst performances

(e.g., prescription of amoxicillin rather than amoxicillin-clavulanate, indications for prescription of pristinamycin, spiramycin-metronidazole or doxycycline). In addition, AMS interventions can target dentists presenting characteristics that were associated with inappropriate prescriptions, such as those located in specific geographic area or those practicing for a long time.

The method of the present study might also be used in other countries, by adapting the PIs and their targets to the national prescribing guidelines and exploring relevant characteristics.

Conclusion

We identified three clusters of dentists according to the appropriateness of their antibiotic prescription practices. Performance practices were suboptimal and presented wide variations between clusters and between PIs. We identified several characteristics associated with the appropriateness of antibiotic prescriptions related to dentists or their patients that might help guiding AMS interventions.

LIST OF ABBREVIATIONS

AMS : antimicrobial stewardship

FDI : the World dental federation

IQR : interquartile range

PI : proxy indicator

UK : United Kingdom

DECLARATIONS

Ethics approval and consent to participate

This retrospective observational study did not modify the medical care of patients, and anonymity of both patients and prescribers was preserved. According to the French law, ethical approval was not required in this context.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the present findings are available from the National Health Insurance but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the National Health Insurance. The study protocol is also available on request.

Competing interests

The authors declare that they have no competing interests.

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None, this work was conducted as part of the routine work.

Authors' contributions

CP and NT conceived the study. NT, CP, OP, JGT and MS designed the methodology. OP conducted the analyses. All the authors interpreted data. MS and MLC drafted the work. All the authors revised the manuscript and approved the final version.

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TABLES

Table 1. Description of the three clusters of antibiotic prescribing practices and performance for the four proxy indicators (n = 3,014 dentists).

	Global N = 3,014 dentists	**Cluster 1** **"Better than average practices"** N = 686 dentists (22.8%) Score [a] : 3/4 (3/4 ; 3/4)	**Cluster 2** **"Average practices"** N = 1241 dentists (41.2%) Score [a] : 2/4 (2/4 ; 2/4)	**Cluster 3** **"Worse than average practices"** N = 1087 dentists (36.1%) Score [a] : 1/4 (1/4 ; 1/4)
Proxy indicator (PI)	**Performances (% of dentists who reached the acceptable target)**			
PI 1 – Amoxicillin / amoxicillin-clavulanate (ratio)*	39.6%	81.4%	38.8%	10.8%
PI 2 – Estimated duration of antibiotic prescriptions (%)*	62.8%	92.4%	73.7%	31.6%
PI 3 – Prescriptions of not indicated antibiotics (%)*	73.0%	96.7%	86.0%	43.3%
PI 4 – Prescriptions of rarely indicated antibiotics (%)*	10.5%	31.1%	7.3%	1.1%

[a] The score is displayed with median (1st quartile ; 3rd quartile) and calculated as [(number of PIs applicable for each dentist and for whom the acceptable target is reached) / (number of PIs applicable for each dentist)].
* p-value < 0.0001 for all PIs

Table 2. Comparison of dentists' and patients' characteristics between the three identified clusters – Bivariate analyses (n = 3,014 dentists).

Characteristics in 2019		Cluster 1 "Better than average practices" N = 686 dentists (22.8%)	Cluster 2 "Average practices" N = 1241 dentists (41.2%)	Cluster 3 "Worse than average practices" N = 1087 dentists (36.1%)	p-value
DENTISTS' CHARACTERISTICS					
Geographic area %	Alsace	19.0	41.0	40.0	**< 0.0001**
	Champagne-Ardenne	17.0	38.4	44.6	
	Lorraine	29.2	42.7	28.1	
Dentist's gender %	Male	23.2	42.8	34.0	**0.019**
	Female	22.3	38.8	38.9	
Practice setting %	Rural (< 5,000 inhabitants)	23.1	41.9	35.1	0.265
	Suburban (5,000 – 20,000 inhabitants)	23.6	42.2	34.1	
	Urban (> 20,000 inhabitants)	21.7	39.6	38.7	
Type of procedure [a] %	Prosthetic	18.8	41.0	40.2	**0.028**
	Prevention	21.9	40.2	37.9	
	Operative dentistry	23.4	42.3	34.3	
	Surgery	40.4	36.2	23.4	
Number of years of practice Median (1st quartile ; 3rd quartile)		14 (3 ; 29)	16 (6 ; 29)	18 (8 ; 30)	**< 0.0001**
Number of patients Median (1st quartile ; 3rd quartile)		744 (504 ; 992)	791 (557 ; 1025)	720 (512 ; 1018)	**0.001**
Number of procedures per patient Median (1st quartile ; 3rd quartile)		2.9 (2.6 ; 3.3)	3.0 (2.7 ; 3.4)	3.0 (2.6 ; 3.5)	**0.004**
PATIENTS' CHARACTERISTICS					

% of patients with chronic diseases Median (1st quartile ; 3rd quartile)	11.3 (9.3 ; 13.5)	11.9 (9.9 ; 14.0)	11.8 (9.9 ; 14.2)	**0.0003**
% of patients with low income Median (1st quartile ; 3rd quartile)	5.0 (2.4 ; 10.4)	4.9 (2.3 ; 9.4)	4.4 (2.1 ; 9.3)	0.073
% of patients < 16 years old Median (1st quartile ; 3rd quartile)	15.3 (11.2 ; 19.5)	14.8 (11.0 ; 18.8)	15.0 (10.7 ; 18.6)	0.197
% of patients > 65 years old Median (1st quartile ; 3rd quartile)	16.3 (11.5 ; 21.8)	17.3 (12.6 ; 22.4)	17.5 (12.7 ; 22.4)	**0.008**

[a] In France, dentists can practice several type of procedure in their daily practice (prosthetic, prevention, operative dentistry, implantology, parodontology, or surgery). In our sample, no dentist practiced a majority of implantology or parodontology in 2019.
Bold indicates a significant p-value (p-value < 0.05).

Table 3. Association between the dentists' and patients' characteristics and the identified clusters – Multivariable polytomous logistic analyses (n = 3,014 dentists).

Characteristics in 2019*		MULTIVARIABLE ANALYSIS			
		Cluster 2 "average practices" VS Cluster 1 "better than average practices"		Cluster 3 "worse than average practices" VS Cluster 1 "better than average practices"	
		Odds Ratio (95% confidence interval)	p-value	Odds Ratio (95% confidence interval)	p-value
Geographic area	Lorraine	1 (reference)	-	1 (reference)	-
	Alsace	1.43 (1.16 ; 1.77)	**0.0009**	2.15 (1.72 ; 2.68)	**< 0.0001**
	Champagne-Ardenne	1.55 (1.18 ; 2.03)	**0.002**	2.83 (2.14 ; 3.73)	**< 0.0001**
Dentist's gender	Male	1 (reference)	-	1 (reference)	-
	Female	1.06 (0.87 ; 1.29)	0.596	1.37 (1.12 ; 1.69)	**0.003**
Number of years of practice [a]		1.01 (1.00 ; 1.01)	0.219	1.02 (1.01 ; 1.03)	**0.0002**
Number of patients		1.000 (1.000 ; 1.001)	**0.004**	1.000 (1.000 ; 1.000)	0.532
Number of procedures per patient		1.16 (1.01 ; 1.34)	**0.041**	1.17 (1.01 ; 1.35)	**0.037**
% of patients with chronic diseases		1.04 (1.01 ; 1.07)	**0.020**	1.04 (1.01 ; 1.08)	**0.023**

[a] Interpretation of results: probability of belonging to cluster 2 (3) multiplied by 1.01 (1.02) as compared to cluster 1 for each additional year of practice.

The characteristics included in this multivariable model were the following: geographic area, dentist's gender, number of years of practice, number of patients, number of procedures per patient, percentage of patients with chronic diseases and percentage of patients with low income. The percentage of patients > 65 years old was not included because of high collinearity with the percentage of patients with chronic diseases (r = 0.74). The type of procedure was not included because of high collinearity with the number of procedures per patient (p < 0.001). The variable percentage of patients with low income was removed from the model because of its non-significance (p = 0.824). The reference class is Cluster 1 "better than average practices". Bold indicates a significant p-value (p-value < 0.05).

Table 4. Comparison of dentists' drug prescribing profile between the three identified clusters – Bivariate analyses (n = 3,014 dentists).

Characteristics in 2019	Cluster 1 "Better than average practices" N = 686 dentists (22.8%)	Cluster 2 "Average practices" N = 1241 dentists (41.2%)	Cluster 3 "Worse than average practices" N = 1087 dentists (36.1%)	p-value
Total drug expenses (€) per patient Median (1st quartile ; 3rd quartile)	9.0 (7.5 ; 11.0)	9.9 (8.1 ; 12.0)	10.9 (8.9 ; 13.0)	**< 0.0001**[a]
Number of units of all drugs per patient Median (1st quartile ; 3rd quartile)	3.6 (2.9 ; 4.4)	3.7 (3.0 ; 4.6)	3.9 (3.2 ; 4.7)	**< 0.0001**[a]
Number of antibiotic prescriptions per 1000 patients Median (1st quartile ; 3rd quartile)	125.6 (83.0 ; 182.9)	143.4 (101.2 ; 201.1)	133.4 (91.5 ; 191.7)	**< 0.0001**
Number of systemic non-steroidal anti-inflammatory prescriptions per 1000 patients Median (1st quartile ; 3rd quartile)	22.0 (6.7 ; 50.0)	28.3 (9.7 ; 60.3)	25.0 (9.3 ; 57.9)	**0.0005**
Number of systemic corticosteroids prescriptions per 1000 patients Median (1st quartile ; 3rd quartile)	0.0 (0.0 ; 8.4)	0.9 (0.0 ; 7.5)	0.9 (0.0 ; 6.5)	0.724

[a] Same OR and p-values when adjusted for patients' health (i.e., the number of procedures per patient and the percentage of patients with chronic diseases).

Bold indicates a significant p-value (p-value < 0.05).

Additional Table 1. Definition of the four PIs and their target.[1]

Proxy indicator (PI)	Numerator description	Denominator description	Target value
PI 1 – Amoxicillin/amocixillin-clavulanate (ratio)	Number of prescriptions of amoxicillin (J01CA04)	Number of prescriptions of amoxicillin-clavulanate (J01CR02)	> 10
PI 2 – Estimated duration of antibiotic prescriptions (%)	Number of prescriptions > 8 days for amoxicillin (J01CA04), amoxicillin-clavulanate (J01CR02), clindamycin (J01FF01) and pristinamycin (J01FG01), and > 4 days for azithromycin (J01FA10)	Total number of prescriptions for these five antibiotics	< 10%
PI 3 – Prescriptions of not indicated antibiotics (%)	Number of prescriptions of lymecycline (J01AA04), minocycline (J01AA08), pivmecillinam (J01CA08), phenoxymethylpenicillin (J01CE02), cloxacillin (J01CF02), cefadroxil (J01DB05), cefuroxime (J01DC02), cefaclor (J01DC04), cefotiam (J01DC07), ceftriaxone (J01DD04), cefixime (J01DD08), cefpodoxime (J01DD13), trimethoprim-sulfamethoxazole (J01EE01), erythromycin (J01FA01), midecamycin (J01FA03), roxithromycin (J01FA06), josamycin (J01FA07), telithromycin (J01FA15), tobramycin (J01GB01), gentamicin (J01GB03), ofloxacin (J01MA01), ciprofloxacin (J01MA02), norfloxacin (J01MA06), lomefloxacin (J01MA07), levofloxacin (J01MA12), moxifloxacin (J01MA14), flumequine (J01MB07), fusidic acid (J01XC01), nitrofurantoin (J01XE01), fosfomycin (J01XX01)	Total number of antibiotic prescriptions	< 1%
PI 4 – Prescriptions of rarely indicated antibiotics (%)	Number of prescriptions of pristinamycin (J01FG01), spiramycin-metronidazole (J01RA04) and doxycycline (J01AA02)	Total number of antibiotic prescriptions	< 5%

Additional Table 2. Results for the four proxy indicators estimating the appropriateness of antibiotic prescriptions by dentists of the Grand Est region in 2019 (n = 3,014 dentists).[1]

Proxy indicator (PI)	Median	IQR (1st quartile ; 3rd quartile)
PI 1 – Amoxicillin / amoxicillin-clavulanate (ratio)	7.0	2.5 ; 17.6
PI 2 – Estimated duration of antibiotic prescriptions (%)	5.1	1.1 ; 19.5
PI 3 – Prescriptions of not indicated antibiotics (%)	0.0	0.0 ; 1.1
PI 4 – Prescriptions of rarely indicated antibiotics (%)	14.2	5.3 ; 37.3

Reference

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Chapitre 4 – Discussion

I – Résumé des principaux résultats

1. Les antibiogrammes ciblés

L'étude ANTIBIO-ciblés a montré un impact positif des antibiogrammes ciblés sur le taux de prescriptions des antibiotiques critiques (20,8% de réduction relative), lié à la réduction des taux de prescriptions de céphalosporines de troisième génération faites à des femmes en documenté. Les antibiogrammes ciblés ont également permis d'améliorer la conformité aux recommandations de prescriptions d'antibiotiques pour les infections urinaires, notamment pour les hommes.

L'évaluation des conséquences négatives potentielles a montré qu'il n'y avait a priori pas d'impact négatif de l'antibiogramme ciblé en termes de nombres de consultations et d'hospitalisations.

Nous avons démontré la faisabilité de la mise en œuvre des antibiogrammes ciblés par les laboratoires de biologie médicale du groupe ATOUTBIO qui y ont dédié environ 23 000 euros et 80 heures de travail supplémentaires et ont pu transmettre les antibiogrammes ciblés à 100% des patients éligibles.

L'acceptabilité par les prescripteurs et par les professionnels de laboratoire était élevée. L'antibiogramme ciblé était décrit comme un outil utile pour guider les prescripteurs dans leur choix d'antibiotiques conformément aux recommandations et pour réduire l'antibiorésistance. La principale contrainte identifiée était la nécessité pour les prescripteurs d'appeler le laboratoire afin d'obtenir l'antibiogramme complet. Mais ces appels ne représentaient que 1,2% de l'ensemble des antibiogrammes ciblés rendus sur l'année et étaient aisément gérables par les professionnels de laboratoire. Tous les professionnels étaient favorables à la généralisation de l'antibiogramme ciblé au niveau national, sous réserve d'avoir une information large des prescripteurs en amont, des outils éducatifs à disposition en complément de l'antibiogramme ciblé, une formation des professionnels de laboratoire pour répondre aux demandes des prescripteurs et une implication de l'ensemble des laboratoires du territoire.

2. Les indicateurs de prescriptions d'antibiotiques

Notre équipe a précédemment développé dix indicateurs proxy estimant la pertinence des prescriptions d'antibiotiques faites par les médecins généralistes.(85) A partir de ce premier travail et de la littérature, nous avons développé et adapté 15 indicateurs quantitatifs et onze indicateurs proxy (accompagnés de leur cible) permettant d'estimer respectivement le volume et la pertinence des prescriptions antibiotiques faites en EHPAD, à l'échelle de l'établissement. Nous avons également développé quatre indicateurs proxy (accompagnés de leur cible) estimant la pertinence des prescriptions antibiotiques à l'échelle du chirurgien-dentiste. Ces indicateurs étaient facilement calculables à large échelle à partir des données de remboursement de l'assurance maladie (SNDS). Ils permettaient d'explorer diverses situations cliniques fréquemment causes de mésusage des antibiotiques. Six des indicateurs proxy des prescriptions en EHPAD et quatre des indicateurs proxy des prescriptions par les chirurgiens-dentistes présentaient des bonnes propriétés clinimétriques.

A partir de ces travaux de développement d'indicateurs proxy (85,92), nous avons identifié trois groupes de prescripteurs selon la pertinence de leurs prescriptions estimée par un score de pertinence calculé à partir des résultats des indicateurs proxy (pratiques moins bonnes que la moyenne, pratiques dans la moyenne et pratiques meilleures que la moyenne). Cela nous a ensuite permis d'identifier des caractéristiques liées au prescripteur, à sa patientèle et à sa pratique, qui soient associées à la pertinence des prescriptions. Nous avons réalisé ce travail pour les médecins généralistes et pour les chirurgiens-dentistes.

II – Les forces

1. Le système national des données de santé

Base de données exceptionnelle en Europe, le SNDS couvre la quasi-totalité de la population française (99%).(75) Tous les antibiotiques étant remboursés en France, l'utilisation du SNDS est particulièrement adaptée à l'étude de ces médicaments, permettant d'obtenir les informations quasi-exhaustives de dispensation d'antibiotiques de la population en ville. Pour les différentes études de cette thèse, nous avons ainsi pu avoir des échantillons quasi-exhaustifs de notre population cible et des effectifs très importants, permettant d'atteindre une puissance suffisante pour mettre en évidence des différences ou des associations significatives. Enfin, le

SNDS permet d'obtenir une mesure fiable des dispensations de médicaments, la base de données étant conçue pour le remboursement.

2. Les antibiogrammes ciblés

L'étude ANTIBIO-ciblés a permis de combler un manque constaté dans la littérature d'études à haut niveau de preuve évaluant l'impact des antibiogrammes ciblés et d'évaluation conjointe de l'impact, de la faisabilité, de l'acceptabilité et des conséquences négatives potentielles.(69)

En effet, il s'agit de la première étude comparative à large échelle visant à évaluer l'impact des antibiogrammes ciblés dans les infections urinaires communautaires sur les prescriptions d'antibiotiques. Son design quasi-expérimental combine une comparaison avant-après (avant la mise en œuvre des antibiogrammes ciblés *versus* après la mise en œuvre des antibiogrammes ciblés) à une comparaison à un groupe témoin (antibiogrammes complets habituels). C'est une étude pragmatique, c'est-à-dire en conditions réelles de pratiques, les prescripteurs étant libres de prescrire l'antibiotique de leur choix. Ainsi les résultats ont une forte validité externe.

L'utilisation de méthodes qualitatives pour l'évaluation de l'acceptabilité, par la conduite d'entretiens individuels et de *focus groups* semi-dirigés, a permis d'apporter des informations complémentaires pour expliquer les résultats quantitatifs obtenus et d'explorer les freins et leviers à la généralisation des antibiogrammes ciblés.

Le nombre et la nature des variables sélectionnées pour l'appariement entre les données des ECBU collectées par les laboratoires et les données du SNDS ont permis d'obtenir un taux d'appariement très satisfaisant de 87,4%.

3. Les indicateurs de prescriptions d'antibiotiques

Nous avons développé les premiers indicateurs proxy permettant d'estimer facilement, à partir de bases médico-administratives, la pertinence des prescriptions antibiotiques faites en EHPAD et des prescriptions antibiotiques faites par les chirurgiens-dentistes sans nécessité d'indication clinique pour être calculés. Pour chaque indicateur proxy, des cibles ont été définies à partir des recommandations françaises d'antibiothérapie par un groupe multidisciplinaire d'experts constitué de spécialistes de maladies infectieuses, spécialistes de santé publique, pharmaciens et professionnels de soins primaires, afin de refléter la pertinence des pratiques de prescription d'antibiotiques. La définition de cibles permet de fixer des

objectifs concrets à atteindre pour améliorer les pratiques de prescription.(86) Nous avons également validé les propriétés clinimétriques en évaluant la mesurabilité, l'applicabilité et la marge d'amélioration de chacun des indicateurs proxy. De plus, nous avons développé le premier ensemble d'indicateurs quantitatifs permettant d'estimer le volume des prescriptions d'antibiotiques faites en EHPAD.

Les bases de données du SNDS ont l'avantage de permettre le calcul de ces indicateurs à large échelle (département, région, pays) et de manière automatisée, de telle sorte qu'ils peuvent être réévalués régulièrement.

Ces travaux peuvent facilement être dupliqués dans d'autres pays en adaptant la définition et les cibles des indicateurs proxy au contexte, aux recommandations nationales en antibiothérapie et aux données disponibles dans les bases nationales.

4. La diffusion des travaux de thèse

Un effort particulier a été entrepris pour partager les résultats de ces travaux aux autorités sanitaires et aux parties prenantes impliquées dans le bon usage des antibiotiques aux niveaux régional et national. Le Ministère en charge de la Santé a été informé de l'ensemble des projets de cette thèse. L'Assurance Maladie est associée à l'ensemble des projets. L'Agence Régionale de Santé (ARS) Grand Est et le centre régional en antibiothérapie AntibioEst sont associés aux travaux sur les antibiogrammes ciblés et ont été informés des travaux sur les indicateurs de prescription des antibiotiques. Les différents projets ont également été valorisés par des présentations lors de congrès nationaux et internationaux. Enfin, des *posts* ont été réalisés sur la page LinkedIn de l'axe de recherche AntibioVac afin de diffuser les différents articles et présentations.(97)

III – Les limites

1. Le système national des données de santé

Les différentes bases de données constituant le SNDS n'ont historiquement pas été conçues pour l'évaluation et la recherche, elles ne sont donc pas complétement adaptées à cette utilisation. En particulier, l'absence d'indication clinique dans le SNDS empêche l'identification du diagnostic pour lequel l'antibiotique a été prescrit.

De plus, les bases de données du SNDS disposent d'informations sur tous les antibiotiques ayant été remboursés. Les données de dispensation sont donc utilisées ici comme

« proxy » des données de prescription. Cela peut entraîner une surestimation de la quantité d'antibiotiques consommés par le patient si son observance n'était pas optimale, ou une sous-estimation des quantités prescrites si le patient n'a pas été cherché son traitement antibiotique à la pharmacie.

Pour l'étude ANTIBIO-ciblés, 12,6% des ECBU n'ont pas pu être appariés avec les données du SNDS. Cette proportion est faible mais nous ne pouvons pas exclure un éventuel biais de sélection, ne disposant pas des informations sur les caractéristiques des ECBU non appariés.

2. Les antibiogrammes ciblés

Le choix du design quasi-expérimental de l'étude ANTIBIO-ciblés a été fait devant la difficulté technique de randomiser les patients ou les laboratoires entre antibiogrammes ciblés et antibiogrammes complets. A l'initiation de l'étude en 2017, peu de groupes de laboratoires étaient en capacité technique de mettre en place les antibiogrammes ciblés. En effet, la mise en place des antibiogrammes ciblés entraîne une réorganisation et des investissements matériels et financiers importants, principalement au niveau du plateau technique où sont envoyés tous les prélèvements réalisés par les laboratoires pour analyse. Ainsi, il aurait été impossible d'un point de vue logistique et organisationnel de ne pas appliquer le rendu des antibiogrammes ciblés à certains laboratoires d'un même groupe ou à certains patients d'un même laboratoire (dans le cas où ils auraient été randomisés dans le groupe témoin). L'absence de randomisation peut entraîner une non comparabilité des deux groupes de l'étude. Cependant, nous avons sélectionné deux groupes de laboratoire qui étaient *a priori* comparables en termes de profil d'activités. De plus nous avons montré qu'ils étaient globalement comparables sur nos deux périodes d'étude. Les variables qui différaient entre les deux groupes ne devraient avoir que peu d'impact sur nos résultats : (i) la prévalence d'*Escherichia coli* dans les ECBU n'influence pas les résultats car nous n'avons analysé que des ECBU positifs à *Escherichia coli* ; (ii) la sensibilité d'*Escherichia coli* à l'amoxicilline-acide clavulanique était plus élevée dans le groupe témoin (antibiogrammes complets) en 2019, mais cela n'a pas ou peu d'impact sur les résultats car les taux de prescription d'amoxicilline-acide clavulanique étaient très bas dans les deux groupes (environ 3%) ; (iii) la sensibilité d'*Escherichia coli* au triméthoprime-sulfaméthoxazole était supérieure dans le groupe témoin en 2019. Ainsi, le groupe témoin devrait avoir plus tendance à prescrire cet antibiotique et donc moins d'antibiotiques critiques, résultant si biais il y a, en une sous-estimation de l'impact des antibiogrammes ciblés sur les antibiotiques critiques.

Nous avons évalué les conséquences négatives potentielles sur la santé des patients, en termes de consultations médicales et d'hospitalisations survenues dans les 30 jours suivant la prescription de l'ECBU. Nos résultats ont montré une absence de différences significatives entre les deux groupes. Cependant, ces résultats sont à interpréter avec précaution car les consultations médicales et hospitalisations sont des mesures indirectes de l'effet sur la santé. De plus, il n'est pas possible d'identifier une relation causale entre les prescriptions d'antibiotiques et les consultations ou hospitalisations, comme nous n'avons pas d'information sur l'indication clinique dans le SNDS.

Nous avons souhaité explorer l'impact des antibiogrammes ciblés sur la conformité aux recommandations. Les recommandations ciblent les infections urinaires masculines dans leur ensemble et nous avons montré une amélioration importante de la conformité aux recommandations pour les patients hommes. Pour les femmes, les recommandations diffèrent selon la situation clinique (cystite ou pyélonéphrite). Il était donc plus complexe d'estimer la conformité aux recommandations pour les femmes, ne disposant pas de l'indication clinique dans les bases du SNDS. Il a été rapporté dans la littérature qu'un médecin généraliste voit une pyélonéphrite pour dix cystites chez ses patientes (98), mais la réalisation d'un ECBU n'étant pas recommandée dans les cystites simples de la femme, il nous était impossible de connaître la proportion de prescriptions d'ECBU pour chaque indication. Nous avons choisi de présenter la conformité aux recommandations selon plusieurs cas de figure : en supposant que toutes les infections sont des cystites, que toutes sont des pyélonéphrites et globalement, quel que soit le type d'infection.

Dans un contexte de design expérimental, le rendu des antibiogrammes ciblés pendant l'étude ANTIBIO-ciblés n'était volontairement pas accompagné d'information détaillée ou d'outils d'aide à la prescription. Ceci a pu générer de l'incompréhension chez les prescripteurs, pouvant limiter leur acceptabilité et leur adhésion, et ainsi sous-estimer l'impact des antibiogrammes ciblés.

Les entretiens individuels et *focus groups* ont été conduits sur la base du volontariat. Les professionnels ayant accepté les entretiens étaient probablement plus intéressés par les antibiogrammes ciblés que ceux ayant refusé. Ainsi, nous ne pouvons pas exclure un biais de sélection, les professionnels interrogés n'étant possiblement pas représentatifs de l'ensemble des professionnels ciblés par l'intervention.

3. Les indicateurs de prescriptions d'antibiotiques

Les différentes études conduites sont des études observationnelles qui ne permettent pas de mettre en évidence de relations causales, mais uniquement des associations qui pourraient donner des pistes pour des évaluations futures et pour orienter les actions de bon usage.

Les indicateurs proxy et leurs cibles, sélectionnées pour refléter la pertinence des pratiques de prescription, ont été définis par un petit groupe d'experts multidisciplinaires et la définition de l'indicateur et de sa cible peuvent être sujets à discussion. Il est important de valider la pertinence et la compréhension de ces indicateurs par un plus large groupe d'experts, avant leur utilisation pratique à large échelle. Ce travail de validation a été réalisé pour les indicateurs des prescriptions faites en EHPAD et pour les indicateurs proxy des médecins généralistes (présenté dans la suite de cette thèse).

Il est important de rappeler que l'identification de profils de prescripteurs (médecins généralistes et chirurgiens-dentistes) était basée sur ces indicateurs proxy qui sont calculés sans indication clinique. Ainsi, ils n'estiment pas directement et de façon exacte la conformité de chaque prescription aux recommandations pour l'indication, mais ils estiment indirectement la pertinence des prescriptions antibiotiques de manière agrégée à l'échelle du prescripteur, avec une marge d'erreur possible.

De plus, nous avons évalué les caractéristiques associées à la pertinence de ces prescriptions antibiotiques parmi les variables qui étaient disponibles ou calculables à partir des données du SNDS. Mais il existe potentiellement d'autres facteurs qui pourraient être liés à ces variables et entraîner un biais de confusion. Par exemple, l'association entre le sexe du prescripteur et la pertinence de ces prescriptions pourrait être liée à la participation plus ou moins importante aux enseignements post-universitaires selon le sexe du prescripteur, comme cela a été montré dans la littérature.(99,100)

III – Les implications et perspectives des antibiogrammes ciblés

1. Les antibiogrammes ciblés dans la stratégie nationale 2022-2025 de prévention des infections et de l'antibiorésistance en santé humaine

Les antibiogrammes ciblés s'ancrent dans l'axe 3 « Renforcement de la prévention des infections et de l'antibiorésistance auprès des professionnels de santé tout au long du parcours de santé du patient » et répondent à l'objectif d' « inciter les professionnels au bon usage des

antibiotiques ».(59) L'action 21 de cet axe vise à « renforcer l'utilisation d'outils existants d'aide à la prescription par les professionnels de santé pour promouvoir les bonnes pratiques ». Dans ce cadre, des recommandations de bonnes pratiques sur les antibiogrammes ciblés pour les infections urinaires à entérobactéries sont en cours d'élaboration par la Société Française de Microbiologie (SFM), le Groupe de Pathologie Infectieuse Pédiatrique (GPIP) et la Société de Pathologie Infectieuse de Langue Française (SPILF), avec une labellisation de l'arbre décisionnel par la Haute Autorité de Santé (HAS).(101) Ces recommandations devraient permettre de généraliser l'utilisation des antibiogrammes ciblés à l'ensemble du territoire national, en facilitant leur intégration dans les logiciels des laboratoires de biologie médicale, le but étant d'avoir une proportion importante de laboratoires qui intègrent le rendu ciblé des antibiogrammes pour les infections urinaires.

Un second aspect de cette action est de renforcer la recherche sur d'autres utilisations des antibiogrammes ciblés, par exemple pour d'autres prélèvements ou par l'absence de rendu de l'antibiogramme dans les cas où une colonisation serait suspectée.

2. Le déploiement des antibiogrammes ciblés suite à l'étude ANTIBIO-ciblés

Le groupe de laboratoires ATOUTBIO, qui a mis en place les antibiogrammes ciblés en septembre 2018 dans le cadre de l'étude ANTIBIO-ciblés, a continué à rendre les antibiogrammes ciblés dans les ECBU positifs à *Escherichia coli* après la fin de l'étude (après décembre 2019). Le principe a également été étendu à d'autres bactéries fréquemment responsables d'infections urinaires : les autres entérobactéries (particulièrement *Proteus spp* et *Klebsiella spp*) et certains *cocci* à Gram positif.

Depuis 2017, les plateaux techniques des laboratoires de biologie médicale se sont consolidés et les systèmes informatiques ont évolué, permettant à davantage de laboratoires d'avoir la capacité de mettre en place le rendu des antibiogrammes ciblés. Les professionnels des laboratoires ATOUTBIO seraient disposés à rencontrer les éditeurs de logiciel d'autres laboratoires de biologie médicale pour partager leur expérience.

Pour aller plus loin dans cette démarche d'accompagnement des prescripteurs et améliorer l'impact des antibiogrammes ciblés et leur acceptabilité, des interventions éducatives devraient compléter ce rendu. Par exemple, ces interventions pourraient être des actions de sensibilisation à l'antibiorésistance, des outils éducatifs et d'aides à la prescription (comme Antibioclic)(65) et des formations sur l'antibiothérapie dans les infections urinaires ou des rappels des recommandations pour la désescalade thérapeutique, notamment dans les cas de pyélonéphrites.

3. Les recommandations pour une extension nationale des antibiogrammes ciblés dans les infections urinaires

L'état d'avancement des travaux menés initialement dans le cadre de la feuille de route interministérielle 2016 pour la maîtrise de l'antibiorésistance puis dans le cadre de la stratégie nationale 2022-2025 a été présenté lors d'une réunion point d'étape organisée par le Ministère en charge de la Santé qui s'est tenue en janvier 2022. Lors de cette réunion, trois expérimentations régionales ont également été présentées, en régions Grand Est (ANTIBIO-ciblés), Hauts-de-France et Bourgogne-Franche-Comté. Nous avons ainsi pu présenter les résultats de l'étude ANTIBIO-ciblés, qui pourront concourir à accompagner le déploiement national des antibiogrammes ciblés.

4. La prochaine étape : l'absence de rendu des antibiogrammes ?

Les antibiogrammes ciblés permettent de limiter les prescriptions inappropriées d'antibiotiques en guidant le prescripteur vers les molécules recommandées. Mais ils n'ont pas d'effet sur les prescriptions inutiles, c'est-à-dire lorsqu'il n'est pas nécessaire de prescrire une antibiothérapie. Une autre stratégie de rendu modifié des antibiogrammes consiste à ne pas rendre l'antibiogramme dans certaines situations. Cette stratégie est particulièrement pertinente dans les cas de bactériurie asymptomatique (colonisation urinaire), c'est-à-dire lorsque des bactéries sont présentes dans les urines mais que le patient ne présente pas de symptômes.(69) En effet, dans les cas de bactériurie asymptomatique, l'antibiothérapie n'est pas recommandée (sauf pour les femmes enceintes à partir du quatrième mois de grossesse et chez les patients avant une procédure urologique invasive programmée).(65)

Peu d'études ont évalué l'impact de l'absence de rendu des antibiogrammes. Une équipe canadienne a réalisé une étude contrôlée randomisée dans deux hôpitaux en 2017.(102) Les ECBU étaient randomisés entre le rendu habituel de l'antibiogramme et l'absence de rendu. Le compte-rendu de l'ECBU dans le groupe où l'antibiogramme n'était pas rendu précisait que l'ECBU était positif mais qu'il pouvait être en lien avec une bactériurie asymptomatique. Si une infection urinaire était suspectée cliniquement, le prescripteur pouvait obtenir les résultats de l'antibiogramme sur simple demande au laboratoire de microbiologie. Des investigateurs ont ensuite évalué si les choix de traiter ou non étaient appropriés selon les cas cliniques : pas d'antibiotiques prescrits pour les bactériurie asymptomatique et prescription d'un antibiotique pour les infections urinaires. Les résultats ont montré une proportion de traitements appropriés

significativement supérieure dans le groupe « absence de rendu de l'antibiogramme » (80,0% *versus* 52,7% pour le groupe ayant rendu l'antibiogramme, p = 0,002). Deux études évaluant les potentielles conséquences négatives n'ont pas mis en évidence de risques associés à l'absence de rendu des antibiogrammes pour les ECBU.(102,103)

Ces résultats sont très encourageants, mais des études avec des effectifs plus importants et un haut niveau de preuve sont nécessaires pour confirmer l'impact et les risques associés à l'absence de rendu des antibiogrammes en fonction du type de prélèvement. Se pose également la question de la faisabilité et de l'acceptabilité par les professionnels, qui doivent nécessairement faire l'objet d'évaluations. Si nous avons montré par l'étude ANTIBIO-ciblés que l'antibiogramme ciblé était bien accepté à la fois par les prescripteurs et par les professionnels de laboratoire, il est à craindre que l'absence de rendu soit moins bien perçu et plus difficile à mettre en place. La collaboration entre les prescripteurs et les microbiologistes en milieu hospitalier peut permettre de mettre en place et d'évaluer l'absence de rendu des antibiogrammes. Il semble plus compliqué, en termes de faisabilité et d'acceptabilité, de réaliser ce type d'intervention dans les laboratoires de ville à ce jour.

Une étude, accompagnée par notre équipe, est en cours au centre hospitalier régional universitaire de Nancy pour évaluer l'impact de l'absence de rendu d'antibiogramme dans les ECBU positifs à *Enterococcus faecalis* sur le volume de prescriptions d'antibiotiques et sur les molécules antibiotiques prescrites.

IV – Les implications et perspectives des indicateurs de prescriptions d'antibiotiques

1. Les indicateurs de prescriptions d'antibiotiques dans la stratégie nationale 2022-2025 de prévention des infections et de l'antibiorésistance en santé humaine

Les indicateurs de prescriptions antibiotiques s'ancrent dans l'axe 5 « Utilisation partagée des données de santé et de surveillance au service de l'action » et répondent à l'objectif de « disposer d'indicateurs utiles aux différents acteurs (autorités sanitaires, professionnels de santé) pour piloter la stratégie nationale, régionale et locale ».(59) L'action 29 de cet axe vise notamment à disposer d'ensembles d'indicateurs de bon usage des antibiotiques accompagnés de leur cible, agrégés au niveau national et régional. Ces indicateurs doivent permettre d'évaluer des actions et aider à la prise de décision dans le pilotage des différentes stratégies. Les

indicateurs existants doivent être mis à disposition facilement pour guider la mise en œuvre d'actions à différentes échelles. L'action 30 de l'axe 5 a pour objectif de développer de nouveaux indicateurs quantitatifs, proxy et de qualité, calculables de manière automatisée à partir de données de routine pour les trois secteurs de soins (en ville, en établissements médico-sociaux et en établissements de santé).

Dans l'axe 3 de la stratégie, l'action 22 vise à « développer de nouvelles interventions promouvant le bon usage des antibiotiques ». L'envoi aux prescripteurs de profils individuels de prescriptions, incluant les indicateurs proxy et leurs cibles et accompagnés d'un plan d'action personnalisé, permettrait d'accompagner les professionnels pour améliorer leurs pratiques de prescription des antibiotiques.

2. La validation par les pairs des indicateurs de prescriptions d'antibiotiques

Afin de valider la compréhension et la pertinence des indicateurs par les prescripteurs, des processus de validation par des consensus formalisés d'experts ont été conduits suite à la publication de nos travaux. Ces processus suivaient une méthode de type Delphi modifiée composée d'un premier tour de questionnaire, d'une réunion de consensus et d'un second tour de questionnaire.

Un premier processus de validation, piloté par la mission nationale PRIMO avec le Centre d'appui pour la Prévention des infections associées aux soins (CPias) Pays de la Loire et le centre régional en antibiothérapie Pays de la Loire, a été conduit en 2021 pour valider les indicateurs quantitatifs et proxy des prescriptions d'antibiotiques faites en EHPAD que nous avons développés.(91) Lors de ce processus Delphi, 14 indicateurs quantitatifs ont été maintenus sans modification (parmi les 21 que nous avons développés). Sur les onze indicateurs proxy développés, trois ont été maintenus sans modification, six ont été modifiés, deux ont été supprimés et un nouveau a été ajouté. Ainsi, ce processus a résulté en une liste de 14 indicateurs quantitatifs et dix indicateurs proxy des prescriptions faites en EHPAD.(104) Ces travaux pourront alimenter les actions de la stratégie nationale 2022-2025 (59), la mission nationale PRIMO étant coordonnée par Santé publique France.

Un second processus de validation a été piloté par le centre régional en antibiothérapie de la région Grand Est (AntibioEst), en collaboration avec l'Assurance Maladie (Direction Régionale du Service Médical (DRSM) du Grand Est et Direction de la Coordination de la Gestion Du Risque (DCGDR) Grand Est) et l'unité de recherche APEMAC de l'Université de Lorraine en 2021 et 2022. Il avait pour objectif de valider les indicateurs proxy développés pour

les prescriptions d'antibiotiques faites par les médecins généralistes.(85) Parmi les dix indicateurs proxy initiaux, trois ont été maintenus sans modification et sept ont été modifiés. Deux nouveaux indicateurs ont été ajoutés. Le processus a ainsi permis de valider une liste de douze indicateurs proxy des prescriptions faites par les médecins généralistes. Le Ministère en charge de la Santé, la Caisse Nationale d'Assurance Maladie (CNAM) et Santé publique France étant conviés aux réunions de ce projet en tant qu'observateurs, il est également probable que ces travaux puissent alimenter le déploiement de la stratégie nationale 2022-2025.(59)

3. L'utilisation des indicateurs de prescriptions d'antibiotiques

Les indicateurs de prescriptions d'antibiotiques peuvent être utiles aux différents acteurs du bon usage des antibiotiques (prescripteurs, établissements, équipes multidisciplinaires en antibiothérapie, centres régionaux en antibiothérapie, autorités de santé, …) dans l'objectif d'améliorer l'usage des antibiotiques. Ils permettent de décrire et comparer l'usage des antibiotiques dans le temps et dans l'espace (entre prescripteurs/établissements) et de faire des retours d'information aux prescripteurs/établissements sur leurs prescriptions. Ils peuvent être utilisés pour guider les interventions de bon usage en ciblant des actions à prioriser, selon les indicateurs proxy ayant obtenu les moins bonnes performances. Par exemple, pour les EHPAD de Lorraine, des actions pourraient viser la réduction des prescriptions d'antibiotiques non indiqués, des sur-prescriptions d'antibiotiques en période hivernale ou encore l'amélioration de la couverture vaccinale antigrippale. Pour les chirurgiens-dentistes de la région Grand Est, une priorité d'action est de réduire les prescriptions d'antibiotiques rarement indiqués en odontologie. Enfin, les indicateurs permettent d'évaluer l'impact des interventions mises en place, en analysant l'évolution avant/après de leurs résultats.

L'identification des caractéristiques liées à la pertinence des prescriptions peut permettre de guider les interventions de bon usage des antibiotiques en ciblant le groupe de prescripteurs avec des pratiques moins bonnes que la moyenne. Il pourrait aussi être envisagé de cibler les prescripteurs présentant certaines des caractéristiques associées à de moins bonnes pratiques de prescription. Par exemple, les interventions de bon usage des antibiotiques à destination des médecins généralistes de la région Grand Est pourraient cibler les hommes exerçant depuis longtemps dans le département de la Haute-Marne, n'ayant pas de mode d'exercice particulier et ayant un nombre élevé de consultations par mois. Pour les chirurgiens-dentistes de la région Grand Est, il pourrait être pertinent de cibler les femmes exerçant en Champagne-Ardenne depuis longtemps et réalisant beaucoup d'actes par patients.

4. Des illustrations de l'utilisation des indicateurs de prescriptions d'antibiotiques

Deux illustrations de l'intérêt et de l'utilisation concrète des indicateurs des prescriptions d'antibiotiques que nous avons développés sont présentées ci-dessous.

La mission nationale SPARES « Surveillance et prévention de la résistance bactérienne en établissement de santé » est conduite par le Centre d'appui pour la Prévention des infections associées aux soins (CPias) Grand Est et pilotée par Santé publique France. Le rapport sur la surveillance de la consommation d'antibiotiques en EHPAD a été publié en mai 2021.(20) Les données 2018 et 2019 des consommations d'antibiotiques en EHPAD avec pharmacie à usage intérieur y sont présentées. Les indicateurs que nous avons développés pour les prescriptions d'antibiotiques faites en EHPAD sans pharmacie à usage intérieur ont été adaptés et utilisés pour la méthodologie de ce rapport. En effet, une adaptation était nécessaire car les données recueillies pour les EHPAD avec pharmacie à usage intérieur sont des données agrégées, et non des données individuelles à l'échelle du patient et de la prescription. Le **Tableau 1** présente les résultats pour quatre indicateurs analysés sur les données 2019 selon le type d'établissement de santé auquel l'EHPAD est rattaché. Deux sont issus des indicateurs quantitatifs et deux des indicateurs proxy. On peut noter par exemple que l'indicateur « ratio antibiotiques (ATB) 1ère intention » correspond à l'indicateur proxy PI 6 de notre étude, pour lequel un objectif cible était fixé > 1. Les résultats pour les EHPAD inclus dans le rapport SPARES sont encourageants pour cet indicateur, le ratio étant compris entre 2,3 et 3,0. La **Figure 13** illustre graphiquement les résultats pour trois des indicateurs, en 2018 et en 2019, parmi les EHPAD ayant recueilli les données de consommation d'antibiotiques sur ces deux périodes.

Tableau 1. Indicateurs de la consommation antibiotiques en 2019 dans 455 EHPAD. Mission SPARES, France, résultats 2019.(20)

Indicateurs	Proportion ATB large spectre*/ Total J01 (%)	Proportion ATB Injectables / Total J01 (%)	Ratio ATB 1re intention**	Proportion ATB non indiqués (%) ***
CHU (N=14)	53,5	10,2	3,0	0,4
CH≤33% (N=145)	47,8	6,8	2,4	0,7
CH>33% (N=230)	54,0	9,1	2,5	0,6
MCO (N=15)	45,2	7,4	2,3	0,6
ESSR (N=14)	45,6	6,9	2,3	0,3
ESLD (N=13)	47,8	6,2	2,3	0,5
PSY (N=17)	52,3	7,2	2,5	0,3
EHPAD (N=7)	55,5	7,7	2,5	0,1
Ensemble (N=455)	51,6	8,2	2,5	0,6

** A moxicilline-acide clavulanique, céphalosporines, carbapénèmes et fluoroquinolones parmi la consommation des ATB de la classe ATC J01*
*** Amoxicilline (J01CA04) + amoxicilline - ac clavulanique (J01CR02) / quinolones (J01M) + céphalosporines (J01D) + MLS (J01F)*
**** Loméfloxacine (J01MA07) + moxifloxacine (J01MA14) + quinolones à visée urinaire (norfloxacine (J01MA06) + télithromycine (J01FA15) + spiramycine-métronidazole (J01RA04) + cefaclor (J01DC04) + cefadroxil (J01DB05) / J01*

ATB : antibiotiques ; CHU : centre hospitalier universitaire ; CH : centre hospitalier ; MCO : établissement privé à but lucratif ou non, ayant une activité prédominante de médecine, chirurgie ou obstétrique ; ESSR : établissement privé à but lucratif ou non, de soins de suite et de réadaptation ; ESLD : établissement de soins de longue durée ; PSY : établissement spécialisé en psychiatrie ; EHPAD : établissement d'hébergement pour personnes âgées dépendantes.

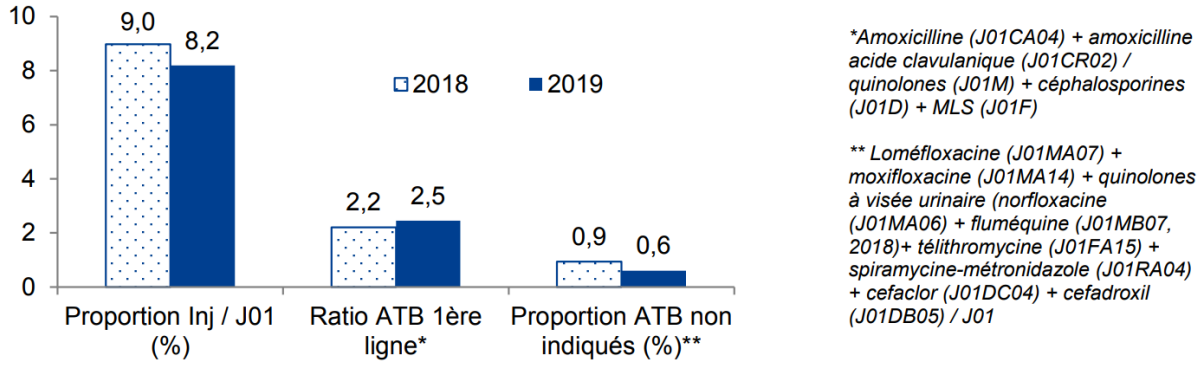

Figure 13. Indicateurs de la consommation antibiotiques en 2018 et 2019 dans la cohorte des 342 EHPAD. Mission SPARES, France, résultats 2019.(20)

Un article faisant l'état des lieux de l'antibiothérapie en odontologie en France en 2019 a été publié en mars 2022 par nos partenaires de l'Université de Lorraine (faculté d'odontologie) et de la Direction Régionale du Service Médical (DRSM) Grand Est.(22) Les **Figures 14, 15 et 16**, extraites de cet article, présentent trois des indicateurs proxy que nous avons développés pour les prescriptions faites par les chirurgiens-dentistes, ici agrégés au niveau régional.

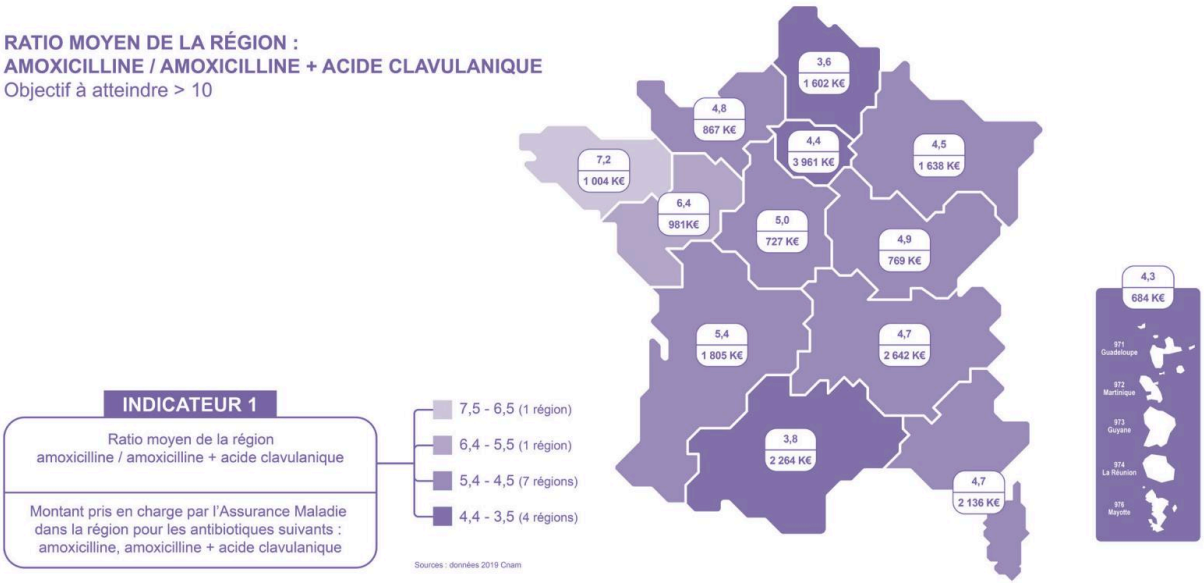

Figure 14. Ratio moyen de prescriptions par les chirurgiens-dentistes pour l'amoxicilline / amoxicilline + acide clavulanique (indicateur 1) par région (illustration Annick Mischler).(22)

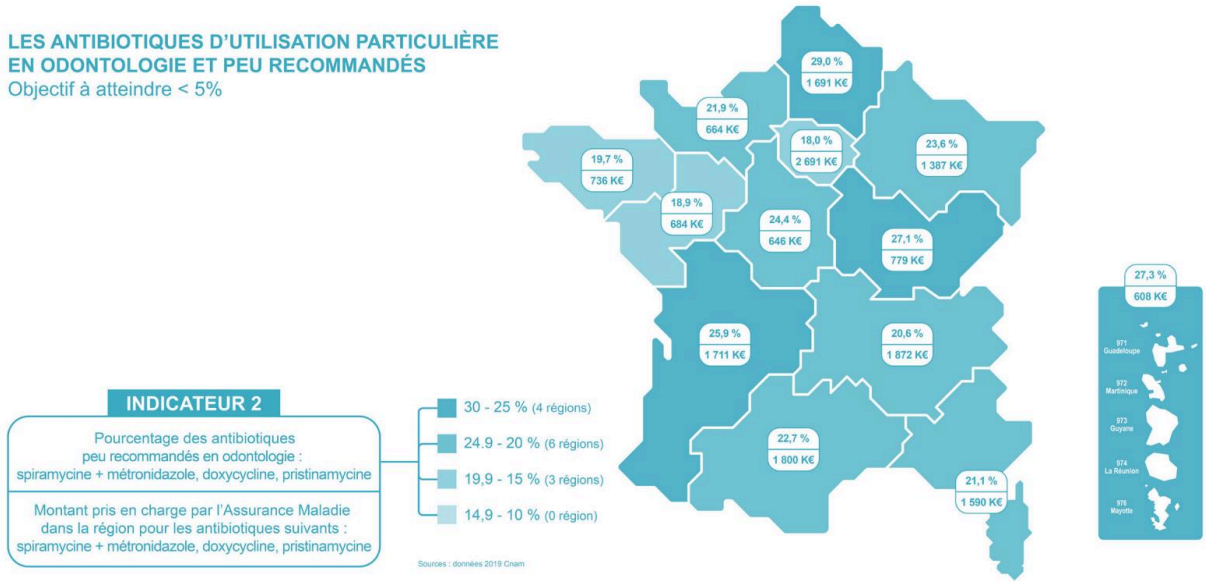

Figure 15. Pourcentage de prescriptions par les chirurgiens-dentistes des antibiotiques peu recommandés par l'ANSM en odontologie (indicateur 2) par région (illustration Annick Mischler).(22)

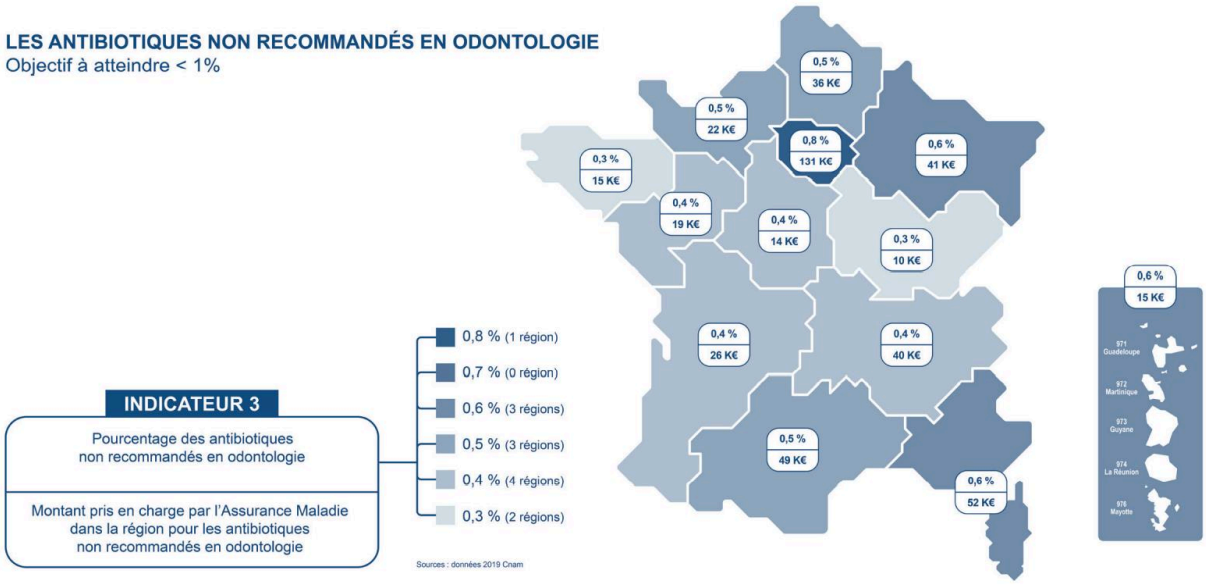

Figure 16. Pourcentage de prescriptions par les chirurgiens-dentistes des antibiotiques non recommandés par l'ANSM en odontologie (indicateur 3) par région (illustration Annick Mischler).(22)

5. Les profils individualisés de prescription

Deux projets incluant des profils individualisés de prescription sont actuellement en cours en région Grand Est. Notre équipe fait partie des comités de pilotage de ces projets. Les profils individualisés de prescription sont composés des indicateurs proxy que nous avons développés et permettent de faire un retour à chaque prescripteur sur ses propres prescriptions. Ces profils pourront être régulièrement envoyés aux prescripteurs afin de les inciter à améliorer leurs pratiques de prescription d'antibiotiques.

Un projet de bon usage des antibiotiques à destination des médecins généralistes de la région Grand Est est piloté par l'Assurance Maladie (Direction Régionale du Service Médical (DRSM) du Grand Est et Direction de la Coordination de la Gestion Du Risque (DCGDR) Grand Est), en collaboration avec le centre régional en antibiothérapie du Grand Est (AntibioEst), l'unité de recherche APEMAC de l'Université de Lorraine, l'Observatoire du MEdicament, des Dispositifs médicaux et de l'Innovation Thérapeutique (Omedit) Grand Est, l'Agence Régionale de Santé (ARS) Grand Est, la Direction Interministérielle de la Transformation Publique (DITP) et la *Behavioural Insights Team.* Des profils individuels de prescription seront transmis aux médecins généralistes chaque année.(105) Ces profils comporteront les résultats individuels des douze indicateurs proxy validés par le processus Delphi précédemment présentés. Des envois trimestriels sont également envisagés en classant les indicateurs proxy selon trois thèmes : (i) favoriser les antibiotiques de première intention,

(ii) prescrire à bon escient et (iii) éviter les prescriptions d'anti-inflammatoires en cas d'infections. Les profils seront accompagnés de ressources éducatives à travers un site internet, des outils d'aide à la prescription et des échanges avec des délégués de l'Assurance Maladie et des membres d'AntibioEst. Le premier envoi des profils de prescriptions est prévu pour le dernier trimestre 2022.

Le projet DentibioRésist de bon usage des antibiotiques par les chirurgiens-dentistes de la région Grand Est est coordonné par l'Université de Lorraine (faculté d'odontologie de Nancy) et la Direction Régionale du Service Médical (DRSM) Grand Est, en partenariat avec le conseil de l'Ordre des chirurgiens-dentistes, les UFR d'odontologie du Grand Est, l'unité de recherche APEMAC de l'Université de Lorraine et le centre régional en antibiothérapie du Grand Est AntibioEst. Ce projet associe l'envoi de profils individualisés de prescription contenant trois des indicateurs proxy que nous avons développés pour les prescriptions des chirurgiens-dentistes à un site internet (106), des campagnes d'échanges confraternels et des formations en e-learning. Les profils individuels ont été envoyés en juin 2021 (données des prescriptions 2019) et en juin 2022 (données des prescriptions 2021). Les **Figures 17 et 18** présentent un exemple de profil individuel de prescriptions (anonymisé). Une évaluation d'impact de ce projet est prévue, accompagnée par notre équipe de recherche.

Les profils individuels de prescription ont été présentés dans le rapport de l'Assurance Maladie sur l'évolution des charges et des produits de l'Assurance Maladie, visant à fournir des propositions concrètes pour améliorer la qualité du système de santé et maîtriser les dépenses en 2023.(107)

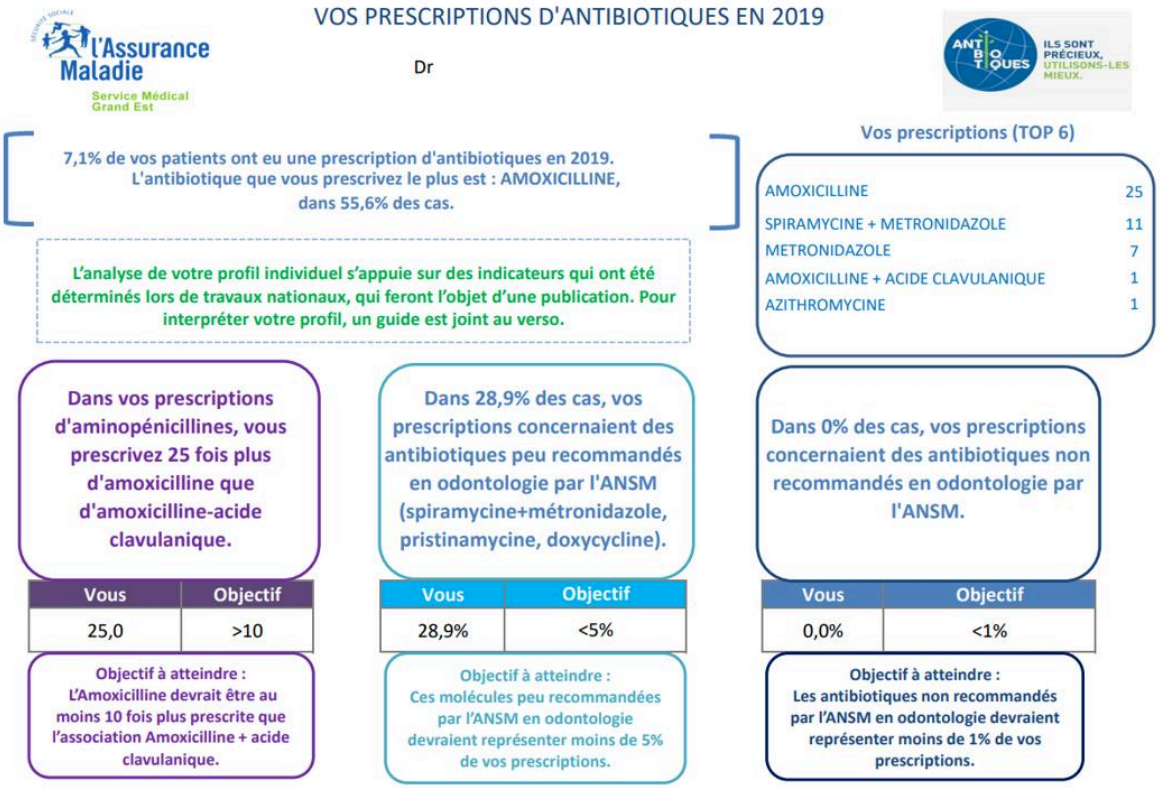

Figure 17. Profils individuels de prescriptions d'antibiotiques à destination des chirurgiens-dentistes de la région Grand Est (recto).

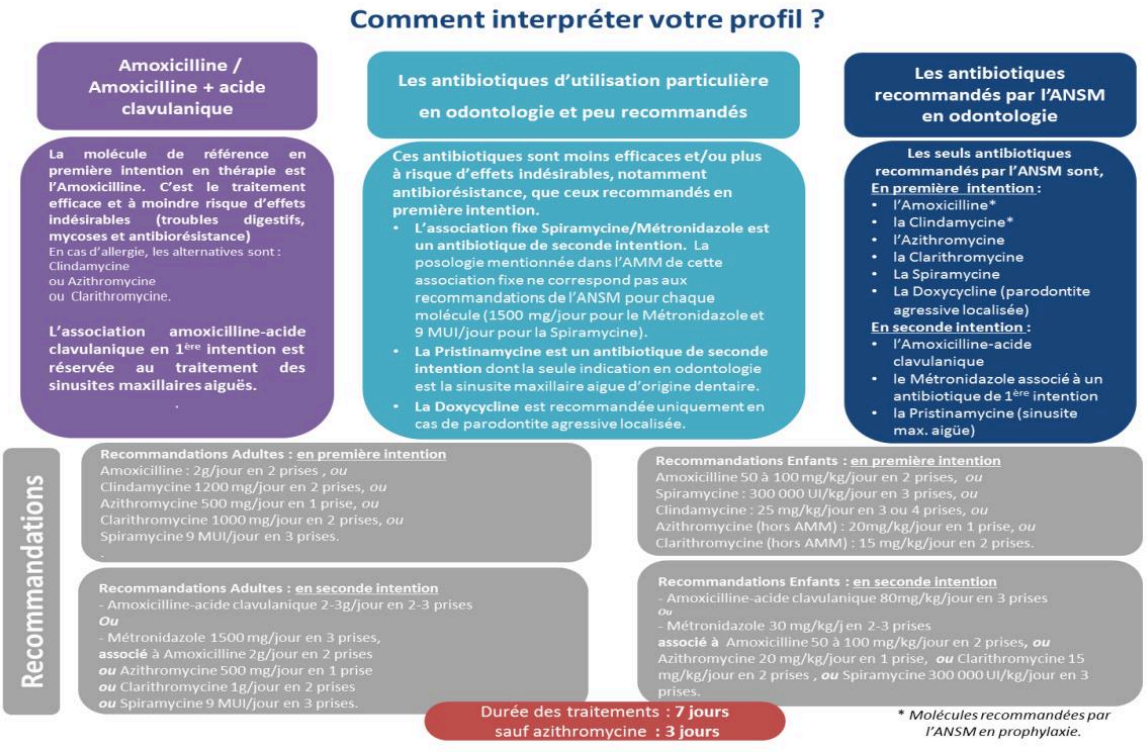

Figure 18. Profils individuels de prescriptions d'antibiotiques à destination des chirurgiens-dentistes de la région Grand Est (verso).

IV – Conclusion

Au cours de cette thèse, des outils permettant d'améliorer les prescriptions d'antibiotiques en soins primaires de ville (notamment par les médecins généralistes et les chirurgiens-dentistes) ont été développés et évalués. Les différents projets ont trouvé application à large échelle en informant les politiques publiques régionale et nationale. Les résultats positifs et innovants de l'évaluation des antibiogrammes ciblés ont permis d'apporter un retour d'expérience pour alimenter les réflexions sur le déploiement national des antibiogrammes ciblés dans les ECBU positifs à entérobactéries. Les indicateurs des prescriptions d'antibiotiques ont été utilisés pour décrire et comparer les prescriptions d'antibiotiques à l'échelle nationale sur une période donnée et pour concevoir des profils individualisés de prescription.

Dans le contexte où l'antibiorésistance est une menace croissante pour la santé publique mondiale, il est crucial de continuer à améliorer les prescriptions et plus globalement l'usage des antibiotiques. Agir pour un meilleur usage des antibiotiques entraîne des bénéfices (i) individuels pour le prescripteur, par l'amélioration de ses pratiques ; (ii) individuels pour le patient, qui sera mieux pris en charge et moins exposé à des risques iatrogènes médicamenteux ; et (iii) collectifs en termes de santé publique, par la prévention de l'émergence de résistances bactériennes et la diminution des coûts qui y sont associés. Il est donc indispensable de mettre en place davantage d'actions visant au bon usage des antibiotiques, afin d'éviter qu'ils ne deviennent inefficaces et que les maladies infectieuses redeviennent l'une des premières causes de mortalité dans le monde.(33)

"*Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine. Unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating.*" – Docteur Keiji Fukuda, sous-directeur général de l'Organisation Mondiale de la Santé (OMS), 30 avril 2014.(108)

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Résumé - L'antibiorésistance est une problématique de Santé publique mondiale. La lutte contre l'antibiorésistance doit passer par l'amélioration de l'usage des antibiotiques, notamment en médecine de ville où 78% des antibiotiques à usage humain sont prescrits. Les travaux de cette thèse s'intéressent à l'évaluation d'interventions visant à améliorer les prescriptions d'antibiotiques en soins primaires de ville et s'articulent autour de deux thématiques : (i) les antibiogrammes ciblés, intervention permettant de favoriser le bon usage des antibiotiques et (ii) les indicateurs de prescriptions d'antibiotiques, outils permettant notamment d'évaluer l'effet d'interventions de bon usage des antibiotiques. Une étude interventionnelle pragmatique, prospective, comparative (antibiogrammes ciblés comparativement aux antibiogrammes complets habituels) de type avant-après (la mise en place des antibiogrammes ciblés) a été conduite en région Lorraine pour évaluer l'impact des antibiogrammes ciblés dans les ECBU positifs à *Escherichia coli* sur les prescriptions d'antibiotiques critiques (amoxicilline-acide clavulanique, céphalosporines de troisième génération et quinolones) en ambulatoire et en EHPAD, ainsi que leur faisabilité et leur acceptabilité. L'évaluation des antibiogrammes ciblés a montré un impact positif, permettant de réduire les taux de prescriptions d'antibiotiques critiques grâce à une diminution des taux de prescriptions de céphalosporines de troisième génération chez les femmes, sans entraîner d'impact négatif sur la morbidité (nombres de consultations et d'hospitalisations). La mise en œuvre des antibiogrammes ciblés était faisable pour les laboratoires de biologie médicale qui y ont dédié 23 000 euros et 80 heures de travail. L'acceptabilité était élevée pour l'ensemble des professionnels interrogés (médecins généralistes et personnels de laboratoire) qui étaient très favorables à la généralisation des antibiogrammes ciblés au niveau national. A partir de la littérature et des bases de données de remboursement de l'Assurance Maladie, 15 indicateurs quantitatifs et 11 indicateurs proxy ont été développés, permettant d'estimer respectivement le volume et la pertinence des prescriptions d'antibiotiques faites en EHPAD (à l'échelle de l'établissement) par les médecins généralistes. Les indicateurs dits « proxy » permettent d'approcher indirectement la qualité des prescriptions à un niveau agrégé sans nécessité de données cliniques pour être calculés. Ils explorent différentes situations cliniques fréquemment causes de mésusage des antibiotiques. Selon la même méthodologie, quatre indicateurs proxy ont été développés pour estimer la pertinence des prescriptions d'antibiotiques faites par les chirurgiens-dentistes (à l'échelle du prescripteur). Les indicateurs proxy ont ensuite été utilisés pour identifier des groupes de prescripteurs selon la pertinence de leurs prescriptions. Cela a permis d'identifier des caractéristiques liées au prescripteur, à sa patientèle et à sa pratique, qui sont associées à la pertinence des prescriptions. Ce travail a été réalisé pour les médecins généralistes et pour les chirurgiens-dentistes. Cette thèse a permis le développement et l'évaluation d'outils permettant d'améliorer et d'évaluer les prescriptions d'antibiotiques en soins primaires de ville. Les différents projets ont trouvé application à large échelle en informant les politiques publiques, régionale et nationale. Les résultats positifs et innovants de l'évaluation des antibiogrammes ciblés ont permis d'apporter un retour d'expérience pour alimenter les réflexions sur le déploiement national des antibiogrammes ciblés dans les ECBU positifs à entérobactéries. Les indicateurs des prescriptions d'antibiotiques ont été utilisés pour décrire et comparer les prescriptions d'antibiotiques à l'échelle nationale sur une période donnée et pour concevoir des profils individualisés de prescription.

Abstract - Antibiotic resistance is a major threat to global public health. To tackle antibiotic resistance, antimicrobial stewardship is crucial to improve antibiotics' use, notably in the outpatient setting where 78% of human antibiotics are prescribed. This PhD subject is the evaluation of interventions to improve antibiotic prescriptions in the outpatient setting. It is organized in two themes: (i) the selective reporting of antibiotic susceptibility testing (AST), intervention to promote antibiotic appropriate use, and (ii) indicators of antibiotics' prescriptions, tools to evaluate the impact of antibiotic stewardship interventions. An interventional, pragmatic, prospective, comparative (selective reporting of AST *versus* complete reporting of AST) before-after (the implementation of the selective reporting of AST) study was conducted in the Lorraine region, to evaluate the impact of selective reporting of AST in *Escherichia coli*-positive urine cultures, on 'critical' antibiotics prescriptions (amoxicillin-clavulanate, third-generation cephalosporins, and quinolones), in the outpatient setting and in nursing homes. Feasibility and acceptability were also evaluated. Selective reporting of AST evaluation showed a positive impact, reducing the prescription rate of critical antibiotics related to a decrease in the prescription rate of third-generation for women. No unintended clinical consequences were observed (numbers of consultations and hospitalizations). The implementation of selective reporting of AST was feasible for laboratories which had dedicated 23,000 euros and 80 working hours. The acceptability was important for all interviewed professionals (general practitioners and laboratories' professionals) who were in favor of the national generalization of the selective reporting of AST. Based on the literature and the Health Insurance reimbursement databases, 15 quantity metrics and 11 proxy indicators were developed to estimate respectively the volume and the appropriateness of antibiotic prescriptions of general practitioners in nursing homes (at the facility level). Proxy indicators indirectly estimate the quality of prescriptions at an aggregated level, without requiring clinical indications for their calculation. They explore various clinical situations frequently responsible for antibiotics misuse. Using the same methodology, four proxy indicators were developed, estimating the appropriateness of antibiotic prescriptions by dentists (at the prescriber level). Proxy indicators were then used to identify characteristics related to prescriber, his/her patients and his/her practice, which were associated with the appropriateness of their prescriptions. This project was conducted for general practitioners and dentists. Through this PhD, tools were developed and evaluated to improve antibiotic prescriptions and their evaluation in the outpatient setting. The different projects had an impact at a larger-scale, informing regional and national stakeholders. The positive and innovative results of the selective reporting of AST were useful to feed discussions on their national generalization for *Enterobacterales*-positive urine cultures. Indicators of antibiotic prescriptions were used to describe and compare national antibiotic prescriptions and to design individualized prescriptions profiles to facilitate feedback to prescribers.