MEASURING ANTIMICROBIAL USE TO PREDICT RESISTANCE OF HEALTHCARE-ASSOCIATED MICROBIOTA

Elise Fortin, M. Sc.

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Montreal

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LIST OF ABBREVIATIONS

3GC:	third-generation cephalosporins
adm:	admissions
ADT :	admissions/discharges/transfers
AICU :	adult intensive care unit
AM:	antimicrobial
Amino:	aminoglycosides
ARC:	aminoglycoside-resistant coliforms
CNISP :	Canadian Nosocomial Infection Surveillance Program
CREKP:	carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.
CRP:	carbapenem-resistant *Pseudomonas* sp.
DDD :	defined daily doses
DNA :	deoxyribonucleic acid
DOT:	days of therapy
EARS-net :	European Antimicrobial Resistance Surveillance Network
EKP:	*E. coli*, *Klebsiella* sp. and *Proteus* sp.
HICPAC :	Healthcare Infection Control Practices Advisory Committee
ICU :	intensive care unit
LOT:	length of therapy
MAE:	mean absolute error
MLIS :	microbiology laboratory information system
MRSA:	methicillin-resistant *Staphylococcus aureus*
NHSN :	National Healthcare Safety Network
NICU:	neonatal intensive care unit
pd:	patient-days
PDD :	prescribed daily doses
PICU:	pediatric intensive care unit
Pip-tazo:	piperacillin-tazobactam
PTRC:	piperacillin-tazobactam-resistant coliforms

PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.

QRC: quinolone-resistant coliforms

QRP: quinolone-resistant *Pseudomonas* sp.

RDD : recommended daily doses

SPIN : *surveillance provinciale des infections nosocomiales*

SPIN-BACTOT: Québec healthcare-associated bloodstream infections surveillance network

TATFAR : Transatlantic Taskforce on Antimicrobial Resistance

WHO : World Health Organization

ABRÉGÉ

En 2011, l'Organisation Mondiale de la Santé, consacrait sa Journée mondiale de la santé à la résistance aux antibiotiques, étant donné son impact sur notre capacité à traiter les infections. Déjà en 2001, des recommandations avaient été faites afin de contrôler la résistance aux antibiotiques; la surveillance de la résistance en milieu hospitalier faisait partie de ces recommandations. Bien qu'il soit difficile de quantifier la relation causale entre l'utilisation des antibiotiques et la résistance, les contextes, les méthodologies et les biais reliés variant beaucoup, cette relation est généralement acceptée. L'utilisation d'antibiotiques étant un facteur modifiable, sa surveillance est également recommandée, en tant que complément à la résistance aux antibiotiques.

Dans la pratique, les réseaux surveillant l'utilisation des antibiotiques et les équipes de recherche ont recours à de nombreuses méthodologies afin de mesurer l'utilisation des antibiotiques. Depuis plusieurs années, l'Organisation Mondiale de la Santé recommande l'utilisation des doses journalières définies par jours-présence. Cet indicateur ne prend toutefois pas en compte le poids des patients, ce qui en limite l'usage dans les populations où les doses sont déterminées en fonction du poids, telles que les populations pédiatriques. Plusieurs autres indicateurs ont été développés, parfois spécifiquement pour contourner ce problème. Par conséquent, il est difficile de comparer les consommations d'antibiotiques mesurées et la meilleure façon de mesurer l'utilisation des antibiotiques, en tant que complément à la surveillance de la résistance, demeure inconnue. Ce projet de thèse visait donc à identifier l'indicateur ou les indicateurs d'utilisation des antibiotiques prédisant le mieux la prévalence et l'incidence de microorganismes résistants dans le microbiome respiratoire des patients hospitalisés aux soins intensifs.

Dans un premier temps, une recension systématique des écrits a été menée afin d'identifier, de définir et de comparer les indicateurs d'utilisation des antibiotiques ayant été utilisés dans des populations incluant des patients pédiatriques, dans le but de complémenter la surveillance de la résistance aux antibiotiques. Vingt-six indicateurs distincts ont été identifiés (combinant 13 numérateurs et 5 dénominateurs) dans les 79 études sélectionnées. Seules deux de ces

études ont étudié la corrélation entre certains indicateurs; une seule a étudié la corrélation entre deux indicateurs et la résistance.

Devant cette absence de données, nous avons demandé à quatre hôpitaux (neuf unités de soins intensifs) de Montréal, au Canada, d'extraire des données individuelles sur tous les patients admis à une unité de soins intensifs entre le 1er avril 2006 et le 31 mars 2010. L'information demandée incluait les dates d'admission, de congé et de transfert, les résultats d'antibiogrammes des cultures respiratoires positives et les ordonnances d'antibiotiques. L'obtention d'extractions de bonne qualité s'est révélée être complexe et a représenté un défi important. Par la suite, nous avons pu procéder à l'atteinte du deuxième objectif, qui consistait à décrire, dans les unités de soins intensifs participantes, l'utilisation d'antibiotiques et la prévalence et l'incidence de résistances cliniquement importantes, en utilisant divers indicateurs et définitions. Les *Staphylococcus aureus* résistants à l'oxacilline et les coliformes résistants au pipéracilline-tazobactam étaient les résistances les plus fréquentes, du point de vue de la prévalence (0,52% et 0,44% des admissions aux soins intensifs) et de l'incidence (6,57 et 7,80 acquisitions / 10 000 jours-présence). Les céphalosporines, les pénicillines et les aminoglycosides étaient les antibiotiques les plus fréquemment prescrits, d'après la plupart des indicateurs. Toutefois, les indicateurs ne détectaient pas tous les mêmes tendances annuelles ni les mêmes différences entre les types d'unités de soins intensifs.

Enfin, des modèles de régression ont permis d'étudier vingt scénarios combinant une résistance donnée avec l'utilisation d'antibiotiques donnés. Dans chaque modèle, ajusté pour le type d'unité de soins intensifs, un indicateur d'utilisation d'antibiotiques servait à prédire la résistance étudiée (prévalence ou incidence), par unité de soins intensifs et par période de quatre semaines. Pour chaque scénario, la justesse de la prédiction atteinte avec un certain indicateur était mesurée (en calculant l'erreur absolue moyenne) puis comparée à la justesse atteinte avec les autres indicateurs. Cette démarche avait pour objectif (troisième objectif) d'identifier l'indicateur d'utilisation des antibiotiques qui prédisait la prévalence et l'incidence de la résistance avec le plus de précision et d'exactitude. Dans les faits, tous les indicateurs se sont révélés équivalents, sauf pour 1 des 20 scénarios étudiés : en tentant de prédire la

prévalence des *Pseudomonas* sp. résistants aux carbapénèmes avec l'utilisation des carbapénèmes, les doses journalières recommandées par 100 admissions ne permettaient pas une aussi grande précision que l'indicateur présentant la plus petite erreur absolue moyenne, soit le nombre de traitements par 100 jours-présence ($p = 0.0006$). Une étude de simulation a donc été développée pour savoir si l'absence de différence observée était un problème de puissance. En utilisant les mêmes erreurs absolues moyennes observées, la simulation a permis de voir si les indicateurs étudiés auraient été considérés statistiquement différents avec de plus grands réseaux d'unités de soins intensifs (donc avec plus d'observations). Seulement 28% de tous les scenarios étudiés auraient permis de distinguer, parmi les divers indicateurs, celui permettant de prédire la prévalence ou l'incidence de la résistance avec le plus de justesse. En général, pour ce faire, de très grands réseaux d'unités de soins intensifs auraient été nécessaires. Cette étude confirme que les résultats observés dans l'étude précédente, soit l'incapacité de distinguer les divers indicateurs de façon statistiquement significative, n'étaient pas attribuables à un manque flagrant de puissance statistique.

Depuis des décennies, des indicateurs d'utilisation des antibiotiques ont été développés, utilisés et discutés, mais l'identification d'un meilleur indicateur fait toujours l'objet de débats. Nous avançons que l'objectif de la mesure doit être pris en compte, soit, dans notre cas, la surveillance de l'utilisation des antibiotiques pour complémenter la surveillance de la résistance aux antibiotiques. Si un indicateur s'était démarqué des autres, il aurait permis une surveillance plus étroite des variations dans la résistance aux antibiotiques, accroissant la capacité à détecter un impact d'interventions ciblant l'utilisation des antibiotiques sur les niveaux de résistance aux antibiotiques. Ces premiers résultats indiquent toutefois qu'un tel indicateur n'existe peut-être pas. Conséquemment, le choix d'un indicateur pourrait reposer sur d'autres critères que la justesse de la précision, tels que la faisabilité (facilité de recueillir l'information et de procéder aux calculs) et les comparaisons externes potentielles, et ce, sans réduire la qualité de leurs activités de surveillance.

ABSTRACT

Given the importance of antimicrobial resistance on our ability to treat infectious diseases, the World Health Organization made it its 2011 World Health Day theme. Already in 2001, recommendations to control antimicrobial resistance had been issued, with a highlight on surveillance of resistance in hospitals. Although the causal relationship between antimicrobial use and antimicrobial resistance is difficult to quantify due to the various settings and indicators used and to related biases, this relationship is generally accepted. Considering that antimicrobial use is modifiable, surveillance of antimicrobial use is recommended as a complement to surveillance of antimicrobial resistance.

In practice, measurement methodologies for surveillance of antimicrobial use vary between networks and investigation teams. For many years now, the World Health Organization has been recommending the use of defined daily doses per patient-days. However, this indicator does not take patients' weight into account, thus limiting the use of defined daily doses in pediatric populations, where prescribed doses are based on patients' weight. Many other indicators have been developed, sometimes to circumvent this specific problem. As a result, it is difficult to make valid comparisons of surveillance results and the optimal way to measure antimicrobial use in hospitals, to complement surveillance of resistance, is still unclear. This thesis project thus aimed to identify the most accurate indicator(s) of antimicrobial use for the prediction of prevalence and incidence of resistant microorganisms in the respiratory microbiota of patients admitted to intensive care units (ICU).

We first performed a systematic literature review to list, define and compare existing indicators of antimicrobial use that have been applied in settings that included pediatric inpatients, to complement surveillance of resistance. Twenty-six different indicators (combining 13 numerators and 5 denominators) were identified from the 79 selected studies. Only two of these studies measured correlation between some indicators; only one looked at the correlation between two indicators and resistance.

As additional evidence on this topic was obviously required, we asked four hospitals (nine intensive care units [ICUs]) in Montreal, Canada, to provide individual-level data on all patients

admitted to an ICU between April 1st, 2006 and March 31st, 2010. We asked for information on admission, discharge and transfer dates, on results of positive respiratory cultures and on antimicrobial prescriptions. In the data collection process, we realized that access to good quality data extractions was a challenge that we had to address. We were then able to carry on with our second objective, which was to describe antimicrobial use, as well as prevalence and incidence of clinically relevant resistances in our participating ICUs, using different definitions and indicators. The highest prevalence and incidence rates were for resistance to oxacillin in *Staphylococcus aureus* (0.52 % of ICU admissions and 6.57 acquisitions / 10,000 patient-days) and to piperacillin-tazobactam in coliforms (0.44% and 7.80 acquisitions / 10,000 patient-days). Cephalosporins, penicillins and aminoglycosides were the most frequently prescribed antimicrobials, according to most indicators. However, indicators had variable sensitivity to detect annual time trends and differences between ICU types.

Finally, regression models were built to study twenty resistance / antimicrobial use scenarios. In each model, adjusted for ICU type, an indicator of antimicrobial use was used to predict a given resistance (prevalence or incidence) in each ICU, per 4-week period. For each scenario, predictive accuracy obtained with each indicator of antimicrobial use was measured (via mean absolute errors) and compared to predictive accuracy reached with other indicators. This was done to identify the indicator of antimicrobial use that predicted prevalence and incidence rates of resistance with the best accuracy (third objective). Results for all indicators were equivalent, except for 1 of the 20 scenarios studied: when predicting prevalence of carbapenem-resistant *Pseudomonas* sp. with carbapenem use, recommended daily doses per 100 admissions were less accurate than courses per 100 patient-days ($p = 0.0006$), which was the indicator presenting the smallest mean absolute error. We then ran a simulation study to determine if the lack of difference observed was a power issue. Using similar mean absolute errors as was found in our study, but with larger networks of ICUs (thus larger numbers of observations), we aimed to determine if we could detect statistically significant differences between indicators. Only 28% of all studied scenarios would have allowed to identify the most accurate indicator for the prediction of resistance prevalence and incidence. In general, large networks of ICUs would be necessary to do so, given differences observed in a previous cohort study. This confirms that the

absence of observed statistically significant differences in our study was not due to a blatant lack of statistical power.

Indicators of population antimicrobial use have been developed, used and discussed for decades now, but the identification of the best indicator is still an object of debate. We believe that the purpose of measurement, surveillance of antimicrobial use as a complement to surveillance of antimicrobial resistance, has to be taken into consideration. Our study has shown that, at least in our context, indicators are equivalent. Had an indicator been more accurate than others, it would have allowed a closer monitoring of variations in antimicrobial resistance frequency, and an increased ability to detect the impact on resistance of interventions targeting antimicrobial use. These first results however indicate that a single best indicator might not exist and that feasibility considerations, such as ease of computation or potential external comparisons could be more decisive in the choice of an indicator for surveillance of healthcare antimicrobial use.

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I would like to thank my supervisors, Dr. Caroline Quach and Dr. Robert W. Platt, as well as Dr. Amee R. Manges, who supervised me until the protocol defence. The quality of their mentorship, their passion for science, their incredible availability, and their frank but non-judgmental remarks, created a wonderful learning environment. The fear of disappointing these people was a non-negligible source of motivation throughout my doctoral years.

I would also like to thank Dr. David L. Buckeridge and Dr. Patricia S. Fontela, the other members of my thesis committee, for their sound scientific advice and their involvement in my research project.

I thank Ms. Milagros Gonzales and Dr. Philippe Ovetchkine, who are co-authors on some of the manuscripts included in this thesis. Their point of view was very informative and improved the presentation of our results. I am also grateful to Ms. Lorie Kloda, Ms. Lindsay Sikora and Dr. Jesse Papenburg for their help with the systematic literature review, to Dr. Lena Coic, Mr. Érick Léveillé, Mr. Jonathan Talbot, Ms. Annie Desjardins and Ms. Sylvie Laperrière, Dr. Anne Fortin, Ms. Isabelle Rocher, Ms. Lucy Montes and Dr. Marc Dionne for their collaboration in the careful review of data, and to Dr. Michal Abrahamowicz for suggesting the idea of a study to assess power to answer the research question. I also address my heartfelt thanks to my PhD cohort colleagues: I highly appreciated the collaborative spirit during courses and protocol development, which has contributed to making the whole doctoral experience pleasant and stimulating.

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PREFACE

Contribution of authors

I defined the research question in collaboration with my initial supervisors, Dr. Caroline Quach and Dr. Amee R. Manges. I then developed the specific objectives and the research protocol, under their supervision, and got advice from the other members of my thesis committee, Dr. Robert W. Platt, Dr. David L. Buckeridge and Dr. Patricia S. Fontela. After the protocol defence, Dr. Platt replaced Dr. Manges as my co-supervisor, as Dr. Manges moved to British Columbia.

For the systematic literature review, I selected, collected and extracted information for all relevant references. Dr. Fontela participated in the selection of eligible references and information extraction, as two reviewers were needed for these steps. For the cohort study, Dr. Quach obtained data from participating hospitals, but I carefully reviewed data extractions until their quality was optimal. I aggregated and analyzed data myself, producing new databases in a format that allowed me to answer the thesis objectives. I was responsible for the initial interpretation of results. After discussing results with my thesis committee, I wrote the first drafts of all manuscripts, which were reviewed at first by Dr. Quach, then by the other co-authors. The manuscript on the simulation study was first reviewed by Dr. Platt. I wrote all chapters of this PhD thesis.

Co-authors of manuscripts presented in this thesis have contributed as follows:

1. Élise Fortin, Patricia S. Fontela, Amee R. Manges, Robert W. Platt, David L. Buckeridge, Caroline Quach. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to paediatrics. *J Antimicrob Chemother* 2014; 69: 1447-56.
   Conception: EF, CQ and PSF; data collection: EF and PSF; data analysis: EF; interpretation: EF, PSF and CQ; writing: EF, PSF, ARM, RWP, DLB and CQ; critical revision: PSF, ARM, RWP, DLB and CQ.
   Permission to reproduce this article in the thesis was granted by all co-authors and by the *Journal of Antimicrobial Chemotherapy*.

2. Élise Fortin, Milagros Gonzales, Patricia S. Fontela, Robert W. Platt, David L. Buckeridge, Caroline Quach. Improving quality of data extractions for the computation of patient-days and admissions *Am J Infect Control* 2014; 43: 174-176.

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   Permission to reproduce this article in the thesis was granted by all co-authors and by the *American Journal of Infection Control*.

3. Élise Fortin, Robert W. Platt, Patricia S. Fontela, Milagros Gonzales, David L. Buckeridge, Philippe Ovetchkine, Caroline Quach. Measurement of antimicrobial resistance and antimicrobial use in nine intensive care units, using different definitions and indicators. To be submitted for publication.

   Conception: EF and CQ; data collection: EF, MG, PO and CQ; data analysis: EF; interpretation: EF, PSF, MG, PO and CQ; writing: EF, RWP, PSF, MG, DLB, PO and CQ; critical revision: RWP, PSF, MG, DLB, PO and CQ.

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4. Élise Fortin, Robert W. Platt, Patricia S. Fontela, David L. Buckeridge, Caroline Quach. Predicting antimicrobial resistance prevalence and incidence from indicators of antimicrobial use: what is the most accurate indicator? To be submitted for publication.

   Conception: EF, RWP, DLB, CQ; data collection: EF and CQ; data analysis: EF; interpretation: EF, RWP, DLB and CQ; writing: EF, RWP, PSF, DLB and CQ; critical revision: RWP, PSF, DLB and CQ.

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5. Élise Fortin, Caroline Quach, Patricia S. Fontela, David L. Buckeridge, Robert W. Platt. A simulation study to assess indicators of antimicrobial use as predictors of resistance: is it

possible to identify the most accurate indicator? Submitted for publication on April 11th, 2015, and minor modifications were asked for on June 15th, 2015.

Conception: EF, CQ and RWP; data collection: EF; data analysis: EF; interpretation: EF and RWP; writing: EF, CQ, PSF, DLB and RWP; critical revision: CQ, PSF, DLB and RWP.

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Statement of originality

The content of this thesis is original work I did to fulfill the requirements of a PhD degree in epidemiology, at McGill University. While I have received guidance from my supervisors, other thesis committee members, and advice from co-authors, this thesis presents my own work.

For decades now, clinicians, public health authorities and administrators have wanted to measure antimicrobial use in populations, including in hospitalized populations. The World Health Organization recommended the use of defined daily doses (DDD) per patient-days as the indicator to follow. However, its use for pediatric populations is not recommended because the indicator cannot account for prescriptions ordered as a factor of patients' weight. Other indicators have been developed, applied and discussed. In a systematic literature review, we were able to list 26 indicators applied to cohorts that included pediatric populations. Such a list did not exist prior to my work. We could also demonstrate that only one study had compared two indicators' correlation with resistance levels. Thus, the need for more exhaustive comparisons became obvious.

To fill this knowledge gap, we created a cohort of all patients admitted to the nine intensive care units (ICUs) of four Montreal hospitals, between April 2006 and March 2010. Our cohort included four adult, 2 pediatric and 3 neonatal ICUs. We first described antimicrobial resistance and antimicrobial use in these participating ICUs, using different definitions and indicators. We then tested time trends and differences between ICU types, for each indicator. Most indicators showed the same trends, but that was not always the case. Past studies did compare indicators, but not as many different indicators as in this study and not in such a systematic way. This

exercise also allowed us to present data on resistance and antimicrobial use from the Province of Quebec, data that are rarely available and published.

Finally, we compared the accuracy of fifteen indicators in their ability to predict resistance prevalence and incidence rates in participating ICUs. Despite years of debate in the scientific community about existing indicators of antimicrobial use, to our knowledge, this exercise had not been done before. We could not identify an indicator or a set of indicators that predicted resistance with better accuracy; a result unlikely attributable to a blatant lack of statistical power, as later demonstrated in a simulation study. However, other investigators might wish to repeat the experiment in different settings to confirm our results. We believe that this thesis proposes a useful methodological framework that not only allows to compare indicators using regression models, but also to determine if observed differences are statistically significant.

This project received approval from the Research Ethics Boards of McGill University and the *Centre Hospitalier Universitaire* Sainte-Justine. No consent from patients was necessary as the data was analyzed anonymously.

CHAPTER 1. INTRODUCTION

Resistance seems to be an unavoidable consequence of antimicrobial use. In 1937, sulfonamides - the first antimicrobials – were developed and in the 1940s, resistance was already reported.[1] As penicillin was introduced, resistant *Staphylococcus aureus* were observed.[2, 3] Use of an antimicrobial exerts a selective pressure on existing microbiota, which promotes the growth of resistant strains, by eliminating others. These strains are then able to proliferate, increasing their probability of transmission.[4-6] Infections caused by resistant microorganisms are not only more difficult to treat, but will often not respond to first-line antimicrobials used empirically and result in more adverse outcomes.[7-14]

Hospitals use massive amounts of antimicrobials and are often faced with an increasing incidence of resistant and multi-resistant microorganisms.[3, 15, 16] Vancomycin-resistant enterococci and staphylococci, methicillin-resistant *S. aureus* and extended spectrum β-lactamase and carbapenemase producing Gram-negative bacteria are healthcare-associated pathogens, which transmission and development need to be controlled.[8, 16, 17] While the implementation of infection prevention and control measures can reduce the impact of resistance (such measures were associated with a decrease in the incidence of methicillin-resistant *S.aureus* bloodstream infections[16, 18]), controlling antimicrobial use, through antimicrobial stewardship programs, is an important intervention that contributes to the control of resistance itself in the inpatient microbiota.[19] Qualitative quality control and surveillance aims to ensure an appropriate use of antimicrobial agents, while quantitative surveillance of population antimicrobial use density allows for benchmarking and monitoring of temporal trends. Integrating surveillance of antimicrobial use with surveillance of bacterial resistance rates can direct efforts to control resistance.[20, 21]

Given the importance of antimicrobial resistance, the World Health Organization made it its 2011 World Health Day theme.[22] Already in 2001, recommendations to control antimicrobial resistance had been issued, with a focus on surveillance of resistance and of antimicrobial use in hospitals.[23] Various surveillance networks currently exist worldwide, using different methodologies. Among these are the European Surveillance of Antimicrobial Consumption

Network, the European Antimicrobial Resistance Surveillance Network, and the National Healthcare Security Network in the United States of America.[16, 21, 24]

The province of Quebec was faced in 2002 with an epidemic of a new, more virulent strain of *Clostridium difficile*, which was thought to be linked with antimicrobial use, in particular quinolones, as this new strain was resistant to quinolones. This proved to be a strong survival benefit for the bacteria. Following the severe morbidity and high mortality in previously healthy adults, the *Ministère de la santé et des services sociaux* implemented an in-depth reorganization of the provincial strategy for surveillance of healthcare-associated infections.[4, 25, 26] The *Comité des infections nosocomiales du Québec*, recognizing the role played by antimicrobial use in the epidemic, and wishing to quantify this major determinant of healthcare-associated infections, recommended the development of a surveillance program of antimicrobial use in hospitals.[27]

In practice, methodologies used for surveillance of antimicrobial use vary between networks and research teams. For decades now, the World health Organization has been recommending the use of defined daily doses per patient-days.[28] However, this indicator does not take patients' weight into account, thus limiting the use of defined daily doses in pediatric, frail elderly and renal insufficient patient populations, where prescribed doses are based on patients' weight or renal function. Many other indicators have been developed, sometimes to circumvent this specific problem. As a result, it is difficult to make valid comparisons of surveillance results. A consensus on the use of a single indicator or of a set of indicators would solve this issue. A good correlation between the indicator of antimicrobial use selected and a clinically important outcome also appears necessary for a surveillance program to be viewed as relevant. However, the optimal way to measure antimicrobial use in hospitals, to complement surveillance of resistance, is still unclear.

This thesis thus aimed to identify the most accurate indicator(s) of antimicrobial use for the prediction of prevalence and incidence of resistant microorganisms in the respiratory microbiota of hospitalized patients (children and adults). To answer this question, three specific objectives were developed:

1) To systematically review existing indicators of antimicrobial use in cohort and repeated point-prevalence studies, including pediatric inpatient populations;

2) To measure population antimicrobial use as well as prevalence and incidence of clinically relevant antimicrobial resistances found in respiratory cultures performed in intensive care unit (ICU) patients, using different indicators and definitions;

3) To identify the indicator of antimicrobial use that predicted prevalence and incidence rates of resistance, in respiratory cultures performed in intensive care unit (ICU) patients, with the best accuracy.

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CHAPTER 2. LITERATURE REVIEW

2.1. Antimicrobial resistance

Resistance to antimicrobial agents is now an expected adverse effect of antimicrobial therapy, along with other adverse drug events such as allergic reactions or toxicity. The development of resistance to an antimicrobial requires the presence of two elements.[1] First, there needs to be a subgroup of potentially resistant microorganisms (i.e., presence of resistance genes). Of note, expressing resistance is often thought to be a disadvantage for microorganisms (decreased fitness) because of the additional energy expenditure required on the microorganism's part to replicate more deoxyribonucleic acid (DNA) and increase protein synthesis.[2] This survival disadvantage will maintain the resistant subgroup in minority until the host (the patient) is exposed to an antimicrobial agent (the second element).[3-5] This exposure will disrupt the patient's microbiota: susceptible strains will be eliminated and resistant strains will have the ability (nutrients and space) to take over the now empty niche.

Table 2.1 illustrates how reliable microorganisms are in their capacity to adapt and evolve when confronted to a new antimicrobial. Resistance to methicillin was reported within a year of its release. Resistance to vancomycin took longer to develop, thus justifying its use as a last-resort antimicrobial; however, it is now commonly reported.

Many different mechanisms can lead to antimicrobial resistance in bacteria. Some bacteria are intrinsically resistant to certain antimicrobials if, for example, they do not have the target for the antimicrobial. Other bacteria will easily mutate or produce enzymes, making the antimicrobial ineffective. These resistance genes are efficiently shared among bacteria via a multitude of mobile genetic elements such as plasmids, transposons, and insertion sequences. Table 2.2 presents clinically important resistant pathogens and a brief description of their main resistance mechanisms.[6, 7]

Table 2.1 Year of release and of first observed resistance for various antimicrobial agents and antimicrobial classes.

Antimicrobial	Year released	Year of first observed resistance
Agent		
Vancomycin[8]	1956	1988
Methicillin[8]	1960	1961
Ampicillin[8]	1961	1973
Piperacillin-tazobactam[9, 10]	1993	1994
Antimicrobial class		
Aminoglycosides[11]	1940s	Late 1950s
Cephalosporins[8]	1960s	Late 1960s
Carbapenems[9, 12]	1985	Late 1980s
Fluoroquinolones[13, 14]	1973	Late 1980s

Note: Superscripts refer to scientific references.

Table 2.2 Clinically important resistant pathogens and related main resistance mechanisms.

Resistant bacteria	**Main resistance mechanisms**
Gram positive bacteria[6]	
S. aureus	-Mutation in the *mecA* gene, which codes for penicillin binding proteins (PBP). It prevents binding
Methicillin	of the antimicrobial.
Enterococcus sp.	
Ampicillin	-Changes in affinity of the enterococcal PBPs. Plasmid-borne resistance to multiple antimicrobials.
Vancomycin	-Genes *vanA* and *vanB*, carried on plasmids or transposons, modify peptidoglycan binding sites in cell wall, preventing binding of antimicrobials.
Gram negative bacteria[7]	
Enterobacter sp. or *Citrobacter* sp.	
Carbapenems	-Production of carbapenemases, which destroy the antimicrobial.
E. coli, *Klebsiella* sp. or *Proteus* sp.	
Carbapenems	-Production of carbapenemases, which destroy the antimicrobial.
3rd-generation cephalosporins	-Production of extended spectrum β-lactamases, which destroy the antimicrobial.
Coliforms	
Aminoglycosides	-Production of aminoglycoside-modifying enzymes, which destroy the antimicrobial.
Piperacillin-tazobactam	-Production of ampC-β-lactamases, which destroy the antimicrobial.
Quinolones	-Mutations in the *gyrA* and *parC* genes, which code for a gyrase and a topoisomerase,

Resistant bacteria	Main resistance mechanisms
	respectively. It prevents binding of the antimicrobial to its targets.
Pseudomonas sp.	
Carbapenems	-Loss or reduction of porins, thus limiting the entry of the antimicrobial in the cell.
	-Efflux pumps to pump the antimicrobial out of the cell.
Piperacillin-tazobactam	-Efflux pumps to pump the antimicrobial out of the cell.
Quinolones	-Mutations in the *gyrA* and *parC* genes, that code for a gyrase and a topoisomerase, respectively. It prevents binding of the antimicrobial to its targets.
	-Efflux pumps to pump the antimicrobial out of the cell.

Note: Superscripts refer to scientific references.

2.2. **Burden of antimicrobial resistance**

Since the 1940s, whenever patients developed resistance to an antimicrobial, clinicians would opt for another agent. Whenever a microorganism became widely resistant to a certain antimicrobial, a new antimicrobial would replace the previous as the recommended treatment. For instance, confronted with increasing levels of resistance to penicillins, third-generation cephalosporins were used more frequently, followed by an increase in resistance to these agents, which in turn was followed by increased carbapenem use and carbapenem resistance levels.[15] However, in the last decades, the number of new antimicrobials has dropped markedly[11, 16] and treatment options for resistant organisms are now quite limited.

Antimicrobial resistance is therefore a worrisome phenomenon because of its potential impact on our ability or inability to treat infections. Resistance is viewed as a major problem by increasing the delay before administration of an appropriate (i.e. effective) antimicrobial treatment or by forcing the administration of a more toxic antimicrobial.[17] For instance, a 2008 meta-analysis of 32 observational studies showed that "the odds of death with inappropriate therapy were 2.34 (1.51 – 3.63) and 2.33 (1.96 – 2.76) times greater for patients with VAP [ventilator-associated pneumonia] and BSI [bloodstream infections], respectively."[18]

Studies attempting to quantify the burden of antimicrobial resistance have faced a multitude of methodological issues such as adjustment for severity of the underlying illness, selection of a proper comparison group, timing of infection onset, outcome definition and definition of appropriate therapy.[17, 19] Investigators address these issues differently, thus increasing the complexity of comparisons between studies.

Nonetheless, in 2014, the World Health Organization (WHO) published the results of a series of systematic literature reviews examining the health and economic burden of five distinct antimicrobial resistance: third-generation-resistant *Escherichia coli*, fluoroquinolone-resistant *E. coli*, third-generation-cephalosporin-resistant *Klebsiella pneumoniae*, carbapenem-resistant *K. pneumoniae* and methicillin-resistant *Staphylococcus aureus*.[20] Selected studies compared patients with resistant strains to patients with susceptible strains. All five resistances were

associated with increased mortality. Patients with fluoroquinolone-resistant *E. coli* or third-generation-cephalosporin-resistant *K. pneumoniae* infections were more likely to be admitted to an intensive care unit. Patients with third-generation-cephalosporin-resistant *K. pneumoniae*, carbapenem-resistant *K. pneumoniae* or methicillin-resistant *S. aureus* infections had prolonged length of stay in the intensive care unit or in hospital. Finally, methicillin-resistant *S. aureus* was associated with a higher risk of septic shock and of discharge to a long-term care facility. These outcomes led to higher hospitalization and treatment costs. Finally, as data will later be presented on resistant *Pseudomonas* sp., it appears relevant to mention the results of another study following hospitalized carriers of *P. aeruginosa*.[21] In this study, emergence of resistance during follow-up was associated with increased mortality, increased risk of bloodstream infection and longer length of stay.

In addition, it is interesting to note that, in two American publications, the proportion of resistance among isolated strains seems to be higher in intensive care units than in other hospital wards, and in inpatients than in outpatients. This could suggest that the heaviest burden of resistance is in intensive care units. However, the proportion of resistant strains is an indicator that has important limitations, especially for burden estimations. This will be discussed shortly.[22, 23]

2.3. **Recommendations for surveillance of antimicrobial resistance in hospitalized patients**

The burden of resistance, given its importance, can justify attempts to control and reduce antimicrobial resistance levels in hospitals. Before any initiative, however, investigators, clinicians and public health authorities must describe resistance levels in their setting. This is achieved through epidemiological surveillance. As mentioned by Sydnor and Perl, in 2011, "surveillance is truly the cornerstone of hospital epidemiology and infection control programs, as it highlights where these programs should focus their energies and allows programs to evaluate the effectiveness of their infection control efforts."[24]

In its 2001 Global Strategy for Containment of Antimicrobial Resistance, the WHO made a series of recommendations, in which governments and health authorities were asked to perform laboratory surveillance of resistance, to conform as much as possible with the WHO antimicrobial resistance surveillance model and to monitor disease burden.[25] In 2014, the WHO again identified a lack of coordinating structures for data sharing. Surveillance methodologies were still very different across countries and surveillance systems.[20] However, the situation seemed better in Europe and in the Americas. A Transatlantic Task Force on Antimicrobial Resistance (TATFAR) was created in 2009 to coordinate efforts between the European Union and the United States of America. TATFAR issued recommendations regarding three areas: antimicrobial use control, prevention of resistant infections and development of new antimicrobial agents. Their recommendations to prevent drug resistant infections especially target healthcare-associated infections, as new resistances tend to arise in healthcare settings.[26] Indeed, because hospitals combine frail and at-risk patients, intensive antimicrobial use and patients from the community admitted for severe infections, they act as both an origin and a reservoir for resistant microorganisms. [25]

In addition to the American participation to TATFAR, the White House clearly indicated its will to address the problem of antimicrobial resistance. In September 2014, a National Strategy for Combating Antibiotic-Resistant Bacteria was published that strengthened the national public health surveillance by "requiring reporting of antibiotic resistance data to NHSN [National Healthcare Security Network] as part of the Centers for Medicare and Medicaid Hospital Inpatient Quality Reporting Program".[27] This publication was followed by a press release, in January 2015, announcing the White House's intention to substantially increase public funding to fight antimicrobial resistance.[28] These political decisions also echoed recommendation issued in 2011 by the Infectious Disease Society of America.[29]

Similarly in 2011, the European Union published its action plan against antimicrobial resistance [30] where it underlined the need for improving surveillance of healthcare-associated infections, as their burden was high and closely related to antimicrobial resistance. It also aimed to reinforce existing surveillance systems devoted to resistance surveillance. Meanwhile, European

countries continue to develop their own national programs. For instance, France's action plan includes surveillance of antimicrobial resistance, with a special focus on resistance in the community, as surveillance is already well developed in hospitals.[31] In the United Kingdom, the British Society for Antimicrobial Chemotherapy Bacteraemia Resistance Surveillance Programme focuses on resistance of bloodstream infections.[32]

In Canada, different surveillance systems monitor antimicrobial resistance. The Canadian Integrated Program for Antimicrobial Resistance Surveillance monitors antimicrobial use and antimicrobial resistance in animals and humans. Resistances under surveillance are however limited.[33] The Canadian Nosocomial Infection Surveillance Program (CNISP) focuses on resistance of healthcare-associated infections in a sample of Canadian hospitals.[34] The Canadian Ward Surveillance Study monitors a wider range of resistances, but in a limited number of hospitals.[35] In the Province of Quebec, the *Surveillance provinciale des infections nosocomiales* (SPIN) and the *Comité d'experts scientifiques sur la résistance aux antibiotiques* both work on resistance surveillance, but SPIN focuses only on healthcare-associated infections.[36]

Finally, microorganisms of interest and their relevant resistance profiles (pathogen/antimicrobial combinations) to follow are selected based on their frequency, their clinical importance, and their emergence.[37] Table 2.3 presents a list of microorganisms followed by a few networks involved in surveillance of antimicrobial resistance in hospitals. In general, these systems have selected the same pathogens (*S. aureus*, *Enterococcus* sp., *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella* sp., *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and coagulase-negative staphylococci). The selected resistance profiles vary more, which could be attributed to the different populations covered.

Table 2.3 Pathogen/antimicrobial combinations in some North American and European surveillance systems.

Microorganism	Antimicrobial tested	WHO[20]	NHSN[38]	EARS-net[39]	CNISP[34]	SPIN[36]
Staphylococcus aureus	oxacillin	X	X	X	X	X
	rifampine			X		
Coagulase-negative staphylococci	oxacillin		X			
Enterococcus sp.	vancomycin		X	X	X	X
	ampicillin		X	X		
	aminoglycosides			X		
Pseudomonas aeruginosa	fluoroquinolones		X	X		X
	carbapenems		X	X		X
	3rd-generation cephalosporins		X	X		X
	piperacillin or piperacillin/tazobactam		X	X		X
	aminoglycosides		X	X		X
	cefepime		X			X
Klebsiella sp.	fluoroquinolones		X	X		X
	carbapenems	X	X	X	X*	X
	3rd-generation cephalosporins	X	X	X		X
	penicillins		X			X
	aminoglycosides		X	X		X

Microorganism	Antimicrobial tested	WHO[20]	NHSN[38]	EARS-net[39]	CNISP[34]	SPIN[36]
Escherichia coli	fluoroquinolones	X	X	X		X
	carbapenems		X		X*	X
	3rd-generation cephalosporins	X	X	X		X
	penicillins		X	X		X
	aminoglycosides		X			X
Acinetobacter baumannii	fluoroquinolones		X			X
	carbapenems		X		X	X
	3rd-generation cephalosporins		X			X
	penicillins		X			X
	aminoglycosides		X			X
	ampicillin-sulbactam		X			X

Note: Numbers in superscript refer to scientific references. WHO: World Health Organization; NHSN: National Healthcare Safety Network, United States of America; EARS-net: European Antimicrobial Resistance Surveillance Network, Europe; CNISP: Canadian Nosocomial Infection Surveillance Program, Canada; SPIN: *Surveillance provinciale des infections nosocomiales*, Province of Quebec.

*Also for all Enterobacteriaceae.

2.4. **Measuring antimicrobial resistance in hospitalized patients**

In North America, laboratories follow standards and guidelines developed by the Clinical and Laboratory Standards Institute to report resistance profiles of isolated microorganisms.[37] These standards and guidelines describe appropriate laboratory methods to determine whether a microorganism is susceptible, intermediate, or resistant to an antimicrobial. They are based on the minimum concentration of antimicrobial that inhibits bacterial growth in vitro, the antimicrobial concentration that can be reached at the site of infection, the route of administration, and the main indications for specific antimicrobials.[40]

Resistance is frequently reported as the proportion, among tested strains, of strains resistant to a certain antimicrobial or class of antimicrobials, and can be described for a group of comparable microorganisms, or for a specific microorganism. For example, the United States of America and the Province of Quebec have respectively reported that 56.8% and 28% of *S. aureus* strains isolated from healthcare-associated bloodstream infections were resistant to methicillin. These percentages were 36.4% and 5% for resistance to vancomycin in *Enterococci* sp.[37, 41] Regardless of methodological problems associated with the definition of duplicate strains (duplicate isolates are excluded based on either their resistance profiles or some pre-determined time span between isolation of strains[42]), this indicator of antimicrobial resistance is important to inform which first-line empirical antimicrobial should be recommended in clinical management guidelines to direct clinicians in their decisions. However, it is less interesting for public health purposes, when the objective is to quantify the absolute frequency of antimicrobial resistance and its burden. For instance, if susceptible strains became less frequently isolated, the proportion of resistant strains would increase, but this could not be interpreted as an increasing number of resistant strains; in this specific example, resistant strains could even be decreasing, but less than susceptible strains.

In 2008, the American Healthcare Infection Control Practices Advisory Committee (HICPAC) issued "recommendations for metrics for multidrug-resistant organisms in healthcare settings".[43] According to HICPAC, an ideal surveillance system for multidrug-resistant organisms should:

1) Monitor resistance profiles with antibiograms (proportion of resistant strains);
2) Estimate exposure burden (e.g. prevalence of resistance in clinical and surveillance isolates, per 100 admissions, in order to reflect colonization);
3) Quantify healthcare acquisition (e.g. incidence rates of hospital-onset resistance in clinical and surveillance isolates, per 1000 patient-days; the hospital-onset criterion is met when the isolate is taken more than 3 days after admission);
4) Estimate infection burden (e.g. cumulative incidence of resistant hospital-onset bloodstream infections).

2.5. Association between antimicrobial use and antimicrobial resistance

Many studies have tried to quantify the association between antimicrobial use and antimicrobial resistance, attempting to establish a causal link between the two factors. In theory, studies using individual information on antimicrobial use and subsequent development of resistance can provide the best evidence for a causal association. In practice, these studies were performed in a wide range of settings, using varying designs: cohorts of patients with cancer, of patients exposed (or not) to antimicrobials or not versus only exposed patients, of outpatients, inpatients, or nursing home residents; cross-sectional studies; case-control studies comparing cases of resistance to all other patients while others used only patients with susceptible strains of the same microorganism as controls; etc.[44-48] Resistance was sometimes measured in infected patients while other studies monitored colonization, and microorganisms studied also varied. In addition, individual studies are also subject to many potential biases. Information on previous antimicrobial exposure can be incomplete, leading to misclassification of exposure; patients are not always tested at random and some patients are tested multiple times, potentially leading to outcome misclassification or selection bias (if tested patients are different from the general population); it is also difficult to collect information on all confounders.[49, 50] Many of these studies have nevertheless found statistically significant associations between resistance and previous exposure to antimicrobials.

Another limitation of individual-level studies that quantify the association between antimicrobial use and resistance is due to the fact that resistance can develop in a patient exposed to antimicrobials who can then transmit resistant strains to other patients, regardless of these patients' exposure to antimicrobials. As for other transmissible infections, an infected individual becomes a risk factor for someone else. It is difficult for individual-level studies to account for this transmission of resistance, even though it might be caused by an initial antimicrobial administration.[49, 51]

Ecological studies can measure the total population effect of antimicrobial use. Here again, settings and resistance / antimicrobial combinations under study can vary. However, ecological studies can be separated in two broad categories. Some studies compare resistance in different countries, hospitals or wards and correlate it with antimicrobial use in corresponding geographical areas. These studies compare different geographical areas over a single time period. Many of these studies have observed higher levels of resistance in geographical areas using more antimicrobials.[52, 53] Other studies rather follow a fixed geographical area in time. These last studies frequently use time series methodologies, which is the closest one can get to the detection of causal associations with an ecological design: it allows to verify whether resistance frequency in a population increases and decreases systematically along with antimicrobial use in this population. In the best cases, a time lag can be observed between antimicrobial use and resistance thus preventing the detection of an increase in antimicrobial use due to increasing resistance.[54-58]

Thus, many investigators consider that antimicrobial use *does* cause resistance, despite methodological limitations. The existence of a plausible biological mechanism (through selection of resistant strains), the detection of dose-response relationships, the detection of associations in studies accounting for temporality and the frequent detection of statistically significant associations among studies (consistency between studies) all support this theory.[50, 59] It has also been suggested that it is now time to take this causal association for granted and carry on with research on interventions to limit the development and the transmission of resistant microorganisms. Consequently, antimicrobial stewardship programs are increasingly being

implemented in hospitals. These programs monitor both qualitative aspects of antimicrobial prescriptions and quantities of antimicrobials used. This quantitative aspect of antimicrobial stewardship is covered by surveillance of antimicrobial use.

2.6. Recommendations for surveillance of antimicrobial use in hospitalized patients

Similarly to surveillance of antimicrobial resistance, surveillance of antimicrobial use is recommended by various authorities worldwide. It has been recommended for hospitals and public health authorities by the WHO in its global strategy for containment of antimicrobial resistance.[25] TATFAR is also working with the American Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control to harmonize methods for surveillance of hospital antimicrobial use in the United States of America and Europe.[26] More specifically, in the United States of America, the Infectious Diseases Society of America has recommended that hospitals provide administrative support to develop surveillance of antimicrobial use and the NHSN collects data on hospital antimicrobial use.[60, 61] In Europe, in addition to many national surveillance systems, the European Surveillance of Antimicrobial Consumption Network has also been monitoring antimicrobial use in hospitals from 27 European countries.[62]

In Canada, the federal framework for action recommends to develop and reinforce surveillance of antimicrobial use, in the community, in hospitals and in animals.[63] The Canadian Integrated Program for Antimicrobial Resistance Surveillance monitors hospital antimicrobial use via hospitals' antimicrobial purchases.[64] The CNISP now also collects data on hospital antimicrobial use; however, only a fraction of CNISP hospitals participate and results are currently not publicly available.[65]

In 2005, following the *Clostridium difficile* crisis, which was thought to be linked with quinolone use, the *Comité des infections nosocomiales du Québec* recommended the development of antimicrobial use surveillance in Quebec hospitals.[66] In 2007, the *Conseil du médicament* published a framework for surveillance of antimicrobial use and of its appropriate use.[67] In

2011, the Quebec Ministry of Health issued a recommendation asking acute care hospitals to implement surveillance of antimicrobial use in hospitalized patients, in collaboration with regional and provincial interlocutors.[68]

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CHAPTER 3. MEASURING ANTIMICROBIAL USE IN HOSPITALIZED PATIENTS

3.1. Preamble

The previous chapter ends on a description of authorities recommending surveillance of hospital antimicrobial use. However, practical aspects of antimicrobial use surveillance are not well defined, especially regarding the choice of indicators to follow. Many different indicators of antimicrobial use have been devised throughout the years. Despite long lasting debates on limitations and qualities of these indicators, it is still unclear what indicator is the best complement to surveillance of antimicrobial resistance. Pediatric populations are also frequently excluded from existing studies, because doses prescribed to children are based on their weight. However, one could assume that surveillance of antimicrobial resistance in pediatric populations is as relevant as in adult populations.

This third chapter thus presents a systemic literature review that I performed, on indicators of antimicrobial use that were applied in settings that included pediatric inpatients, to complement surveillance of resistance. This systematic review was published in 2014 in the *Journal of Antimicrobial Chemotherapy*. The number of the chapter has been added before the tables' and figures' original numbers, to facilitate orientation through the thesis. This is however the only change that was made to the article. Please note that what is usually referred to as "indicators" in the rest of the thesis, is rather labeled "measures" in the following article.

The results of the systematic review highlight that the indicator of antimicrobial use that best predicts antimicrobial resistance prevalence and rates, for surveillance purposes, had still not been identified and that additional evidence on this topic was a necessity.

3.2. Measuring antimicrobial use in hospitalized patients: a systematic review of available measures applicable to pediatrics

AUTHORS

É. Fortin[1,2], P. S. Fontela[3], A. R. Manges [1,4], R. W. Platt [1], D. L. Buckeridge [1], C. Quach [1,2,3]

1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Canada

2) Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Québec and Montréal, Canada

3) Department of Pediatrics, The Montreal Children's Hospital, McGill University, Montréal, Canada

4) School of Population and Public Health, University of British Columbia, Vancouver, Canada

ABSTRACT

Objectives. Measures quantifying antimicrobial use in a population have been described previously, but the optimal measure to use for surveillance of antimicrobial resistance in hospital settings, especially when including pediatric populations, is unknown. This systematic review of literature aims to list, define and compare existing measures of antimicrobial use that were applied in settings that included pediatric inpatients, to complement surveillance of resistance.

Methods. We identified cohort studies and repeated point-prevalence studies presenting data on antimicrobial use in a population of inpatients or validations / comparisons of antimicrobial measures through a systematic search of literature using MEDLINE, EMBASE, CINAHL and LILACS (1975-2011) and citation tracking. Study populations needed to include pediatric hospitalized patients. Two reviewers independently extracted data on study characteristics and results.

Results. Overall, 3878 records were screened and 79 studies met selection criteria. Twenty-six distinct measures were found; the most frequently used being defined daily doses (DDD) / patient-days and exposed patients / patients. Only 2 studies compared different measures quantitatively, showing 1) a positive correlation between % exposed and antimicrobial-days / patient-days and 2) a strong correlation between doses / patient-days and agent-days / patient-days (r=0.98), with doses / patient-days correlating more with resistance rates (r=0.80 vs 0.55).

Conclusions. The measure of antimicrobial use that best predicts antimicrobial resistance prevalence and rates, for surveillance purposes, has still not been identified; additional evidence on this topic is a necessity.

INTRODUCTION

The increasing prevalence of microorganisms resistant to antimicrobials and of strains resistant to multiple classes of antimicrobials is concerning.[1-5] Resistant microorganisms are transmitted from patient to patient and are further selected following antimicrobial exposure.[6] Controlling antimicrobial use, through antimicrobial stewardship programs, is thus an important intervention for the control of resistance in the inpatient microbiota.[2] Qualitative work aims to ensure an appropriate use of antimicrobial agents, while quantitative surveillance of populational antimicrobial use density allows benchmarking and monitoring of temporal trends. Integrating surveillance of antimicrobial use with surveillance of bacterial resistance rates can direct efforts to control resistance.[7, 8]

Measures quantifying antimicrobial use in hospitalized populations have been described previously.[8-12] A numerator will either quantify presence, volume or duration of exposure to antimicrobials and will be divided by a denominator that describes the population at risk of exposure to antimicrobials (person or person-time). However, none of these measures completely capture the complete picture of antimicrobial consumption and thus the selection of the measure that should be recommended for surveillance of resistance is not an obvious choice. Moreover, if one also aims to do surveillance for pediatric populations (e.g., pediatric and neonatal intensive care units or pediatric hospitals), an additional challenge arises, as prescriptions for neonates and pediatric patients are based on patients' weight, which is not seen in adult populations. Many measures that quantify volume of antimicrobials used depend on doses administered, but do not take into account prescriptions based on body weight. This is why, for instance, the World Health Organization (WHO) does not recommend the use of defined daily doses (DDD) for pediatric patients[9], which in turns explains why pediatric patients are often excluded from studies employing or evaluating antimicrobial use measures[11-15], although these populations are exposed to antimicrobials and develop resistance, much like in adult populations.[16-19]

We are currently considering the implementation of quantitative antimicrobial use surveillance in Québec hospitals, which would complement surveillance of antimicrobial resistance, but aiming to include pediatric populations. We aimed to describe existing measures of antimicrobial use in cohort and repeated point-prevalence studies including pediatric inpatient populations, understand how well these measures correlated, and compare their ability to predict future antimicrobial resistance prevalence and rates.

METHODS

SEARCH STRATEGY

We developed a review protocol and screened MEDLINE (OvidSP interface), EMBASE (OvidSP interface), CINAHL and LILACS for eligible studies published between 1975 and September 2011, to include the final steps of the development of the ATC/DDD system, adopted by the WHO in 1981.[9] Lists of search terms (see the online supplementary data) were built around the following concepts: a) children or infants; b) utilization; c) anti-infective; d) surveillance or measurement. The related subheadings were exploded when judged appropriate. To address potentially biased reporting of research results, we hand-searched all abstracts published in 2011 in two proceedings (Infection Diseases Society of America, Society for Healthcare Epidemiology of America).[20] Reference lists of selected articles were screened manually. Finally, for eligible studies comparing measures of antimicrobial use only, we used Google Scholar to identify studies citing them.

STUDY ELIGIBILITY

Selected designs included cohort studies and repeated point-prevalence studies, presenting data on antimicrobial use in a population, validations of antimicrobial use measures or comparisons of antimicrobial measures. Only repeated point-prevalence studies were kept because of the longitudinal aspect provided by the repetition of the

study. Study populations were required to include pediatric hospitalized patients. Only publications in English, French or Spanish were included. Publications were excluded when the purpose was to measure antimicrobial use and outcomes in individuals rather than in a population. Whenever resistance was mentioned as a concern in the introduction, objectives, discussion or conclusion, we understood that resistance was one of the measurement's purpose and these studies were retained. Similarly, studies where the purpose was not clear were kept to prevent the exclusion of more global studies comparing measures. Studies that described antimicrobial expenses solely for budget purposes, total drug use in a hospital or that studied allergic reactions were excluded. Editorials, reviews and commentaries were also excluded from the final analyses, but references were screened for eligible studies.

STUDY SELECTION

Two reviewers (EF and PSF) independently screened the titles and abstracts of the records retrieved by the electronic search. Subsequently, the same two reviewers independently reviewed the full text of all potentially eligible studies. For each step, results obtained were compared after screening of the first records. Discrepancies between reviewers were resolved through discussion to respect the review's objectives.

DATA EXTRACTION

Two reviewers (EF and PSF) independently extracted relevant information (in duplicate). The first ten studies were used as a pilot to clarify any ambiguity. Data to be extracted were divided into three sections:

1) Identification and description of studies: design, type and number of geographical units (hospital or ward), population characteristics (e.g., age limits, ICUs or teaching hospitals), cohort size, period covered by the data, number and width of time intervals, and purpose of the measurement (antimicrobial resistance, various, unknown).

2) Description of measures: units, antimicrobials selected, details on the computation, granularity of the data (individual or group), and strengths and limitations (according to authors and reviewers).

3) Comparison of measures: when antimicrobial use measures were compared to at least one other measure (another antimicrobial use measure or the presence of antimicrobial resistance), information was noted on how measures were compared (qualitatively or quantitatively), how they agreed and whether time lags were considered.

ANALYSIS OF SELECTED STUDIES

Frequency distributions of studies and identified measures were produced, and a narrative synthesis of results was performed. The potential influence of study design (i.e. type and number of geographical units and time intervals; population characteristics), purpose of measurement and selected antimicrobials were explored by stratifying or restricting the analyses on these characteristics. Study power was qualitatively assessed based on the number of observations (cohort size and time points), especially for studies comparing measures.

In studies where measures were not compared, we focused on the measures chosen rather than on the results, so power and biases were not relevant. For studies on the correlation between different measures, selection bias was not an issue because these studies simply described the strength of the relation between two measures of the same concept (antimicrobial use) in the same population. However, choices in the computation of measures could lead to different correlation coefficients and so details on computation were extracted. In studies comparing the ability of different measures to predict resistance, results could be influenced by biases.[21, 22] Therefore, the potential biases that we considered were the following: 1) inclusion of unused doses in the calculation of antimicrobial use measures, 2) consideration of potential time lags between antimicrobial use density and resistance rates, 3) occurrence of interventions

targeting either antimicrobial use or transmission of resistant microorganisms between patients during study period, 4) definition of resistance, and 5) choices of geographical unit, time intervals, antimicrobial classes and resistances.

RESULTS

SELECTED STUDIES

A flow chart of eligible study selection is presented in Figure 3.1.[23] Reviewers screened 3878 records; 79 studies met selection criteria. Study designs could differ substantially, as shown in Table 3.1. Selected studies included 19 surveillance cohorts, 56 other cohort studies and four repeated point-prevalence studies. Twenty-six studies (33 %) used more than one measure; although 79 studies were selected, information was extracted on 119 measures. In eight studies (10%), results obtained with different measures were compared, and quantitative methods (correlation coefficients) were used in two of these studies,[12, 24-30] one of which also compared the correlation of each measure with antimicrobial resistance.[26]

MEASURES OF ANTIMICROBIAL USE

Thirteen different numerators and five different denominators were used and are detailed in Tables 3.2 and 3.3. They were combined to produce 26 distinct measures (Table 3.4). Several measures referred to similar concepts. Measures using DDD, recommended daily doses (RDD), RDD in mg/kg, prescribed daily doses (PDD) and undefined doses combine information on quantities prescribed and duration of therapy, using different values in their definition of what is a standard daily dose. Grams and costs also estimate quantities and duration of therapy. Agent-days and antimicrobial-days measure the duration of treatments. Other measures reported exposure to antimicrobials: any exposure (proportion of patients exposed), number of treatment periods, of courses or of agents.

ASSOCIATIONS AND CORRELATIONS BETWEEN MEASURES

Table 3.5 summarizes the eight studies that compared different measures.[12, 24-30] Three studies commented on the quantitative results obtained using different measures. Antachopoulos demonstrated an underestimation of the number of doses prescribed to pediatric and neonatal populations when using DDD / patient-days[24]; Berrington mentioned that DDD were closer to agent-days than to antimicrobial-days[12]; Valcourt *et al.* obtained identical values for PDD and agent-days.[30] Although a few authors have mentioned the limited interpretation of DDD measures in pediatric populations,[10, 24-33] Berild *et al.* noted that DDDs were still easier to interpret than costs, since costs could also reflect changes in preferred agents used and in prices.[25] Four studies used sets of measures and underlined the relationships between the proportion of exposed patients, the duration of treatment and the quantity of antimicrobials prescribed;[27-30] they showed how, for example, a stable proportion of exposed patients combined with a decrease in the duration of treatment led to a reduction in total quantities prescribed to patients.[29] Valcourt *et al.* also pointed out that the average duration of treatment was related to the average length of stay (potential exposure time).[30]

Di Pentima *et al.* showed that quinolone RDD in mg/kg/patient-days and quinolone-days/patient-days were highly correlated (r=0.98) in one hospital during the eight-year follow up.[26] When analyses were restricted to either levofloxacin or ciprofloxacin, the correlation (r) was 0.86 and 0.96, respectively. The study of Gerber *et al.*, with data from 40 hospitals, reported a positive correlation (r not provided) between the proportion of exposed patients and antimicrobial-days/patient-days; correlation was computed for total antimicrobial use and was then restricted to broad-spectrum antimicrobials.[27] Authors mentioned that hospitals where a greater proportion of patients receive antimicrobials also prescribed treatments for longer durations, a correlation that could have been different in another population.

PREDICTION OF ANTIMICROBIAL RESISTANCE

Only one study calculated the correlation of two different measures with rates of resistance.[26] Di Pentima *et al.* reported that quinolone RDD in mg/kg /patient-days were more positively correlated to rates of resistance in Gram-negative rods than quinolone-days (r=0.803 versus r=0.553).

DISCUSSION

To our knowledge, this is the first systematic review of available measures of antimicrobial use in inpatient populations that also include pediatric patients. Although many measures were found, few were compared quantitatively, and only one study calculated the correlation between antimicrobial use measures and resistance.

MEASURES OF ANTIMICROBIAL USE

Twenty-six different measures were found in the literature, the most frequently used being DDD / patient-days and exposed / patients. The limitations of the DDD / patient-days method in pediatrics have been mentioned, but this well-known and clearly defined measure can still be used in specific situations, such as to follow antimicrobial use density in a population where patients' average weight is constant. Other authors preferred to develop new measures such as RDD in mg/kg and RDD numerators or the kg-days denominator. Confronted with such a variety of measures, it is important to understand how these measures compare to one another in order to choose the most appropriate measure that could be used in the surveillance of resistance rates.

An important limitation of many of our eligible studies was the use of ill-defined measures. Whenever possible, numerators were renamed according to definitions provided by Berrington and de With *et al.*[12, 14] Measures using DDD were usually well documented because this method is well-known and easy to reference.[9] On the other hand, standard doses were not always provided for PDD, RDD and RDD in mg/kg

measures and not all publications explained how these standard daily doses were defined. In some publications, it was not always possible to distinguish agent-days from antimicrobial-days or courses from treatment periods. Authors also only seldom specified if they had kept prescribed but unused doses in their measures, which is particularly important if one is measuring antimicrobial use to determine its association with resistance. Regarding denominators, it was not always clear if the day of discharge was excluded or not in values of patient-days/bed-days, even though potentially important variations in rates of healthcare-associated infections can be observed when using different denominator definitions.[34, 35]

ASSOCIATIONS AND CORRELATIONS BETWEEN MEASURES

Of the 26 measures identified, 17 were compared to at least one other measure, but only four measures were compared quantitatively. According to these results, RDD in mg/kg / patient-days and agent-days / patient-days were strongly correlated, and so were the measures exposed / patients and antimicrobial-days / patient-days. When RDD in mg/kg is a good representation of daily doses actually prescribed to pediatric patients, it approximates agent-days; it was therefore not a surprise to find that this measure was highly correlated with days of therapy. The magnitude of the correlations between two measures varied, as analyses were restricted to certain classes of agents. Obviously, as all identified measures aim to quantify antimicrobial use in a population, a relatively high level of correlation is expected between them.[36] Indeed, expected similarities and differences between measures can be used in sets of measures to better understand changes occurring in antimicrobial use in a population, [37] as was done in the four studies analyzing how the proportion of exposed patients, the duration of treatment and the quantity given can all have an impact on a population's global antimicrobial use.

PREDICTION OF ANTIMICROBIAL RESISTANCE

In the single study comparing the correlation of two measures of antimicrobial use with resistance rates, in children, RDD in mg/kg was more strongly correlated with resistance than agent-days.[26] RDD in mg/kg / patient-days might be a more precise measure; on a particular day and for a particular patient, agent-days can be equal to either zero or one, while the number of standard doses can take any value greater than or equal to zero. The same type of reasoning could apply to patient-days, which combine information on the number of admissions and patients' length of stay thus offering a wider range of possible values. On the other hand, in a situation where exposure could be highly misclassified (including unused doses or days, or doses and days prescribed by the hospital but administered to discharged patients, for example), it is possible that a simple measure of exposure (yes or no) would better reflect reality.

NEXT STEPS

The result of this last study would require confirmation by other studies comparing more measures, a wider range of agents, microorganisms and resistance definitions, using analytic methods such as regression models, and considering potential time lags. These factors could all have an influence on the various measures' ability to predict resistance. In our case, because of our particular interest in healthcare-associated resistance, prediction of incidence of resistant healthcare-associated infections, as well as prediction of prevalence and acquisition of resistance in inpatients' microbiome (2008 HICPAC recommendations[38]) would be especially relevant. However, such a study would probably not have to compare all measures identified in this review. For instance, DDDs and RDDs include the information provided by grams and costs, but in a more standardized manner, which simplifies comparisons between agents and prevents the introduction of temporal bias due to market fluctuations. Market fluctuations also limit the use of costs as a denominator. Moreover, as PDDs and agent-days are equivalent, only one of these measures can be kept. Finally, as patients' weights are not always

known (especially in adults), RDDs and RDD in mg/kg could be combined into a single measure.

LIMITATIONS

There are limitations to this review. First, it only includes studies that were published or presented at conferences; some research teams could have studied this topic without communicating their results. Inability to demonstrate a difference between measures, even though interesting, could have led to publication bias. Moreover, studies where antimicrobial use was only one factor among many others could have been missed, but antimicrobial exposure is such an important determinant of resistance that this seems improbable. We have screened abstracts from two conferences held in the United States of America to minimize the publication bias, but screening additional abstracts, from other conferences held elsewhere in the world could have reduced this bias even further. Second, due to insufficient measure definitions and to the use of a variable nomenclature for equivalent measures, we might have misclassified identified measures. For an easier interpretation of published results, we encourage our colleagues to carefully define their measures. Third, some of our studies only presented pediatric or neonatal data; we however hypothesize that measures meaningful for pediatric populations can also be generalized to adult populations, while the reverse is not necessarily true. Fourth, a large variety of designs had to be considered. Studies compared different measures and their data came from different settings varying by time interval and number of geographical units. This heterogeneity can be important because in some settings, two measures provide similar information (e.g. admissions and patients are more similar if the time interval is longer). Agents and microorganisms under study can also vary: the study that compared measures to resistance rates focused on quinolones and Gram-negative rods. Results could be different for other agents and microorganisms. Finally, because of our particular interest in long-term surveillance, we excluded single point-prevalence studies while keeping repeated point-

prevalence studies, although one could object that both types of studies use similar metrics.

Because so little quantitative data were found, vague definitions of measure and design heterogeneity have probably not influenced our conclusions. Adding single point-prevalence studies would probably make exposed / patients the most frequent measure, but would probably not bring additional comparisons of measures' ability to predict resistance because of the limited number of measures applicable in point-prevalence studies. Our conclusions might be likely to differ substantively if a large number of studies were missed due to the search strategy or in the case of substantial publication bias.

CONCLUSION

The choice of a measure of antimicrobial use depends on the purpose of the measurement. It is hypothesized frequently that the regulation of antimicrobial use could lead to better control of resistant microorganisms. In this context, surveillance systems were developed not only to monitor resistant microorganisms, but also to monitor antimicrobial use. However, little information is available to guide policy makers in the choice of the ideal measure for a surveillance system, particularly when including pediatric populations. Our results showed that the measure of antimicrobial use that is the most appropriate is still unclear. Along with a certain degree of standardization, additional evidence on this topic is required.

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TRANSPARENCY DECLARATIONS

All authors: no conflict of interest to declare.

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Table 3.1. Description of selected studies.

Study characteristics	Studies	
	N	%
Design		
Repeated point-prevalence study	4	5
Surveillance cohort	19	24
Other cohort study	56	71
Purpose of measurement		
Antimicrobial resistance	68	86
Not specified	11	14
Measures		
1	53	67
2	21	27
3	2	3
4	2	3
10	1	1
Measured antimicrobials		
All	60	76
Specific agents	19	24
Unused doses		
Not specified	64	81
Included	5	6
Excluded	9	11
Excluded doses returned to pharmacy	1	1
Age groups included		
Children and neonates only	47	59
Adults also included	32	41
Type of geographical units		

Study characteristics	Studies	
	N	%
Hospitals	17	22
Departments	6	8
Wards	56	71
Geographical units (range)	1-75	---
Time intervals (range)	1 day – 6.5 years	---
Time points (range)	1 – 61	---
Comparison of measures		
No	71	90
Yes	8	10
Qualitative	6	75
Quantitative (correlation)	2	25
Correlation with resistance		
No	78	99
Yes	1	1

Table 3.2. Frequency distribution and description of numerators found in selected studies.

Category / units	Description*	Studies**	
		N	%
Exposures			
Exposed	Patients prescribed / administered antimicrobials, regardless of quantity or duration.	39	49.4
Treatment periods	Number of distinct periods of consecutive days when a patient is prescribed / administered at least one antimicrobial. A treatment combining different antimicrobials is counted as 1 treatment period.	5	6.3
Courses	Number of distinct periods of consecutive days when a patient is prescribed / administered a specific antimicrobial. Therefore, the sum of courses will not equal treatment periods.	4	5.1
Agents	Number of different antimicrobials to which a patient was exposed.	3	3.8
Quantity			
DDD	Defined daily doses, as defined by the ATC/DDD system. One DDD is the average quantity (in grams) given to a 70 kg adult for 1 day. These values are identical worldwide.	33	41.8
Currency	Costs of prescribed / administered antimicrobials.	6	7.6
Grams	Grams of prescribed / administered antimicrobials.	4	5.1
RDD in mg/kg	Standard daily doses vary according to the weight of the patient. This measure	4	5.1

Category / units	Description*	Studies**	
		N	%
	was developed for pediatric populations. This measure is usually named DDD in mg/kg, but because these standards are not defined by the ATC/DDD system, RDD in mg/kg seems to be a more appropriate name.		
Doses	These doses were not defined in the studies.	2	2.5
RDD	Recommended daily doses. Similar to DDD, but the standard daily doses are defined by local guidelines.	1	1.3
PDD	Prescribed daily doses. Similar to DDD, but the doses actually prescribed / administered are considered to be the standard.	1	1.3
Duration			
Agent-days	Patient-days when a specific antimicrobial was prescribed / administered.	12	15.2
Antimicrobial-days	Patient-days when any antimicrobial was prescribed / administered (alone or in combination). Therefore, the sum of agent-days will not equal antimicrobial-days.	5	6.2

* Terminology in this table may not match the one used in studies. Numerators extracted were sometimes renamed depending on the description provided by the authors.

** Some studies used more than one measure; although 79 studies were selected, information was extracted on 119 measures and percentages do not add up to 100%.

Table 3.3. Frequency distribution and description of denominators found in selected studies.

Category / units	Description*	Studies**	
		N	%
Person-time			
Patient-days	Sum of days spent in hospitals or wards by all patients. No distinction is made between patient-days and bed-days.	62	78.5
kg-days	Sum of [expected weight (in kg) of patients at a certain age X the number of patient-days of that age].	1	1.3
Person			
Patients	Patients included in the study.	32	40.5
Admissions	Admissions to wards or hospitals.	22	27.8
Other			
Currency	Costs of all prescribed / administered drugs.	2	2.5

* Terminology in this table may not match the one used in studies. Denominators extracted were sometimes renamed depending on the description provided by the authors.

** Some studies used more than one measure; although 79 studies were selected, information was extracted on 119 measures and percentages do not add up to 100%.

Table 3.4. Frequency distribution of measures of antimicrobial use found in selected studies.

Category / measure*	Studies**		
	N	%	References***
Exposure / Person-time			
Treatment periods / patient-days	2	2.5	12, 39
Exposed / patient-days	1	1.3	39
Courses / patient-days	1	1.3	12
Quantity / Person-time			
DDD / patient-days	31	39.2	10, 12, 16, 24, 25, 30, 32, 33, 40-62
Grams / patient-days	4	5.1	28, 63-65
Currency / patient-days	3	3.8	17, 25, 40
RDD in mg/kg / patient-days	3	3.8	24, 26, 66
Doses / patient-days	2	2.5	67, 68
RDD in mg/kg / kg-days	1	1.3	69
RDD / patient-days	1	1.3	70
PDD / patient-days	1	1.3	30
Duration / Person-time			
Agent-days / patient-days	9	11.4	12, 26, 30, 71-76
Antimicrobial-days / patient-days	4	5.1	12, 27, 67, 77
Exposure / Person			
Exposed / patients	27	34.2	16-19, 25, 27, 28, 30, 44, 47, 71, 76, 78-92
Exposed / admissions	11	13.9	29, 59, 70, 75, 77, 93-98
Treatment periods / admissions	2	2.5	12, 99
Courses / admissions	2	2.5	12, 100
Agents / patients	2	2.5	71, 87
Treatment periods / patients	1	1.3	80
Courses / patients	1	1.3	79
Agents / admissions	1	1.3	96

Category / measure*	Studies**		
	N	%	References***
Quantity / Person			
DDD / admissions	2	2.5	12, 31
Currency for antimicrobials / patients	1	1.3	43
Duration / Person			
Agent-days / admissions	3	3.8	12, 29, 101
Antimicrobial-days / admissions	1	1.3	12
Quantity / Other			
Currency for antimicrobials / currency for all drugs	2	2.5	43, 71

* Terminology in this table may not match the one used in studies. Measures extracted were sometimes renamed depending on the description provided by the authors.

** Some studies used more than one measure, so although 79 studies were selected, information was extracted on 119 measures and percentages do not sum up to 100%.

***As references 39 to 101 are cited only in Table 3.4, they are listed in the online supplementary data rather than in the references' section.

Table 3.5. Studies comparing different measures of antimicrobial use.

#	Comparison method	Measures compared	Geographical unit	Time intervals (n x interval)	Agents	Summary of results
12	Descriptive	DDD/PD DDD/admissions agent-days/PD agent-days/admissions AM-days/PD* AM-days/admissions courses/PD courses/admissions tx periods/PD* tx periods/admissions	13 departments (1 pediatric)	1 x 1 year	All	•Correlation analyses were done, but data from the pediatric department were excluded from these analyses. Patient-days give lower measure estimate than admissions. •DDD are closer to agent-days than to antimicrobial-days. •Measures accounting for combinations are lower than the others.
24	Descriptive	DDD/PD* RDD in mg/kg / PD	3 wards (adult, pediatric, neonatal)	1 x 1 year	Ceftriaxone	•The adjusted doses gave higher values, especially in neonatology.
25	Descriptive	DDD/PD currency/PD	1 department (1 NICU* and 1 pediatric	7 x 1 year	All	•Costs and DDD show the same trends, but while the interpretation of DDDs appears straightforward, costs are

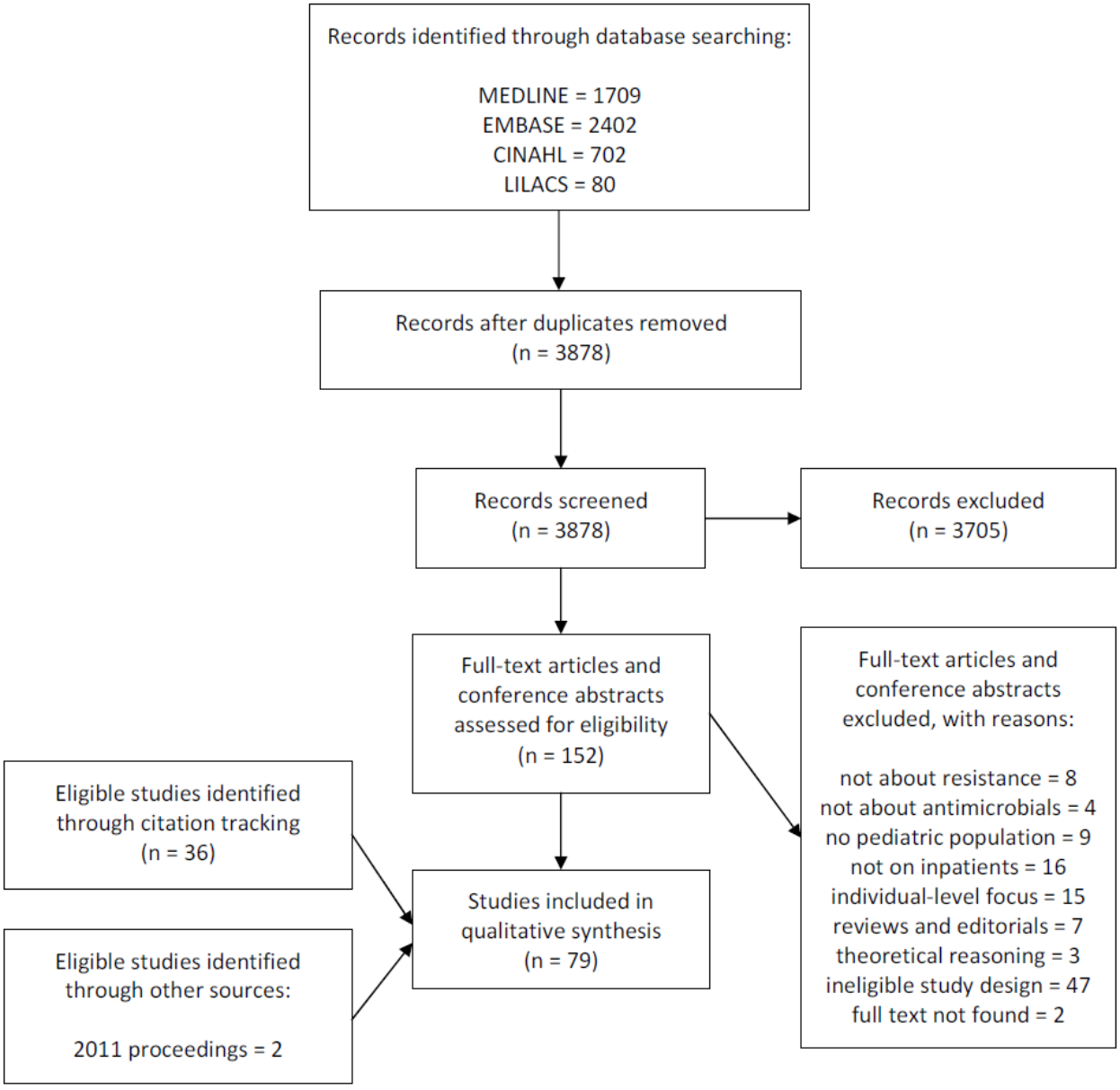
#	Comparison method	Measures compared	Geographical unit	Time intervals (n x interval)	Agents	Summary of results
			ward)			influenced by changes in prescribed antimicrobials and in deals with drug companies.
28	Descriptive	grams/PD exposed/patients	1 NICU	4 x 6 months	All	•The proportion of exposed patients, the number of admissions and the average weight of treated patients have not changed, so the authors explain the observed decrease of grams/patient-days by the shorter duration of treatment.
29	Descriptive	exposed/admissions agent-days/admissions	1 NICU	10 x 1 year	All	•Even though the proportion of exposed patients remained stable, the mean duration of treatment decreased, which resulted in a decrease in antimicrobial use.
30	Descriptive	DDD/PD PDD/PD* agent-days/PD exposed/patients*	3 wards (PICU*, NICU, CICU*)	1 x 1 year 2x1 year (PICU)	Vancomycin Linezolid	•In critically ill children, drug use density of vancomycin is significantly less when measured with DDD compared to PDD, a more appropriate method in children. •The simplest and most accurate method of assessing drug use density is agent-

#	Comparison method	Measures compared	Geographical unit	Time intervals (n x interval)	Agents	Summary of results
						days, which allows comparison of drug use density between different pediatric facilities or clinical units. PDD and agent-days are identical at the group level. •The proportion of patients who are exposed is similar in the 3 ICUs, but agent-days vary because of different average lengths of stay in each ICU.
26**	Correlation	RDD in mg/kg /PD agent-days/PD	1 hospital	8 x 1 year	Ciprofloxacin Levofloxacin	•Quinolones doses/1000 patient-days and days of therapy/1000 patient-days are strongly correlated (r=0.9777 for quinolones, r=0.848 for levofloxacin only and r=0.955 for ciprofloxacin only).
27**	Correlation	exposed/patients AM-days/PD	40 hospitals	1 x 1 year	All Broad-spectrum	•The authors conclude that the two measures are correlated because hospitals who expose more patients also prescribe for longer durations of treatment. However, correlation coefficients are not provided, only p-values.

* AM = antimicrobial; CICU = cardiac intensive care unit; DDD = defined daily dose; exposed = exposed patients; NICU = neonatal intensive care unit; PD = patient-days; PDD = prescribed daily dose; PICU = pediatric intensive care unit; tx = treatment.

**Measures were compared using correlation coefficients; other studies made a qualitative description.

Figure 3.1. Flow diagram of the selection of studies.



SUPPLEMENTARY DATA

Table 3.6. Databases and search terms.

MEDLINE	**EMBASE**	**CINAHL**	**LILACS**
(OvidSP; keywords and subject headings)	(OvidSP; keywords and subject headings)	(keywords and CINAHL headings)	(keywords)
1. exp Child/	1. child/	S1) (MH "Child+") OR (MH "Infant+") OR (MH "Hospitals, Pediatric") OR (MH "Pediatrics+")	children or child or pediatrics or infant or neonatology [Words]
2. exp Pediatrics/	2. exp pediatrics/	S2) "child*"	and utilization or consumption or prescribing [Words]
3. exp Infant/	3. infant/	S3) "pediatric*"	and antiinfective or antimicrobial or antibacterial or antibiotic [Words]
4. child*.mp.	4. child*.mp.	S4) "infan*"	

MEDLINE	EMBASE	CINAHL	LILACS
(OvidSP; keywords and subject headings)	(OvidSP; keywords and subject headings)	(keywords and CINAHL headings)	(keywords)
5. pediatric*.mp.	5. pediatric*.mp.	S5) "neonat*"	
6. infan*.mp.	6. infan*.mp.	S6) (MH "Drug Utilization")	
7. neonat*.mp.	7. neonat*.mp.	S7) (MH "Drugs, Prescription") OR (MH "Prescriptions, Drug")	
8. exp Drug Utilization/	8. exp drug utilization/	S8) "utilization"	
9. prescriptions/ or exp drug prescriptions/	9. exp prescription/ or exp prescription drug/	S9) "consumption"	
10. utilization.mp.	10. utilization.mp.	S10) "prescri*"	
11. consumption.mp.	11. consumption.mp.	S11) (MH "Antiinfective Agents+")	
12. prescri*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	12. prescri*.mp.	S12) "antiinfective*"	

MEDLINE	**EMBASE**	**CINAHL**	**LILACS**
(OvidSP; keywords and subject headings)	(OvidSP; keywords and subject headings)	(keywords and CINAHL headings)	(keywords)
13. exp Anti-Infective Agents/	13. exp antibiotic agent/ or exp antiinfective agent/	S13) "anti-infective*"	
14. anti-infective*.mp.	14. anti-infective*.mp.	S14) "antibacterial*"	
15. antimicrobial*.mp.	15. antimicrobial*.mp.	S15) "antimicrobial*"	
16. antibacterial*.mp.	16. antibacterial*.mp.	S16) "antibiotic*"	
17. antibiotic*.mp.	17. antibiotic*.mp.	S17) (MH "Epidemiology+")	
18. exp Epidemiology/	18. epidemiology/	S18) (MH "Weights and Measures+")	
19. exp Population Surveillance/	19. exp drug surveillance program/ or exp disease surveillance/	S19) (MH "Evaluation+")	
20. exp "Weights and Measures"/	20. exp technique/	S20) "surveillance"	
21. epidemiolog*.mp.	21. epidemiolog*.mp.	S21) "epidemiolog*"	
22. surveillance.mp.	22. surveillance.mp.	S22) "monitor*"	

MEDLINE	**EMBASE**	**CINAHL**	**LILACS**
(OvidSP; keywords and subject headings)	(OvidSP; keywords and subject headings)	(keywords and CINAHL headings)	(keywords)
23. monitor*.mp.	23. monitor*.mp.	S23) "measur*"	
24. measur*.mp.	24. measur*.mp.	S24) "quantif*"	
25. quantif*.mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]	25. quantif*.mp.	S25) "evaluat*"	
26. stewardship.mp.	26. stewardship.mp.	S26) "stewardship"	
27. 1 or 2 or 3 or 4 or 5 or 6 or 7	27. 1 or 2 or 3 or 4 or 5 or 6 or 7	S27) S1 or S2 or S3 or S4 or S5	
28. 8 or 9 or 10 or 11 or 12	28. 8 or 9 or 10 or 11 or 12	S28) S6 or S7 or S8 or S9 or S10	
29. 13 or 14 or 15 or 16 or 17	29. 13 or 14 or 15 or 16 or 17	S29) S11 or S12 or S13 or S14 or S15 or S16	
30. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	30. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	S30) S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or	

MEDLINE	EMBASE	CINAHL	LILACS
(OvidSP; keywords and subject headings)	(OvidSP; keywords and subject headings)	(keywords and CINAHL headings)	(keywords)
		S25 or S26	
31. 27 and 28 and 29 and 30	31. 27 and 28 and 29 and 30	S31) S27 and S28 and S29 and S30	
32. limit 31 to (yr="1975 - Current" and (english or french or spanish))	32. limit 31 to ((english or french or spanish) and yr="1975 -Current")	S32) S27 and S28 and S29 and S30 (Limiters - Language: English, French, Spanish; Published Date from: 19750101-20111231)	

Additional references from Table 3.4

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CHAPTER 4. IMPROVING QUALITY OF DATA EXTRACTIONS

4.1. Preamble

Indicators for surveillance of antimicrobial resistance and of antimicrobial use in intensive care units (ICUs) can be computed using hospital administrative databases. Microbiology laboratory information systems (MLIS) can provide information on microorganisms isolated from patients during their stay in the ICU, along with susceptibility profiles. Pharmacy databases will provide information on antimicrobial prescriptions for these same patients; additional information can also be available on the actual distribution of these prescriptions to the ICUs. Finally, admission/discharge/transfer (ADT) data is also necessary to compute indicators' denominators: patient-days spent in the ICU, ICU number of admissions and patients present in the ICU.

Ideally, data extractions could be performed independently for all three data sources, based on dates and ICU, before being merged and analyzed. In reality, however, obtaining useful data extractions is much more complicated. Many hospitals will use different information systems, sometimes home-made, and within hospitals, different databases can collect similar information in different ways (for instance, through time and across databases, different names and codes can be given to a same ICU). Although healthcare workers and administrative staff can easily consult the data contained in the various databases to get specific information on a given patient, they do not always know how to correctly extract data on many patients, for a given ward and a given period of time. Changes brought to information systems can also create conversion problems, when old information is incorrectly imported in the new system.

A brief communication published in the *American Journal of Infection Control* summarizes a careful review of ADT data extractions received from four Montreal hospitals (nine ICUs), covering a period from April 1st, 2006 to March 31st, 2010. Steps followed allowed us to improve accuracy, completeness and consistency of extractions.

This publication is reproduced in the next section. The number of the chapter has been added before the tables' and figures' original numbers, to facilitate orientation through the thesis. This is however the only change that was made to the article. Although one step involved merging ADT data with MLIS data, the review of MLIS data itself is discussed further in the third section of this chapter. Finally, the review of pharmacy data extractions is described in the last section of the chapter.

After these procedures, we believe our databases were ready for use, although they were probably still not perfectly clean. Yet, perfect data is not necessary for surveillance purposes, as long as trends remain and can be detected. More preoccupying is the time it took to obtain suitable data extractions, as an eventual surveillance system would aim to detect emerging problems in a timely manner.

4.2. Improving quality of data extractions for the computation of patient-days and admissions

AUTHORS

Élise Fortin, PhD(c);[1,2] Milagros Gonzales, MSc;[3] Patricia S. Fontela, MD PhD;[3] Robert W. Platt, PhD[1]; David L. Buckeridge, MD PhD[1]; Caroline Quach, MD MSc[1,2,3]

1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada;

2) Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Québec and Montréal, Québec, Canada;

3) Department of Pediatrics, The Montréal Children's Hospital, McGill University, Montréal, Québec, Canada.

ABSTRACT

We describe how admissions / discharges / transfers datasets were carefully reviewed for the computation of patient-days and admissions used to monitor resistance and antimicrobial use, in nine intensive care units. A visual inspection of datasets and comparisons with other data sources improved accuracy, completeness and consistency of computations.

INTRODUCTION

In the context of healthcare-associated infections surveillance, numbers of patient-days or admissions are necessary for the computation of infection rates.[1, 2] Surveillance of antimicrobial use and of related antimicrobial resistance in inpatient populations also frequently requires the use of patient-days or admissions.[3-5] While working on the development of such a surveillance system, we asked four hospitals for admissions / discharges / transfers (ADT) data extractions for all patients admitted to intensive care units (ICU). Other authors have reported difficulties in the utilization of hospital databases, as was our case.[5] No user manual was available, nor was an official gold standard, to validate our computations of counts of admissions and patient-days. However, other data sources were available and were used to improve the quality of our data. The objective of this publication is thus to describe encountered problems and steps taken to improve three dimensions of our data's quality: completeness, consistency and accuracy.

METHODS

We asked four hospitals (nine ICUs) in the Province of Quebec to provide individual-level data on all patients admitted to an ICU between April 1st 2006 and March 31st 2010 (1st database: individual-level ADT, extracted by the admission service of medical archives departments). Using these data, we computed numbers of patient-days and admissions per ICU and per 28-day period, starting on April 1st of each year. For the same time period, we had also asked the microbiology laboratories for a download of all specimens with culture results and antimicrobial susceptibility tests results for all ICU patients, taken during their stay at the ICU (2nd database: microbiology laboratory information system or MLIS). For seven of the nine ICUs, we had access to Excel files prepared by medical archivists containing aggregated counts of patient-days and admissions per 28-day period and per ICU (3rd database: aggregated ADT). Finally, for eight ICUs, we could

also use patient-days reported to the provincial surveillance of central line-associated bloodstream infections in ICUs (SPIN-BACC network; 4th database: SPIN); these data were entered by infection prevention and control teams, who sometimes also had access to and used the 3rd database.[6] In databases 1 and 4, patient-days are defined as the sum of days spent in ICUs by individual patients, where admission and discharge days each counted for half a day.

The first two databases were merged at the individual level, using unique identifiers, as well as admission, discharge and specimen collection dates; we checked whether collection dates occurred during ICU stays. Counts of patient-days and admissions obtained from the 1st database were compared to those reported in the 3rd and 4th databases. These last databases were merged to have a single comparator, with values for all 28-day periods and all ICUs. Values were identical for 94% of observations, whenever values were available in the two databases; the value closest to values obtained from the first database were kept for the 6 percent remaining. These steps allowed to improve the 1st database regarding: 1) inclusion of all necessary variables and observations for all concerned ICU admissions (completeness); 2) similar identification of ICUs through time and across databases (consistency); 3) computation of exact numbers of patient-days and admissions (accuracy).[7] The McGill University and hospitals Research Ethics Board approved this study. Computers and databases were password protected and workstations were located in rooms that were locked outside of working hours.

RESULTS

Table 4.1 presents steps followed, problems detected and dimensions of data quality that were evaluated through each step. Re-extraction of data or discussions with medical archivists and information technologies staff were often needed. While exploring data extracted, merging individual ADT and MLIS data, and comparing patient-

days and admissions obtained with different data sources, we detected issues such as missing data and erroneous dates, whose causes and solutions were not necessarily known. For example, the peak in patient-days observed in period 4 of 2008-2009 in two ICUs of the same hospital (Figure 4.1) suggested a computer bug; discussions with local data managers were necessary to link the problem to a change of software with incorrect data conversion and to understand how to resolve the issue. Once all corrections were made, the median absolute difference, in percentage, between annual patient-days obtained in each ICU with individual-level ADT and those obtained with the comparator was 2.1 % of the comparator value (interquartile range: 0.7 % - 10.0 %). For 75 % of these values, individual-level ADT gave lower numbers of patient-days than the comparator.

DISCUSSION

In their validation of pharmacy and ADT data from the ICUs of 4 hospitals, Schwartz *et al.* demonstrated the importance of good programming and communication when using databases coming from "disparate information systems".[5] Set in similar conditions, our experience also shows that problems arising as early as during the extraction step could compromise the quality of surveillance denominators. Our careful review of data has allowed us to verify and, when necessary, to improve 1) completeness of our data extractions, 2) consistency of ICU definitions through time and databases; 3) consistency between counts of admissions and counts of patient-days resulting from these admissions and 4) accuracy of these counts, which are now free of any obviously spurious value.

This was not an easy task, as data extractions were done by overloaded local staff who could not always explain discrepancies between databases because they only dealt with one database and because similar information (e.g. ICU identification) could be coded differently in each data source. A good communication with all stakeholders was

essential during the entire process. Production of time series was also considered a logical step in the context of surveillance, as it allowed the identification of discrete out-of-range data, which could impair the valid analysis of time trends.

Unfortunately, even though our 28-day counts of admissions and patient-days are now close to counts obtained in other denominator sources, they are not identical. Since the scale of errors varied between ICUs, rate comparisons between ICUs might be biased, in unknown directions and, given that none of our databases is considered to be a gold standard, the true values cannot be identified. The fact that previous computations of patient-days could not be reproduced is worrisome because unexplained. Yet, counts are usually close, making the overall significance in denominators' difference unlikely to have an impact on surveillance rates. The remaining solution to further validate our counts would be to compare our individual data with medical records, a time-consuming step that would not be sustainable in a surveillance setting. We did not consider this was necessary for our purposes: although it is essential to have a good understanding of the various data sources and thus to manipulate and analyze the data using different strategies, a proper surveillance system of hospital antimicrobial use and antimicrobial resistance will have to produce good (but not necessarily perfect) data in a timely manner. In fact, timeliness is an important dimension of data quality in surveillance that could not be evaluated in this retrospective study.

A system where hospital databases would be validated through pre-programmed algorithms and where data would be merged using appropriate data fields into a single database could save time,[8] and could be used to monitor various aspects of infection control such as healthcare-associated infections, antimicrobial use and antimicrobial resistance, inappropriate treatments, financial burden of hospital infections, etc.[9] According to our experience, once a valid list of admissions is obtained with unique identifier, a standardized ward identifier and ward admission and discharge dates, it can be merged with the entire MLIS data and other datasets such as pharmacy data, to

retain only information relevant to selected admissions. Problems related to *ad hoc* manual data extractions could thus be prevented.

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Figure 4.1. Example of problems detected in the individual-level ADT data extraction of one ICU, by comparison with aggregated ADT data and with another distribution of individual-level ADT data.

Filled arrow indicates an increase in patient-days that did not occur in aggregated ADT data nor in numbers of admissions; when distributed according to the discharge period of patients, the problem appeared to be specific to period 4 of year 2008-2009 and was detected in another ICU as well. Empty arrow indicates a sudden increase in patient-days in all data sources, that also corresponded to an increase in admissions.

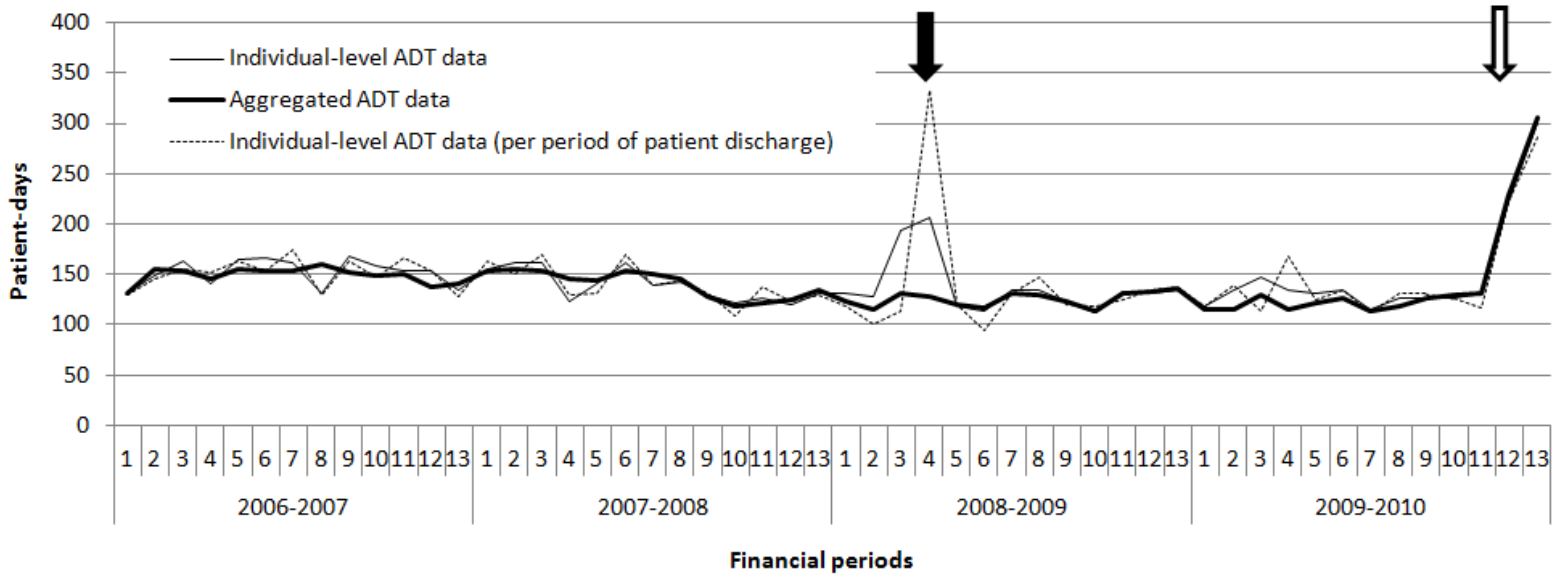

Table 4.1. Steps followed, problems detected and dimensions of data quality evaluated.

Steps	Description	Problems detected	Data quality dimension
Visual inspection of data	Check extracted variables	- ICU* codes are different from one database to the other and can change in time.	Consistency
	Produce time series for each ICU for: - patient-days - admissions	- In some ICUs, patients discharged after March 31st, 2010 were missing, causing an apparent decrease of patient-days and admissions towards the end of the study period. - Some ICUs were merged during the study period. - Sudden increase of admissions and patient-days in one ICU during the study period, because the number of beds more than doubled (Figure).	Completeness and accuracy Consistency Accuracy
Comparison with MLIS data	Individual-level ADT data were merged with MLIS data.	- Based on ICU admission and discharge dates, 4179 susceptibility tests done in ICUs could not be related to an admission in ADT data, because ADT extractions were incomplete.	Completeness
Comparison with other data sources	Compare time series of patient-days and admissions produced in	- One hospital combined intermediate care unit with an ICU, in the provincial database. - In one hospital, the numbers of admissions and	Consistency Consistency

Steps	Description	Problems detected	Data quality dimension
	step 1 to time series obtained using aggregated ADT and SPIN data. If values are not the same, try to reproduce aggregated ADT and SPIN data by combining different ICU codes.	patient-days were widely underestimated in one ICU and widely overestimated in the other ICU. However, numbers of admissions were similar, suggesting that our values of patient-days, obtained directly from these admissions, were the correct ones. - In the ICUs of one hospital, patient-days were very close to aggregated ADT data, except at the beginning of 2008. Admissions were similar to aggregated data. A distribution of patient-days per financial period of discharge showed that the excess of patient-days was only related to patients discharged in June 2008, when the hospital converted its data into a new system (Figure).	Accuracy

*ADT: admissions / discharges / transfers; ICU: intensive care unit; MLIS: microbiology laboratory information system; SPIN: provincial surveillance network.

4.3. Microbiological laboratories information systems

A similar strategy was used to review MLIS data extractions. A visual inspection of birth dates highlighted the fact that for one hospital, data was extracted only for neonates (excluding older patients), but also for neonates that had not been admitted to the neonatal ICU. Descriptive time series of the numbers of tests performed in each ICU (i.e. plots of the counts of cultures performed per 4-week period, in each ICU) allowed the detection of different problems: absence of tests for periods of time ranging between three 4-week periods in an ICU, a year in two other ICUs, but sometimes for the entire study period. Data was re-extracted, providing more complete MLIS data extractions. Extractions provided information on microorganisms isolated, sampling dates and sampling sites, susceptibility profiles as well as hospital, ICU and patient identifiers.

4.4. Hospital pharmacies databases

Pharmacy data extractions were easier to use, as they included data for the entire hospitals, rather than only for ICUs. The final ADT data extractions were merged with pharmacy data, to select all prescriptions that were active during patients' ICU stays. Variables kept were hospital, ICU and patient identifiers, patient's birth date, patient's weight, agent prescribed, prescribed start and stop dates, dose, frequency and administration route. Administration dates were not available and dates of distribution of prescriptions in wards were incomplete, so only prescription dates could be used. Time series then allowed the identification of ICUs that were merged during the study period, to maintain consistent ICU definitions through time. *A posteriori*, using a valid ADT extraction (with unique patient identifiers, hospital and ICU identifiers and ICU admission and discharge dates) might have been the simplest way to select the relevant pharmacy as well as MLIS data, presuming such an ADT extraction can be obtained.

CHAPTER 5. ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL USE IN NINE INTENSIVE CARE UNITS

5.1. Preamble

This chapter presents a description of the frequency of clinically relevant resistances in the respiratory microbiota of all patients in our cohort. It also describes the frequency of antimicrobial use. These are necessary steps before studying the prediction of resistance using population antimicrobial use. This description, as one might now foresee, can be done in various ways. In the scientific literature, a variety of definitions and indicators are used to quantify resistance and antimicrobial use. Several were applied in the following manuscript before testing for time trends or differences between intensive care unit (ICU) types. Trends detected depend on the cohort's ICU mix and might not be representative of other groups of ICUs. However, in addition to a good description of the cohort, the manuscript shows clearly that different indicators of a same phenomenon (antimicrobial use) can follow different trends. This manuscript was submitted for publication on April 7th, 2015. The number of the chapter has been added before the tables' and figures' original numbers, to facilitate orientation through the thesis. This is however the only change that was brought to the manuscript.

While only two indicators of resistance frequency were used (prevalence among admitted patients and incidence rate per 10,000 patient-days), ten distinct indicators of antimicrobial use were computed. In the systematic literature review previously presented, 13 numerators and five denominators were identified, combined in 26 indicators that had actually been used. As mentioned in the discussion, some numerators' and denominators' interest appeared more limited. After computing the remaining seven numerators (defined daily doses, recommended daily doses, agent-days, antimicrobial-days, courses, treatment periods and exposed patients) and three denominators (patient-days, admissions and patients present), it appeared that agent-days and courses were almost identical to antimicrobial-days and treatment periods, respectively. The latter were thus excluded from further analyses. In the end, five numerators and three denominators were selected and analyzed. However, in the following description of antimicrobial resistance and antimicrobial use in our cohort, only indicators with patient-days or

ICU admissions are presented. In fact, ICU admissions and patients present in the ICU become very similar over long time intervals. As we present data over four years or per year, indicators using patients present in the ICU provided redundant information and are not presented in this chapter.

Finally, a choice was made to follow resistance in respiratory isolates taken from ICU patients. As the manuscript only briefly explains this choice, the justification is provided in this preamble. Although the systematic screening of all inpatients' stools could have provided a more complete portrait of resistance in inpatients' microbiota, this expensive and time-consuming methodology – that would ideally use microarrays or sequencing, would not be sustainable in a real-life setting for surveillance of resistance. Culture results obtained for clinical reasons are a more realistic source of information. We also hypothesized that ICU patients, who are frequently intubated, undergo frequent respiratory cultures, as a routine practice to investigate potential causes of clinical instability in the patient. These cultures would thus not only provide information on infected patients, but also on colonized patients. Moreover, unlike stool cultures where only pathogens are looked for – with use of selective culture media to eliminate commensals, respiratory tract cultures are more likely to be worked on extensively. This was a way to get closer to the concept of microbiota. Adding cultures from other wards and infection sites would not only have compromised this, but it would have also led to a potential confounding of resistance time trends depending on changes in sampling practices through time.

5.2. Measurement of Antimicrobial Resistance in the Respiratory Microbiota and Antimicrobial Use in Nine Intensive Care Units, Using Different Definitions and Indicators

AUTHORS

Élise Fortin, PhD(c)[1,2]; Robert W. Platt, PhD[1]; Patricia S. Fontela, MD PhD[3]; Milagros Gonzales, MSc[3]; David L. Buckeridge, MD PhD[1]; Philippe Ovetchkine, MD[4]; Caroline Quach, MD MSc [1,2,3]

1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada;

2) Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Québec and Montréal, Québec, Canada;

3) Department of Pediatrics, The Montréal Children's Hospital, McGill University, Montréal, Québec, Canada;

4) Department of Pediatrics, Division of Infectious Diseases, CHU Sainte-Justine – University of Montréal, Montréal, Québec, Canada.

ABSTRACT

Objective. Limited data exists on antimicrobial use and on levels of resistance in Québec inpatients' microbiota. Using different indicators and definitions, this study aimed to describe population antimicrobial use as well as prevalence and incidence of clinically relevant antimicrobial resistances found in respiratory cultures performed in intensive care unit (ICU) patients.

Methods. This retrospective cohort study included all patients admitted to nine ICUs, between April 2006 and March 2010. Prevalence and incidence of clinically relevant resistances in respiratory cultures were described and population antimicrobial use was measured using ten different indicators based on either dosage, duration of treatment or exposure to antimicrobials.

Results. Indicators had variable sensitivity to detect time trends and differences between ICU types. However, the highest prevalence and incidence rates in respiratory isolates were in *Staphylococcus aureus* resistance to oxacillin (0.52 % of ICU admissions and 6.57 acquisitions / 10,000 patient-days) and coliforms resistance to piperacillin-tazobactam (0.44% and 7.80 acquisitions / 10,000 patient-days). Cephalosporins, penicillins and aminoglycosides were the most frequently prescribed antimicrobials, according to most indicators.

Conclusions. Given the observed heterogeneity between indicators, one should consider referring to sets of indicators, allowing for the selection of indicators representing different aspects of antimicrobial use, resistance levels and of patient case-mix.

INTRODUCTION

Given the importance of antimicrobial resistance, the World Health Organization (WHO) made it its 2011 World Health Day theme.[1] Already in 2001, recommendations to control antimicrobial resistance had been issued, with a focus on surveillance of resistance and of antimicrobial use in hospitals.[2] Various surveillance networks currently exist worldwide, notably, the European Surveillance of Antimicrobial Consumption (ESAC), the European Antimicrobial Resistance Surveillance Network (EARS-Net), and the National Healthcare Security Network (NHSN) in the United States.[3-5]

Across networks, frequency of resistance has been estimated using different methodologies and definitions: in isolates from healthcare-acquired infections versus all clinical isolates, intermediate strains have been grouped with resistant or susceptible strains, and varying definitions of multiresistance. [6-8] For surveillance of antimicrobial use, debate is also ongoing: the WHO recommends the use of defined daily doses (DDDs) per patient-days.[9] ESAC measures antimicrobial use in point prevalence surveys while the NHSN prefers days of treatment per patient-days. Other indicators also exist, but publications comparing many indicators in a single study are rare.[3, 5, 10] However, as existing studies have shown how different indicators can highlight different aspects of antimicrobial use, some authors recommend the use of sets of indicators to get a complete portrait of the situation.[11-14]

Using different indicators and definitions, this study aimed to describe the burden (prevalence and incidence) of clinically relevant antimicrobial resistances found in respiratory cultures performed in patients from nine intensive care units (ICUs), and to describe population antimicrobial use in these ICUs, as would be done in a surveillance setting. Results obtained with the various methodologies were also compared.

METHODS

STUDY DESIGN AND POPULATION

This retrospective cohort study included all patients admitted to ICUs in four hospitals located in Montreal, Canada, between April 1st, 2006 and March 31st, 2010. Participating ICUs included three neonatal ICUs (NICUs), two pediatric ICUs (PICUs) and four adult ICUs. This project received approval from the Research Ethics Boards of McGill University and the *Centre Hospitalier Universitaire* Sainte-Justine.

Admission – Discharge – Transfer (ADT) data were extracted for all ICU patients. Our data included unique identifying numbers, ICU identification and dates of admission and discharge to and from hospitals and ICUs. After a careful review, these data were used to compute numbers of ICU admissions (including transfers from other wards) and ICU patient-days.[15]

ANTIMICROBIAL RESISTANCE

Using microbiology laboratory information systems, a database of bacteria isolated from ICU patients was built. Only positive cultures were available. Variables extracted were: unique identifying number, ICU identification, sampling site, sample collection date, identified microorganism, antimicrobial tested and resistance profile (susceptible, intermediate or resistant). This database was merged with ADT data, to link cultures with specific care episodes. Endotracheal and other respiratory samples were selected. We assumed that most ICU patients were intubated at some point during their ICU stay and that respiratory cultures were done for intubated patients as part of the investigation for unstable ICU patients. This was thus an attempt to describe the respiratory microbiota, regardless of the presence of an infection.

For the measurement of resistance prevalence and incidence, clinically relevant antimicrobial resistances (microorganism / antimicrobial combinations) were selected. Coliforms were analyzed as a group and included the following microorganisms: *Enterobacter* sp., *Escherichia coli*, *Hafnia alvei*, *Klebsiella* sp., *Morganella morganii*, *Providencia rettgeri*, *Raoultella* sp., *Serratia* sp. and microorganisms coded as "Coliforms". Based on the SHEA and HICPAC recommendations for metrics for multidrug-resistant organisms in healthcare settings,

prevalence of resistance per 100 ICU admissions was measured to estimate exposure burden. Incidence of resistance per 10,000 patient-days was also measured to quantify healthcare acquisition.[16] Prevalence of resistance to specific antimicrobials was measured by counting the number of ICU admissions where a resistant strain of a given microorganism was isolated. Resistance to a specific antimicrobial was counted as an incident case when a resistant microorganism was detected in a patient with a previously susceptible organism or in a patient with no positive culture at least 2 days after admission to ICU; patient-days were computed excluding the first 2 days after ICU admission, based on dates, as these patient-days had an event probability equal to zero. Two alternative definitions of resistance incidence were also used, the first one using, as recommended by the SHEA and HICPAC, a 3-day window after admission (rather than a 2-day window) and the second one counting intermediate strains along with resistant strains (rather than resistant strains only).

ANTIMICROBIAL USE

Hospital pharmacy databases provided the following information on all prescriptions for antimicrobials issued for patients included in the study: unique identifying number, age, weight, antimicrobial prescribed, posology and prescription start and stop dates. These databases described prescribed drugs and not necessarily drugs administered to a patient. Only agents belonging to class J01 of the Anatomical Therapeutic Chemical (ATC) classification system (anti-infectives for systemic use) were kept for analysis, except for oral and rectal doses of metronidazole, which were also included despite not being part of class J01.[17] Doses and days of treatment prescribed for use before or after ICU admission were excluded, but those used on the ICU admission or discharge dates were kept.

Antimicrobial use was measured using 10 different indicators previously identified in a systematic review of indicators used for populations that included pediatric patients.[10] These indicators were obtained by combining 5 numerators [defined daily doses (DDDs), recommended daily doses (RDDs), agent-days, exposed patients, and number of courses] with 2 denominators (ICU patient-days and ICU admissions). DDDs were computed dividing quantities prescribed by the standard values specified on the website of the ATC/DDD system.[17] RDD were

computed similarly, but standard values for the computation of RDDs were based on doses recommended in the 2008 Sanford Guide, the 2012 Red Book, The Montreal Children's Hospital drug formulary and Nelson 2012; pediatric patients' weight was accounted for in RDD computations (RDDs in mg/kg).[18-21] A table of standard values is available as supplementary material. Agent-days were the numbers of days when each specific antimicrobial was prescribed; in a combined therapy, each agent prescribed for a day counts for one agent-day. Exposure was the number of patients prescribed an antimicrobial agent, regardless of quantity or duration. Courses were the number of distinct periods of consecutive days when a patient was prescribed a specific antimicrobial. All ICU patient-days were included in the computation of denominators, as antimicrobial exposure was measured for the entire ICU stay; ICU admission and discharge day each counted for half a day. Indicators were computed by antimicrobial agent and class of antimicrobials, in accordance with the Anatomical Therapeutic Chemical Classification System.

STATISTICAL ANALYSES

The various definitions of resistance were compared using the global values obtained for the population as a whole; incidence rates were compared using a mid-P test for differences in rates. Bivariate additive regression models were used to detect the presence of time trends (per year) or of differences by ICU type (NICU, PICU, adult ICU). Binomial regression was used for resistance prevalence, Poisson regression, for incidence of resistance and indicators of antimicrobial use. Statistical analyses were performed using SAS 9.2.

RESULTS

Between April 2006 and March 2010, 28,919 patients were admitted to participating ICUs, for a total of 192,422 patient-days and a median length of stay of 2.0 days. In adult ICUs, there were 16,955 admissions and 79,432 patient-days, in PICUs, 6,064 admissions and 29,696 patient-days, and in NICUs, 5,900 admissions and 83,294 patient-days. Respective median lengths of stay were 2.0, 2.0 and 5.0 days.

ANTIMICROBIAL RESISTANCE

Prevalence and incidence of selected resistances observed in respiratory isolates are presented in Table 5.1, with results on alternative definitions for incidence rates. The highest prevalence and incidence rates were oxacillin resistance in *Staphylococcus aureus* and piperacillin-tazobactam resistance in coliforms. The lowest resistance rates were vancomycin or ampicillin resistance in *Enterococcus* sp. and carbapenems resistance in *E. coli*, *Klebsiella* sp. and *Proteus* sp. These rare resistances were not analyzed in regression models. Incidence rates obtained when using a 3-day window were not statistically different from those obtained with a 2-day window. When including intermediate strains in computations, rates were different for only two resistances: piperacillin-tazobactam in coliforms and quinolones in *Pseudomonas* sp.

Prevalence differences for time trends and ICU type are presented in Table 5.2. Increasing prevalences were observed for quinolones and to piperacillin-tazobactam resistance in coliforms and third-generation cephalosporins resistance in *E. coli*, *Klebsiella* sp. and *Proteus* sp. Resistance prevalence was usually lower in NICUs than in adult ICUs; however, aminoglycosides resistance in coliforms was more prevalent than in adult ICUs. Resistance prevalence was also lower in PICUs for quinolone resistance in coliforms and *Pseudomonas* sp. as well as for carbapenem resistance in *Pseudomonas* sp.

Incidence rate differences for time trends and ICU type are presented in Table 5.3. Again, increasing time trends were observed for resistance to piperacillin-tazobactam in coliforms and to third-generation cephalosporins in *E. coli*, *Klebsiella* sp. and *Proteus* sp. Incidence rates were usually lower in NICUs than in adult ICUs, except for third-generation cephalosporins resistance in *E. coli*, *Klebsiella* sp. and *Proteus* sp. Incidence was also lower in PICUs for oxacillin resistance in *S. aureus*, to quinolones in coliforms and to carbapenems in *Pseudomonas* sp.

ANTIMICROBIAL USE

ICU antimicrobial use, as measured using ten different indicators, is described in Table 5.4. At least one antimicrobial was prescribed for 56 % of ICU admissions, for a total of 77,390 DDDs, 122,807 RDDs, 147,638 agent-days and 36,547 courses. As the number of patient-days was much higher than the number of admissions, indicators per 100 admissions were higher than

indicators per 100 patient-days. Cephalosporins were usually the most frequently used antimicrobials, followed by penicillins and aminoglycosides. However, using agent-days, cephalosporins ranked third, while with DDDs, aminoglycoside use appeared much less frequent. Clindamycin, macrolides, trimethoprim and sulfamides and monobactams were systematically the least frequently used antimicrobial classes.

Tables 5.5 and 5.6 summarize the results of regression models exploring time trends and variations per ICU type (detailed results are provided as supplementary data in Tables 5.8 and 5.9). Most indicators for aminoglycosides, penicillins and quinolones use followed a statistically significant decreasing trend ($p \leq 0.05$). All indicators of carbapenem use increased, while most indicators for clindamycin, macrolide and penicillin and β-lactamase inhibitors use remained stable. When focusing on diverging indicators, those using admissions as denominators, and RDDs or DDDs as numerators detected increases more frequently. Those using patient-days and courses or agent-days detected decreases more frequently. In the analysis of variations per ICU type, use was generally lower in NICUs than in adult ICUs, except for aminoglycosides and penicillins, for which use was higher in NICUs (except with DDD / 100 patient-days); results varied for clindamycin and trimethoprim and sulfamides. Indicators that diverged from the majority used admissions as a denominator. In PICUs, carbapenem (except when using RDD), glycopeptide and quinolone use was lower than in adult ICUs, while aminoglycoside, penicillin, cephalosporin, clindamycin and macrolide use was higher than in adult ICUs; results varied for penicillins and β-lactamase inhibitors and trimethoprim and sulfamides. In these two cases, indicators standing out used patient-days or DDDs.

DISCUSSION

We described antimicrobial resistance and use in nine ICUs. Prevalence and incidence of clinically relevant resistances in respiratory isolates were described and population antimicrobial use was measured using ten different indicators based on either dosage, duration of treatment or exposure to antimicrobials. Indicators had variable sensitivity to detect time trends and differences between ICU types.

ANTIMICROBIAL RESISTANCE

Overall, resistance is relatively rarely detected in ICU patients' respiratory cultures. In a recent study in Canadian hospitals, Simor *at al.* reported a prevalence of 0.3% of methicillin-resistant *S. aureus* (MRSA) and 0 % of vancomycin-resistant *Enterococci* (VRE) in strains from infected patients, but of 4.2% and 0.5%, respectively, when adding colonization.[22] When comparing our resistance prevalence (0.5% and 0.01% for MRSA and VRE respectively) to those of Simor's, one may wonder if our data suggest lower resistance prevalence or rather indicate that our data mainly represent infections and not colonization.

The fact that selected resistances ranked similarly with incidence and prevalence, along with the relatively similar numbers of cases, suggest that a high proportion of prevalent cases are actually acquired (or revealed) during ICU stays. This phenomenon is of course more apparent with the 2-day window definition of incident cases. Datta *et al.* had previously demonstrated that different time windows could produce different incidence rates of MRSA healthcare-associated infections.[23] In our population, the 2- and 3-day window definitions provided statistically equivalent estimates of incidence rates, but results might differ in larger cohorts. Therefore, the 2-day window was preferred because of the larger numerator and improved precision. When patients who acquired an intermediate strain were counted as incident cases of resistance, two of the ten resistance incidence rates significantly increased (resistance to piperacillin-tazobactam in coliforms and to quinolones in *Pseudomonas* sp.). This is coherent with a CANWARD publication, in which intermediate strains were more frequent in these microorganism / antimicrobial combinations than in others.[24]

Of all resistances, only oxacillin-resistant *S. aureus* showed a decreasing trend over time, which was not statistically significant. Significant increasing trends were observed in coliforms (piperacillin-tazobactam, quinolones and third-generation cephalosporins), suggesting prevention efforts should be directed towards controlling these resistances. Also, a gradient in resistance, from neonates to adults, was observed in our cohort, a finding that was reported in the past.[25] In our data, an exception to this trend was observed for prevalence of resistance to aminoglycosides, which was significantly higher in NICUs; however, incidence remained lower

than in adult ICUs. This could be explained by the longer median length of stay in NICUs (more patient-days). This result is nonetheless interesting when put in parallel with the fact that aminoglycoside use was also higher in NICUs.

ANTIMICROBIAL USE

Cephalosporins, penicillins and aminoglycosides were the most frequently prescribed antimicrobials, according to most indicators. Grohskopf *et al.* reported that, in NICUs and PICUs, around 25% of patients were exposed to cephalosporins, 15% to ampicillin and 20% to aminoglycosides; these values are very similar to those observed in our study (25%, 15% and 17%, respectively), which included a majority of pediatric or neonatal ICUs.[26] Aminoglycoside use was also similar to use reported by Dumartin *et al.* on pediatric wards (1.9 versus 1.7 DDD / 100 patient-days) and in ICUs (8.8 RDD / 100 patient-days versus 9.0 DDD / 100 patient-days), but penicillin and third generation cephalosporin use were lower in our study.[27] RDDs are closer to agent-days than DDDs, an expected result as RDDs should better reflect actually prescribed daily doses than DDDs; it is interesting to note that RDDs generally underestimated agent-days in our cohort. In the case of quinolones and carbapenems, RDDs underestimated agent-days even more than DDDs, although our cohort includes a majority of pediatric and neonatal ICUs. This is attributable to the fact that DDDs and RDDs account not only for duration of treatment, but also for quantities given, which do not always correspond to standard doses. It also depends on antimicrobial agents most frequently used in populations studied ("antimicrobial-mix"), and how much their DDDs and RDDs differ from each other and from actually prescribed daily doses. For instance, in our study, RDDs for parenteral ciprofloxacin, imipenem and meropenem were lower than their DDD and were also the most used agents in their respective classes. Aminoglycosides were prescribed more frequently in NICUs than in adult ICUs, thus magnifying the discrepancy between DDDs and RDDs in mg/kg prescribed to neonates. The same phenomenon was observed for penicillins. These discrepancies were also reflected in the results of regression models for aminoglycoside, penicillin and carbapenem use.

In general, antimicrobial use was lower in NICUs compared to adult ICUs, except for aminoglycoside and penicillin use, which were higher in NICUs. This makes sense as treatment

options are more limited in this population, leading to a more intense use of available agents. Also, as median length of stay in NICUs is longer, patients have more time to be exposed to antimicrobials; this can explain why, in the few cases where lower use was observed in adult ICUs, admissions were used as denominator. Antimicrobial use was frequently higher in PICUs than in adult ICUs. Whenever indicators disagreed, DDDs tended to underestimate antimicrobial use, compared to most indicators; this is expected, as DDDs are not adjusted for patients' weight, but this underestimation was not systematic. Interestingly, decreasing trends were observed for two of the most frequently prescribed antimicrobial classes, penicillins and aminoglycosides. Indicators giving opposite results also provide interesting information. For instance, for penicillins and β-lactamase inhibitors, agent-days per patient-days decreased, but RDDs per admissions increased. A closer look at the data indicates that the decrease was mostly driven by adult ICUs, while the increase came from PICUs and NICUs, where prescribed daily doses appear to have increased through time. For clinicians and public health authorities, these observations all point out to the usefulness of using sets of indicators to better understand their populations' antimicrobial use.

LIMITATIONS

Interpretation of these results has a few limitations. First of all, we limited our description of resistance to respiratory cultures; other sources might have provided different estimates of resistance, with different relative frequencies of isolated microorganisms. However, in studies presenting separately urine and respiratory tract isolates, proportions of resistant and intermediate strains were not dramatically different.[6, 24] Importantly, we were interested in measuring the burden of resistance. This is why we did not measure the proportion of resistance among all isolated strains (resistant, intermediate and susceptible), as this last metric would inform on the choice of empirical treatment rather than on the burden. Also, our study aimed to reproduce a surveillance setting limited to ICU patients, which probably led to higher levels of resistance and antimicrobial use than in entire hospitals. Although we used 2- and 3-day windows in our incidence computations, as used in definitions of healthcare-associated infections, some resistances might need more time to be selected and revealed and incidence might be underestimated. However, median length of stay in ICUs (and in acute care hospitals

from the same jurisdiction)[28] is short and longer time-windows would have excluded a very large proportion of patients from incidence computations. We thus chose to remain close to recommended windows. For measurement of antimicrobial use, administration and distribution start and stop dates were not always available so our results rather describe prescribed antimicrobials. This measurement error might probably lead to an overestimation of antimicrobial use in our ICUs. In the case of interrupted or delayed treatments, this might have affected indicators using DDDs, RDDs and agent-days more than other indicators; in the case of courses never started, all indicators would be overestimated. Finally, objectives were to describe resistance and antimicrobial use in our cohort; however, because analyses aggregated data per ICU type and per year, we do not believe these results should be used to study the association between antimicrobial use and resistance. Finer stratification of data would be necessary for this purpose.

This study described antimicrobial use and resistance in nine ICUs, using different measures of resistance, different definitions of incident resistance and also using ten indicators of antimicrobial use. Although most of the time, these measures gave similar estimates and detected similar trends, this was not always the case, suggesting that in some situations, a set of indicators may be preferable, selecting indicators showing different aspects of antimicrobial use (we would suggest admissions and patient-days as denominators and exposed, agent-days and DDDs as numerators, based on this study) and of resistance levels (resistant versus resistant and intermediate strains). Purpose of measurement should also orient indicator selection, but indicators predicting resistance with the best accuracy have yet to be identified.

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Table 5.1. Prevalence and incidence rates of different resistant microorganisms isolated from respiratory cultures, in nine intensive care units, April 2006 to March 2010.

	Prevalence (28,919 admissions)		Incidence					
			2-day window, resistant only (146,154 patient-days)		3-day window, resistant only (127,979 patient-days)		2-day window, resistant or intermediate (146,154 patient-days)	
	n	% [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]
Staphylococcus aureus / Oxacillin	149	0.52 [0.44 ; 0.60]	96	6.57 [5.35 ; 7.99]	79	6.17 [4.92 ; 7.65]	96	6.57 [5.35 ; 7.99]
Enterococcus sp. / Vancomycin	2	0.01 [0.00 ; 0.02]	2	0.14 [0.02 ; 0.45]	1	0.08 [0.00 ; 0.39]	2	0.14 [0.02 ; 0.45]
Enterococcus sp. / Ampicillin	10	0.01 [0.00 ; 0.02]	8	0.55 [0.25 ; 1.04]	7	0.55 [0.24 ; 1.08]	8	0.55 [0.25 ; 1.04]
Enterococcus faecalis / Ampicillin	2	0.01 [0.00 ; 0.02]	2	0.14 [0.02 ; 0.45]	2	0.16 [0.03 ; 0.52]	2	0.14 [0.02 ; 0.45]
Enterobacter sp. or *Citrobacter* sp. / Carbapenems	2	0.01 [0.00 ; 0.02]	2	0.14 [0.02 ; 0.45]	2	0.16 [0.03 ; 0.52]	3	0.21 [0.05 ; 0.56]

	Prevalence (28,919 admissions)		Incidence					
			2-day window, resistant only (146,154 patient-days)		3-day window, resistant only (127,979 patient-days)		2-day window, resistant or intermediate (146,154 patient-days)	
	n	% [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]	n	Rate per 10,000 patient-days [95 % C. I.]
Coliforms / Quinolones	96	0.33 [0.27 ; 0,41]	73	5.00 [3.94 ; 6.24]	67	5.24 [4.09 ; 6.61]	89	6.09 [4.92 ; 7.46]
Coliforms / Pip-tazo	126	0.44 [0.36 ; 0.52]	114	7.80 [6.46 ; 9.33]	108	8.44 [6.96 ; 10.15]	156	10.67 [9.10 ; 12.45]
Coliforms / Aminoglycosides	62	0.21 [0.16 ; 0.27]	52	3.56 [2.69 ; 4.63]	45	3.52 [2.60 ; 4.66]	72	4.93 [3.88 ; 6.17]
EKP / 3GC	40	0.14 [0.10 ; 0.19]	30	2.05 [1.41 ; 2.89]	27	2.11 [1.42 ; 3.03]	41	2.81 [2.04 ; 3.77]
EKP / Carbapenems	7	0.02 [0.01 ; 0.05]	5	0.34 [0.13 ; 0.76]	5	0.39 [0.14 ; 0.87]	6	0.41 [0.17 ; 0.85]
Pseudomonas sp. / Quinolones	47	0.16 [0.12 ; 0.22]	38	2.60 [1.19 ; 3.35]	36	2.81 [2.00 ; 3.85]	71	4.86 [3.82 ; 6.09]
Pseudomonas sp. / Carbapenems	95	0.33 [0.27 ; 0.40]	78	5.34 [4.25 ; 6.63]	74	5.78 [4.57 ; 7.22]	85	5.82 [4.67 ; 7.16]
Pseudomonas sp. / Pip-tazo	58	0.20 [0.15 ; 0.26]	45	3.08 [2.27 ; 4.08]	42	3.28 [2.40 ; 4.39]	45	3.08 [2.27 ; 4.08]

Note: /GC: 3rd-generation cephalosporins; EKP: *Escherichia coli*, *Klebsiella* sp. or *Proteus* sp.; Pip-tazo: piperacilline-tazobactam.

Table 5.2. Bivariate prevalence differences, per year and per type of intensive care unit, for selected resistant microorganisms isolated in respiratory cultures.

	Resistance prevalence difference (%, 95 % C. I.)							
	S. aureus	**Coliforms**			**EKP**	**Pseudomonas sp.**		
	Oxacillin	**Quinolones**	**Piperacillin-tazobactam**	**Amino-glycosides**	**3GC**	**Quinolones**	**Carbapenems**	**Piperacillin-tazobactam**
Year	-0,03 [-0,10 ; 0,04]	**0,07 [0,01 ; 0,12]**	**0,21 [0,15 ; 0,27]**	0,04 [0,00 ; 0,09]	**0,05 [0,02 ; 0,09]**	0,02 [-0,02 ; 0,07]	0,02 [-0,04 ; 0,08]	0,03 [-0,01 ; 0,08]
ICU type								
Adult	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
PICU	-0,13 [-0,35 ; 0,09]	**-0,46 [-0,58 ; -0,34]**	-0,09 [-0,27 ; 0,10]	0,00 [-0,12 ; 0,13]	-0,07 [-0,17 ; 0,03]	**-0,12 [-0,21 ; -0,04]**	**-0,37 [-0,51 ; -0,24]**	-0,05 [-0,18 ; 0,08]
NICU	**-0,58 [-0,72 ; -0,43]**	**-0,39 [-0,53 ; -0,25]**	0,03 [-0,18 ; 0,23]	**0,18 [0,01 ; 0,34]**	-0,06 [-0,17 ; 0,04]	-*	**-0,40 [-0,53 ; -0,28]**	**-0,12 [-0,23 ; 0,00]**

Note: statistically significant differences are in **bold** (p value < 0.05). 3GC: third-generation cephalosporins; EKP: *Escherichia coli*, *Klebsiella* sp. or *Proteus* sp.; ICU: intensive care unit; NICU: neonatal ICU; PICU: pediatric ICU.

*0 prevalent case of resistance to quinolones.

Table 5.3. Bivariate incidence rate differences, per year and per type of intensive care unit, for selected resistant microorganisms isolated in respiratory cultures.

	Resistance incidence rate difference (%, 95 % C. I.)							
	S. aureus	**Coliforms**			**EKP**	**Pseudomonas sp.**		
	Oxacillin	**Quinolones**	**Piperacillin-tazobactam**	**Amino-glycosides**	**3GC**	**Quinolones**	**Carbapenems**	**Piperacillin-tazobactam**
Year	-0,89 [-2,08 ; 0,30]	0,40 [-0,64 ; 1,44]	**3,35 [2,22 ; 4,48]**	0,69 [-0,18 ; 1,57]	**0,67 [0,05 ; 1,28]**	0,35 [-0,36 ; 1,07]	0,39 [-0,58 ; 1,37]	0,38 [-0,41 ; 1,16]
ICU type								
Adult	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
PICU	**-7,92 [-12,79 ; -3,06]**	**-11,53 [-14,83 ; -8,22]**	-2,71 [-7,96 ; 2,53]	-0,52 [-3,97 ; 2,93]	-1,15 [-3,84 ; 1,54]	-1,31 [-3,22 ; 0,59]	**-11,79 [-15,32 ; -8,27]**	-2,45 [-5,72 ; 0,83]
NICU	**-14,23 -17,55 ; -10,91]**	**-11,82 [-14,90 ; -8,74]**	**-8,67 [-12,00 ; -5,33]**	**-2,60 [-4,79 ; -0,40]**	-2,78 [-4,53 ; 1,03]	-*	**-12,58 [-15,74 ; -9,41]**	**-4,91 [-7,10 ; -2,73]**

Note: statistically significant differences are in **bold** (p value < 0.05). 3GC: third-generation cephalosporins; EKP: *Escherichia coli*, *Klebsiella* sp. or *Proteus* sp.; ICU: intensive care unit; NICU: neonatal ICU; PICU: pediatric ICU.

*0 prevalent case of resistance to quinolones.

Table 5.4. Antimicrobial use in nine intensive care units, as measured using ten different indicators.

	Antimicrobial use									
	Per 100 patient-days					Per 100 admissions				
	DDD*	RDD*	Exposed	Agent-days	Courses	DDD	RDD	Exposed	Agent-days	Courses
Aminoglycosides	1,9	8,8	2,5	12,7	3,0	12,9	58,8	16,5	84,5	19,6
Penicillins	6,0	12,1	2,6	13,8	3,3	40,1	80,3	17,3	91,9	22,0
Ampicillin	2,8	8,4	2,2	9,3	2,4	18,9	56,1	14,6	61,8	16,0
Carbapenems	3,0	2,8	0,5	4,0	0,6	19,8	18,7	3,5	26,5	4,0
Glycopeptides	5,1	6,8	2,1	9,0	2,5	33,7	45,2	14,1	60,2	16,7
Quinolones	5,4	4,2	1,0	4,6	1,1	35,9	28,2	6,4	30,6	7,3
Cephalosporins	7,7	13,0	3,8	11,1	4,2	51,0	86,7	25,2	73,7	27,7
3rd-generation cephalosporins	2,1	3,7	0,8	3,5	0,9	13,8	24,7	5,6	23,2	6,0
Clindamycin	0,7	1,2	0,3	1,2	0,3	4,7	8,2	2,1	8,2	2,2
Macrolides	1,3	2,2	0,4	1,6	0,4	8,4	14,8	2,8	10,8	3,0
Penicillins and β-lactamase inhibitors	6,4	8,5	2,0	11,7	2,4	42,7	56,4	13,4	78,0	16,3
Piperacillin-tazobactam	1,9	2,6	0,5	3,3	0,6	12,4	17,5	3,5	21,8	3,9
Trimethoprim and sulfamides	0,3	0,9	0,3	3,1	0,3	2,2	6,1	2,0	20,9	2,1
Monobactams	0,0	0,0	0,0	0,0	0,0	0,2	0,2	0,0	0,3	0,0
Other antimicrobials	2,4	3,2	0,8	3,8	0,8	16,0	21,3	5,1	25,1	5,6
Metronidazole	2,3	3,1	0,7	3,6	0,8	15,2	20,4	4,9	23,9	5,3

*DDD: defined daily doses; RDD: recommended daily doses.

Table 5.5. Summary of bivariate Poisson regression results on time trends in antimicrobial use.

Antimicrobial class	**Decrease**	**Stable**	**Increase**
Aminoglycosides	All other indicators	RDD / 100 admissions	-
Penicillins	All other indicators	Exposed / 100 admissions Courses / 100 admissions	-
Carbapenems	-	-	All indicators
Glycopeptides	-	Exposed / 100 patient-days Exposed / 100 admissions Agent-days / 100 patient-days Agent-days / 100 admissions Courses / 100 patient-days Courses / 100 admissions	DDD / 100 patient-days DDD / 100 admissions RDD / 100 patient-days RDD / 100 admissions
Quinolones	All indicators	-	-
Cephalosporins	All other indicators	DDD / 100 patient-days Agent-days / 100 admissions	DDD / 100 admissions RDD / 100 patient-days RDD / 100 admissions
Clindamycin	Courses / 100 patient-days	All other indicators*	DDD / 100 admissions
Macrolides	DDD / 100 patient-days DDD / 100 admissions	All other indicators	

Antimicrobial class	Decrease	Stable	Increase
Penicillins and β-lactamase inhibitors	Agent-days / 100 patient-days Courses / 100 patient-days	All other indicators	RDD / 100 admissions
Trimethoprim and sulfamides	Agent-days / 100 patient-days	All other indicators	DDD / 100 patient-days DDD / 100 admissions RDD / 100 admissions

* The models for DDD / 100 patient-days and RDD / 100 patient-days did not converge.

Table 5.6. Summary of bivariate Poisson regression results on variations in antimicrobial use per type of intensive care unit.

Antimicrobial class	**ICU type (Adult ICUs as reference)**					
	Neonatal ICU use is…			**Pediatric ICU use is…**		
	Lower	**Not different**	**Higher**	**Lower**	**Not different**	**Higher**
Aminoglycosides	DDD / pd*		All other indicators			All indicators
Penicillins	DDD / pd		All other indicators			All indicators
Carbapenems	All indicators			All other indicators		RDD / pd RDD / adm
Glycopeptides	All indicators			All indicators		
Quinolones	All indicators			All indicators		
Cephalosporins	All other indicators		Agent-days / adm*			All indicators
Clindamycin	All other indicators	RDD / adm	Exposed / adm Agent-days / adm Courses / adm			All indicators
Macrolides	All indicators					All indicators
Penicillins and β-lactamase inhibitors	All indicators			DDD / pd DDD / adm RDD / pd	Exposed / pd Courses / pd RDD / adm	All other indicators
Trimethoprim and sulfamides	All other indicators	Agent-days / pd Exposed / adm	RDD / pd RDD / adm		DDD / pd DDD / adm	All other indicators

Antimicrobial class	ICU type (Adult ICUs as reference)					
	Neonatal ICU use is…			Pediatric ICU use is…		
	Lower	Not different	Higher	Lower	Not different	Higher
		Courses / adm	Agent-days / adm			

*pd: per 100 patient-days; adm: per 100 admissions.

SUPPLEMENTARY DATA

Table 5.7. Standard values used in the computation of defined daily doses (DDD) and recommended daily doses (RDD).

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)								
						Neonates						
						0 - 7 days old			8 - 28 days old			
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
Tetracyclines	Demeclocycline	PO	600	600							
	Doxycycline	PO	100	150	3						
		IV	100								
	Minocycline	PO	200	200							
	Tetracycline	PO	1000	1000	37,5						
	Tigecycline	IV	100	100							
Penicillins	Amoxicillin	PO	1000	1125	90						30
	Ampicillin	IV	2000	7200	200	100	100	150	150	150	200
	Cloxacillin	PO	2000	3000	100	75	75	112,5	75	112,5	150
		IV	2000	6000	150	75	75	112,5	75	112,5	150
	Penicillin G	IV	3600	12000	150	60	60	90	60	90	120
	Penicillin V	PO	2000	1300	37,5						

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)							
						Neonates					
						0 - 7 days old			8 - 28 days old		
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
	Piperacillin	IV	14000	16800	400	100	100	200	200	200	300
Penicillins (and enzyme inhibitors)	Amioxicillin-clavulanate	PO	1000	1125	90			30			30
	Piperacillin-tazobactam	IV	14000	12000	400	100	100	200	200	200	300
	Ticarcillin-clavulanate	IV	15000	14400	300	150	150	225	225	225	300
Cephalosporins	Cefazolin	IV	3000	2600	75	40	40	40	40	40	60
	Cephalexin	PO	2000	2600	37,5						
	Cefaclor	PO	1000		30						
	Cefoxitin	IV	6000	6000	120						40
	Cefprozil	PO	1000	750	22,5	22,5	22,5	22,5	22,5	22,5	22,5
	Cefuroxime	IV	3000	4125	150	100	100	150	150	150	150
		PO	500	1500	25						
	Cefepime	IV	2000	3600	100						
Cephalosporins (3rd generation)	Cefixime	PO	400	400	8						
	Cefotaxime	IV	4000	5150	150	100	100	150	100	150	150
	Ceftazidime	IV	4000	3750	150	100	100	100	150	150	150

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)							
						Neonates					
						0 - 7 days old			8 - 28 days old		
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
	Ceftriaxone	IV	2000	1875	100	50	50	50	50	50	75
Monobactams	Aztreonam	IV	4000	8000	120	60	60	90	90	90	120
Carbapenems	Ertapenem	IV	1000	1000	30						
	Imipenem-cilastatin	IV	2000	2500	80	50	50	50	50	75	75
	Meropenem	IV	2000	4000	60	40	40	40	60	60	60
Sulfonamides and trimethoprim	Sulfadiazine	PO	600	3000	100	100	100	100	100	100	100
	Trimethoprim-sulfamethoxazole	PO	1200	1600	10	1,2	1,2	1,2	1,2	1,2	1,2
		IV	5500	5250	15	1,2	1,2	1,2	1,2	1,2	1,2
	Trimethoprim	PO	400	200	10	1,2	1,2	1,2	1,2	1,2	1,2
		IV	400		10	1,2	1,2	1,2	1,2	1,2	1,2
Macrolides	Azithromycin	PO	300	250	5	5	5	5	10	10	10
		IV	500	250	5	5	5	5	10	10	10
	Clarithromycin	PO	500	750	15						
	Erythromycin	PO	1000	1125	40	20	20	20	30	30	30
		IV	1000	1500	40	20	20	20	30	30	30

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)							
						Neonates					
						0 - 7 days old			8 - 28 days old		
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
Lincosamides	Clindamycin	PO	1200	775	25	10	10	15	10	15	15
		IV	1800	2000	30	10	10	15	15	15	20
Aminoglycosides	Amikacin	IV	1000	1050	30	10	15	20	10	22,5	30
	Gentamicin	IV	240	350	7,5	2,85	5	5	5	5	5
		PO				10	10	10	10	10	10
	Streptomycin	IV	1000	1050							
	Tobramycin	In	300	600	600						
		IV	240	350	7,5	2,85	5	5	5	5	5
Quinolones	Ciprofloxacin	PO	1000	1000	30	30	30	30	30	30	30
		IV	500	720	30	30	30	30	30	30	30
	Levofloxacin	PO	500	500	16	16	16	16	16	16	16
		IV	500	500	16	16	16	16	16	16	16
	Moxifloxacin	PO	400	400							
		IV	400	400							
Glycopeptides	Vancomycin	IV	2000	2000	40	25	25	36	30	30	44

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)							
						Neonates					
						0 - 7 days old			8 - 28 days old		
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
		PO	2000	1250	40	40	40	40	40	40	40
		Re		2000							
Amphenicols (grouped with "others")	Chloramphenicol	IV	3000	4000	75	25	25	25	25	25	30
Streptogramins (grouped with "others")	Quinupristin-dalfopristin	IV	1500	1575	22,5						
Others	Colistimethate	In	240	160							
		IV	240	175							
	Daptomycin	IV	280	280	7	12	12	12	12	12	12
	Fusidate	PO	1500	1500							
	Linezolid	PO	1200	1200	30	20	20	30	30	30	30
		IV	1200	1200	30	20	20	30	30	30	30
	Metronidazole	PO	2000	1500	30	7,5	7,5	15	15	15	30

Antimicrobial class	Antimicrobial agent	Route	DDD (in mg)	RDD (in mg)							
						Neonates					
						0 - 7 days old			8 - 28 days old		
			All patients	Adult patients	Pediatric patients	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg	< 1.2 kg	1.2 - 2.0 kg	≥ 2.0 kg
		IV	1500	1500	30	7,5	7,5	15	15	15	30
	Nitrofurantoin	PO	200	300	6						

Table 5.8. Bivariate Poisson regression results on time trends in antimicrobial use of various antimicrobial classes, according to ten different indicators.

Antimicrobial class	Indicator	Rate difference per year
Aminoglycosides	Agent-days / admissions	-0,0363 [-0,0458 ; -0,0269]
	Agent-days / patient-days	-0,0072 [-0,0087 ; -0,0058]
	Courses / admissions	-0,0069 [-0,0114 ; -0,0023]
	Courses / patient-days	-0,0014 [-0,0021 ; -0,0008]
	DDD / admissions	-0,0067 [-0,0104 ; -0,0030]
	DDD / patient-days	-0,0013 [-0,0018 ; -0,0007]
	Exposed / admissions	-0,0046 [-0,0088 ; -0,0004]
	Exposed / patient-days	-0,0010 [-0,0017 ; -0,0004]
	RDD / admissions	-0,0041 [-0,0121 ; 0,0039]
	RDD / patient-days	-0,0019 [-0,0031 ; -0,0007]
Penicillins	Agent-days / admissions	-0,0243 [-0,0341 ; -0,0144]
	Agent-days / patient-days	-0,0055 [-0,007 ; -0,0041]
	Courses / admissions	-0,0030 [-0,0079 ; 0,0018]
	Courses / patient-days	-0,0009 [-0,0016 ; -0,0002]
	DDD / admissions	-0,0259 [-0,0322 ; -0,0197]
	DDD / patient-days	-0,0047 [-0,0056 ; -0,0037]
	Exposed / admissions	-0,0024 [-0,0066 ; 0,0019]
	Exposed / patient-days	-0,0007 [-0,0014 ; -0,0001]
	RDD / admissions	-0,0108 [-0,0200 ; -0,0016]
	RDD / patient-days	-0,0033 [-0,0047 ; -0,0019]
Carbapenems	Agent-days / admissions	0,0145 [0,0092 ; 0,0197]
	Agent-days / patient-days	0,0016 [0,0009 ; 0,0024]
	Courses / admissions	0,0028 [0,0007 ; 0,0048]
	Courses / patient-days	0,0003 [0,0000 ; 0,0006]
	DDD / admissions	0,0140 [0,0096 ; 0,0185]
	DDD / patient-days	0,0017 [0,0010 ; 0,0024]
	Exposed / admissions	0,0032 [0,0013 ; 0,0051]

Antimicrobial class	Indicator	Rate difference per year
	Exposed / patient-days	0,0004 [0,0001 ; 0,0007]
	RDD / admissions	0,0173 [0,0130 ; 0,0216]
	RDD / patient-days	0,0022 [0,0016 ; 0,0029]
Glycopeptides	Agent-days / admissions	0,0051 [-0,0028 ; 0,0130]
	Agent-days / patient-days	-0,0005 [-0,0017 ; 0,0007]
	Courses / admissions	-0,0008 [-0,0050 ; 0,0034]
	Courses / patient-days	-0,0005 [-0,0011 ; 0,0002]
	DDD / admissions	0,0109 [0,0049 ; 0,0169]
	DDD / patient-days	0,0009 [0,0000 ; 0,0018]
	Exposed / admissions	0,0017 [-0,0022 ; 0,0056]
	Exposed / patient-days	0,0000 [-0,0006 ; 0,0005]
	RDD / admissions	0,0195 [0,0126 ; 0,0263]
	RDD / patient-days	0,0020 [0,0010 ; 0,0030]
Quinolones	Agent-days / admissions	-0,0346 [-0,0403 ; -0,0289]
	Agent-days / patient-days	-0,0058 [-0,0067 ; -0,0050]
	Courses / admissions	-0,0066 [-0,0094 ; -0,0038]
	Courses / patient-days	-0,0011 [-0,0016 ; -0,0007]
	DDD / admissions	-0,0361 [-0,0423 ; -0,0299]
	DDD / patient-days	-0,0062 [-0,0071 ; -0,0052]
	Exposed / admissions	-0,0046 [-0,0072 ; -0,0019]
	Exposed / patient-days	-0,0008 [-0,0012 ; -0,0004]
	RDD / admissions	-0,0325 [-0,0380 ; -0,0270]
	RDD / patient-days	-0,0055 [-0,0063 ; -0,0046]
Cephalosporins	Agent-days / admissions	0,0007 [-0,0080 ; 0,0095]
	Agent-days / patient-days	-0,0014 [-0,0027 ; -0,0001]
	Courses / admissions	-0,0085 [-0,0139 ; -0,0030]
	Courses / patient-days	-0,0018 [-0,0027 ; -0,0010]
	DDD / admissions	0,0110 [0,0037 ; 0,0184]
	DDD / patient-days	0,0006 [-0,0005 ; 0,0017]
	Exposed / admissions	-0,0074 [-0,0125 ; -0,0022]

Antimicrobial class	Indicator	Rate difference per year
	Exposed / patient-days	-0,0016 [-0,0024 ; -0,0009]
	RDD / admissions	0,0272 [0,0177 ; 0,0367]
	RDD / patient-days	0,0023 [0,0009 ; 0,0037]
Clindamycin	Agent-days / admissions	0,001 [-0,0018 ; 0,0039]
	Agent-days / patient-days	0,0000 [-0,0004 ; 0,0004]
	Courses / admissions	-0,0015 [-0,0030 ; 0,0000]
	Courses / patient-days	-0,0003 [-0,0005 ; 0,0000]
	DDD / admissions	0,0035 [0,0014 ; 0,0056]
	DDD / patient-days	0,0000 [0,0000 ; 0,0000]
	Exposed / admissions	-0,0010 [-0,0024 ; 0,0005]
	Exposed / patient-days	-0,0002 [-0,0004 ; 0,0000]
	RDD / admissions	0,0017 [-0,0011 ; 0,0046]
	RDD / patient-days	0,0008 [0,0008 ; 0,0008]
Macrolides	Agent-days / admissions	0,0006 [-0,0028 ; 0,0041]
	Agent-days / patient-days	-0,0001 [-0,0006 ; 0,0004]
	Courses / admissions	-0,0004 [-0,0022 ; 0,0013]
	Courses / patient-days	-0,0001 [-0,0004 ; 0,0001]
	DDD / admissions	-0,0048 [-0,0078 ; -0,0018]
	DDD / patient-days	-0,0009 [-0,0014 ; -0,0005]
	Exposed / admissions	-0,0006 [-0,0024 ; 0,0011]
	Exposed / patient-days	-0,0002 [-0,0004 ; 0,0001]
	RDD / admissions	0,0006 [-0,0033 ; 0,0046]
	RDD / patient-days	-0,0002 [-0,0008 ; 0,0004]
Penicillins and β-lactamase inhibitors	Agent-days / admissions	-0,0001 [-0,0092 ; 0,009]
	Agent-days / patient-days	-0,0017 [-0,003 ; -0,0003]
	Courses / admissions	-0,0019 [-0,0061 ; 0,0022]
	Courses / patient-days	-0,0006 [-0,0012 ; 0,0000]
	DDD / admissions	0,0064 [-0,0003 ; 0,0132]
	DDD / patient-days	0,0001 [-0,0009 ; 0,0011]
	Exposed / admissions	0,0002 [-0,0036 ; 0,0039]

Antimicrobial class	Indicator	Rate difference per year
	Exposed / patient-days	-0,0002 [-0,0008 ; 0,0003]
	RDD / admissions	0,0109 [0,0032 ; 0,0187]
	RDD / patient-days	0,0005 [-0,0007 ; 0,0016]
	Agent-days / admissions	-0,0036 [-0,0085 ; 0,0013]
	Agent-days / patient-days	-0,0010 [-0,0018 ; -0,0003]
	Courses / admissions	-0,0003 [-0,0018 ; 0,0012]
	Courses / patient-days	-0,0001 [-0,0003 ; 0,0001]
Trimethoprim and	DDD / admissions	0,0054 [0,0041 ; 0,0068]
sulfamides	DDD / patient-days	0,0008 [0,0006 ; 0,001]
	Exposed / admissions	0,0000 [-0,0015 ; 0,0015]
	Exposed / patient-days	0,0000 [-0,0003 ; 0,0002]
	RDD / admissions	0,0027 [0,0001 ; 0,0054]
	RDD / patient-days	0,0003 [-0,0001 ; 0,0007]

Table 5.9. Bivariate Poisson regression results on variation in antimicrobial use of various antimicrobial classes per type of intensive care unit, according to ten different indicators.

Antimicrobial class	Indicator	Rate differences (adult ICUs as reference)	
		Neonatal ICU	Pediatric ICU
Aminoglycosides	Agent-days / admissions	2,9484 [2,9041 ; 2,9928]	0,898 [0,8732 ; 0,9229]
	Agent-days / patient-days	0,2010 [0,1978 ; 0,2042]	0,1829 [0,1778 ; 0,1879]
	Courses / admissions	0,6838 [0,6624 ; 0,7053]	0,1932 [0,1815 ; 0,2050]
	Courses / patient-days	0,0459 [0,0444 ; 0,0475]	0,0393 [0,0369 ; 0,0417]
	DDD / admissions	0,058 [0,0491 ; 0,0669]	0,3326 [0,3167 ; 0,3484]
	DDD / patient-days	-0,0026 [-0,0035 ; -0,0017]	0,0675 [0,0642 ; 0,0707]
	Exposed / admissions	0,5698 [0,5502 ; 0,5895]	0,1645 [0,1536 ; 0,1753]
	Exposed / patient-days	0,0381 [0,0366 ; 0,0395]	0,0334 [0,0312 ; 0,0357]
	RDD / admissions	1,9207 [1,8849 ; 1,9564]	0,7815 [0,7586 ; 0,8044]
	RDD / patient-days	0,1314 [0,1288 ; 0,1340]	0,1593 [0,1546 ; 0,1640]
Penicillins	Agent-days / admissions	3,2369 [3,1902 ; 3,2836]	0,8319 [0,8074 ; 0,8564]
	Agent-days / patient-days	0,2172 [0,2138 ; 0,2207]	0,1691 [0,1641 ; 0,1741]
	Courses / admissions	0,7500 [0,7275 ; 0,7726]	0,2133 [0,2008 ; 0,2258]
	Courses / patient-days	0,0498 [0,0482 ; 0,0515]	0,0433 [0,0408 ; 0,0459]
	DDD / admissions	0,1607 [0,1415 ; 0,1799]	0,3287 [0,3071 ; 0,3503]
	DDD / patient-days	-0,0313 [-0,0335 ; -0,0292]	0,0644 [0,0599 ; 0,0688]
	Exposed / admissions	0,5651 [0,5454 ; 0,5847]	0,1772 [0,1657 ; 0,1886]
	Exposed / patient-days	0,0369 [0,0354 ; 0,0383]	0,036 [0,0336 ; 0,0383]
	RDD / admissions	2,7873 [2,7437 ; 2,8309]	0,6369 [0,6148 ; 0,6591]
	RDD / patient-days	0,1831 [0,1798 ; 0,1863]	0,1291 [0,1246 ; 0,1337]
Carbapenems	Agent-days / admissions	-0,1428 [-0,1564 ; -0,1292]	-0,1061 [-0,1204 ; -0,0918]
	Agent-days / patient-days	-0,0552 [-0,0571 ; -0,0532]	-0,0246 [-0,0276 ; -0,0216]
	Courses / admissions	-0,0277 [-0,0328 ; -0,0227]	-0,0183 [-0,0239 ; -0,0127]
	Courses / patient-days	-0,0091 [-0,0098 ; -0,0083]	-0,0042 [-0,0054 ; -0,0030]
	DDD / admissions	-0,2700 [-0,2785 ; -0,2614]	-0,1473 [-0,1596 ; -0,1350]

Antimicrobial class	Indicator	Rate differences (adult ICUs as reference)	
		Neonatal ICU	Pediatric ICU
	DDD / patient-days	-0,0596 [-0,0613 ; -0,0578]	-0,0327 [-0,0353 ; -0,0301]
	Exposed / admissions	-0,0259 [-0,0306 ; -0,0213]	-0,0162 [-0,0214 ; -0,0109]
	Exposed / patient-days	-0,0081 [-0,0088 ; -0,0074]	-0,0037 [-0,0048 ; -0,0026]
	RDD / admissions	-0,0408 [-0,0526 ; -0,0290]	0,0300 [0,0166 ; 0,0435]
	RDD / patient-days	-0,0299 [-0,0314 ; -0,0283]	0,0044 [0,0016 ; 0,0072]
Glycopeptides	Agent-days / admissions	-0,1034 [-0,1257 ; -0,0810]	-0,1051 [-0,1272 ; -0,0830]
	Agent-days / patient-days	-0,0993 [-0,1022 ; -0,0964]	-0,0274 [-0,0320 ; -0,0229]
	Courses / admissions	-0,1095 [-0,1198 ; -0,0992]	-0,064 [-0,0756 ; -0,0525]
	Courses / patient-days	-0,0367 [-0,0383 ; -0,0352]	-0,0150 [-0,0174 ; -0,0126]
	DDD / admissions	-0,4912 [-0,5024 ; -0,4800]	-0,3370 [-0,3519 ; -0,3220]
	DDD / patient-days	-0,1072 [-0,1095 ; -0,1049]	-0,0735 [-0,0766 ; -0,0704]
	Exposed / admissions	-0,1041 [-0,1134 ; -0,0948]	-0,0554 [-0,0662 ; -0,0447]
	Exposed / patient-days	-0,0324 [-0,0338 ; -0,0310]	-0,0129 [-0,0152 ; -0,0107]
	RDD / admissions	-0,2486 [-0,2655 ; -0,2318]	-0,0271 [-0,0476 ; -0,0067]
	RDD / patient-days	-0,0901 [-0,0925 ; -0,0876]	-0,0102 [-0,0145 ; -0,0060]
Quinolones	Agent-days / admissions	-0,4677 [-0,4784 ; -0,457]	-0,3636 [-0,3771 ; -0,3502]
	Agent-days / patient-days	-0,1013 [-0,1035 ; -0,0990]	-0,0787 [-0,0815 ; -0,0759]
	Courses / admissions	-0,1162 [-0,1214 ; -0,1110]	-0,0982 [-0,1045 ; -0,0920]
	Courses / patient-days	-0,0250 [-0,0261 ; -0,0239]	-0,0211 [-0,0225 ; -0,0198]
	DDD / admissions	-0,5653 [-0,5767 ; -0,5540]	-0,4382 [-0,4527 ; -0,4237]
	DDD / patient-days	-0,1208 [-0,1232 ; -0,1184]	-0,0947 [-0,0978 ; -0,0917]
	Exposed / admissions	-0,1018 [-0,1067 ; -0,0970]	-0,0847 [-0,0906 ; -0,0788]
	Exposed / patient-days	-0,0218 [-0,0229 ; -0,0208]	-0,0182 [-0,0195 ; -0,017]
	RDD / admissions	-0,4425 [-0,4528 ; -0,4322]	-0,3683 [-0,3806 ; -0,3559]
	RDD / patient-days	-0,0954 [-0,0976 ; -0,0932]	-0,0794 [-0,0820 ; -0,0768]
Cephalosporins	Agent-days / admissions	0,0459 [0,0254 ; 0,0664]	1,3501 [1,3149 ; 1,3853]
	Agent-days / patient-days	-0,0601 [-0,0626 ; -0,0576]	0,2716 [0,2644 ; 0,2788]
	Courses / admissions	-0,0884 [-0,1001 ; -0,0766]	0,3504 [0,3301 ; 0,3708]
	Courses / patient-days	-0,0381 [-0,0397 ; -0,0364]	0,0695 [0,0653 ; 0,0737]

Antimicrobial class	Indicator	Rate differences (adult ICUs as reference)	
		Neonatal ICU	Pediatric ICU
	DDD / admissions	-0,4841 [-0,4960 ; -0,4723]	0,4292 [0,4024 ; 0,4560]
	DDD / patient-days	-0,1083 [-0,1107 ; -0,1060]	0,0828 [0,0773 ; 0,0883]
	Exposed / admissions	-0,1017 [-0,1126 ; -0,0907]	0,2946 [0,2754 ; 0,3138]
	Exposed / patient-days	-0,0373 [-0,0389 ; -0,0357]	0,0582 [0,0543 ; 0,0622]
	RDD / admissions	-0,1456 [-0,1659 ; -0,1252]	1,5174 [1,4793 ; 1,5556]
	RDD / patient-days	-0,0927 [-0,0955 ; -0,0900]	0,3045 [0,2967 ; 0,3123]
Clindamycin	Agent-days / admissions	0,0388 [0,0315 ; 0,0461]	0,1986 [0,1862 ; 0,2110]
	Agent-days / patient-days	-0,0018 [-0,0026 ; -0,0011]	0,0403 [0,0377 ; 0,0428]
	Courses / admissions	0,0088 [0,0050 ; 0,0126]	0,0494 [0,0431 ; 0,0557]
	Courses / patient-days	-0,0008 [-0,0012 ; -0,0004]	0,0100 [0,0087 ; 0,0113]
	DDD / admissions	-0,0368 [-0,0400 ; -0,0336]	0,0734 [0,0644 ; 0,0823]
	DDD / patient-days	-0,0081 [-0,0088 ; -0,0075]	0,0146 [0,0128 ; 0,0165]
	Exposed / admissions	0,0069 [0,0033 ; 0,0105]	0,0499 [0,0435 ; 0,0562]
	Exposed / patient-days	-0,0009 [-0,0013 ; -0,0005]	0,0101 [0,0088 ; 0,0114]
	RDD / admissions	0,0015 [-0,0043 ; 0,0074]	0,2134 [0,2005 ; 0,2264]
	RDD / patient-days	-0,0052 [-0,0059 ; -0,0045]	0,0432 [0,0406 ; 0,0459]
Macrolides	Agent-days / admissions	-0,0695 [-0,0759 ; -0,0631]	0,1153 [0,1027 ; 0,1278]
	Agent-days / patient-days	-0,0189 [-0,0199 ; -0,0178]	0,0226 [0,0201 ; 0,0252]
	Courses / admissions	-0,0230 [-0,0260 ; -0,0199]	0,0316 [0,0250 ; 0,0383]
	Courses / patient-days	-0,0056 [-0,0061 ; -0,0050]	0,0062 [0,0048 ; 0,0076]
	DDD / admissions	-0,0971 [-0,1019 ; -0,0923]	0,0269 [0,0168 ; 0,0370]
	DDD / patient-days	-0,0209 [-0,0219 ; -0,0199]	0,0046 [0,0025 ; 0,0067]
	Exposed / admissions	-0,0222 [-0,0252 ; -0,0192]	0,0271 [0,0208 ; 0,0335]
	Exposed / patient-days	-0,0054 [-0,0060 ; -0,0049]	0,0053 [0,0040 ; 0,0066]
	RDD / admissions	-0,1346 [-0,1419 ; -0,1273]	0,067 [0,0535 ; 0,0804]
	RDD / patient-days	-0,0325 [-0,0338 ; -0,0312]	0,0122 [0,0094 ; 0,0150]
Penicillins and β-lactamase inhibitors	Agent-days / admissions	-0,3744 [-0,3960 ; -0,3528]	0,2179 [0,189 ; 0,2468]
	Agent-days / patient-days	-0,1421 [-0,1452 ; -0,1390]	0,0370 [0,0310 ; 0,0430]
	Courses / admissions	-0,1107 [-0,1201 ; -0,1013]	0,0209 [0,0079 ; 0,0340]

Antimicrobial class	Indicator	Rate differences (adult ICUs as reference)	
		Neonatal ICU	Pediatric ICU
	Courses / patient-days	-0,0338 [-0,0353 ; -0,0324]	0,0026 [-0,0001 ; 0,0053]
	DDD / admissions	-0,5964 [-0,6086 ; -0,5841]	-0,3069 [-0,3251 ; -0,2886]
	DDD / patient-days	-0,1297 [-0,1322 ; -0,1272]	-0,0683 [-0,0721 ; -0,0645]
	Exposed / admissions	-0,1055 [-0,1136 ; -0,0973]	0,0124 [0,0006 ; 0,0243]
	Exposed / patient-days	-0,0295 [-0,0308 ; -0,0282]	0,0011 [-0,0013 ; 0,0036]
	RDD / admissions	-0,4673 [-0,4838 ; -0,4507]	0,0019 [-0,0220 ; 0,0257]
	RDD / patient-days	-0,127 [-0,1298 ; -0,1243]	-0,0057 [-0,0106 ; -0,0008]
Trimethoprim and sulfamides	Agent-days / admissions	0,1046 [0,0939 ; 0,1152]	0,6516 [0,6303 ; 0,6730]
	Agent-days / patient-days	0,0001 [-0,0009 ; 0,0011]	0,1326 [0,1282 ; 0,1370]
	Courses / admissions	0,0018 [-0,0015 ; 0,0050]	0,0502 [0,0438 ; 0,0566]
	Courses / patient-days	-0,0014 [-0,0018 ; -0,001]	0,0102 [0,0088 ; 0,0115]
	DDD / admissions	-0,0248 [-0,0274 ; -0,0221]	0,0038 [-0,0012 ; 0,0088]
	DDD / patient-days	-0,0055 [-0,006 ; -0,0050]	0,0005 [-0,0005 ; 0,0016]
	Exposed / admissions	0,0002 [-0,0028 ; 0,0033]	0,0478 [0,0415 ; 0,0540]
	Exposed / patient-days	-0,0014 [-0,0018 ; -0,0011]	0,0097 [0,0084 ; 0,0109]
	RDD / admissions	0,0353 [0,0294 ; 0,0411]	0,1954 [0,1838 ; 0,2070]
	RDD / patient-days	0,0007 [0,0002 ; 0,0012]	0,0398 [0,0374 ; 0,0422]

CHAPTER 6. ACCURACY OF DIFFERENT INDICATORS OF ANTIMICROBIAL USE IN PREDICTING ANTIMICROBIAL RESISTANCE

6.1. Preamble

The main part of the project aimed to verify if a certain indicator (or group of indicators) was able to follow trends in resistance with more accuracy than others. To ensure that this work would be useful to public health staff and to infection control and prevention teams, we tried to reproduce a surveillance setting as much as possible.

Although antimicrobial use surveillance is recommended by the World Health Organization, and despite the existence of many different indicators, studies statistically attempting to determine which indicator is the most relevant for surveillance of resistance are very rare. The following manuscript presents our own attempt to answer this question. This manuscript will shortly be submitted for publication

Surveillance may be performed in two distinct manners: comparing entities (intensive care units [ICUs], hospitals, countries) or following time trends within these entities. We focused on the study of time trends. Indicators (resistance in respiratory isolates and antimicrobial use) were recomputed per 4-week period, to predict resistance within participating ICUs. Although the study objective relates to prediction of prevalence and incidence rates rather than causality, this design limits potential biases such as reverse causality, where antimicrobial use is adapted to observed resistance levels.

We selected the most frequent resistances among clinically relevant resistances described in the previous chapter. We tried to predict these resistances using antimicrobial use of one or more antimicrobial classes. We measured antimicrobial use using 15 different indicators: the same ten as in the previous section, but with an additional denominator: patients present in the ICU.

6.2. Predicting antimicrobial resistance prevalence and incidence from indicators of antimicrobial use: what is the most accurate indicator?

AUTHORS

Élise Fortin, PhD(c)[1,2]; Robert W. Platt, PhD[1]; Patricia S. Fontela, MD PhD[1,3]; David L. Buckeridge, MD PhD[1]; Caroline Quach, MD MSc[1,2,3]

1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada;

2) Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Québec and Montréal, Québec, Canada;

3) Department of Pediatrics, The Montréal Children's Hospital, McGill University, Montréal, Québec, Canada.

ABSTRACT

Objective. The optimal way to measure antimicrobial use in hospital populations, as a complement to surveillance of resistance is still unclear. Using respiratory isolates and antimicrobial prescriptions of nine intensive care units (ICUs), this study aimed to identify the indicator of antimicrobial use that predicted prevalence and incidence rates of resistance with the best accuracy.

Methods. Retrospective cohort study including all patients admitted to three neonatal (NICU), two pediatric (PICU) and four adult ICUs between April 2006 and March 2010. Ten different resistance / antimicrobial use combinations were studied. After adjustment for ICU type, indicators of antimicrobial use were successively tested in regression models, to predict resistance prevalence and incidence rates, per 4-week time period, per ICU. Binomial regression and Poisson regression were used to model prevalence and incidence rates, respectively. Multiplicative and additive models were tested, as well as no time lag and a one 4-week-period time lag. For each model, the mean absolute error (MAE) in prediction of resistance was computed. The most accurate indicator was compared to other indicators using t-tests.

Results. Results for all indicators were equivalent, except for 1/20 scenarios studied. When predicting prevalence of carbapenem-resistant *Pseudomonas* sp. with carbapenem use, recommended daily doses per 100 admissions were less accurate than courses per 100 patient-days ($p=0.0006$).

Conclusions. A single best indicator to predict antimicrobial resistance might not exist. Feasibility considerations such as ease of computation or potential external comparisons could be decisive in the choice of an indicator for surveillance of healthcare antimicrobial use.

INTRODUCTION

Although the causal relationship between antimicrobial use and antimicrobial resistance is difficult to quantify due to the various settings and measures studied and to related biases, this relationship is generally accepted.[1-3] The European Surveillance of Antimicrobial Comsumption (ESAC) has shown that countries using antimicrobials more intensively tend to also present higher levels of resistance.[4] Considering that antimicrobial use is modifiable, surveillance of antimicrobial use is often recommended as a complement to surveillance of antimicrobial resistance in hospitals.[5-8]

In practice however, methodologies vary between networks and research teams. For surveillance of antimicrobial use, the World Health Organization recommends the use of defined daily doses (DDDs) per patient-days.[9] ESAC rather measures hospital antimicrobial use in point prevalence surveys (proportion of patients receiving treatment), while the American National Healthcare Safety Network prefers agent-days (days of therapy [DOT]) per patient-days, among others.[6, 10, 11] Authors have suggested that the solution might reside in the monitoring of sets of indicators, but composition of these sets also varies: DDD and locally defined daily doses per patient-days[12]; daily doses per admissions and per patient-days[13, 14]; DOT, length of therapy (LOT) and the DOT:LOT ratio[15]. Although many authors have exposed either the limitations of different indicators, their own choice of indicator, or the necessity for more research to identify the most appropriate indicator(s) for surveillance of antimicrobial use, ultimately, very few published studies have actually compared these indicators' ability to predict resistance levels.[1, 11, 15-18]

Public health authorities or hospital epidemiologists wishing to develop a coordinated program devoted to the surveillance of hospital antimicrobial use have to identify one or a few of these indicators for their surveillance. However, the optimal way to measure antimicrobial use in hospital populations, to complement surveillance of resistance, is still unclear. Using respiratory isolates and antimicrobial prescriptions of nine intensive care units, and assuming a causal association between antimicrobial use and resistance, this study thus aimed to identify the indicator of antimicrobial use that predicted prevalence and incidence rates of resistance with

the best accuracy. Specifically, the objective was not, however, to demonstrate the existence of a causal association between antimicrobial use and resistance, nor was it to quantify such an association without bias.

METHODS

STUDY DESIGN AND POPULATION

This was a retrospective cohort study on all patients admitted to ICUs of four hospitals located in Montreal, Canada, between April 1st, 2006 and March 31st, 2010. Participating ICUs included three neonatal ICUs (NICU), two pediatric ICUs (PICU) and four adult ICUs. The study design focused on recreating a surveillance context to identify the best indicator of antimicrobial use for surveillance activities, in this case, an ICU-based surveillance. This project has received approval from the Research Ethics Boards of McGill University and the *Centre Hospitalier Universitaire* Sainte-Justine.

ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL USE

Susceptibility tests performed on positive respiratory tract cultures were selected. We assumed that a large proportion of ICU patients were intubated at some point during their ICU stay and that respiratory cultures were done for intubated patients as part of the investigation for unstable ICU patients. This was thus an attempt to describe the respiratory microbiota, regardless of the presence of an infection. Intermediate strains were counted with susceptible as non-resistant strains. Based on the SHEA and HICPAC recommendations for metrics for multidrug-resistant organisms in healthcare settings, prevalence of resistance per 100 ICU admissions was measured to estimate exposure burden and incidence of resistance per 10,000 patient-days was also measured to quantify healthcare acquisition.[19] Prevalence of resistance was measured by counting the number of ICU admissions where a resistant strain of a given microorganism was isolated. Resistance was considered incident when a resistant microorganism was detected in a patient with a previously susceptible organism or with no positive culture at least 2 days after admission to ICU; patient-days were computed excluding

the first 2 days after ICU admission, based on dates. Incidence rates and prevalence were computed per 4-week period, for each ICU.

Hospital pharmacy databases provided information on all prescriptions for antimicrobials issued for patients included in the study. Only agents belonging to class J01 of the Anatomical Therapeutic Chemical (ATC) classification system (anti-infectives for systemic use) were kept for analysis.[20] Doses and days of treatment prescribed for use before or after ICU admission were excluded (as these would not be included in an ICU-based surveillance), but we included those used on the ICU admission or discharge dates, or in between. Population antimicrobial use was measured using fifteen different indicators. These indicators were obtained by combining five numerators (defined daily doses [DDDs], recommended daily doses [RDDs], agent-days, exposed patients, and number of courses) with three denominators (ICU patient-days, ICU admissions and ICU patients), all previously identified in a systematic review of indicators used for populations that included pediatric patients.[11] For a given 4-week period, "ICU admissions" only include patients admitted to the ICU during the period, while "ICU patients" include all patients present in the ICU at some point in time during the period. Indicators of antimicrobial use were computed per 4-week period, for each ICU.

Ten different resistance / antimicrobial use combinations were studied and are listed in the first column of Tables 6.1 and 6.2, for a total of 20 scenarios: 10 for prediction of prevalence and 10 for prediction of incidence rates. These combinations were selected based on the frequency of resistant strains and on their clinical relevance. In two combinations, use of three classes of antimicrobials was taken into account, as *Staphylococcus aureus* resistant to methicillin and *Escherichia coli*, *Klebsiella* sp. and *Proteus* sp. resistant to carbapenems can also present other resistances.

STATISTICAL ANALYSES

For each combination, scatterplots of resistance and antimicrobial use according to the different indicators were produced to visualize aggregation of data at the ICU level and time series were produced to see trends. After adjustment for ICU type, indicators of antimicrobial use were successively tested in regression models, to predict resistance prevalence and incidence rates,

per 4-week time period, per ICU. Binomial regression was used to model prevalence and Poisson regression, to model incidence rates. Multiplicative (log link) and additive (identity link) models were tested, as well as no time lag and a one 4-week-period time lag; in total, for each scenario, 60 models were compared (15 indicators x 2 regression links x 2 time lags). As there were repeated measurements for every ICU (51 measurements with a 1-period time lag, 52 measurements without a time lag), generalized estimating equations were used to account for correlated values at the ICU level.

For each model, the mean absolute error (MAE) was computed. The MAE is a statistic used in the analysis of time series, to quantify the difference (or error) between observed values (prevalence or incidence rates) and values predicted by a model.[21] Predictive accuracy of different regression models can be compared using t-tests, to determine whether differences observed in predictions are statistically significant. Absolute values of these errors were computed per 4-week period and per ICU, and were then averaged, to produce the MAE of each model. The most accurate indicators were the ones with the smallest MAEs. MAEs were then compared using t-tests. In a given scenario, the most accurate model was compared to all other models (59 t-tests), beginning with the least accurate model. A Holm correction was applied to account for multiple comparisons, to keep an overall α of 0.05.[22] As an indication, when comparing the smallest MAE to the largest one, the t-test p-value had to be smaller than 0.0008 to reject the null hypothesis. Analyses were performed using SAS 9.3.

RESULTS

MAEs for the most, second most and least accurate indicators, for each combination, are presented in Table 6.1 (prevalence) and Table 6.2 (incidence rate). The most and least accurate indicators were usually not statistically different, except in the prediction of resistance prevalence in *Pseudomonas* sp. When using carbapenem use to predict prevalence of carbapenem-resistant *Pseudomonas* sp., the indicator with the smallest MAE was courses per 100 patient-days (no time lag, using an identity link), which was significantly more accurate (p =

0.0006) than the least accurate model, RDD per 100 admissions (with a 1-period time lag, using a log link).

In regression models, additive models (identity link) frequently failed at producing coefficients and predicting prevalence or incidence. This was the case for 40 / 600 models for prediction of resistance prevalence and for 99 / 600 models for prediction of incidence rates, while all multiplicative models (log link) converged and produced coefficients. This problem was due to the fact that predicted values below 0 or above 1 in the case of binomial regression, or simply below 0 for Poisson regression, were obtained with additive models.

Examples of descriptive graphs produced are presented in Figures 6.1 and 6.2. Figure 6.1 presents a scatterplot of prevalence of carbapenem-resistant *Pseudomonas* sp. per 100 admissions against carbapenem use in courses per 100 patient-days, the most accurate indicator for this combination. Data was aggregated per ICU; it was also aggregated per year rather than per period, to make the graph clearer. This is representative of most scatterplots produced, showing an apparent clustering of antimicrobial use at the ICU level. Figure 6.2 presents time series of piperacillin-tazobactam, quinolone and carbapenem use per 4-week period, all ICUs combined. Each graph presents the most accurate and the least accurate indicators for the prediction of resistance in *Pseudomonas* sp.. As observed in MAE comparisons, indicators are visually more similar for piperacillin-tazobactam use and quinolone use than with carbapenem use, for which the only difference in predictive accuracy of resistance prevalence was observed.

DISCUSSION

To our knowledge, this comparison of population antimicrobial use indicators' ability to predict resistance is novel, even though this knowledge gap had been highlighted in the scientific literature previously. Using respiratory tract isolates and antimicrobial prescriptions from nine intensive care units, this study compared the accuracy of fifteen indicators of population antimicrobial use in predicting prevalence and incidence rates of different resistances in the respiratory microbiota. A statistically significant difference between MAEs was observed for

only 1 of the 20 scenarios studied: carbapenem use to predict prevalence of carbapenem-resistant *Pseudomonas* sp. This difference identified one indicator that did not perform as well; however, no single indicator (or no set of indicators) stood out as better than the others.

IDENTIFYING THE MOST ACCURATE INDICATOR

The absence of difference between indicators that was observed for most scenarios could be explained by different factors. These are not limitations, but rather reflect the reality of ICUs and of their use of antimicrobials. First, as described in Figure 6.1, throughout the four years of the study, levels of antimicrobial use and resistance tended to correlate at the ICU level; after adjusting for ICU type, there was thus less variation that could be explained with indicators of antimicrobial use. In addition, all indicators were attempting to measure similar variations in time: no exposure is equal to a value of zero for all numerators, which will tend to increase or decrease together with different magnitudes. Also, ICUs' median lengths of stay are very short (5 days in neonatal ICUs and 2 days in other ICUs, data not published); for an ICU admission of two days, the difference between the number of agent-days, the number of courses and the simple exposure cannot be as large as for a longer admission. Of note, the situation would not necessarily have been dramatically different using hospital-wide data, as the median length of stay in Québec acute-care hospitals was 4 days.[23] Finally, although resistance / antimicrobial use combinations studied included entire antimicrobial classes (sometimes even three), a single agent can sometimes constitute most of an antimicrobial class usage. For instance ampicillin-days represented 67% of all penicillin agent-days; therefore, even if the standard DDD and RDD for ampicillin are very different, indicators of ampicillin use using DDDs, RDDs or agent-days will tend to follow the same time trends, and respective indicators of penicillin use will be driven by ampicillin use. In this study, rather than the actual values of indicators, what mattered were variations in time and across ICUs, and correlation of indicators with resistance measures; most indicators did not differ at these levels. Whenever a difference was found, it was between the most accurate and the least accurate indicators, but most indicators' MAEs were not different from the indicator with the smallest MAE.

Actually, statistically different MAEs were observed only for one scenario, involving prevalence of resistance to carbapenems in *Pseudomonas* sp.. *Pseudomonas* sp. are prone to the development of resistance, especially to imipenem: they might react more swiftly to an exposure to antimicrobials, amplifying the possibility to detect differences between indicators of antimicrobial use.[24] Another interesting observation regarding this scenario is that, although a large proportion of prevalent cases are also incident cases, no statistically significant difference between indicators was detected in their prediction of incidence rates. As admissions last longer in neonatal ICUs than in other ICUs, prevalence and incidence rates do not follow the same trends, despite their similar numerators.

LIMITATIONS

In this study, different indicators of antimicrobial use usually had similar accuracy in the prediction of resistance prevalence or incidence in the respiratory microbiota. Interpretation of results is however limited by assumptions made in the study design. In this study, we assumed that surveillance would ideally include pediatric populations, which have been frequently excluded from antimicrobial use surveillance.[15, 17, 25, 26] We also assumed that ICUs would perform surveillance on a 4-week period basis, without information on antimicrobial use before ICU admission, and that neonatal, pediatric and adult ICUs would be considered different enough to be treated separately. We also limited our cohort to ICU patients and to respiratory tract cultures performed for these patients, in an attempt to include colonizing microorganisms rather than only microorganisms infecting patients. All this was done to be as representative and similar as possible to a real surveillance setting, but results could differ if other assumptions were made. Second, our results describe prescribed antimicrobials rather than administered or dispensed antimicrobials, which probably lead to some degree of overestimation of antimicrobial use in our ICUs. As we were interested in prediction of resistance time trends, this might not be as critical as for a study estimating association between antimicrobial use and resistance. Also, a study with more participating ICUs would have allowed the use of hierarchical models with random intercepts, rather than population average models using generalized estimating equations. More participating ICUs would have also allowed us to compare ICUs and perform benchmarking, but this was not our objective. Finally, with nine ICUs followed during

four years, the study population was large enough to detect significant associations between some indicators and resistance levels, but a lack of power to detect differences between indicators is possible (not enough ICU-4-week-periods observed).

Indicators of population antimicrobial use have been developed, used and discussed for decades now, but the identification of the best indicator is still an object of debate. We believe that the purpose of measurement, surveillance of antimicrobial use as a complement to surveillance of antimicrobial resistance, has to be taken into consideration. Our study has shown that, at least in our context, indicators are equivalent. Had an indicator been more accurate than others, it would have allowed a closer monitoring of variations in antimicrobial resistance frequency, and an increased ability to detect the impact on resistance of interventions targeting antimicrobial use. These first results however indicate that a single best indicator might not exist and that feasibility considerations, such as ease of computation or potential external comparisons could be more decisive in the choice of an indicator for surveillance of healthcare antimicrobial use.

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Figure 6.1. Scatterplot of prevalence of carbapenem-resistant Pseudomonas sp. per 100 admissions and carbapenem use in courses per 100 patient-days, per year and per intensive care unit (ICU).

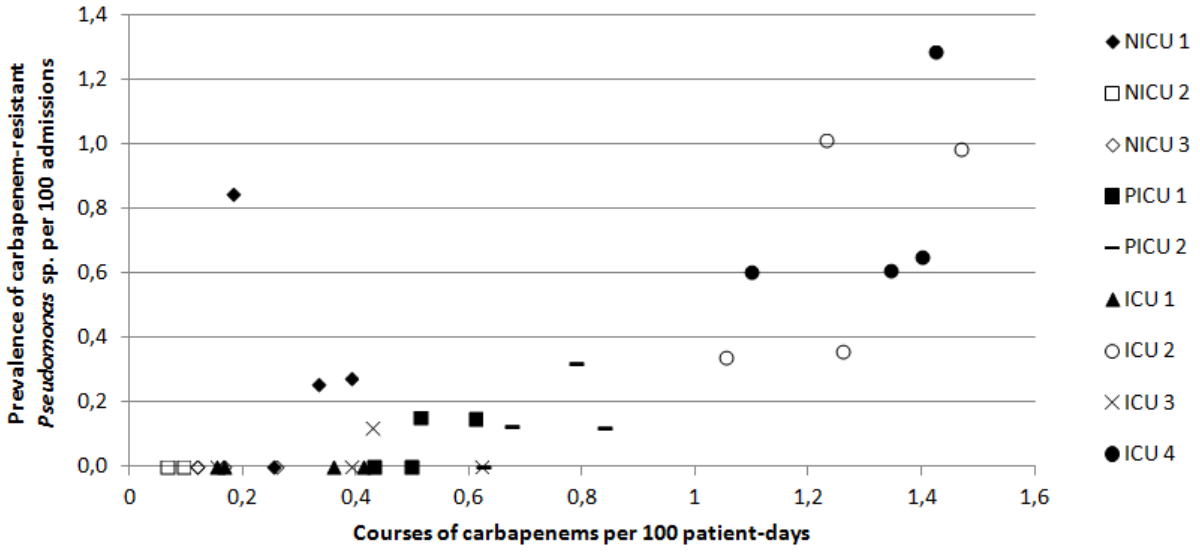

Figure 6.2. Time series of piperacillin-tazobactam, quinolone and carbapenem use per 4-week period, all ICUs combined.

Part A: quinolone use in courses per 100 admissions and exposed per 100 admissions; part B: carbapenem use in courses per 100 patient-days and in RDD per 100 admissions; part C: piperacillin-tazobactam use in agent-days per 100 patient-days and RDD per 100 admissions.

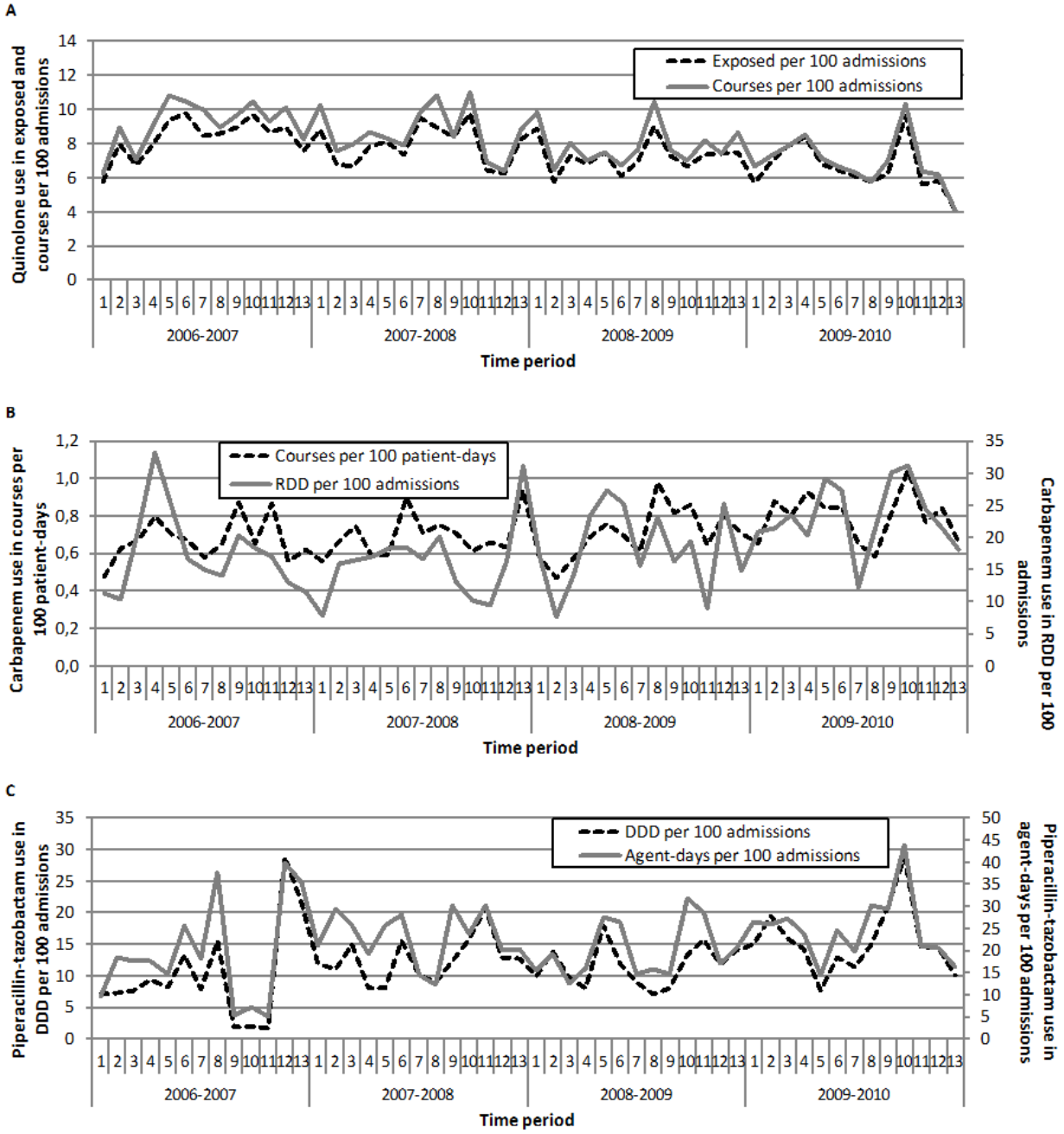

Table 6.1. Most accurate, second most accurate and least accurate indicators in predicting resistance prevalence, for selected resistance /antimicrobial combinations.

Resistance / antimicrobial use*	Models adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 100 adm)	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)***
MRSA / penicillins	NICU Others (ref.)	DDD / patients	Id	0.55	DDD / adm	Id	0.55	1.00	Agent-days / adm	Log	0.58	0.52
MRSA / penicillins + 3GC + quinolones	NICU Others (ref.)	DDD / adm	Log	0.53	DDD / patients	Log	0.53	0.94	Courses / pd	Log	0.58	0.29
Pip-tazo-resistant coliforms / pip-tazo	Unadjusted	DDD / adm	Id	0.62	RDD / patients	Id	0.62	0.99	Agent-days / adm	Log	0.70	0.33
Quinolone-resistant coliforms / quinolones	NICU PICU AICU (ref.)	DDD / adm (1)	Id	0.32	DDD / adm	Id	0.32	0.94	Exposed / pd (1)	Log	0.38	0.12
Aminoglycoside-resistant coliforms /aminoglycosides	Unadjusted	DDD / pd	Id	0.38	DDD / patients	Id	0.39	0.97	DDD / adm (1)	Log	0.41	0.51

Resistance / antimicrobial use*	Models adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 100 adm)	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)***
Carbapenem-resistant EKP / carbapenems	Unadjusted	Agent-days / pd	Id	0.21	Courses / pd	Id	0.21	0.95	RDD / adm (1)	Log	0.24	0.36
Carbapenem-resistant EKP / 3GC + aminoglycosides + quinolones	Unadjusted	DDD / adm	Id	0.21	DDD / patients	Id	0.21	0.97	Agent-days / adm	Id	0.26	0.30
Pip-tazo-resistant *Pseudomonas* sp. / pip-tazo	Unadjusted	DDD / adm (1)	Id	0.30	DDD / patients (1)	Id	0.31	0.95	Agent-days / adm (1)	Log	0.33	0.70
Quinolone-resistant *Pseudomonas* sp. / quinolones	Unadjusted	Courses / adm (1)	Id	0.16	Exposed / patients (1)	Id	0.16	0.98	Exposed / adm (1)	Id	0.34	0.0043
Carbapenem-resistant	NICU PICU	Courses / pd	Id	0.31	Agent-days / pd	Id	0.32	0.85	RDD / adm (1)	Log	0.43	0.0006

Resistance / antimicrobial use*	Models adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 100 adm)	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 100 adm)	Difference (p-value)***
Pseudomonas sp. / carbapenems	AICU (ref.)											

Note: (1): with a time lag of one 4-week period; 3GC: third-generation cephalosporins; AICU: adult intensive care unit; adm: admissions; EKP: *Escherichia coli*, *Klebsiella* sp., *Proteus* sp.; Id: identity; MAE: mean absolute error; MRSA: meticillin-resistant *Staphylococcus aureus*; NICU: neonatal intensive care unit; pd: patient-days; PICU: pediatric intensive care unit; pip-tazo: piperacillin-tazobactam.

*Resistance / antimicrobial use: “resistance” designates the resistant microorganism prevalence that was predicted using the population use of the designated ”antimicrobial use”.

**Level of statistical significance, after a Holm correction for multiple comparisons: 0.05 / 1 = 0.05.

***Level of statistical significance, after a Holm correction for multiple comparisons: 0.05 / 59 = 0.0008.

Table 6.2. Most accurate, second most accurate and least accurate indicators in predicting resistance incidence rates, for selected resistance /antimicrobial combinations.

Resistance / antimicrobial use*	Model adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 10,000 pd)	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)***
MRSA / penicillins	NICU PICU AICU (ref.)	Agent-days / patients (1)	Log	9.8	Courses / patients (1)	Log	9.8	0.97	Courses / pd	Id	10.4	0.50
MRSA / penicillins + 3GC + quinolones	NICU PICU AICU (ref.)	Exposed / adm (1)	Log	8.6	Exposed / patients (1)	Log	8.6	0.97	Exposed / pd	Id	10.4	0.03
Pip-tazo-resistant coliforms / pip-tazo	NICU Others (ref.)	RDD / patients (1)	Id	11.5	DDD / patients (1)	Id	11.6	0.97	Agent-days / adm (1)	Log	12.7	0.28
Quinolone-resistant coliforms / quinolones	NICU PICU AICU (ref.)	Courses / adm	Log	6.9	Courses / patients	Log	6.9	0.96	Exposed / pd (1)	Log	7.6	0.32
Aminoglycoside-resistant coliforms	Unadjusted	DDD / adm	Id	6.0	Courses / pd	Id	6.0	0.99	Agent-days / adm (1)	Log	6.2	0.67

Resistance / antimicrobial use*	Model adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 10,000 pd)	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)***
/aminoglycosides												
Carbapenem-resistant EKP / carbapenems	NICU Others (ref.)	Agent-days / pd	Id	3.5	Courses / pd	Id	3.5	0.93	RDD / patients (1)	Id	4.2	0.14
Carbapenem-resistant EKP / 3GC + aminoglycosides + quinolones	NICU Others (ref.)	DDD / patients	Id	3.8	DDD / adm	Id	3.8	1.00	Exposed / pd (1)	Log	4.2	0.43
Pip-tazo-resistant *Pseudomonas* sp. / pip-tazo	NICU Others (ref.)	Agent-days / patients	Log	5.3	Agent-days / adm	Log	5.4	0.93	Courses / pd (1)	Log	5.8	0.42
Quinolone-resistant *Pseudomonas* sp.	Unadjusted	DDD / adm	Id	3.5	DDD / patients	Id	3.5	0.94	Exposed / pd	Log	4.3	0.10

Resistance / antimicrobial use*	Model adjusted for ICU type	Most accurate			Second most accurate				Least accurate			
		Indicator	Regression link	MAE (cases / 10,000 pd)	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)**	Indicator	Regression link	MAE (cases / 10,000 pd)	Difference (p-value)***
/ quinolones												
Carbapenem-resistant *Pseudomonas* sp. / carbapenems	NICU PICU AICU (ref.)	Courses / pd	Log	7.1	DDD / pd	Log	7.2	0.95	Courses / pd (1)	Log	8.0	0.21

Note: (1): with a time lag of one 4-week period; 3GC: third-generation cephalosporins; AICU: adult intensive care unit; adm: admissions; EKP: *Escherichia coli*, *Klebsiella* sp., *Proteus* sp.; Id: identity; MAE: mean absolute error; MRSA: meticillin-resistant *Staphylococcus aureus*; NICU: neonatal intensive care unit; pd: patient-days; PICU: pediatric intensive care unit; pip-tazo: piperacillin-tazobactam.

*Resistance / antimicrobial use: “resistance” designates the resistant microorganism incidence that was predicted using the population use of the designated ”antimicrobial use”.

**Level of statistical significance, after a Holm correction for multiple comparisons: 0.05 / 1 = 0.05.

***Level of statistical significance, after a Holm correction for multiple comparisons: 0.05 / 59 = 0.0008.

CHAPTER 7. POST HOC ASSESSMENT OF CONDITIONS THAT WOULD ALLOW THE IDENTIFICATION OF THE MOST ACCURATE INDICATOR

7.1. Preamble

In chapter 6, fifteen different indicators of antimicrobial use offered similar accuracy in the prediction of prevalence and incidence of resistance in nine intensive care units' (ICUs) respiratory cultures. Different explanations were offered to explain this absence of difference. Among these explanations was a potential lack of power due to the limited number of ICUs in the study cohort. Chapter 7 thus presents a simulation study that explores the conditions under which the choice of a specific indicator could improve antimicrobial use surveillance, by providing a better accuracy in prediction of resistance time trends.

The manuscript reproduced in the next section was submitted for publication on April 11th, 2015. Reviewers asked for minor modifications and the subsequent changes are reflected in the thesis. The number of the chapter has been added before the tables' and figures' original numbers, to facilitate orientation through the thesis. This is however the only change that was made to the manuscript.

7.2. A Simulation Study to Assess Indicators of Antimicrobial Use as Predictors of Resistance: Does It Matter Which Indicator Is Used?

AUTHORS

Élise Fortin[1,2], Caroline Quach[1,2,3], Patricia S. Fontela[1,3], David L. Buckeridge[1], Robert W. Platt[1]

1) Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, Québec, Canada

2) Direction des risques biologiques et de la santé au travail, Institut national de santé publique du Québec, Québec and Montréal, Québec, Canada

3) Department of Pediatrics, The Montréal Children's Hospital, McGill University, Montréal, Québec, Canada

ABSTRACT

Objective. Indicators of antimicrobial use have been described previously, but few studies have compared their accuracy in prediction of antimicrobial resistance in hospital settings. This study aimed to identify conditions under which significant differences would be observed in the predictive accuracy of indicators in the context of surveillance of intensive care units (ICUs).

Methods. Ten resistance / antimicrobial use combinations were studied. We used simulation to determine if Québec's network of 81 ICUs or the National Healthcare Safety Network (NHSN) of 2952 ICUs are large enough to allow the detection of predetermined differences between the most accurate and 1) the second most accurate indicator, and 2) the least accurate indicator, in more than 80% of simulations. For each indicator, we simulated absolute errors in prediction for each ICU and each 4-week period, for surveillance lasting up to 5 years. Absolute errors were generated following a binomial distribution, using mean absolute errors (MAEs) observed in 9 ICUs as the average proportion; simulated MAEs were compared using t-tests. This was repeated 1000 times per scenario.

Results. When comparing the two most accurate indicators, 80% power was reached less often with the Québec network versus the NHSN (0/20 versus 2/20 scenarios, with 5 years of surveillance data), a finding reinforced when comparing the most and least accurate indicators (3/20 versus 20/20 scenarios). When simulating 1 year of data, scenarios reaching an 80% power dropped to 0/20, comparing the two most accurate indicators with the larger network, and to 1/20, comparing the most and least accurate indicators with the smaller network.

Conclusion. Most of the time (72%), identifying an indicator of antimicrobial use predicting antimicrobial resistance with a better accuracy was not possible. The choice of an indicator for an eventual surveillance system could rely on criteria other than predictive accuracy.

INTRODUCTION

Surveillance of both antimicrobial resistance and population antimicrobial use are necessary to understand the magnitude of resistance problems in hospitals and obtain data for the development of tailored interventions. In Canada, surveillance of selected resistant microorganisms is already ongoing but surveillance of hospital antimicrobial use is very limited.[1-3] The Québec Ministry of Health has thus recommended the development of local surveillance in Québec healthcare facilities.[4] The optimal way to measure antimicrobial use in hospital populations, to complete surveillance of resistance, is however unclear and has been the object of long lasting debates.[5-9]

The World Health Organization recommends the use of defined daily doses per patient-days, the American National Healthcare Safety Network prefers days of treatment (agent-days) per patient-days, while the European Surveillance of Antimicrobial Consumption measures hospital antimicrobial use with point prevalence surveys (proportion of patients receiving treatment).[10-12] A variety of indicators have also been used, such as grams per patient-days, currency per patient-days, recommended daily doses in mg/kg per patient-days, exposed patients / admissions, agent-days / admissions.[8, 13-16] Various sets of indicators have been suggested.[6, 17-19] Although some studies did compare a few indicators, very few studies compared their ability to predict levels of antimicrobial resistance in hospitals. We conducted a systematic literature review aiming to identify such studies, as long as they included pediatric populations and we found only one study comparing indicators' correlation with resistance.[20] This study compared two of the 26 different indicators reported in the literature.[21]

In a recent study comparing the accuracy of 15 indicators of antimicrobial use in predicting resistance of the respiratory microbiota (both prevalence and incidence of resistance), no indicator was clearly superior to the others (unpublished manuscript). However, only nine intensive care units (ICUs) participated in the study (4 adult ICUs, 2 pediatric ICUs and 3 neonatal ICUs), raising the question of a potential lack of power to discriminate between the accuracy of indicators. This simulation study aimed to

determine under which conditions significant differences would be observed among indicators in the predictive accuracy of antimicrobial resistance. We aimed to determine if, given previously observed non-statistically significant differences between indicators in absolute errors, differences could be detected in two simulated larger networks of ICUs. Our secondary objective was to evaluate the impact of follow-up duration on our results.

METHODS

This study was approved by the Research Ethics Boards of McGill University and of the *Centre Hospitalier Universitaire* Sainte-Justine. No consent from patients was necessary as the data was analyzed anonymously.

VARIABLES

Resistance / antimicrobial use combinations

Ten resistance / antimicrobial use combinations (combinations) were studied: 1) methicillin-resistant *Staphylococcus aureus* (MRSA) / penicillin use; 2) MRSA / penicillin, third-generation cephalosporins (3GC) and quinolone use; 3) piperacillin-tazobactam-resistant coliforms (PTRC) / piperacillin-tazobactam use; 4) quinolone-resistant coliforms (QRC) / quinolone use; 5) aminoglycoside-resistant coliforms (ARC) / aminoglycoside use; 6) carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp. (CREKP) / carbapenem use; 7) CREKP / aminoglycoside, 3GC and quinolone use; 8) piperacillin-tazobactam-resistant *Pseudomonas* sp. (PTRP) / piperacillin-tazobactam use; 9) quinolone-resistant *Pseudomonas* sp. (QRP) / quinolone use and 10) carbapenem-resistant *Pseudomonas* sp. (CRP) / carbapenem use. These combinations were chosen based on their clinical relevance and on the frequency of resistance. Prevalence of resistance per 100 admissions and incidence rates per 10,000 patient-days were both studied, analyzed per ICU and per 4-week period. Penicillins, 3GC, quinolones (more precisely,

fluoroquinolones), piperacillin-tazobactam, aminoglycosides and carbapenems respectively correspond to codes J01CA-E-F, J01DD, J01MA, J01CR05, J01G and J01DH, according to the Anatomical Therapeutic Chemical classification system.[10]

Indicators of antimicrobial use

In a systematic review of indicators of antimicrobial use in hospitalized patients populations that included pediatric populations, 26 indicators were identified, combining 13 numerators and 5 denominators.[20] This study focused on 5 numerators and 3 denominators. Numerators were: 1) defined daily doses (DDD; one DDD is the average quantity, in grams, given to a 70 kg adult for 1 day; values are identical worldwide), 2) recommended daily doses (RDD; similar to DDD, but the standard daily doses are defined by local guidelines; accounted for pediatric patients' weight in mg / kg), 3) agent-days (patient-days when a specific antimicrobial was prescribed), 4) courses (distinct periods of consecutive days when a patient is prescribed a specific antimicrobial) and 5) exposed patients (patients prescribed antimicrobials). Other numerators identified in the systematic review were not kept for these analyses. The information provided by grams and costs is reflected in DDDs and RDDs, but blurred through market fluctuations; prescribed daily doses and agent-days should be equivalent, so only agent-days were kept; as patients' weights are not always known (especially in adults), RDDs and RDD in mg/kg were combined into a single measure. Finally, as we stratified our indicators per antimicrobial class, antimicrobial-days and treatment periods became almost identical to agent-days and courses (respectively) to warrant additional analyses. Denominators were patient-days, admissions (including transfers from other wards) and patients present. Costs and kg-days, also identified in the systematic review, were not kept in the analyses because, once again, market fluctuations also limit the use of costs and patients' weights are not always known. Fifteen indicators of use of different antimicrobial classes were thus studied, per ICU and per 4-week period.

Predictive accuracy

The accuracy of indicators in predicting of the prevalence of resistant respiratory microbiota organisms was measured using mean absolute errors (MAEs).[22] A MAE is a measure of accuracy used in the prediction of time series as it measures the mean difference between observed and model-predicted values; MAEs obtained with different models can be compared using t-tests. In the original cohort study, regression models were used to model prevalence and incidence rates of resistance, per ICU and per 4-week period, successively using the fifteen indicators of antimicrobial use, after adjusting for ICU type (adult, pediatric or neonatal). For each combination, 60 models were built for prevalence (15 indicators x 4-week time lag or no time lag x additive or multiplicative models) and 60 others for incidence rates. MAEs were computed for each model (MAEs stratified per ICU type are presented in S1 Table and S2 Table). Errors are the observed prevalence (or observed incidence) minus prevalence (or incidence) predicted by the model. Absolute values of these errors are then averaged, to obtain the MAE. A smaller MAE indicates a more accurate model. For example, in predicting CRP prevalence with carbapenem use, the most accurate model was an additive model with carbapenem use measured in courses per 100 patient-days. With no time lag, this model had a MAE of 0.31 cases per 100 admissions (0.46 for adult ICUs, 0.26 for pediatric ICUs and 0.15 for neonatal ICUs). The second most accurate model was also additive, used no time lag and used carbapenem use measured in agent-days per 100 patient-days for a MAE of 0.32 cases per 100 admissions (0.48 for adult ICUs, 0.24 for pediatric ICUs and 0.14 for neonatal ICUs). Finally, the least accurate model was multiplicative, had a MAE of 0.43 cases per 100 admissions (0.50 for adult ICUs, 0.20 for pediatric ICUs and 0.50 for neonatal ICUs) and used carbapenem use measured in recommended daily doses per 100 admissions, with a 4-week-period time lag. The online supporting information illustrates this example (7.S1 Fig.).

SIMULATION PROCEDURES

Forty scenarios were studied for each combination (Table 7.1): 1) for the prediction of prevalence, ten scenarios where the most accurate indicator was compared to the second most accurate indicator (two networks of ICUs x five different durations of surveillance) and ten scenarios where the most accurate indicator was compared to the least accurate indicator; 2) the same twenty scenarios were also simulated for the prediction of incidence rates. One thousand independent simulations were performed per scenario. For each simulation run, the same seed was used to produce the absolute errors for the two indicators to be compared (but with different mean absolute errors) because the original study compared MAEs obtained while trying to predict the same outcome and were thus dependent. As a result, compared indicators were simulated using the same seed, but each scenario's 1000 simulations were independent. Indicators were compared using the Satterthwaite t-test method, as we could not assume that compared MAEs would always have equal variances. Simulations were performed using SAS 9.3; datasets were created in data steps, creating random binomial variables using call ranbin routines.

For each scenario, we generated datasets containing the absolute errors for each of the indicators of antimicrobial use compared, per ICU and per 4-week period of surveillance. For scenarios investigating the prediction of resistance prevalence, absolute errors represented differences between two proportions (observed – predicted). Absolute error per 4-week period = x / average number of admissions per 4-week period, where X ~ Bin (average number of admissions per 4-week period, observed MAE). For scenarios investigating the prediction of resistance incidence rates, absolute errors represented differences between two rates and number of admissions was replaced by number of patient-days. As observed MAEs varied according to ICU type, random variables were generated stratifying per ICU type.

Patient-days and admissions per type of ICU (pediatric, neonatal and adult) followed the structure of two existing networks of ICUs: the Québec healthcare-associated

bloodstream infections surveillance network (SPIN-BACTOT, 2009-2010) and the American National Healthcare Security Network (NHSN, 2009).[23, 24] Characteristics of these networks are summarized in Table 7.2. Patient-days were available for both SPIN-BACTOT and NHSN ICUs, but admissions were unknown. The average number of patient-days per period was computed. From data observed in the nine ICUs participating to the original cohort study, we computed the ratio of admissions per patient-day, per ICU type (0.21 for adult ICUs, 0.21 for pediatric ICU and 0.07 for neonatal ICUs). We then estimated the average periodic number of admissions in SPIN-BACTOT and NHSN by multiplying this ratio by the number of patient-days reported in each network. Simulations were run for surveillance durations ranging from 13 to 65 periods 4-week periods (from 1 to 5 years).

For each simulation, a t-statistic comparing the smallest MAE to the other MAEs was computed and p-values stored. The methodology used in the initial cohort study presumed that all indicators were compared to the most accurate one: all 60 models of a given scenario were ranked according to their MAE; if the least accurate model was not statistically different from the most accurate one, then all other models were assumed to not be different. A Holm correction was thus applied to account for multiple comparisons. For scenarios comparing the two most accurate indicators, when 80% of simulations had a p-value below 0.05 (0.05 / 1), we considered that this scenario had an 80% power to detect a difference between the two indicators compared. The significance level was rather 0.0008 (0.05 / 59) when comparing the most and the least accurate indicators.

RESULTS

ACCURACY IN THE PREDICTION OF RESISTANCE PREVALENCE

Using a network of ICUs similar to SPIN-BACTOT's ICU network (70 adult ICUs, 4 pediatric ICUs and 7 neonatal ICUs), we were unable to distinguish the best of the two most

accurate indicators, regardless of surveillance duration (Fig. 7.1A). Differences could be found between the most and the least accurate indicators in 80% of simulations for two combinations (Fig. 7.1B). These differences could only be detected after 5 years of surveillance for QRC / quinolone use. For QRP / quinolone use, a difference was observed even after only 1 year of surveillance.

With a network of ICUs similar to NHSN (2591 adult ICUs, 178 pediatric ICUs and 183 neonatal ICUs), the two most accurate indicators could only be distinguished for two combinations (Fig. 7.1C). For CRP / carbapenem use, 2 years of surveillance were sufficient while for QRC / quinolone use, 3 years were necessary. Differences could always be found between the most and the least accurate indicators, for all 10 combinations except MRSA / penicillin use, for which at least 2 years of data were necessary.

ACCURACY IN THE PREDICTION OF RESISTANCE INCIDENCE RATES

With a network of ICUs similar to SPIN-BACTOT's ICU network, the two most accurate indicators could never be distinguished (Fig. 7.2A). Also, 80% power could be reached for only 1 of 10 scenarios in the detection of differences between the most and the least accurate indicators (MRSA / penicillin, 3GC and quinolone use), and it necessitated 3 years of surveillance data. (Fig. 7.2B).

With a network of ICUs similar to NHSN, even though more simulations detected differences, 80% power was never reached when comparing the two most accurate indicators (Fig. 7.2C). Differences could always be found between the most and the least accurate indicators, for all 10 combinations, however, 3 years of data were necessary for ARC / aminoglycoside use.

DISCUSSION

This simulation study has allowed us to compare predictive accuracy of different indicators of antimicrobial use, while exploring conditions for which a specific indicator should be selected among others, to improve surveillance. We estimated the power necessary to distinguish indicators of antimicrobial use regarding their accuracy in predicting antimicrobial resistance in networks of ICUs. Networks of ICUs were simulated, similar in size and structure to a provincial network (SPIN-BACTOT) and to a much larger network (NHSN). Absolute errors were simulated for each ICU, per 4-week period and mean absolute errors were compared. Results of this study show us that network size and surveillance duration influence power to detect differences between MAEs, but that most of the time, MAEs (i.e. indicators of antimicrobial use) showed similar predictive accuracies.

The size of ICU networks had an important impact on our ability to distinguish indicators of antimicrobial use. Indeed, when comparing the two most accurate indicators, 80% power was reached less often with the Québec network versus the NHSN (0 / 20 scenarios versus 2 / 20 scenarios, respectively, with 5 years of surveillance data). This was especially true when comparing the most and least accurate indicators (3 / 20 scenarios versus 20 / 20 scenarios, respectively). In the scenarios less likely to detect differences between MAEs (comparing the two most accurate indicators in the provincial network), duration of surveillance did not influence the capacity to reach 80% power: such a network was underpowered to detect differences, even with five years of data. Similarly, duration of surveillance was irrelevant in the scenarios most likely to detect differences between MAEs (comparing the most and the least accurate indicators in the large national network), as a single year of data was usually sufficient to reach 80% power. However, the accumulation of more data through increased surveillance duration did make a difference in other scenarios: when simulating only 1 year of surveillance data, scenarios allowing to reach 80% power dropped from 2 to 0 / 20, comparing the

two most accurate indicators in the larger network, and from 3 to 1 / 20, comparing the most and the least accurate indicators in the smaller network.

Interpretation of results is limited by assumptions made in the simulation procedures. First, we assumed that the ideal design was to predict resistance at the ICU level rather than pooled provincial or national resistance prevalence or incidence rate. We also assumed that surveillance would be performed on a 4-week or monthly basis rather than on an annual basis, to follow time variations. In this setting, the larger the number of participating ICUs and the finer the time intervals, the more observations are produced, increasing power to detect differences between indicators. Even if a surveillance system was to eventually pool all data in a single annual estimate of resistance, in a project like ours, trying to identify the indicator that predicts resistance levels with the best accuracy, finer observation units allowed us to reduce a potential ecological bias. Second, we assumed that values observed in the initial cohort study (admissions: patient-days ratios and MAEs) are representative of entire networks of ICUs; we also assumed that ICU type (adult, pediatric and neonatal ICUs) is the only relevant element in the structure of ICU networks. As the number of studies comparing predictive accuracy of indicators of population antimicrobial use is quite small, we performed this simulation study using available information (MAEs we already had). Third, available information for our simulations related to ICUs, rather than hospitals. Length of stay is longer when considering the entire hospital and antimicrobial use varies between wards.[8] Although this simulation study is certainly a first hint on the population size necessary to identify a more accurate indicator, results might differ at the hospital level. Similar studies at hospital level would be an interesting complement to our findings. Finally, as statistically significant differences were not observed in the initial cohort study, the present simulation study could not identify the most accurate indicator (or indicators, as they could vary between combinations); our study was rather designed to estimate power that could be reached with different ICU networks sizes and surveillance durations, to eventually identify the most accurate indicator of antimicrobial

use. However, we believe that the lack of evidence of differences reflects absence of differences, rather than being inconclusive.

CONCLUSION

Network size and surveillance duration influence power to detect differences between indicators. However, most of the time, identifying an indicator of antimicrobial use predicting antimicrobial resistance with a better accuracy was not possible. The choice of an indicator for an eventual surveillance system could rely on criteria other than predictive accuracy, such as feasibility (ease of data collection and computation) and the potential for external comparisons, without decreasing the quality of their surveillance activities. Results also confirm that the incapacity to observe statistically significant differences in this previous study was not due to a blatant lack of statistical power. Ideally, both the cohort and the simulation studies should be reproduced, using other surveillance conditions in confirmatory studies. Our studies are however a first answer to a long existing question; they also propose a methodological framework for future studies on this topic.

LIST OF ABBREVIATIONS

3GC: third-generation cephalosporins

Amino: aminoglycosides

ARC: aminoglycoside-resistant coliforms

CREKP: carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.

CRP: carbapenem-resistant *Pseudomonas* sp.

ICU: intensive care unit

MAE: mean absolute error

MRSA: methicillin-resistant *Staphylococcus aureus*

NHSN: National Healthcare Security Network

Pip-tazo: piperacillin-tazobactam

PTRC: piperacillin-tazobactam-resistant coliforms

PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.

QRC: quinolone-resistant coliforms

QRP: quinolone-resistant *Pseudomonas* sp.

SPIN-BACTOT: Québec healthcare-associated bloodstream infections surveillance network

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Table 7.1. Scenarios studied to assess power to detect differences between indicators in predicting prevalence and incidence rates of resistance (1000 simulations per scenario).

Measure of resistance	**Resistance**	**Antimicrobial use**	**SPIN-BACTOT network (Most accurate indicator vs…)**		**NHSN (Most accurate indicator vs…)**	
			Second most accurate	**Least accurate**	**Second most accurate**	**Least accurate**
Prevalence (/1000 admissions)	MRSA	Penicillins	1 year of data 2 years of data 3 years of data 4 years of data 5 years of data	1 year of data 2 years of data 3 years of data 4 years of data 5 years of data	1 year of data 2 years of data 3 years of data 4 years of data 5 years of data	1 year of data 2 years of data 3 years of data 4 years of data 5 years of data
	MRSA	Penicillins + 3GC + quinolones				
	PTRC	Piperacillin-tazobactam				
	QRC	Quinolones				
	ARC	Aminoglycosides				
	CREKP	Carbapenems				
	CREKP	Aminoglycosides + 3GC + quinolones				
	PTRP	Piperacillin-tazobactam				
	QRP	Quinolones				
	CRP	Carbapenems				
Incidence rate (/10,000 patient-days)	MRSA	Penicillins	1 year of data 2 years of data	1 year of data 2 years of data	1 year of data 2 years of data	1 year of data 2 years of data
	MRSA	Penicillins + 3GC + quinolones				
	PTRC	Piperacillin-tazobactam				
	QRC	Quinolones				

Measure of resistance	Resistance	Antimicrobial use	SPIN-BACTOT network (Most accurate indicator vs…)			NHSN (Most accurate indicator vs…)	
			Second most accurate	Least accurate		Second most accurate	Least accurate
	ARC	Aminoglycosides	3 years of data	3 years of data		3 years of data	3 years of data
	CREKP	Carbapenems	4 years of data	4 years of data		4 years of data	4 years of data
	CREKP	Aminoglycosides + 3GC + quinolones	5 years of data	5 years of data		5 years of data	5 years of data
	PTRP	Piperacillin-tazobactam					
	QRP	Quinolones					
	CRP	Carbapenems					

Note: 3GC: third-generation cephalosporins; amino: aminoglycosides; ARC: aminoglycoside-resistant coliforms; CREKP: carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.; CRP: carbapenem-resistant *Pseudomonas* sp.; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; NHSN: National Healthcare Security Network; pip-tazo: piperacillin-tazobactam; PTRC: piperacillin-tazobactam-resistant coliforms; PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.; QRC: quinolone-resistant coliforms; QRP: quinolone-resistant *Pseudomonas* sp.; SPIN-BACTOT: Québec healthcare-associated bloodstream infections network.

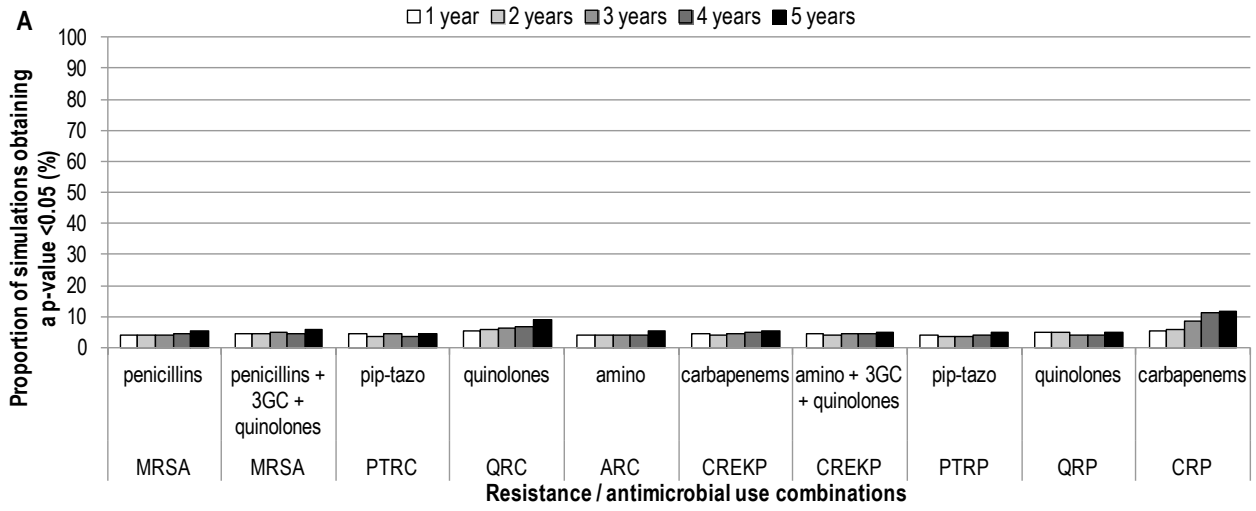
Table 7.2. Description of the SPIN-BACTOT and NHSN networks.

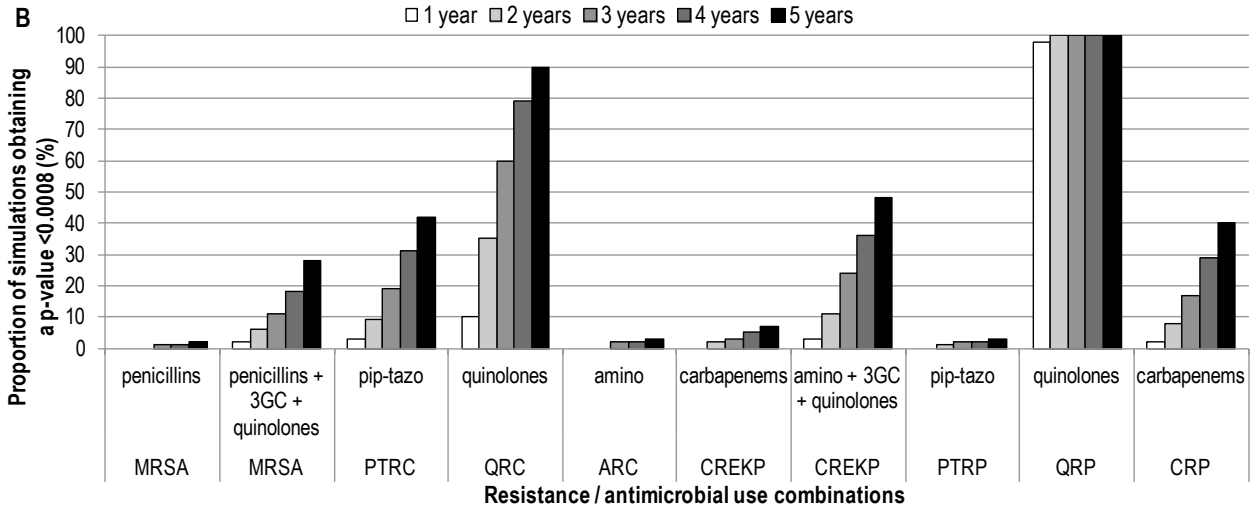
ICU type	SPIN-BACTOT				NHSN		
	ICUs (N)	Patient-days (N, /4-week period and / ICU)	Admissions (N, estimated, /4-week period and / ICU)		ICUs (N)	Patient-days (N, per 4-week period and / ICU)	Admissions (N, estimated, /4-week period and / ICU)
Adult	70	199	42		2591	255	54
Pediatric	4	120	25		178	253	52
Neonatal	7	514	36		183	867	61

Note: ICU: intensive care unit; NHSN: National Healthcare Security Network; SPIN-BACTOT: Québec healthcare-associated bloodstream infections network.

Figure 7.1. Proportion of simulations detecting differences between indicators in predicting resistance prevalence, for ten combinations and five durations.

A) Network of ICUs similar to SPIN-BACTOT's ICU network, comparing the two most accurate indicators. B) Network of ICUs similar to SPIN-BACTOT's ICU network, comparing the most accurate indicator to the least accurate. C) Network of ICUs similar to the NHSN, comparing the two most accurate indicators. 3GC: third-generation cephalosporins; amino: aminoglycosides; ARC: aminoglycoside-resistant coliforms; CREKP: carbapenem-resistant E. coli, Klebsiella sp. and Proteus sp.; CRP: carbapenem-resistant Pseudomonas sp.; ICU: intensive care unit; MRSA: methicillin-resistant Staphylococcus aureus; NHSN: National Healthcare Security Network; pip-tazo: piperacillin-tazobactam; PTRC: piperacillin-tazobactam-resistant coliforms; PTRP: piperacillin-tazobactam-resistant Pseudomonas sp.; QRC: quinolone-resistant coliforms; QRP: quinolone-resistant Pseudomonas sp.; SPIN-BACTOT: Québec healthcare-associated bloodstream infections network.


A
1 year
2 years
3 years
4 years
5 years
Proportion of simulations obtaining a p-value <0.05 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations


B
1 year
2 years
3 years
4 years
5 years
Proportion of simulations obtaining a p-value <0.0008 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations

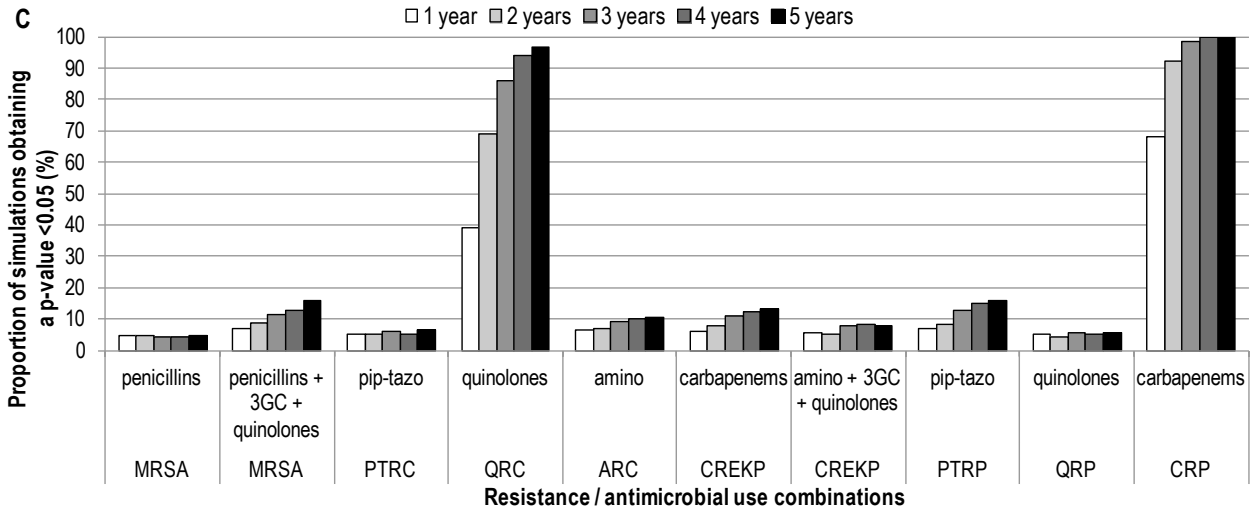
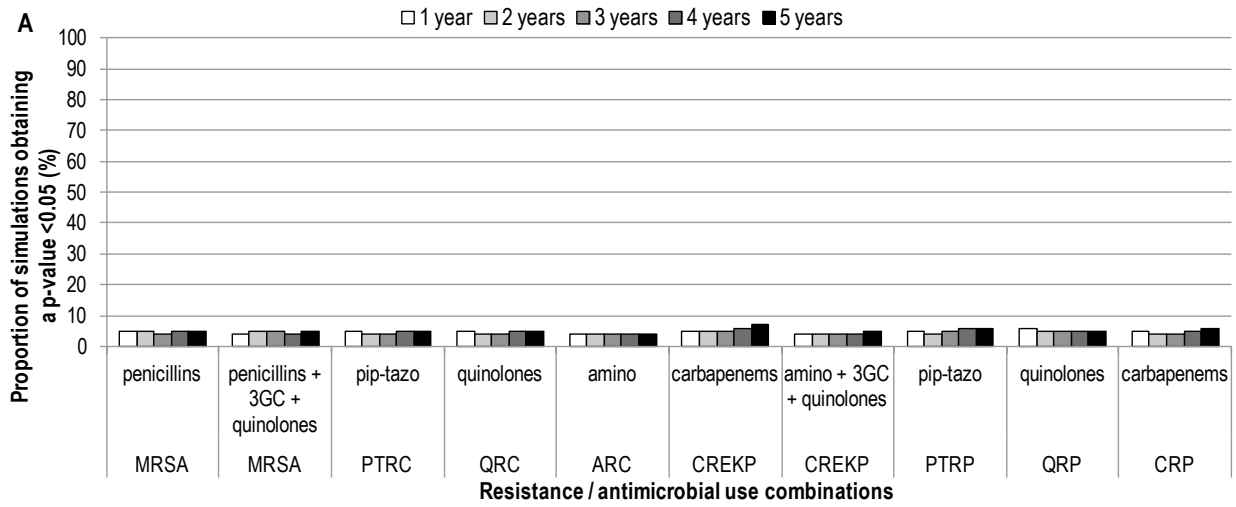
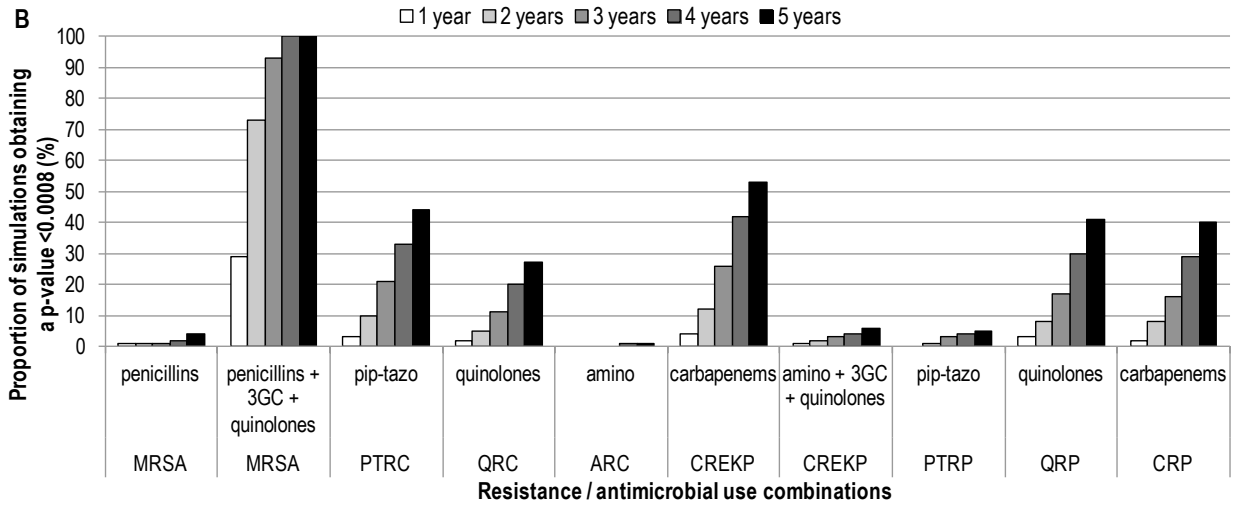
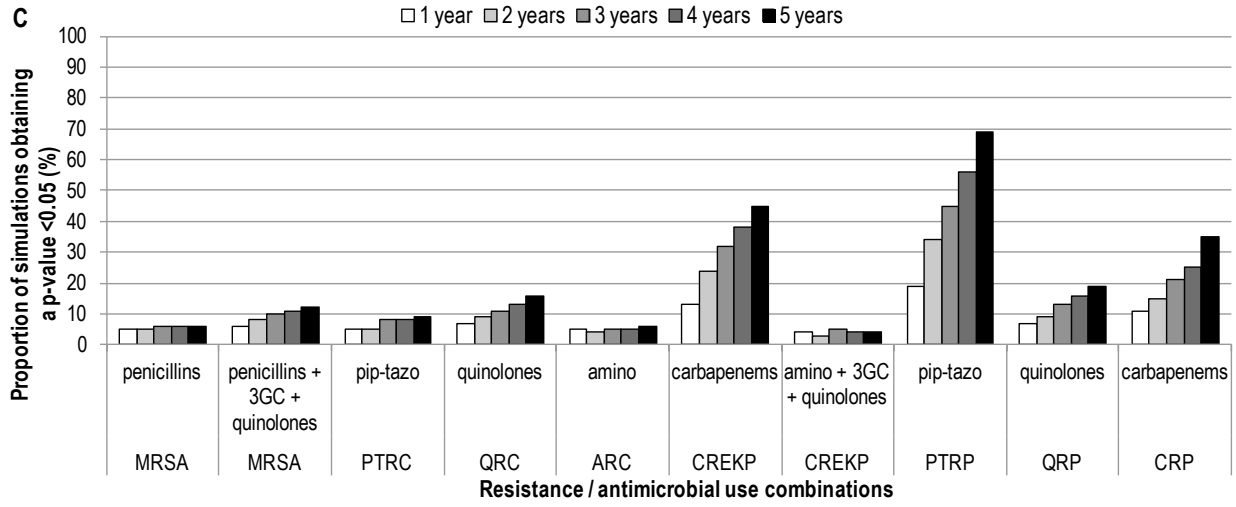

C
1 year
2 years
3 years
4 years
5 years
Proportion of simulations obtaining a p-value <0.05 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations

Figure 7.2. Proportion of simulations detecting differences between indicators in predicting resistance incidence rates, for ten combinations and five durations.

A) Network of ICUs similar to SPIN-BACTOT's ICU network, comparing the two most accurate indicators. B) Network of ICUs similar to SPIN-BACTOT's ICU network, comparing the most accurate indicator to the least accurate. C) Network of ICUs similar to the NHSN, comparing the two most accurate indicators. 3GC: third-generation cephalosporins; amino: aminoglycosides; ARC: aminoglycoside-resistant coliforms; CREKP: carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.; CRP: carbapenem-resistant *Pseudomonas* sp.; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; NHSN: National Healthcare Security Network; pip-tazo: piperacillin-tazobactam; PTRC: piperacillin-tazobactam-resistant coliforms; PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.; QRC: quinolone-resistant coliforms; QRP: quinolone-resistant *Pseudomonas* sp.; SPIN-BACTOT: Québec healthcare-associated bloodstream infections network.


A
1 year 2 years 3 years 4 years 5 years
Proportion of simulations obtaining a p-value <0.05 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations


B
1 year 2 years 3 years 4 years 5 years
Proportion of simulations obtaining a p-value <0.0008 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations


C
1 year 2 years 3 years 4 years 5 years
Proportion of simulations obtaining a p-value <0.05 (%)
100
90
80
70
60
50
40
30
20
10
0
penicillins
penicillins + 3GC + quinolones
pip-tazo
quinolones
amino
carbapenems
amino + 3GC + quinolones
pip-tazo
quinolones
carbapenems
MRSA
MRSA
PTRC
QRC
ARC
CREKP
CREKP
PTRP
QRP
CRP
Resistance / antimicrobial use combinations

SUPPORTING INFORMATION

Figure 7.S1. Methodology followed to identify the most accurate, the second most accurate and the least accurate indicators, in predicting prevalence of carbapenem-resistant *Pseudomonas* sp. in nine intensive care units.

DDD: defined daily doses; ICU: intensive care unit; MAE: mean absolute error; RDD: recommended daily doses.

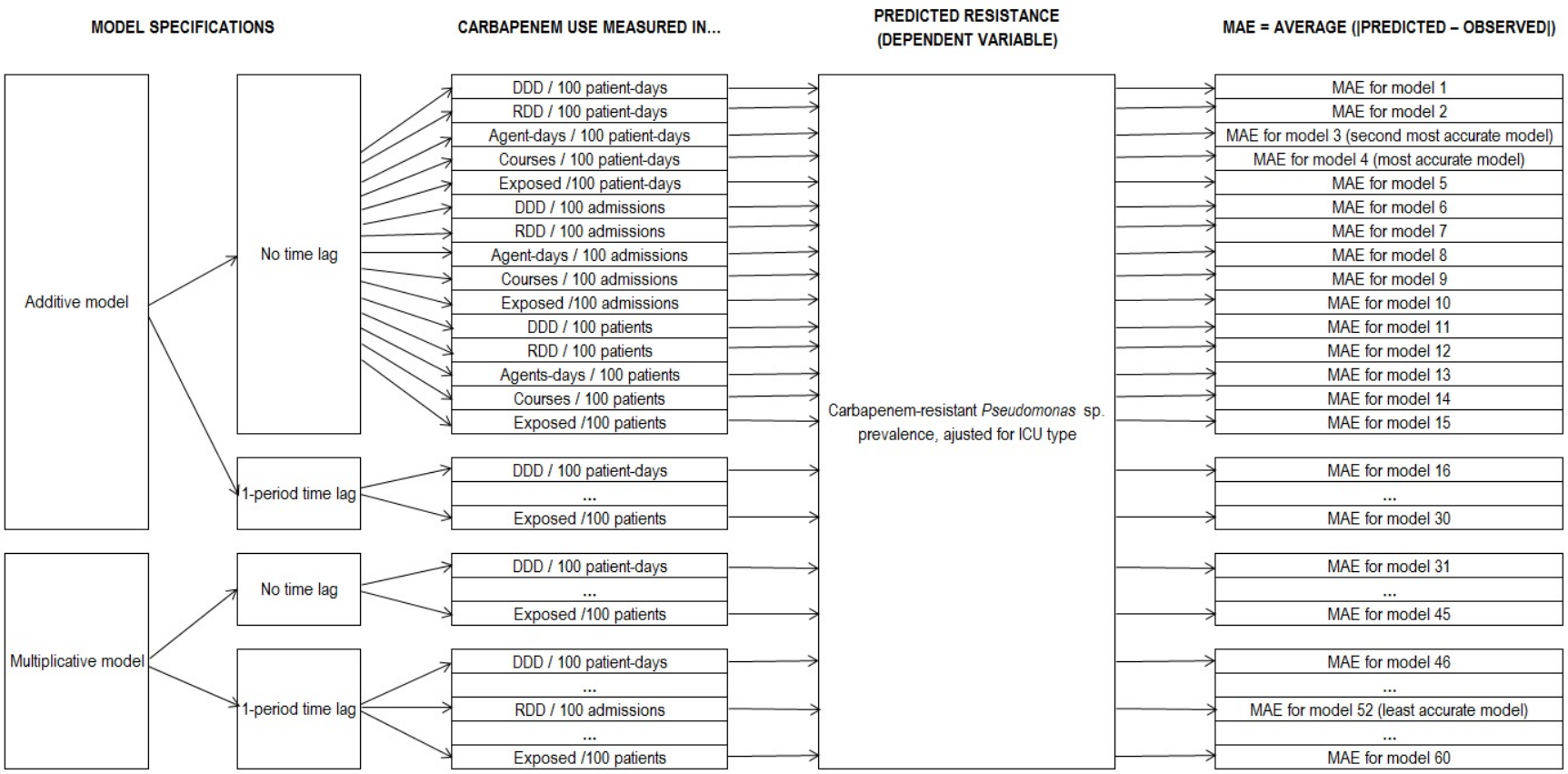


Table 7.S1. Most accurate, second most accurate and least accurate indicators in predicting prevalence of antimicrobial resistance, for different scenarios, with their regression link and their mean absolute error.

Resistance / antimicrobial use	Adjustment for ICU type	Most accurate indicator	Regression link	MAE	Second most accurate indicator	Regression link	MAE	Least accurate indicator	Regression link	MAE
ARC / aminoglycosides	none	DDD / pd	identity	0,003839	DDD / patients	identity	0,003857	DDD / adm (1)	log	0,004102
CREKP / 3GC + aminoglycosides + quinolones	none	DDD / adm	identity	0,002113	DDD / patients	identity	0,002123	agent-days / adm	identity	0,002604
CREKP / carbapenems	none	agent-days / pd	identity	0,002119	courses / pd	identity	0,002134	RDD / adm (1)	log	0,002360
CRP / carbapenems	adult	courses / pd	identity	0,004593	exposed / pd	identity	0,004791	RDD / adm (1)	log	0,005014
	pediatric	courses / pd	identity	0,002635	exposed / pd	identity	0,002406	RDD / adm (1)	log	0,001955
	neonatal	courses / pd	identity	0,001501	exposed / pd	identity	0,001448	RDD / adm (1)	log	0,005014
MRSA / 3GC + penicillins + quinolones	adult + pediatric	DDD / adm	log	0,007135	DDD / patients	log	0,007188	courses / pd	log	0,007889
	neonatal	DDD / adm	log	0,001671	DDD / patients	log	0,001659	courses / pd	log	0,001615
MRSA / penicillins	adult + pediatric	DDD / patients	identity	0,007541	DDD / adm	identity	0,007535	agent-days / adm	log	0,007882
	neonatal	DDD / patients	identity	0,001438	DDD / adm	identity	0,001452	agent-days / adm	log	0,001638
PTRC / piperacillin-	none	DDD / adm	identity	0,006238	RDD / patients	identity	0,006245	agent-days / adm	log	0,007014

Resistance / antimicrobial use	Adjustment for ICU type	Most accurate indicator			Second most accurate indicator			Least accurate indicator		
		Indicator	Regression link	MAE	Indicator	Regression link	MAE	Indicator	Regression link	MAE
tazobactam										
PTRP / piperacillin-tazobactam	none	DDD / adm (1)	identity	0,003034	DDD / patients (1)	identity	0,003055	agent-days / adm	log	0,003275
QRC / quinolones	adult	DDD / adm (1)	identity	0,005160	DDD / adm	identity	0,004998	exposed / pd (1)	log	0,006352
	pediatric	DDD / adm (1)	identity	0,001025	DDD / adm	identity	0,001471	exposed / pd (1)	log	0,000886
	neonatal	DDD / adm (1)	identity	0,002052	DDD / adm	identity	0,002034	exposed / pd (1)	log	0,001980
QRP / quinolones	none	courses / adm (1	identity	0,001574	exposed / patients	identity	0,001580	exposed / adm (1)	identity	0,003387

Note: 3GC: third-generation cephalosporins; adm: admissions; ARC: aminoglycoside-resistant coliforms; CREKP: carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.; CRP: carbapenem-resistant *Pseudomonas* sp.; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; pd: patient-days; PTRC: piperacillin-tazobactam-resistant coliforms; PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.; QRC: quinolone-resistant coliforms; QRP: quinolone-resistant *Pseudomonas* sp.

Table 7.S2. Most accurate, second most accurate and least accurate indicators in predicting incidence rates of antimicrobial resistance, for different scenarios, with their regression link and their mean absolute error.

Resistance / antimicrobial use	Adjustment for ICU type	Most accurate indicator			Second most accurate indicator			Least accurate indicator		
		Indicator	Regression link	MAE	Indicator	Regression link	MAE	Indicator	Regression link	MAE
ARC / aminoglycosides	none	DDD / adm	identity	0,000598	courses / pd	identity	0,000598	agent-days / adm (1)	log	0,000622
CREKP / 3GC + aminoglycosides + quinolones	adult +pediatric	DDD / patients	identity	0,000492	DDD / adm	identity	0,000491	exposed / pd (1)	log	0,000547
	neonatal	DDD / patients	identity	0,000158	DDD / adm	identity	0,000159	exposed / pd (1)	log	0,000169
CREKP / carbapenems	adult + pediatric	agent-days / pd	identity	0,000437	courses / pd	identity	0,000445	RDD / patients (1)	identity	0,000550
	neonatal	agent-days / pd	identity	0,000169	courses / pd	identity	0,000166	RDD / patients (1)	identity	0,000165
CRP / carbapenems	adult	courses / pd	log	0,001369	DDD / pd	log	0,001383	courses / pd (1)	log	0,001548
	pediatric	courses / pd	log	0,000259	DDD / pd	log	0,000255	courses / pd (1)	log	0,000278
	neonatal	courses / pd	log	0,000145	DDD / pd	log	0,000141	courses / pd (1)	log	0,000142
MRSA / 3GC + penicillins + quinolones	adult	exposed / adm (1)	log	0,001324	exposed / patient (1)	log	0,001332	exposed / pd	identity	0,001696
	pediatric	exposed / adm (1)	log	0,001061	exposed / patient (1)	log	0,001060	exposed / pd	identity	0,001128
	neonatal	exposed / adm (1)	log	0,000109	exposed / patient (1)	log	0,000109	exposed / pd	identity	0,000108
MRSA / penicillins	adult	agent-days / patients (1)	log	0,001598	courses / patients (1)	log	0,001592	courses / pd	identity	0,001693
	pediatric	agent-days / patients (1)	log	0,001069	courses / patients (1)	log	0,001083	courses / pd	identity	0,001130

Resistance / antimicrobial use	Adjustment for ICU type	Most accurate indicator			Second most accurate indicator			Least accurate indicator		
		Indicator	Regression link	MAE	Indicator	Regression link	MAE	Indicator	Regression link	MAE
	neonatal	agent-days / patients (1)	log	0,000010	courses / patients (1)	log	0,000107	courses / pd	identity	0,000107
PTRC / piperacillin-tazobactam	adult + pediatric	RDD / patients (1)	identity	0,001384	DDD / patients (1)	identity	0,001389	agent-days / adm (1)	log	0,001567
	neonatal	RDD / patients (1)	identity	0,000687	DDD / patients (1)	identity	0,000691	agent-days / adm (1)	log	0,000674
PTRP / piperacillin-tazobactam	adult + pediatric	agent-days / patients	log	0,000699	agent-days / adm	log	0,000713	courses / pd (1)	log	0,000764
	neonatal	agent-days / patients	log	0,000198	agent-days / adm	log	0,000185	courses / pd (1)	log	0,000198
QRC / quinolones	adult	courses / adm	log	0,001368	courses / patients	log	0,001377	exposed / pd (1)	log	0,001526
	pediatric	courses / adm	log	0,000167	courses / patients	log	0,000167	exposed / pd (1)	log	0,000171
	neonatal	courses / adm	log	0,000125	courses / patients	log	0,000125	exposed / pd (1)	log	0,000127
QRP / quinolones	none	DDD / adm	identity	0,000349	DDD / patients	identity	0,000353	exposed / pd	log	0,000433

Note: 3GC: third-generation cephalosporins; adm: admissions; ARC: aminoglycoside-resistant coliforms; CREKP: carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp.; CRP: carbapenem-resistant *Pseudomonas* sp.; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*; pd: patient-days; PTRC: piperacillin-tazobactam-resistant coliforms; PTRP: piperacillin-tazobactam-resistant *Pseudomonas* sp.; QRC: quinolone-resistant coliforms; QRP: quinolone-resistant *Pseudomonas* sp.

CHAPTER 8. SUMMARY AND CONCLUSIONS

8.1. Summary

Although the causal relationship between antimicrobial use and antimicrobial resistance is difficult to quantify due to the various settings and indicators used and to related biases, this relationship is generally accepted. Considering that antimicrobial use is modifiable, surveillance of antimicrobial use is recommended as a complement to surveillance of antimicrobial resistance aiming to limit its development and transmission. In practice, methodologies for surveillance of antimicrobial use vary between networks and research teams. As a result, it is difficult to make valid comparisons of surveillance results and the optimal way to measure antimicrobial use in hospitals, to complement surveillance of resistance, is still unclear.

This thesis thus aimed to identify the most accurate indicator(s) of antimicrobial use for the prediction of prevalence and incidence of resistant microorganisms in the respiratory microbiota of patients admitted to ICUs (children as well as adults). To answer this question, three specific objectives were developed:

1) To systematically review existing indicators of antimicrobial use in cohort and repeated point-prevalence studies including pediatric inpatient populations;

2) To measure population antimicrobial use as well as prevalence and incidence of clinically relevant antimicrobial resistances found in respiratory cultures performed in intensive care unit (ICU) patients, using different indicators and definitions;

3) To identify the indicator of antimicrobial use that predicted prevalence and incidence rates of resistance, in respiratory cultures performed in ICU patients, with the best accuracy.

In order to identify the most accurate indicator for surveillance of antimicrobial use, to be used as a complement to surveillance of antimicrobial resistance, a list of existing indicators had to be built. This was in reality the objective of a systematic literature review that compiled all indicators used in cohort and repeated point-prevalence studies, between 1975 and 2011, and

where antimicrobial resistance was mentioned as a justification to measure antimicrobial use. Because a surveillance program would aim to include pediatric hospitals and pediatric wards, and because the most often used indicator (DDDs per patient-days) is known to underestimate antimicrobial use in pediatric populations, selected studies had to include pediatric populations.

Seventy-nine studies met selection criteria. Of note, many eligible studies did not define their measures clearly, thus lessening the possibility for readers to compare their own results. Twenty-six distinct indicators were found (13 numerators and five denominators). Numerators could be categorized as measuring quantity, duration or simple exposure, while denominators measured person-time, person or total expenses. Indicators most frequently used were DDD / patient-days and exposed patients / patients. Of the 26 indicators identified, 17 were compared with at least one other indicator, but only four were compared quantitatively. Only 2 studies compared different measures quantitatively, showing 1) a positive correlation between proportion of patients exposed and antimicrobial-days / patient-days and 2) a strong correlation between doses / patient-days and agent-days / patient-days (r=0.98), with doses / patient-days correlating more with resistance rates (r=0.80 vs. 0.55). These results demonstrated clearly that little evidence was available to guide policy makers in the choice of the ideal indicator for a surveillance system, particularly when including pediatric populations. To us, this was a confirmation that our project was necessary.

The work to come, however, did not have to carry on with all indicators identified in the systematic literature review. Market fluctuations limited the use of expenses as an indicator. Information provided per grams of antimicrobials is included and standardized in recommended daily doses (RDD) and DDD computations. Prescribed daily doses should mathematically be equal to agent-days. Kg-days cannot be used for adult populations because patients' weight is usually unknown. Finally, as adult patients' weight is frequently unknown and as RDD in mg/kg is more useful for paediatrics, RDD and RDD in mg/kg could be combined into a single indicator. In the end, seven numerators (DDD, RDD, agent-days, antimicrobial-days, courses, treatment periods and exposed patients) and three denominators (patient-days, admissions and patients present) appeared interesting to us, for a potential of 21 indicators to study and compare. As

the project progressed, when computing these numerators and denominators for some ICUs, it appeared that agent-days and courses were almost identical to antimicrobial-days and treatment periods, respectively. Antimicrobial-days and treatment periods would thus also be excluded from final analyses, leaving 15 indicators.

A cohort was then built and included all patients admitted to the nine ICUs of four hospitals between April 1st, 2006 and March 31st, 2010. Data extractions were obtained from each hospital's admission/discharge/transfer system, microbiology laboratory information system and pharmacy database.

Obtaining good data extractions represented an important challenge. These databases are independent and each hospital has its own databases. Moreover, administrative staffs are not necessarily used to perform data extractions from these systems. As a consequence, the careful review of the data took months and revealed many problems, such as missing data, varying ICU identifiers or false dates created when information systems were changed. Steps followed during this review of data extractions included a visual inspection of data and comparisons with laboratory data and other data sources. Data were re-extracted until their completeness, accuracy and consistency were judged satisfactory. Experiencing difficulties in obtaining good quality extractions from hospital databases is a well-known problem that, somehow, is still unsolved. Although perfect data is not necessary for surveillance purposes, the time it took to obtain these suitable data extractions is problematic, since an eventual surveillance system would aim to detect emerging problems in a timely manner.

A preliminary step, before studying the prediction of resistance with indicators of antimicrobial use, consisted in describing resistance in respiratory isolates and antimicrobial use in participating ICUs. Prevalence and incidence of clinically relevant resistances in respiratory cultures were measured. ICU antimicrobial use was also measured, using ten different indicators based on either dosage, duration of treatment or exposure to antimicrobials. Indicators were presented aggregated for the entire follow-up period (April 2006 to March 2010), but were also computed per ICU and per year. Over a year or a four-year period, patients present and patients admitted are almost identical; this is why the five indicators using number of patients as

denominator were not discussed in this part of the thesis. Bivariate additive regression models were used to detect the presence of time trends (per year) or of differences by ICU type (neonatal, pediatric or adult). Binomial regression was used for resistance prevalence, Poisson regression, for incidence of resistance and indicators of antimicrobial use.

Overall, resistance was relatively rare in ICU patients' respiratory cultures. Methicillin-resistant *S. aureus* and piperacillin-tazobactam-resistant coliforms were the most frequent resistances and they were detected in only 0.52% and 0.44% of all admitted patients. Incidence rates of these resistances were also the highest, at 6.57 and 7.80 cases per 10,000 patient-days, respectively. Ampicillin- or vancomycin-resistant *Enterococcus* sp. were very rare (prevalence of 0.01%), as well as carbapenem-resistant *Enterobacter* sp. and *Citrobacter* sp. (prevalence of 0.01%) and carbapenem-resistant *E. coli*, *Klebsiella* sp. and *Proteus* sp. (prevalence of 0.02%). Significant increasing trends were observed in coliforms (piperacillin-tazobactam, quinolones and third-generation cephalosporins), suggesting prevention efforts should be directed towards controlling these resistances. Also, a gradient in resistance, from neonates to adults, was observed in our cohort.

Cephalosporins, penicillins and aminoglycosides were the most frequently prescribed antimicrobials, according to most indicators (25.2%, 17.3% and 16.5% of admitted patients were exposed, respectively). RDDs were closer to agent-days than DDDs, an expected result as RDDs should better reflect prescribed daily doses than DDDs; it is interesting to note that RDDs generally underestimated agent-days in our cohort. Discrepancies between these indicators highly depend on antimicrobial agents most frequently used in populations studied ("antimicrobial-mix"), and how much their DDDs and RDDs differ from each other and from actually prescribed daily doses. For instance, aminoglycosides were prescribed more frequently in neonatal ICUs than in adult ICUs, thus magnifying the discrepancy between DDDs and RDDs in mg/kg prescribed to neonates. Other examples are parenteral ciprofloxacin, imipenem and meropenem for which RDDs were lower than DDDs, while these agents were also the most used in their respective antimicrobial classes.

In general, antimicrobial use was lower in neonatal ICUs compared to adult ICUs, except for aminoglycoside and penicillin use, which were higher in neonatal ICUs. This makes sense as treatment options are more limited in this population, leading to a more intense use of available agents. Antimicrobial use was frequently higher in pediatric ICUs than in adult ICUs. Whenever indicators diverged, as expected, DDDs tended to show lower antimicrobial use in pediatric and neonatal ICUs, compared to most indicators. Interestingly, decreasing trends were observed for two of the most frequently prescribed antimicrobial classes, penicillins and aminoglycosides.

In summary, after analyzing differences between indicators of antimicrobial use regarding the trends they detected, chapter 5 concluded on the observation that a set of indicators could be preferable to a single indicator, as different indicators reflect different aspects of antimicrobial use. Varying lengths of stay between ICUs could justify the use of at least two indicators, one using ICU admissions and another using ICU patient-days. In our cohort, exposed patients, DDDs and agent-days would have allowed us to detect the main trends and discrepant trends as well.

However, surveillance of antimicrobial use is often performed to complement surveillance of resistance in patients. This is why, in chapter 6, we compared indicators' accuracy in prediction of antimicrobial resistance, after adjustment for intensive care unit type. Of the clinically relevant resistances measured in the previous study, the eight most frequent were selected and re-computed per 4-week period and per ICU. Ten different resistance / antimicrobial use combinations were studied, for a total of 20 scenarios, as both prevalence and incidence rates of each combination' resistance were studied. All 15 indicators of antimicrobial use of related antimicrobial classes or agents were also computed per 4-week period and per ICU. After adjustment for ICU type, indicators of antimicrobial use were successively tested in regression models, to predict respiratory isolates' resistance prevalence and incidence rates, per 4-week time period, per ICU. Generalized estimating equations were used to account for correlated values at the ICU level. Multiplicative and additive models were tested, as well as no time lag and a one 4-week-period time lag; in total, for each scenario, 60 models were compared (15 indicators x 2 regression links x 2 time lags).

For each model, the mean absolute error (MAE) was then computed. The MAE is a statistic used in the analysis of time series, to quantify the difference between observed values and values predicted by a model. An error was the difference between observed frequency of resistance and the frequency predicted by the regression model, computed for each 4-week period, in each ICU. Absolute values of these errors were computed and averaged, to produce the MAE of each model. The most accurate indicators were the ones with the smallest MAEs. Predictive accuracy of different models of a given scenario was then compared using t-tests, to determine whether differences observed in predictions were statistically significant.

A statistically significant difference between MAEs was observed for only 1 of the 20 scenarios studied: carbapenem use to predict prevalence of carbapenem-resistant *Pseudomonas* sp. This difference identified one indicator that did not perform as well ($p = 0.0006$); however, no single indicator (or no small set of indicators) stood out as better than the others. This almost complete absence of difference can be explained by 1) adjustment for ICU type, while a strong correlation of resistance and antimicrobial use existed at the ICU level; 2) the fact that indicators tend to increase or decrease together, describing similar trends; 3) limited differences in indicators' range due to a very short median length of stay in ICUs; 4) similar variations in DDDs, RDDs and agent-days, for some combinations, as a single agent constituted most of an antimicrobial class usage.

As no specific indicator stood out as a better predictor of resistance, chapter 7 presented a simulation study exploring conditions (network size and surveillance duration) that could eventually allow for the detection of statistical differences between indicators' predictive accuracy. Ten different resistance / antimicrobial use combinations were studied. Simulations were run to find out if Quebec's network of ICUs or the National Healthcare Safety Network ICUs (81 and 2952 ICUs, respectively) could have allowed the detection of predetermined differences between the most accurate and 1) the second most accurate indicator, and 2) the least accurate indicator, in more than 80% of simulations. For each indicator, simulated absolute errors were generated, for each ICU and each 4-week period, over surveillance durations ranging from 1 to 5 years.

Less than a third of all 400 scenarios studied (112 / 400) had an 80% power to detect a difference between compared indicators. This 80% power was reached more frequently with the larger network (103 / 200 scenarios versus 9 / 200 scenarios with the smaller network) or with longer durations of surveillance (25 / 80 scenarios following ICU for 5 years versus 19 / 80 scenarios following ICUs for 1 year only). ICU network size and surveillance duration both influenced the number of simulated absolute errors (or simulated observations) used in t-tests and, consequently, power to detect differences between indicators. However, most of the time, identifying an indicator of antimicrobial use predicting antimicrobial resistance with a better accuracy was not possible.

This last study confirmed that the incapacity to observe statistically significant differences in this previous study was not due to a blatant lack of statistical power. Had an indicator been more accurate than others, it would have allowed a closer monitoring of variations in antimicrobial resistance frequency, and an increased ability to detect the impact on resistance of interventions targeting antimicrobial use. Our actual results rather demonstrate that the choice of an indicator for surveillance of antimicrobial use is not critically limited by predictive accuracy of resistance levels, and that it could very well rely on criteria such as differences in simple trend detections, as discussed in chapter 5, but also on practical and feasibility criteria such as ease of computation and external comparisons and actual practices in hospitals.

8.2. **Conclusion**

This thesis presents the results of a systematic approach to answer to a question where evidence-based information was lacking. A systematic review of the literature allowed us to identify 26 indicators of antimicrobial use that had been used in cohorts or repeated point-prevalence studies that included pediatric populations. Only two of these indicators had been compared regarding their ability to predict resistance frequency. It became obvious that data was necessary to orient the choice of an indicator for surveillance of antimicrobial use in hospital populations, to be used as a complement to surveillance of antimicrobial resistance. We thus created a cohort of all patients admitted to one of nine participating ICUs, between April 2006 and March 2010. Using extractions from hospitals' administrative databases is a

challenge commonly mentioned by investigators and our project was no exception to this rule. We were still able to describe prevalence and incidence rates of clinically relevant resistances in these patients' respiratory cultures, and to describe antimicrobial use in our cohort, using different indicators of antimicrobial use. Although most indicators detected the same time trends and the same differences between ICU types, they did not always agree; disparities provided useful information. Finally, we compared fifteen indicators' accuracy in predicting the most frequent clinically relevant resistances. Predictive accuracy was measured with mean absolute errors, measures that could be compared using t-tests. A statistically significant difference between MAEs was observed for only 1 of the 20 scenarios studied, where only one indicator stood out as worse than all others. A simulation study confirmed that this incapacity to identify a single most accurate indicator was not attributable to a blatant lack of statistical power. The choice of an indicator for an eventual surveillance system is thus not critically limited by predictive accuracy of resistance levels and could rely on criteria other than predictive accuracy, such as feasibility, potential for external comparisons and actual practices, without decreasing the quality of surveillance activities.

While computing the different indicators of antimicrobial use presented in this thesis, it became obvious that certain indicators are easier to compute than others. For instance, DDDs and RDDs can be computed using aggregated pharmacy data. On the contrary, counting the number of exposed patients, agent-days, antimicrobial-days, courses and treatment periods necessarily mean that individual data have to be available. In addition, courses and treatment periods necessitate taking into account consecutive days of therapy, with one or more agents. Stratifying the indicators can also be very simple with some indicators, but require more efforts with other indicators. In this case, DDDs, RDDs, agent-days and antimicrobial-days collected per month and per ward can simply be summed up to obtain hospital antimicrobial use. However, exposed patients, courses or treatment periods counted in wards or during two consecutive time periods are not collapsible. For instance, a patient exposed to one course of an antimicrobial can be transferred during treatment; wards would count the exposure once each, but at the hospital level, it remains a single exposure. Summing them up will overestimate hospital use; indicators have to be recomputed with each additional stratification of data. At the

denominator level, the number of patients presents the same peculiarity. As statistical resources are limited in hospitals, this is an important aspect to take into account.

In addition, certain indicators will facilitate external comparisons. DDDs per patient-days is the indicator most frequently used in publications and uses international standards. Exposed patients per patients, despite computational limitations, is another frequently used indicator that can allow comparisons with point-prevalence studies. Agent-days per patient-days are also used in the United States and can represent an interesting comparison for a North American territory such as the Province of Quebec. RDDs cannot be compared to external data unless standard doses used are the same. Finally, courses and treatment periods are frequently used in studies on the appropriate use of antimicrobials, but less frequently for quantitative surveillance of population antimicrobial use.

Finally, as indicators of antimicrobial use appear equivalent in their prediction of resistance, an important aspect to take into account when choosing the indicator for a provincial surveillance of antimicrobial use is what is already ongoing in hospitals. In September and October 2014, a web-based questionnaire was thus sent to chief pharmacists in the Province of Quebec acute care hospitals. The study aims to describe 1) available pharmacy data; 2) hospitals' actual practices in qualitative and quantitative surveillance of antimicrobial use; 3) hospitals' motivation to perform surveillance of antimicrobial use. This study is not part of the thesis project and data analysis is still ongoing. However, it is a logical step given our previous results and results should be helpful in the choice of an indicator.