EVALUATING PHARMACEUTICAL POLICIES USING CROSS-NATIONAL COMPARISONS AND TIME SERIES ANALYSIS

Yared Santa Ana Tellez

The research presented in the PhD thesis was conducted under the umbrella of the Utrecht World Health Organization (WHO) Collaborating Centre for Pharmaceutical Policy and Regulation, which is based at the Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, The Netherlands. The Collaborating Centre aims to develop new methods for independent pharmaceutical policy research, evidence based policy analysis and conceptual innovation in the area of policy making and evaluation in general.

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EVALUATING PHARMACEUTICAL POLICIES USING CROSS-NATIONAL COMPARISONS AND TIME SERIES ANALYSIS

Vergelijking van effecten van geneesmiddelenbeleid tussen landen en met tijdreeksanalyses
(met een samenvatting in het Nederlands)

Evaluación de políticas farmacéuticas usando comparaciones entre países y análisis de series de tiempo
(con resumen en Español)

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TABLE OF CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

BACKGROUND

Economic development and productivity depend on a healthy society. Health is linked to human well-being, but is also a means to improve income levels [1]. Access to effective and safe medicines is one of the key drivers to ensure a population's health. Access to medicines has been defined as "having essential medicines continuously available and affordable at public or private health facilities or medicine outlets that are within one hour's walk from the homes of the population" [2]. However, many people lack access to medicines worldwide [3,4]. This can be due to numerous reasons, among which are: inefficient medicine distribution systems, inadequate funding, and inaccurate forecasting [2,3,5]. In situations where medicines are available and affordable, poor health outcomes can still occur as a consequence of poor quality and inappropriate prescribing, dispensing and use of medicines [6].

Pharmaceutical policies provide a framework to coordinate activities in the pharmaceutical sector [7], and regulate the interplay between the government, the pharmaceutical industry, wholesalers, retailers, health professionals and patients. Pharmaceutical policies can be implemented on each health system level (Table 1). These policies aim to promote equitable access to medicines through medicine registration, reimbursement, and distribution at all health sector levels. Moreover, pharmaceutical policies at this level aim to ensure that the medicines provided to the population are safe, effective and of high quality [8,9]. Likewise, these policies aim to promote the appropriate use of medicines in the population at a health service delivery or individual household community level.

Table 1. Examples of pharmaceutical policies by health system level, adapted from Bigdeli, et al. (10)

Health system level	**Examples of policies to improve access to medicines**
Individual household community	Policies to improve medicine use by: • providing medicine information to patients • encouraging better prescribing and dispensing practices
Health service delivery	Policies to improve procurement efficiency by: • ensuring adequate, equitable and sustainable financing • regulating prices of medicines • encouraging better prescription and dispensing practices • monitoring quality of health services and medicines
Health sector	Policies to improve the governance of the pharmaceutical sector by: • regulating registration and selection of medicines • ensuring appropriate procurement and distribution
International level	Improve national or international market dynamics by: • reducing corruption and government bureaucracy • facilitating economic trade • encouraging global pharmaceutical research development for treatment of diseases affecting low and middle income countries

Pharmaceutical policies implemented nationally act on each health system level described previously. For the design and implementation of pharmaceutical policies, it is necessary to take into account country characteristics such as: the health system structure, income level, current pharmaceutical policies and the pharmaceutical market situation. Policies can have a differentiated effect across countries due to diverse country settings. For example, health system structures vary between high income countries and middle and low income countries [10]. In high income countries, health insurances often fund medicines, and private channels supply them. Most of these countries have implemented universal health coverage and the coverage of medicines is either pre-paid or reimbursed. In middle and low income countries, healthcare is usually stratified in public and private sectors [11,12]. In the public sector, government or social insurances purchase and distribute medicines through public healthcare facilities or facilities coordinated by social insurances. On the other hand, patients receiving healthcare in the private sector usually pay out of their pocket to access medicines through established retail outlets or drug sellers [12]. Therefore, the distinction between health providers has to be taken into account, since policies may only affect one of the sectors or differentially affect both.

Pharmaceutical policies, as other type of policies, should be constantly reviewed, modified and improved in accordance with new developments in the pharmaceutical market, as well as changes in laws and epidemiological profiles. Although, in an ideal world, each policy should be evaluated and modified if necessary, in reality, there is a lack of monitoring and evaluation of such policies. As a consequence, decisions are often made in the absence of good evidence of their impact [13].

Drug utilization studies are used to evaluate pharmaceutical policies. They provide information on how medicines are used in daily practice. They can describe the extent of medicine use in a certain area, such as a specific region, country, city or hospital. This information can be used to compare patterns of prescribing, dispensing and utilization of medicines between countries, i.e., cross-national comparisons [14]. The results of cross-national comparisons of drug utilization can be employed to develop best prescribing and dispensing practices, as well as to explore differences in medicine exposure in relation to specific outcomes, and optimize pharmaceutical policies aimed to improve the use of medicines.

HISTORY OF DRUG UTILIZATION RESEARCH

Drug utilization research began in the 1960s [15]. One of the first works in the field reported the consumption of medicines between 1966 and 1967, and highlighted the importance of comparing antibiotic use between different countries. Afterwards, in the 1970s, a comparison of the use of insulins and oral-antidiabetic drugs between Northern Ireland, Norway, and Sweden was published, which found that the use of these medicines was different within and between countries [16]. Other publications followed, mostly from Europe. These studies were mainly quantitative, comparing and describing patterns of use of medicines between countries and regions [17,18]. Early works on drug utilization research mostly focused on describing patterns of use of antibiotics, antidiabetic medicines, and psychotropic medications [16,19,20].

The World Health Organization (WHO) has been fundamental in the development of drug utilization research. In 1969, the WHO organized its first meeting on Drug Consumption in

Oslo, where the need for a common classification system of medicines and for a technical unit of comparison in drug utilization studies was discussed. This discussion formed the base for the later development of the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) as standard measurement of medicine use. WHO also provided the definition of drug utilization which is "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" [15].

Since the 1970s, drug utilization research has expanded its main objectives to include determinants of differences in the use of medicines and the evaluation of changes in patterns of medicine use. Such studies for example evaluate the effect of clinical guidelines for treatment of a certain disease on the use of medicines. Additionally, studies have evaluated changes in the use of (specific) medicines after a pharmaceutical policy was implemented [21].

METHODS OF ANALYZING THE IMPACT OF INTERVENTIONS ON DRUG UTILIZATION

There are several methods to address the impact of potential causes, e.g. interventions, economic conditions, or changes in policies, on relevant outcomes such as DDD/TID (defined daily dose per 1000 inhabitants per day), PDD/TID (prescribed daily doses per 1000 inhabitants per day), number of medicines prescribed, number of claims, or volume of medicines sold. These methods usually consist of causal inference designs. They include quasi-experiments, regression analyses, panel methods (fixed and random effects), difference-in-differences, instrumental variable estimations, regression discontinuity designs, interrupted time series analyses, and quantile regressions [21,22].

A frequently used method to assess the impact of pharmaceutical policies to date is interrupted time series analysis. This is the strongest and most commonly used quasi-experimental design to assess the impact of an intervention when a randomized controlled trial is not possible [23]. Interrupted time series is a special type of time series analysis where an intervention occurs at a specific point and the series are broken off by the introduction of the intervention. If the intervention has an impact, the post-intervention estimates can reflect two effects: a change in level (step change) at the intervention point, which indicates an immediate effect of the intervention, and a change in slope before and after the intervention, which can show a long-lasting effect of the intervention on the rate by which the outcome changes [23].

DATA SOURCES FOR DRUG UTILIZATION RESEARCH

Access to reliable information is essential to study the use of medicines [24]. However, in many settings, the availability of information sources depends highly on the development of the existent healthcare system and country resources. When the data sources are available, suitable decision-making depends on the in-country capacity of information retrieval, analysis and formatting results in a clear manner. In many high-income settings, routinely collected administrative data is usually the main source for policy evaluation and current drug utilization assessment in particular. These data are collected from registries of drug sales and drug

allocation at various levels of the drug distribution chain. All relevant data can be collected at the prescription level, or at point of delivery, where the patient hands over the prescription in a pharmacy and receives the medicines [15]. Other sources of information are databases of pharmaceutical and medical billing and prescriptions. In some cases, this type of data can be linked with diagnosis information. In short, the main sources of data for drug utilization studies and monitoring and evaluation of pharmaceutical policies in high-income countries are health insurance databases and electronic health records.

In contrast, in the majority of low- and middle-income countries, this type of information is scarce. This is mainly due to the absence of health insurance databases recording prescribing and electronic health records. Dispensing records are often kept on paper. Besides, there is a lack of comprehensive pharmacovigilance systems and insufficient monitoring of medicines in the market. Nevertheless, the importance of electronic health records for healthcare improvement has been recognized in low- and middle-income countries. Subsequently, some countries are developing national electronic medical record systems [25]. However, access to this information for research purposes is not warranted, or due to recent system set ups, data might be insufficient. Hence, in these cases, estimations on drug utilization have been conducted using retail sales data [26]. Market research companies such as IMS Health collects this type of data. IMS Health uses national sample surveys completed at different points of the pharmaceutical sales distribution channels, for example, from manufacturer to wholesaler, or from wholesalers to retailers. IMS Health usually collects data on medicine prices and volume of medicines sold [27].

Although several countries are committed to move towards universal healthcare, it is difficult to reach effective health coverage. Effective coverage has been defined as the fraction of potential health gain that is actually delivered to the population through the health system, given its capacity [28]. Besides health coverage, it is important to take into account that health services utilization relies on medicine availability. If the availability of affordable medicines is not warranted, population in the lowest levels of income may be unable to pay the indirect costs of public health institutions services, borrow money, or have expenditure sufficiently large to push households into poverty. These indirect costs may include transportation costs, unpaid sick leave, time, and co-payments [29]. When medicines are not available in the public sector, the patients can get them in the private sector by out-of-pocket expenditure. In Latin America and Caribbean, the average out-of-pocket health expenditure as a percentage of total expenditure on health is 33% [30], and the variability of this indicator in 2014 ranged from 6% in Cuba to 64% in Venezuela. Besides, the percentage of expenditure in medicines has been reported to be the largest expenditure of out-of-pocket disbursements, having the greatest impact in low-income households [31]. Thus, it is important to study the consumption of medicines in the private sector. But the recollection of this type of data is lacking, contrasting other regions as North America or Europe, where the consumption of prescribed medicines is recorded via reimbursement mechanisms of payer. Therefore, the evaluation of national pharmaceutical policies in these settings is a challenging task because pharmaceutical policies are not taken into account in health systems reforms [29] and data sources for evidence-based decisions are lacking.

The combination of research carried out using different methodologies on different data sources enriches the knowledge needed for the improvement of national pharmaceutical policies and drug utilization in different settings. Previous publications at the WHO Collaborating Centre for Pharmaceutical Policy and Regulation have focused on the assessment of access to medicines and pharmaceutical policies in different settings. Access to medicines has been analyzed using price and availability data [5] and between countries [32,33]. In Europe, the use of medicines has been studied between countries in relation to health system characteristics [34], and different pricing policies and their effects on the use of medicines have been evaluated in the context of the economic recession [35]. Additionally, methodological approaches have been developed to examine pharmaceutical policies and access to medicines in developing countries [36]. This thesis builds on these works by addressing the effect of different pharmaceutical policies implemented at the national level on the use of medicines in high-income and middle-income countries with a variety of data sources. The methodological techniques for policy evaluation such as time series analysis are emphasized with the assessment of intended and unintended effects of pharmaceutical policies in Latin American countries.

OBJECTIVE OF THE THESIS

The creation of electronic health-information systems opens a window of opportunity for the assessment of medicines use. The analysis of these data sources and others such as medicine claims and sales data can provide a convenient and relatively inexpensive approach to study existent pharmaceutical policies. Study results can be useful for decision-makers in their process of evidence-based policymaking. Therefore, the overall objective of this thesis is to evaluate the effects of pharmaceutical policies implemented at a national level on the use of medicines in different countries with different income levels. In this thesis, we analyzed different types of policies (OTC sales regulation, generic policies and decisions of approval and reimbursement of medicines) and different data sources as case studies from the public and private sector. In addition, the studies contained in this thesis explore and strengthen methods for policy evaluation, with a focus on time series analysis.

THESIS OUTLINE

This thesis consists of nine studies structured in five chapters. After the introduction, **Chapter 2** contains three subchapters on cross-national comparisons in drug utilization research. **Chapter 2.1** presents an overview of cross-national comparison studies, summarizing their characteristics in terms of data and methodological approach to evaluate the use of medicines between countries. **Chapter 2.2** presents the development of an evaluation checklist. This checklist is intended to assist in the evaluation of the strengths and limitations of cross-national comparisons of drug utilization studies. The results of this evaluation will be used to develop good practice guidelines to conduct, analyze and report these types of studies. In **Chapter 2.3,** time series regressions are used to assess cross-national differences in the uptake of insulin analogues in four Scandinavian countries and the United Kingdom as an example of a cross-national comparative study.

Interrupted time series analysis has been used largely in drug utilization studies, specifically in the evaluation of the effect of pharmaceutical policies. For the evaluation of pharmaceutical policies, up to now there has been a strong focus on segmented time series analysis. **Chapter 3** focuses on this methodology. **Chapter 3.1** provides technical details on the use of reference groups when evaluating policies using interrupted time series analysis. Then in **Chapter 3.2** the evaluation of the effect of the introduction of the mandatory offer of generic substitution in the use of medicines for chronic diseases in South Africa is conducted using interrupted time series analysis.

Chapter 4 presents the evaluation of the OTC sales restriction of antibiotics and studies on the unintended effects of the reinforcement of the policy in Mexico and Brazil. This chapter begins with the overall impact evaluation of the policy reinforcement in both countries (**Chapter 4.1**), followed by **Chapter 4.2**, where the seasonal variation in the use of penicillins before and after the policy change is measured. In **Chapter 4.3**, the importance of the quality of databases and appropriate methodologies to better assess this type of interventions is highlighted, in response to an editorial letter, showing different results of the evaluation of the OTC sales restriction of antibiotics in Brazil. **Chapter 4.4** assesses the unintended effects of this policy by measuring the changes in the use of therapeutic groups that can be perceived as substitutes of antibiotics to relieve cold symptoms.

To finalize, in **Chapter 5**, the general discussion draws lessons from the studies conducted in this thesis. In this chapter, the methodological challenges and areas of improvement to conduct drug utilization studies are addressed. It highlights the importance of appropriate methods applied in different databases for the evaluation of the effects of pharmaceutical policies on the use of medicines in different settings.

REFERENCES

1. World Health Organization. WHO | Health and development [Internet]. World Health Organization; Available from: http://www.who.int/hdp/en/
2. United Nations Development Group. Indicators for Monitoring the Millennium Development Goals [Internet]. New York; 2003. Available from: http://mdgs.un.org/unsd/mdg/Resources/Attach/Indicators/HandbookEnglish.pdf
3. World Health Organization. The World Medicines Situation [Internet]. Geneva, Switzerland; 2004. Available from: http://apps.who.int/medicinedocs/pdf/s6160e/s6160e.pdf
4. MDG Gap Task Force. Millenium Development Goal 8. Taking Stock of the Global Partnership for Development [Internet]. 2015. Available from: http://www.un.org/millenniumgoals/pdf/MDG_Gap_2015_E_web.pdf
5. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet. 2009 Jan 17;373(9659):240–9.
6. Mills A, Brugha R, Hanson K, McPake B. What can be done about the private health sector in low-income countries? Bull World Health Organ. 2002 Jan;80(4):325–30.
7. Panamerican Health Organization. PAHO WHO | Pharmaceutical policies [Internet]. 2014 [cited 2016 Feb 16]. Available from: http://www.paho.org/hq/index.php?option=com_content&view=category&layout=blog&id=1265&Itemid=1177
8. World Health Organization. How to Develop and Implement a National Drug Policy (Second Edition) [Internet]. Available from: http://apps.who.int/medicinedocs/en/d/Js2283e/4.1.2.html
9. Almarsdóttir AB, Traulsen JM. Studying and evaluating pharmaceutical policy--becoming a part of the policy and consultative process. Pharm World Sci. 2006 Feb;28(1):6–12.
10. Cutler DM, Zeckhauser RJ. The anatomy of health insurance. Handbook of Health Economics. Elsevier Science B.V.; 1999. p. 565–643.
11. Berendes S, Heywood P, Oliver S, Garner P. Quality of private and public ambulatory health care in low and middle income countries: systematic review of comparative studies. PLoS Med. 2011 Apr;8(4):e1000433.
12. Kanavos P, Das P, Durairaj V, Laing R, Abegunde DO. Options for financing and optimizing medicines in resource-poor countries [Internet]. 2010. Available from: http://www.who.int/healthsystems/topics/financing/healthreport/34Medicinesrev.pdf
13. Adam T, Hsu J, de Savigny D, Lavis JN, Røttingen J-A, Bennett S. Evaluating health systems strengthening interventions in low-income and middle-income countries: are we asking the right questions? Health Policy Plan. 2012 Oct;27 Suppl 4:iv9–19.
14. Gillström A, Wettermark B. Literature Review Cross-national comparison of DU activities [Internet]. 2011. Available from: http://www.pharmacoepi.org/pub/1c094bf0-2354-d714-513c-1bcc98255a3c
15. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf
16. Bergman U, Elmes P, Halse M, Halvorsen T, Hood H, Lunde PK, et al. The measurement of drug consumption. Drugs for diabetes in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol. 1975 Feb 28;8(2):83–9.
17. Bergman U. The history of the Drug Utilization Research Group in Europe. Pharmacoepidemiol Drug Saf. 2006 Feb;15(2):95–8.
18. Lee D, Bergman U. Studies of Drug Utilization. In: Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology. Oxford, UK: Wiley-Blackwell; 2012. p. 379–401.
19. Grímsson A, Idänpään-Heikkilä J, Lunde M, Olafsson O, Westerholm B. [Consumption of psychotropic drugs in Finland, Iceland, Norway and Sweden]. Nord Med. 1977 Feb;92(2):49–54.
20. Griffiths K, McDevitt DG, Andrew M, Baksaas I, Lunde PK, Bergman U, et al. Validation of observed differences in the utilization of antihypertensive and antidiabetic drugs in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol. 1985 Jan;29(1):1–8.
21. Wooldridge JM. Introductory econometrics. 4th ed. South Western CENGAGE learining; 2009.

22. Angrist JD, Pischke J-S. Mostly harmless econometrics: An empiricist's companion [Internet]. 2008. Available from: http://www.development.wne.uw.edu.pl/uploads/Main/recrut_econometrics.pdf

23. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299–309.

24. Cameron A, Ewen M, Auton M, Abegunde D. The World Medicines Situation 2011. Medicines prices, availability and affordability [Internet]. 2011. Available from: http://www.who.int/medicines/areas/policy/world_medicines_situation/WMS_ch6_wPricing_v6.pdf

25. World Health Organization. Atlas of eHealth country profiles: the use of eHealth in support of universal health coverage: based on the findings of the third global survey on eHealth 2015. [Internet]. 2015. Available from: http://apps.who.int/iris/bitstream/10665/204523/1/9789241565219_eng.pdf?ua=1

26. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014 Aug;14(8):742–50.

27. IMS Health [Internet]. [cited 2016 Feb 18]. Available from: http://www.imshealth.com/en

28. Ng M, Fullman N, Dieleman JL, Flaxman AD, Murray CJL, Lim SS. Effective coverage: a metric for monitoring Universal Health Coverage. PLoS Med. Public Library of Science; 2014 Sep 22;11(9):e1001730.

29. Homedes N, Ugalde A, Rovira Forns J. The World Bank, pharmaceutical policies and Health Reforms in Latin America. 2005.

30. The World Bank. Out-of-pocket health expenditure data (% of total expenditure on health) [Internet]. 2016 [cited 2016 May 13]. Available from: http://data.worldbank.org/indicator/SH.XPD.OOPC.TO.ZS

31. Dmytraczenko T, Almeida G. Toward Universal Health Coverage and Equity in Latin America and the Caribbean - The World Bank [Internet]. Dmytraczenko T, Almeida G, editors. Washington, D.C.; 2015. Available from: https://openknowledge.worldbank.org/bitstream/handle/10986/22026/9781464804540.pdf?sequence=2

32. Kaplan WA, Wirtz VJ, Stephens P, Barra AG, Albuquerque I, Sooksriwong C, et al. The Market Dynamics of Generic Medicines in the Private Sector of 19 Low and Middle Income Countries between 2001 and 2011: A Descriptive Time Series Analysis. Lexchin J, editor. PLoS One [Internet]. Public Library of Science; 2013 Sep 30 [cited 2016 Jul 17];8(9):e74399. Available from: http://dx.plos.org/10.1371/journal.pone.0074399

33. Stephens P, Ross-Degnan D, Wagner AK, Baghdadi G, Fikree F, Pasha O, et al. Does access to medicines differ by gender? Evidence from 15 low and middle income countries. Health Policy (New York). Elsevier; 2013 Apr;110(1):60–6.

34. Hoebert JM, Mantel-Teeuwisse AK, van Dijk L, Bijlsma JWJ, Leufkens HGM. Do rheumatoid arthritis patients have equal access to treatment with new medicines?: tumour necrosis factor-alpha inhibitors use in four European countries. Health Policy. Ireland; 2012 Jan;104(1):76–83.

35. Leopold C, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, et al. Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: interrupted time series analyses. Int J Equity Health. 2014;13:53.

36. Waning B, Kaplan W, Fox MP, Boyd-Boffa M, King AC, Lawrence DA, et al. Temporal trends in generic and brand prices of antiretroviral medicines procured with donor funds in developing countries. J Generic Med [Internet]. SAGE Publications; 2010 Apr [cited 2016 Jul 17];7(2):159–75. Available from: http://jgm.sagepub.com/lookup/doi/10.1057/jgm.2010.6

CHAPTER 2

CROSS-NATIONAL COMPARISONS IN DRUG UTILIZATION RESEARCH

CHAPTER 2.1

CROSS-NATIONAL COMPARISONS OF DRUG UTILIZATION - AN ANALYSIS OF DATA AND METHODOLOGICAL APPROACHES USED

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ABSTRACT

Background

2.1

Cross-national comparison of drug utilization (CNC DU) studies provide valuable information about medicines use in different countries and regions by examining patterns of prescribing, dispensing and consumption of medicines. Over the years, with different initiatives carried out mostly in Europe, the use of medicines has been compared using administrative databases. Still there is room for improvement in conducting these comparative studies, particularly in methods to make these comparisons fully reliable. A comprehensive overview of these comparisons might help to identify commonalities and differences in methodological approaches and provide the basis for future guidelines to improve the reporting of this type of studies.

Objective

To summarize the characteristics of CNC of drug utilization studies in terms of data and methodological approaches used to evaluate the use of medicines between countries

Methods

We searched CNC DU studies published between 2000 and 2015 assessing the use of medicines globally. in different geographical areas: Europe, Asia, Africa, Oceania and Americas. Complete texts of all potentially relevant articles were retrieved and scrutinized. For each article selected we extracted overall publication and CNC characteristics such as number of countries involved, therapeutic group(s) studied, number of years covered in the study and description of the time frame. We focused on databases description (level at which the data was generated (wholesaler, pharmacy records) and whether the primary objective of the data was administrative or no) and methodology used, e.g. units and terminology to describe exposure data. Data were analyzed descriptively.

Results

We retrieved 104 CNC DU studies. These studies included the comparison of use of medicines in 92 different countries, 40 of them from Europe, 28 from Asia, 13 from Americas, 9 from Africa and 2 from Oceania. Thirty-two studies compared 10 or more countries; 14 studies compared 4 countries and the maximum number of countries included in one comparison was 68. Twenty-eight studies were cross-sectional and 16 analyzed time periods of over 10 years. Most of the studies were descriptive (n=72) and the rest (n=32) were analytical. Twenty-three studies focused on the assessment of antibiotics use, followed by antihypertensives, anti-depressants, opioids and NSAIDs. Nearly half of the studies (n=56) based their analysis on only one type of database, while the other half based their analysis on data combinations. The unit of measurement most used (n=45) was the defined daily dose per 1,000 inhabitants per day (DDD/TID).

Conclusion

CNC of drug utilization studies have included countries from different regions of the world, although Europe was the continent where by far most of these studies have been conducted. However, the lack of reporting the databases characteristics might reduce the validity of the comparisons. IMS Health was the main information source in other continents where the availability of databases is lacking.

BACKGROUND

In 1969, the World Health Organization (WHO) organized its first meeting on Drug Consumption in Oslo, where the need for a common classification system of medicines and for a technical unit of comparison in drug utilization studies was discussed. This discussion formed the base for the later development of the Anatomical Therapeutic Chemical (ATC) classification system and the defined daily dose (DDD) as standard measurement of medicine use [1]. Since the beginning of Drug Utilization Research (DUR) it has been recognized that cross-national comparisons (CNC) of medicine use are important to identify potential problems on the rationality of prescription and use of medicines [1]. Some of the first studies of drug utilization research had the objective to assess the risks and benefits of medicines besides describing the trends of medicine use [1,2].

In Europe the initial drug utilization studies focused on assessing differences in drug utilization of antidiabetic agents, antihypertensives and psychotropic medication use between countries [3–5]. One specific aspect that challenges the comparison of drug utilization between countries is the difference in characteristics of (national) data sources used for these studies. Data characteristics such as coverage in population and coverage and codification of medicines, usually differ between data sources and countries. Therefore, to facilitate this type of comparison several methodological innovations have been created over the past years. These innovations include the development of the Anatomical Therapeutic Chemical (ATC) classification as an international classification system for medicines and the development of the defined daily dose (DDD) as a standard measure of drug use [1,2,6]. Additionally, there have been recent attempts to harmonize description of data sources and data validity to improve the quality of comparisons [7–9].

The aims of the CNC define the inclusion criteria of medicines in the analysis, and can influence the comparison itself. For example, when assessing the general use of medicines of a given therapeutic group, it is required to analyze a large selection of products in the whole pharmaceutical market this can challenge the selection of medicines under study because even when a medicine is available in each country, there may be differences in pharmacological strengths, pharmaceutical forms and package sizes.

The most comprehensive initiative to compare the use of medicines between countries was taken in the early 2000s with the creation of the European Surveillance of Antimicrobial Consumption (ESAC) project. The aim of the ESAC project was to collect data which were publicly available, comparable, and reliable on antibiotic use across Europe [10]. The results of the project highlighted the many challenges of comparing data sources and emphasized the need for methodological rigor to assure the validity of study design to conduct reliable CNCs [7].

Similar studies to the ESAC project were carried out by the Euro-Med-Stat-project supported by the European Union with the aim to describe the trends in utilization and prescribing of statins and other lipid lowering drugs in Europe by comparing data on statin utilization and expenditure from different administrative databases (mainly reimbursement data) with those from a commercial source (IMS Health) [8,11]. IMS Health is the main commercial data source in Europe and other continents, and it has been widely used in drug utilization research including CNC worldwide. Walley et al. found substantial differences between data

from different sources concluding that standards for data collection as well as the standardized application using the ATC/DDD methodology are urgently needed [8].

Apart from sales data, CNCs may also be conducted based on other data sources such as electronic medical records, disease based registries or questionnaires to physicians or patients. Such studies may be even more difficult to conduct since healthcare systems vary widely between countries [2].

In 2008, a structured CNC poster session was held in Copenhagen Denmark at the 24th International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE), presenting available data from more than 20 countries [12]. This was followed up in 2010, at the 26th ICPE in Brighton, United Kingdom where a workshop was arranged with the aim to explore and analyze various methodological issues in conducting CNC of drug consumption data. The discussions focused on database content and validity, classification and measurement of utilization units, expenditure units, and prescribing quality indicators in CNC [13]. Later on, during the 2011 ISPE/EuroDURG meeting in Antwerp, Belgium a poster session on CNC was organized and a literature review on CNC of Drug Utilization activities in Europe was published [14].

The efforts and initiatives mentioned above are examples of CNCs that have provided great experience to the field of drug utilization research. Nevertheless, there is still room for improvement in conducting these comparative studies, particularly in data assessment and methods. A comprehensive global overview of the methodological characteristics of these comparisons might help to identify commonalities and differences in methodological approaches and provide the basis for future guidelines to improve the reporting of this type of studies. Therefore, the objective of the present work was to summarize the characteristics of CNC of drug utilization studies in terms of data and methodological approach (descriptive or analytical) to evaluate the use of medicines between countries.

METHODS

Selection of studies

We searched studies assessing CNC of drug utilization among different geographical areas. Studies were included if they met all of the following criteria: (1) comparison of exposure data on volume between countries, and (2) comparison of at least two countries or regions (geographical areas with at least the number of inhabitants of the smallest European country) within different countries. Selected studies needed to have the intention to measure exposure at population level, either by using data from nation-wide level such as electronic medical records, administrative health care records or commercial databases or by analyzing data already collected for another purpose (secondary use of data) as proposed in the Guide on Methodological Standards in Pharmacoepidemiology by ENCePP 2013 [15].

The following types of studies were excluded: studies that compared data from individual hospitals, individual practices or nursing homes, case studies, case series, epidemiological-based studies collecting information from population surveys, qualitative studies, editorials and narrative reviews.

Search strategy

Electronic searches of PubMed/Medline and EMBASE were carried out in December 2015, including studies from 2000 onwards. We selected articles published in 2000 or thereafter to be able to compare and to add the results from two previous literature reviews in Europe and Latin America [14,16]. The search strategy included MeSH terms for Drug Utilization studies associated with each geographical area in the world. Searches were conducted separately for Europe, since most of the CNC studies were conducted only in European countries. A similar search was conducted for other regions of the world; Asia, Africa and Oceania were grouped together in one search key. For the American continent the same key search was applied but only for the period between November 2013 and December 2015, since a previous literature review covered the period from 2000 to November 2013 [16]. Details about the search keys can be found in the supplementary material.

We restricted the search to studies published in English, German, Spanish or French. Independently, two authors (YS and CD) screened all identified records to exclude clearly irrelevant citations and highlighted the relevant citations. Additionally, we screened the articles selected in two previous literature reviews [14,16] and added relevant citations that were not retrieved by our key search but by snowballing and experts recommendation. A modified flow chart from PRISMA guidelines with the detailed search flow can be seen in Figure 1.

Data extraction and analysis

Complete texts of all potentially relevant articles were retrieved and scrutinized. For each article selected we extracted overall publication and CNC characteristics. Since our overarching aim was to summarize the information available on CNC of drug utilization studies by describing the data sources and methodologies used in the existing studies, we summarized and described the following aspects of each study:

1) Search engine where each study was found (PubMed, EMBASE or both), 2) Number of countries involved in the CNC and if the comparison only covered European countries, 3) Name of the countries studied, 4) Kind of product(s) studied and the terminology used to describe them, 5) Number of years covered in the study and description of the time frame. With this information, we classified the studies as cross-sectional when they just reported the use of medicine in a specific point in time, and we classified studies as longitudinal when they analyzed more than two points in time, 6) Databases description: level at which the data was generated (for example: wholesaler, pharmacy records), whether the primary objective of the data was administrative or not, 7) Data coverage report, if the authors reported coverage related to the population and products that were covered, and 8) Methodological approach (descriptive or analytical) and units of analysis used.

Descriptive studies provide information about the amount of medicines used, analytical studies aim to explore factors that could explain the differences in the use of medicines [2]. We did not make any exclusion due to study quality, since quality assessment was out of the scope of this research.

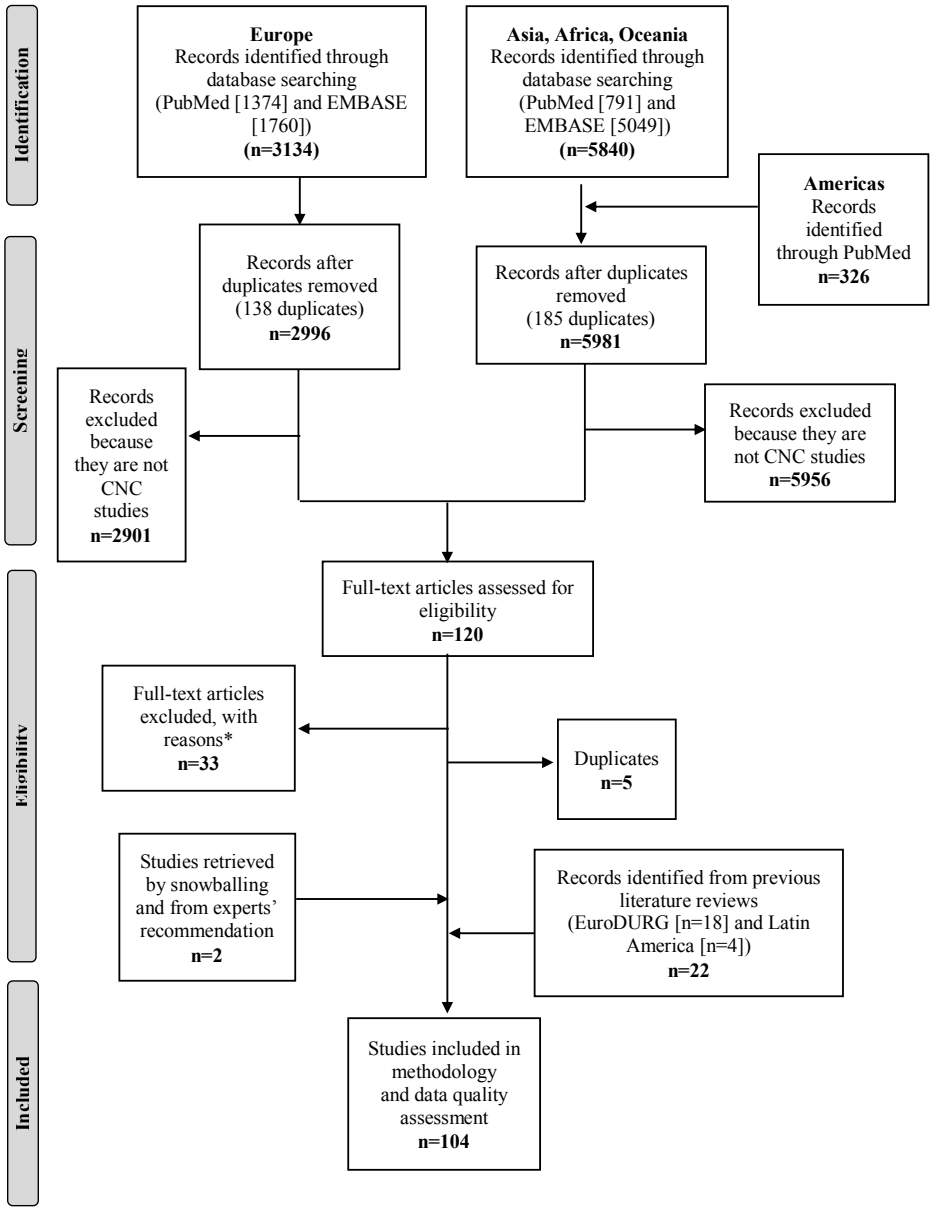

Figure 1. Literature search on cross-national comparison of drug utilization studies in the world. Flowchart of search and review process.

RESULTS

Characteristics of included studies

The search strategy resulted in the inclusion of 104 studies, see Figure 1. These studies included the comparison of use of medicines in 92 different countries, 40 of them from Europe, 28 from

Asia, 13 from the Americas, 9 from Africa and 2 from Oceania (Figure 2). The countries that were included in most of the studies were the United Kingdom (n=68), followed by the Netherlands and Germany in 49 studies each, Denmark (n=48) and Sweden (n=46). Among the countries most frequently included in CNC were also countries outside of Europe; the United States in 15 studies, Canada in 9 studies and Mexico in 7 studies. Asian and African countries such as China, Japan, Indonesia, South Africa, Egypt and Kenya were studied infrequently. Thirty-two studies compared 10 or more countries; 14 studies compared 4 countries and the maximum number of countries included in one comparison was 68.

Twenty-eight studies (27%) were cross-sectional and 16 (15%) analyzed time periods of over 10 years. All other studies (n=60, 58%) assessed data longitudinally, but over shorter time periods. Most of the studies were descriptive (n=72), the remaining (n=32) were analytical studies i.e. they explored factors that might explain patterns of medicines use. Twenty-three studies focused on the assessment of antibiotics use, 13 of these studies were derived from the ESAC project. Following antibiotics, the therapeutic groups that were most frequently studied were antihypertensives (n=7), anti-depressants (n=7), opioids (n=6) and NSAIDs (n=6). Other therapeutic groups studied in lower frequency were and anti-epileptics (n=4), proton pump inhibitors (n=3) and anti-psychotics (n=3).

Nearly half of the studies (n=56) based their analysis on only one type of database, while the other half base their analysis on data combinations. Outside of Europe, CNC studies mostly used IMS Health sales data in the American region; while in Asia and Africa researchers constructed the data with information of health facilities and patients. Fifty-six studies used one type of database in the analysis, 34 of them just in Europe, see Figure 3.

Figure 2. Density of countries included in cross-national comparison of drug utilization studies between 2000 and 2015.

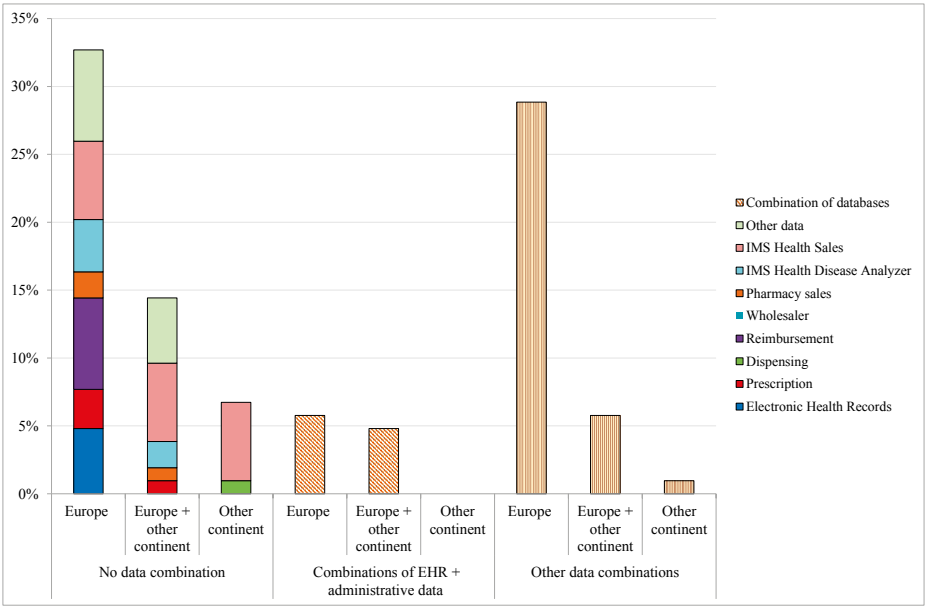

Figure 3. Percentage of studies with different combinations of data sources to compare the use of medicines between countries. We classified studies into those that just compare European countries, studies that compare European countries with countries from other continents, and studies that compare countries from continents other than Europe.

Most of the studies mentioned the data coverage (n=57), although some in more detail than others and 11 studies referred to another publication to consult databases characteristics, the rest did not mention coverage information or representativeness. The unit of measurement most used was the defined daily dose per 1,000 inhabitants per day (DDD/TID) (n=45), other units of measurement used were proportions (n=33). The rest of the studies (n=28 studies), used a variety of measures such as number units, number of prescriptions, milligrams, etc. The majority of the studies were descriptive (72 studies). All the studies selected are summarized in Table B in the supplementary data section.

DISCUSSION

Cross-national comparisons of drug utilization studies identified in this review showed different characteristics in their data sources and methodological approaches. These characteristics were summarized providing and overview of the current state of CNC studies globally. Most of the studies compared the use of medicines between European countries while only 7% of the studies compared the use of medicines in other countries of the world. The therapeutic group that was studied the most was the antibiotics, followed by medicines for cardiovascular diseases.

We found that although most of the studies report some details about coverage and representativeness of the data sources, still a big percentage of the studies (35%) do not report

these details, being this the major weakness in these studies. Without this information is difficult to determine the coverage in terms of population and medicines hampering the reliability of the comparisons between countries.

The understanding of data characteristics is paramount for the correct assessment of comparisons of medicine use between countries and regions. Although many studies documented the information about data sources used, some others just reported the database name or did not report the main objective of the data source.

In this review, we found that 46% of the studies compared the use of medicines between countries using data sources created with different purposes, such as the comparison between prescription and dispensing data. Prescription and dispensing datasets capture different levels of medicines consumption, for example the scenario where the patient pays directly for a prescribed medicine but this medicine is not covered by the insurance therefore is not reimbursed, or the scenario where the patient gets a prescription but decides not to get the medicine Therefore, it is necessary to interpret the results of each CNC taking into account these differences.

In Europe, most of the CNC studies were conducted using prescription and reimbursement databases. In some well-developed countries such as Denmark, Sweden and Norway, it is possible to link different data sources such as electronic health records, prescription data and dispensing data. These links make possible the assessment of population characteristics facilitating the assessment of factors that could explain the differences in the use of medicines [17].

In most of the low and middle income countries, the availability of data sources is inadequate [18] contrary to high income countries where as mentioned above administrative data sources contain data on prescription, dispensing and reimbursement allowing the study of use of medicines [9]. CNC studies that compared countries outside of Europe used IMS Health sales data and samples from health care facilities. Regions, such as Latin America, used primary data or IMS Health data. IMS Health collects data from multiple sources of information along the medicines supply chain, for example manufacturers, wholesalers, and community pharmacies [19].

Independently of the income level of each country, data sources have to be fully understood and reported in terms of coverage both at population and drug level. When comparing data sources from different countries, it is necessary to take into account the health system structure of each country. It should be clarified if the data comes from public or private insurer and their corresponding representativeness in each of the countries in the comparison. Previous initiatives have been carried out to summarize the data sources available to conduct pharmacoepidiemiological and drug utilization studies. The PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) project compiled and yearly updated information on nationwide administrative databases that collect drug consumption data and until February 2015. This compilation can be very useful to explain the results of CNC studies providing information on data coverage. In the PROTECT project, different data sources were used to develop methodological standards and innovative tools to strengthen the monitoring of the benefit/risk profile of medicines in Europe and to increase early detection and assessment of adverse drug reactions [20].

This review summarizes the main characteristics of CNC of drug utilization studies from 2000 onwards. Despite the recent increase in studies outside of Europe, the CNC of drug utilization in Africa, Asia, Oceania and Americas remains extremely limited. One of our main obstacles of the key search used, was the inability to retrieve all the articles from Europe that were found in a previous literature review [14], these articles (18) were added during the final step of the selection process in addition to two studies retrieved by snowballing. Therefore, we are expecting that some CNC studies conducted during the years covered in this review were not reached. However, the results found give an overview on the existent state of CNC studies.

As countries gradually adopt and implement new regular data collection over coming years, it is imperative that drug utilization studies document the data characteristics in terms of population and drug coverage, to facilitate interpretation of use of medicines between countries.

To improve the knowledge generated with CNC of drug utilization studies, collaboration between countries could be very important. First, to homogenize data coding, and second, to exchange experiences in data collection. Multi-country exercises should help to improve and standardize reporting and tools for comprehensive regular data collection.

CONCLUSION

CNC of drug utilization studies have included countries from different regions of the world, although Europe was the continent where by far most of these studies have been conducted. This is mostly due to the high availability of databases to study and compare the use of medicines across European countries. However, the lack of reporting the databases characteristics might reduce the validity of the comparisons. IMS Health was the main information source in other continents where the availability of databases is lacking. The present work highlights the need for better guidance on conduct and reporting of CNCs to set a base for their correct assessment.

REFERENCES

1. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf
2. Elseviers M, Wettermark B, Almarsdottir AB, Andersen M, Benko R, Bennie M, et al. Drug Utilization Research: Methods and Applications. Wiley-Blackwell; 2016. 568 p.
3. Bergman U, Elmes P, Halse M, Halvorsen T, Hood H, Lunde PK, et al. The measurement of drug consumption. Drugs for diabetes in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol. 1975 Feb 28;8(2):83–9.
4. Grímsson A, Idänpään-Heikkilä J, Lunde M, Olafsson O, Westerholm B. [Consumption of psychotropic drugs in Finland, Iceland, Norway and Sweden]. Nord Med. 1977 Feb;92(2):49–54.
5. Griffiths K, McDevitt DG, Andrew M, Baksaas I, Lunde PK, Bergman U, et al. Validation of observed differences in the utilization of antihypertensive and antidiabetic drugs in Northern Ireland, Norway and Sweden. Eur J Clin Pharmacol. 1985 Jan;29(1):1–8.
6. World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD Index [Internet]. 2012. 2012. Available from: http://www.whocc.no/atc_ddd_index/
7. Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. Br J Clin Pharmacol. 2004 Oct;58(4):419–28.
8. Walley T, Folino-Gallo P, Schwabe U, Van Ganse E, Stephens P. Comparison of national administrative and commercial databases to monitor expenditure and costs of statins across Europe. Eur J Clin Pharmcol. 2004 Sep;60(7):503–11.
9. Ferrer P, Ballarín E, Sabaté M, Rottenkolber M, Amelio J, Hasford J, et al. Drug Consumption Databases in Europe. Available from: http://www.imi-protect.eu/documents/DUinventoryFeb2015.pdf
10. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579–87.
11. The EURO-MED-STAT Group. EURO-MED-STAT: monitoring expenditure and utilization of medicinal products in the European Union countries: a public health approach. Eur J Public Health. 2003 Sep;13(3 Suppl):95–100.
12. Abstracts of the 24th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Pharmacoepidemiol Drug Saf. 2008 Aug;17(S1):S1–294.
13. Abstracts of the 26th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, 19-22 August 2010, Brighton, UK. Pharmacoepidemiol Drug Saf. John Wiley & Sons, Ltd.; 2010 Aug;19(S1):S1–347.
14. Gillström A, Wettermark B. Literature Review Cross-national comparison of DU activities [Internet]. 2011. Available from: http://www.pharmacoepi.org/pub/1c094bf0-2354-d714-513c-1bcc98255a3c
15. European Medicines Agency. Guide on Methodological Standards in Pharmacoepidemiology [Internet]. 2010. Available from: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideMethStandardsPE_Rev3.pdf
16. Durán CE, Christiaens T, Acosta Á, Vander Stichele RH, Acosta A, Vander Stichele RH. Systematic review of Cross-National Drug Utilization Studies in Latin America: methods and comparability. PDS. 2015 Jan;25(1):16–25.
17. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. Denmark; 2010 Feb;106(2):86–94.
18. Bachhav SS, Kshirsagar NA. Systematic review of drug utilization studies & the use of the drug classification system in the WHO-SEARO Region. Indian J Med Res. Medknow Publications; 2015 Aug;142(2):120–9.
19. IMS Health. IMS The Uniform System of Classification [Internet]. 2008 [cited 2014 Oct 3]. Available from: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Health Services Research Network/USC_Classiification_Process_2011.pdf
20. Drug Consumption Databases in Europe. http://www.imi-protect.eu/documents/DUinventory_October2012_MASTER.pdf. Barcelona; 2013.

SUPPLEMENTARY MATERIALS

Search key for Europe:

("Databases, Factual"[Mesh] OR "Electronic Health Records"[Mesh] OR "International Agencies/statistics and numerical data"[Mesh] OR "Registries/statistics and numerical data"[Mesh] OR "Commerce/statistics and numerical data"[Mesh] OR "Reimbursement, Incentive/statistics and numerical data"[Mesh] OR "Cross-Cultural Comparison"[Mesh] OR (("international" [All Fields] OR "cross-national" [All Fields] OR "cross-country"[All Fields]) AND Compar*)) AND ("Europe"[Mesh] OR "European Union"[Mesh]) AND ("Drug Utilization"[Mesh] OR "Pharmacoepidemiology"[Mesh] OR "Drug Prescriptions"[Mesh] OR "Drug Therapy, Combination"[Mesh] OR "Drug Therapy, Computer-Assisted"[Mesh] OR "Inappropriate Prescribing"[Mesh] OR "Self Medication"[Mesh] OR "Polypharmacy"[Mesh] OR "Pharmaceutical Preparations/statistics and numerical data"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical Preparations/utilization"[Mesh] OR "Drug Combinations"[Mesh] OR "Drugs, Essential"[Mesh] OR "Drugs, Generic"[Mesh] OR "Nonprescription Drugs"[Mesh] OR "Prescription Drugs"[Mesh])

Time frame: January 2000 – December 2015

Search key for Africa, Asia and Oceania

("Databases, Factual"[Mesh] OR "Electronic Health Records"[Mesh] OR "International Agencies/statistics and numerical data"[Mesh] OR "Registries/statistics and numerical data"[Mesh] OR "Commerce/statistics and numerical data"[Mesh] OR "Reimbursement, Incentive/statistics and numerical data"[Mesh] OR "Cross-Cultural Comparison"[Mesh] OR (("international" [All Fields] OR "cross-national" [All Fields] OR "cross-country"[All Fields]) AND Compar*)) AND ("Africa"[Mesh] OR "Asia"[Mesh] OR "Oceania"[Mesh]) AND ("Drug Utilization"[Mesh] OR "Pharmacoepidemiology"[Mesh] OR "Drug Prescriptions"[Mesh] OR "Drug Therapy, Combination"[Mesh] OR "Drug Therapy, Computer-Assisted"[Mesh] OR "Inappropriate Prescribing"[Mesh] OR "Self Medication"[Mesh] OR "Polypharmacy"[Mesh] OR "Pharmaceutical Preparations/statistics and numerical data"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical Preparations/utilization"[Mesh] OR "Drug Combinations"[Mesh] OR "Drugs, Essential"[Mesh] OR "Drugs, Generic"[Mesh] OR "Nonprescription Drugs"[Mesh] OR "Prescription Drugs"[Mesh])

Time frame: January 2000 – December 2015

Search key for the Americas:

("Databases, Factual"[Mesh] OR "Electronic Health Records"[Mesh] OR "International Agencies/statistics and numerical data"[Mesh] OR "Registries/statistics and numerical data"[Mesh] OR "Commerce/statistics and numerical data"[Mesh] OR "Reimbursement, Incentive/statistics and numerical data"[Mesh] OR "Cross-Cultural Comparison"[Mesh] OR (("international" [All Fields] OR "cross-national" [All Fields] OR "cross-country"[All Fields]) AND Compar*)) AND

("Americas"[Mesh]) AND ("Drug Utilization"[Mesh] OR "Pharmacoepidemiology"[Mesh] OR "Drug Prescriptions"[Mesh] OR "Drug Therapy, Combination"[Mesh] OR "Drug Therapy, Computer-Assisted"[Mesh] OR "Inappropriate Prescribing"[Mesh] OR "Self Medication"[Mesh] OR "Polypharmacy"[Mesh] OR "Pharmaceutical Preparations/statistics and numerical data"[Mesh] OR "Pharmaceutical preparations/therapeutic use"[Mesh] OR "Pharmaceutical Preparations/utilization"[Mesh] OR "Drug Combinations"[Mesh] OR "Drugs, Essential"[Mesh] OR "Drugs, Generic"[Mesh] OR "Nonprescription Drugs"[Mesh] OR "Prescription Drugs"[Mesh])

Time frame: November 2013 – December 2015

Table A. Studies excluded with reasons for exclusion *

Number of articles	Reasons for exclusion
1	Article in Italian with abstract in English.
1	Full text not available.
1	Description of datasets for the ESAC studies, drug utilization not studied.
3	No CNC study.
1	Commentary.
6	Unclear representativeness of data.
4	Comparison of small regions of Europe.
2	Not addressing drug utilization.
4	Sample data source and methods not explained.
7	CNC studies analyzing data from one country and comparing the results from other countries reported in other sources of information.
5	Conference abstracts

Table B. Selected articles and characteristics

Num.	PMID	Authors Year	Number of countries involved	Kind of products
1	16236045	Walley T, et al. 2005	13	Statins
2	18162422	Hamunen K, et al. 2008	7	Opiods
3	19453723	Eurap Study Group.2009	38	Antiepileptic drugs
4	19091608	Hamunen K, et al. 2009	5	Opiods
5	20691035	Zahl P-H, et al. 2010	4	SSRI, TCA
6	21682002	De Natale R, et al. 2011	5	Glaucoma: prostaglandin analog (PGA) and b-blocker (BB) and other monotherapy antigalucoma medicines
7	21923448	Parkin L, et al. 2011	2	Antibiotics, antiasthmatics, proton pump inhibitors, statins, oral hypoglycemics, antidepressants, antipsychotics, ADHD drugs
8	21564162	Sen EF, et al. 2011	2	Cough and cold medicines
9	20860726	Zoega H, et al. 2011	5	ADHD
10	22079753	Hoebert JM, et al. 2012	4	TNF-alfa inhibitors
11	21792563	Ponizovsky AM, et al. 2012	2	Opioids
12	23018106	Benchimol EI, et al. 2013	4	Inflammatory bowel disease-related medication
13	23114457	Clay E, et al. 2013	9	Benzodiazepines and benzodiazepine receptor agonists
14	23608219	Kostev K, et al. 2013	2	Insulin
15	24252465	Valkhoff VE, et al. 2013	4	NSAIDs
16	23775052	Wilby KJ, et al. 2013	4	Antidepressants
17	24575970	de Groot MCH, et al. 2014	5	Antiepileptic
18	24997585	Holstiege J, et al. 2014	5	Systemic antibiotics
19	24657114	Versporten A, et al. 2014	17	Antibiotics

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
1997-2003	DDD/TID	Descriptive		7				5	1			
2002	DDD/TID	Descriptive						6			1	
1999-2005	Other	Descriptive										32
2002-2006	DDD/TID	Descriptive						4			1	
1975-2006	DDD/TID	Descriptive						4				
1995-2006	Proportion	Descriptive		1					5			
2004-2006	Proportion	Descriptive		2								
2005-2008	Proportion	Descriptive	2									
2007	Proportion	Descriptive		4				1				1
2003-2007	DDD/TID	Descriptive			1	2	1	1		2		
2000-2008	DDD/TID	Descriptive				1		1				
2004-2009	Proportion	Descriptive	2	1		1						
2005-2011	Other	Descriptive								9		
2005-2010	Proportion	Analytic							2			
1999-2011	Other	Descriptive		3				2			1	
2007-2011	Other	Descriptive								4		
2001-2009	Other	Analytic	1	2							3	
2005-2008	Other	Analytic	1		1	3						
2011	DDD/TID	Descriptive							17			

Table 2. (continued)

Num	PMID	Authors Year	Number of countries involved	Kind of products
20	12086284	Christiaens TCM, et al. 2002	2	Antibiotics
21	12069022	Molstad S, et al. 2002	15	Antibiotics
22	14533757	EURO-Med-Stat Group. 2003	15	Lipid reducing agents
23	15128388	Alonso J, et al. 2004	6	Psychotropic drugs
24	15316702	Walley T, et al. 2004	14	Statins
25	15920930	De Conno F, et al. 2005	9	Opiods
26	15708101	Goossens H, et al. 2005	26	Antibiotics
27	15640272	Hjardem E, et al. 2005	2	Biological drugs for rheumatoids arthritis
28	17086563	Arellano FM, et al. 2006	2	Cox 2, NSAIDs
29	16735414	Ferech M, et al. 2006	34	Antibiotics
30	16865360	Melander A, et al. 2006	10	Anihypergicaemic drugs
31	16988753	Stolk P, et al. 2006	6	Antihypertensive
32	16698845	Vander Stichele RH, et al. 2006	15	Antibiotics
33	17366456	Goossens H, et al. 2007	28	Antibiotics
34	18164600	Bauer M, et al. 2008	12	Antidepressants
35	18538009	Deschepper R, et al. 2008	24	Antibiotics
36	18091761	Haynes K, et al. 2008	2	Digoxin
37	18155900	Kos M, et al. 2008	8	Oncology
38	18160392	Rosman S, et al. 2008	2	URTI medications

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
1997	DDD/TID	Descriptive	2					2				
1994 and 1997	Other	Descriptive		2					11			
2002	DDD/TID	Descriptive		1				4			1	
2001-2003	Proportion	Analytic										6
2000	DDD/TID	Descriptive				14				12		
2001-2003	DDD/TID	Descriptive								8		
1997-2002	DDD/TID	Descriptive		1		1	4	9			1	1
200-2003	Proportion	Descriptive									2	
1995-2004	Other	Analytic						1			1	
2003	DDD/TID	Descriptive			1	1	4	9			3	7
1994-2003	DDD/TID	Descriptive					1	9				
2003	DDD/TID	Descriptive				2	2	2				
1997-2002	DDD/TID	Descriptive		1		3	2	6			2	1
2004	DDD/TID	Descriptive			1	1	4	9	1		1	2
2004-2005	Proportion	Analytic									12	
2004	Other	Analytic			1	1	2	9			3	2
1991-2004	Other	Descriptive	1			1						
2001-2005	Other	Analytic								8		
2003	Other	Analytic	2									

Table 2. (continued)

Num	PMID	Authors Year	Number of countries involved	Kind of products
39	18489520	Stolk P, et al. 2008	9	Clopidogrel
40	19029175	Sturkenboom MCJM, et al. 2008	3	Various (Check comments sections for full list)
41	16715536	Zito JM, et al. 2006	4	Antidepressant
42	18817536	Zito JM, et al. 2008	3	Psiychotropic
43	19052566	Balkrishnan R, et al. 2009	5	Angiotensin receptor blockers
44	19249102	Bramness JG, et al. 2009	3	Lithium
45	19222726	Elseviers M, et al. 2009	5	Phosphate binders
46	19621220	Ravera S, et al. 2009	12	Fequently used medicinal products with a known potential to increase the risk of road traffic accidents
47	20003427	Stolk P, et al. 2009	6	Orphan drugs
48	21155704	Godman B, et al. 2010	18	proton pump inhibitors and statins
49	20014174	Inotai A, et al. 2010	6	NSAIDS
50	20451614	Neubert A, et al. 2010	3	Analgesics and NSAIDs
51	20847018	Strang J, et al. 2010	2	Methadone
52	21622674	Adriaenssens N, et al. 2011	16	Antivirals
53	21182150	Coloma PM, et al. 2011	4	NSAIDs
54	21107828	Mijatović V, et al. 2011	3	NSAIDs
55	20811908	Sen EF, et al. 2011	3	Asthma
56	21378066	Svendsen K, et al. 2011	4	Opioids

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
1998-2005	DDD/TID	Descriptive			4	5						
2000-2005	Other	Descriptive	3									
2000	Other	Analytic	2		1	1						
2000	Other	Analytic	1		1	1						
2005-2006	Other	Descriptive							5			
2005-2006	DDD/TID	Descriptive		3								
2002-2007	Proportion	Descriptive									5	
2000-2005	DDD/TID	Descriptive		2		1	3	4				2
2000 - 2006 (November)	DDD/TID	Analytic	1		3	2						
2001-2007	Proportion	Descriptive				18						
2002 - 2007	DDD/TID	Descriptive								6		
2000-2005	Proportion	Analytic	2						1			
1993-2008	Other	Descriptive		2								
2008	DDD/TID	Descriptive			1	5		7			1	2
1998-2007 (time frames dependent on databases used)	Proportion	Analytic	3		3							
2005-2008	DDD/TID	Descriptive			1		2					
2000-2005	Other		2					1				
2002	DDD/TID	Descriptive		1	1		1				1	

Table 2. (continued)

Num	PMID	Authors Year	Number of countries involved	Kind of products
57	21831028	Vončina L, et al. 2011	6	renin-angiotensin
58	21235461	Zarb P, et al. 2011	17	Antibiotics
59	22833612	Ng-Mak DS, et al. 2012	3	Triptans
60	22928490	Valkhoff VE, et al. 2012	3	NSAIDs, coxibs and gastroprotective agents, rofecoxib
61	22706960	Filippini M, et al. 2013	21	
62	23397325	Holstiege J, et al. 2013	5	Antibiotics
63	22941408	Piccinni C, et al. 2013	2	Antiarrytmic
64	24278396	Raschi E, et al. 2013	12	Antipyschotics
65	24793010	Abbing-Karahagopian V, et al. 2014	5	Antidepressants
66	25300384	Chevalier P, et al. 2014	2	Opioids
67	.	Godman B, et al. 2014	4	Risperidone
68	25062657	Leopold C, et al. 2014	2	Antipsychotic
69	24322966	Malo S, et al. 2014	2	Antibiotics
70	25339902	et al. 2014	7	Losartan
71	25785934	Poluzzi E, et al. 2015	13	Antihistamines
72	12207637	De Ponti F, et al. 2002	7	Non-antiarrhytimic drugs
73	14962875	Walley T. 2004	14	Statins
74	15762983	Fretheim A, et al. 2005	10	Antihypertensives
75	16735416	Coenen S, et al. 2006	25	Antibiotics
76	16735415	Ferech M, et al 2006	25	Antibiotics

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
2001-2007	DDD/TID	Descriptive				6						
2003	Other	Descriptive									17	
2006 -2008	Other	Descriptive							3			
Cohort	Proportion	Analytic		3								
1997-2007	Other	Analytic			1	1	3	7				
2005-2008	Proportion	Descriptive	1		1	3						
2009-2011	DDD/TID	Analytic		2								
2005-2010	DDD/TID	Descriptive									12	
2001-2009	Proportion	Analytic	5									
2008-2012	Other	Descriptive		1					1			
2005-2011	DDD/TID	Analytic				4						
2007-2011	Other	Analytic							2			
2010	DDD/TID	Descriptive		1	1							
2 years before and after generic losartan (country dependent)	Proportion	Analytic				7						
2005-2009/2010	DDD/TID	Analytic				13						
1998	DDD/TID	Descriptive						7				
2000	DDD/TID	Descriptive				14						
2000	DDD/TID	Descriptive								1		
1997-2003	DDD/TID	Descriptive			1	1	3	8				3
1997-2003	DDD/TID	Descriptive			1	1	3	8			1	2

Table 2. (continued)

Num	PMID	Authors Year	Number of countries involved	Kind of products
77	18329721	Demyttenaere K, et al. 2008	6	Antidepressants and benzodiazepines
78	18097697	Jönsson B, et al. 2008	30	Rheumatoid arthritis
79	20110034	Obradovic M, et al. 2009	8	Oncologics
80	19505202	Paradis PE, et al. 2009	4	Topiramate
81	19076158	Raschi E, et al. 2009	14	Antibiotics
82	20142264	Adriaenssens N, et al. 2010	20	Antimycotics and antifungals
83	19817815	Hsia Y, et al. 2010	3	Antiepileptic
84	20203082	Kemp A, et al. 2010	7	Non a specific group
85	20222132	Rosa MM, et al. 2010	26	Antipakinsonian NMDA antagonists MAO inhibitors Levodopa derivate Dopamine agonists Comtinhibitors Anticholinergics
86	21833180	Godman B, et al. 2011	19	PPIs and statins.
87	21440221	Montes J-M. 2011	4	Ziprasidone
88	21689139	Neubert A, et al. 2011	8	Anti-diabetic
89	21573227	Wells WA, et al. 2011	10	Tuberculosis
90	25807553	Duber HC, et al. 2015	3	Antiretrovirals
91	11934139	Diop AH, et al. 2002	3	Tuberculosis
92	21318025	Fix BV, et al. 2011	3	Anti smoking
93	23559528	Tett SE, et al. 2013	2	Gastroprotective
94	25706152	Rottenkolber M, et al. 2015	5	long-acting beta-2-agonists

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
2001-2003	Proportion	Analytic									6	
2000-2006	Other	Descriptive								3		
1997 - 2007	Proportion	Descriptive						2		6		
1998-2008	Proportion	Analytic								4		
1998 and 2005	DDD/TID	Descriptive			1	7		5		1		
2005 -2007	DDD/TID	Descriptive			1	6	2	8			1	2
2001-2005	Proportion	Analytic	1	1					1			
2007	Proportion	Descriptive									7	
2003-2007	DDD/TID	Descriptive								26		
2001-2007	Proportion	Descriptive		5		8						6
Unclear	Proportion	Descriptive									4	
2008	Proportion	Descriptive		7					1			
	Proportion	Descriptive								1		
2007-2008	Proportion	Descriptive									3	
2011-2012												
1996	Other	Descriptive									3	
2006 - 2008	Proportion	Descriptive									3	
2001 -2005	DDD/TID				2							
2002-2009	Proportion			4	2	1						

Table 2. (continued)

2.1

Num	PMID	Authors Year	Number of countries involved	Kind of products
95	25660252	Kim SC, et al. 2015	3	Osteoporosis medications
96		Santa-Ana-Tellez Y, et al. 2014	2	Antibiotics
97		Wilby KJ, et al. 2013	4	Antidepresants
98		Verstappen SM, et al. 2015	4	Reumathoid Arthritis treatment
99	24146761	Santa-Ana-Tellez Y, et al. 2013	2	Antibiotics (J01)
100	23551290	Wirtz VJ, et al. 2013	4	Antibiotics (J01)
101	23379471	Wirtz VJ, et al. 2013	8	Antibiotics (J01)
102	20414511	Wirtz VJ, et al. 2010	8	Antibiotics (J01)
103	24098644	Kaplan WA, et al. 2013	19	Not specified in text. Specified in appendix
104	25022435	Van Boeckel et al. 2014	68	Antibiotics (no ATC)

Time frame	Unit of analysis	Descriptive or analytic	EHR	Prescription	Dispensing	Reimbursement	Wholesaler	Pharmacy sales	IMS Health analyzer	IMS Health sales	Other	Unclear
2004 -2012	Proportion	Descriptive	1		1	2						
2007-2012	DDD/TID	Analytic								2		
2007-2011	Other	Descriptive								4		
Unknown	Proportion	Descriptive									4	
2007-2012	DDD/TID	Analytic								2		
1995 - 2009	DDD/TID	Analytic								4		
1999 - 2009	DDD/TID	Descriptive								8		
1997 - 2007	DDD/TID	Descriptive								8		
2001 -2011	Proportion									19		
2000-2010	Other	Descriptive								68		

CHAPTER 2.2

DEVELOPMENT OF A CHECKLIST TO EVALUATE CROSS-NATIONAL COMPARISONS OF DRUG UTILIZATION STUDIES

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ABSTRACT

Cross-national comparisons of drug utilization (CNC DU) studies provide valuable information about the use of medicines in different countries, but methods for the comparability between data sources of different countries has not been extensively reported. A checklist to evaluate and review cross-national comparisons of drug utilization (CNC DU) studies was therefore developed based on a literature search of this type of publications and previous publications about CNC DU assessment. The checklist addresses the main potential comparability problems in CNC DU studies in a systematic manner by facilitating the identification and extraction of relevant information related to data sources and methods from CNC DU studies. Hence, with the information extracted, the validity of the comparisons can be assessed taking into account the potential comparability problems in terminology, units of measure, population coverage and drug coverage between data sources used in a CNC DU study. The developed checklist will serve as a basis to develop good practice guidelines for designing, conducting, analyzing and reporting CNC DU studies.

INTRODUCTION

Cross-national comparisons of drug utilization (CNC DU) studies provide valuable information about the use of medicines in different countries. Besides, these studies are useful to explore differences in the exposure to medicines in relation to specific outcomes. In addition, they may help to optimize pharmaceutical policies to improve medicines use in the community [1].

The availability and quality of data on medicines use at country level has improved as a consequence of new methods of data collection. This provides more opportunities to conduct CNC DU studies. Although CNC DU research has been ongoing for several decades, a consensus on good practices to conduct these types of studies has not been reached. Some of the previous studies in drug utilization research have proposed assessment checklists directed at population based administrative claims data [2]. A checklist could facilitate the validity assessment of national data collection systems for international comparisons. However, a standard and generally applicable checklist for evaluation, implementation and report of CNC DU has yet to be developed. The proposed checklist has to take into account a broad array of data sources from different settings and could serve as the basis for good practice recommendations to conduct CNC DU studies. Furthermore, the checklist could provide guidance in the development and standardization of methods used in CNC DU studies and could increase the usefulness of these studies in the policy decision- making process.

OBJECTIVE

The primary aim of this work is to develop a checklist to assess the validity of cross-national comparison of drug utilization (CNC DU) studies intended to estimate exposure to medication on a population-based level and to guide the reporting of these studies.

METHODS

A review checklist was developed to facilitate the validity assessment of CNC DU studies and to guide the reporting of their results. The development of this checklist comprised six steps: 1) development of the first draft of the checklist; 2) first pilot testing of the checklist with subsequent revision; 3) second pilot testing; 4) checklist adjustment; 5) third pilot and final revision; 6) test for external validity. These steps will be described in detail below:

Development of the first draft of the checklist

A working group of experts ('Working Group' called from here on) from IMI-PROTECT (The Initiative Medicines Initiative - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium), EuroDURG (European Drug Utilization Group), Heymans Institut of Pharmacology, University of Ghent, the Boston WHO Collaborating Centre in Pharmaceutical Policy, and the Utrecht WHO Collaborating Centre for Pharmaceutical Policy and Regulation, searched for and examined previous articles that addressed the comparability of CNC DU studies [3]. Among the literature reviewed was a study by Durán et al, which used a checklist to assess the comparability of CNC DU in Latin America [4]. This checklist for the assessment of Latin American studies was based on two previously developed checklists:

i) one developed by Gillstrom et al. for a literature review on CNC of DU activities in Europe presented at the ISPE/EuroDURG meeting in Antwerp, Belgium 2011 [5], and ii) another checklist used for assessing the database characteristics and data validity which was adapted from the methodological checklist of the ESAC project [2].

The checklist designed by Durán et al, consisted of 34 items stratified in six domains, namely: general data (six items), study design and population (five items), data description (five items) and data validity (five and eleven items, respectively), drugs terminology and units of measure (five items), and limitations (two items). The Working Group decided to adapt the Durán et al checklist and added four more items to improve the general description of the research articles: 1) unique identifier number used in PubMed (PMID), 2) therapeutic group(s) studied, 3) description of the study design, and 4) description of the time frame. For further detail consult Table A in the supplementary material.

First pilot testing of the checklist and subsequent revision

The developed checklist was pilot tested using five randomly selected CNC DU articles retrieved from a literature review of CNC DU in Europe [3]. Four members of the Working group carried out the pilot test: ME, VW, LI and YS. Details of the research articles used in this first pilot can be found in Table B in the supplementary material.

Comments regarding ease of reading and flow of items on the checklist were provided and minor changes to some items and the checklist layout were made to increase face validity. The Working Group added instructions for using the checklist to ensure correct application. Close-ended items were also added to the checklist. An option of inability to answer the items due to lack of information in the research article or inability to give an answer was added to avoid non-response bias.

Second pilot testing and revisions of the checklist

Ten reviewers tested the subsequently revised checklist with 38 items stratified in the same domains used by Durán et al. Twenty randomly selected articles of CNC DU from the already mentioned literature review were scored (Supplemental material Table C). Each article was reviewed and scored by at least two reviewers in this second pilot phase. Each researcher assessed three to four research articles and the percentage of agreement per section was calculated.

This second pilot showed moderate agreement between reviewers (Supplemental material Table D). The following potential reasons for the moderate agreement were identified: i) lack of enough detail in the instructions to score each item, ii) lack of a glossary, ii) lack of ability to score all items for each data source separately in case multiple data sources were used within one study. Therefore, the Working Group decided to extensively modify the checklist.

Checklist adjustment

The checklist was modified by four of the reviewers (RVS, CD, ME and YS) who expanded it to 67 items divided in six domains: general data, study design, drug terminology and units, population coverage, drug coverage, and overall evaluation. During this stage, items in each

domain were modified to facilitate the ability to score each data source contained in each research article. Instructions were modified in accordance to the added items and domain stratification and a short glossary was added to ease the assessment.

Third pilot and revision of the checklist

The Working Group tested the checklist once more. In this stage, five research articles were analyzed, and five different researchers reviewed each article (Table E, supplementary material). The Working Group discussed the results and made final revisions and adjustments. Agreements on terminology were made during a face-to-face meeting, and the checklist was shortened to 50 items to avoid redundancy and strengthen the content validity. The instructions were improved regarding readability, clarity, and ease of use. After these modifications, the checklist was sent out for external revision.

External validity

To test the clarity and external validity of the checklist, researchers in the drug utilization field who did not participate in the checklist development will review it.

RESULTS

Inter-rater agreement for each pilot is reported in the supplementary material (Tables D, F1-F6). Areas where the agreement was low were discussed and an additional explanation in the user guide was written down.

The final version of the checklist is described below. The checklist is structured in six domains and can be completed in an Excel file. Each domain is displayed in a different spreadsheet with dropdown menus that contain the possible answers for each question.

I. **General data.** The purpose of the first section is to register the general characteristics of the research article. These include: main author and background (academia or industry), year of publication and (number of) countries involved in the comparison. In this section information of the data sources used for each country or region included in the study is also captured.

It is important that the information is captured separately for each data source because in some studies different data sources from the same country have been utilized. See Table 1 for further details.

II. **Study design.** The second section aims to register the type of study design (cross-sectional, longitudinal dynamic/open cohort, longitudinal closed cohort, cohort study with outcome, intervention study), the population studied (general population, age group specific, gender specific or disease specific population), the geographical level of analysis, i.e. national, regional or local (city) and time range of the study. This section aims to help the reviewer to understand how well the analyses can be generalized to a wider population. This is important since any difference between the study population and wider population should

be reported to be able to judge the representativeness of the results. Tables 2a and 2b show in detail the items and possible answers for this section.

III. **Terminology and units.** This section aims to register the terminology used in the study, the therapeutic group(s) or medicine(s) that were compared, and units applied to quantify the outcomes. The use of a standardized methodology is important to be able to compare the use of medicines in different countries and data sources. The terminology most commonly used in drug utilization research are: Anatomical Therapeutic Chemical (ATC) classification, the European Pharmaceutical Market Research Association (EPhMRA) classification, medicine name, RxNorm, Snomed, etc. The information should be indexed in the checklist through the use of ATC terminology for all the studies, including those that applied a different terminology than the ATC classification. Table 3 shows in detail the items contained in this section. In this domain of the checklist one potential comparability problem is assessed:

   i. Potential comparability problem due to terminology and measurement units assignment: A potential comparability problem might be present when there are problems in terminology and assignment of measurement units in the data set, for example errors of attribution of marketed medicines to the ATC classification, or other.

IV. **Population coverage:** refers to the percentage of population captured by the data source out of the total population being studied. Potential comparability problems may occur due to under- or over-reporting of important segments of the population. Each data source used in the cross-national comparison is constructed under different situations, for example reimbursement data in different countries can vary depending on the coverage and health system structure, which may limit their comparability. See Table 4 for detailed information of each item in this section. In this domain of the checklist three potential comparability problems are assessed:

   i. Potential comparability problem due to data coverage. This potential comparability problem might exist when data is not representative (in case of samples) or the data is distorted or incomplete (in case of census data). This is more likely to occur in countries where health care systems are strongly fragmented.

   ii. Potential comparability problem due to ambulatory / hospital mix. This problem occurs in countries where it is not possible to stratify between ambulatory and hospital data. It refers to the proper determination of the mix between ambulatory and hospital care (attribution of polyclinic prescribing by specialists, day clinics, nursing homes, kindergartens, hospital distribution to primary care patients of special medicines classes, such as medicines to treat HIV and oncological medicines).

iii. Potential comparability problem due to parallel import/export. The validity of the population exposure estimate may be distorted in countries with data collection based on distribution data and with substantial parallel export.

V. Drug coverage. This section is designed to analyze under-reporting of over-the-counter medicines, potential comparability problems due to reimbursement coverage and potential comparability problems related to terminology and/or units of measure. Table 5 contains detailed information of the items and possible answers for each item. The hospital/outpatient data collection refers to the difference in utilization according to the type of care: ambulatory or hospital care and the potential existing overlap between both.

i. Potential comparability problem due to reimbursement coverage. This potential comparability problem might occur in studies using data from reimbursement/claims sources. Some medicines are not recorded in these data sources because they are not covered by health insurances, or patients opt to pay out of pocket. It also applies to countries where medicines are covered under the concept of an essential medicines list.

ii. Potential comparability problem due to prescription status (Prescription Only Medicines and Over the Counter (OTC) medicines). This potential comparability problem can occur with sales data, because OTC sales are not taken into account as part of the national consumption. It also applies in studies where data collection systems based on reimbursement data and/or on prescription data, and on dispensing data where only the reimbursed medicines are recorded.

VI. Overall evaluation. This section summarizes the potential comparability problems assessed in previous sections. The reliability of individual data sources and the validity of the comparison between countries is assessed using the information of data sources used (population and drug coverage), and the potential comparability problems found per country or region included in the comparison. In this section it is required that the reviewer assesses the study validity using scale from 1 to 6. In addition, it is required to summarize the main limitations and methodological pitfalls noticed by the authors of the research article under review as well as the limitation noted by the reviewers, see Table 6 for details of this section.

Table 1. General data section.

PMID article	First Author	Year	Reference	Background of the first author	Number of countries involved	Number of European countries involved	Number of databases	Drug group(s) compared (Express in ATC if possible)
Combination of numbers	First author, et al.	Year	Journal citation	Academia or Industry	5	3	7	[Free text]

Table 2a. Study design section

PMID article	Name of Countries involved (Add one country per line)	Database name or provider name	Temporal aspect of the study
Combination of numbers	Country 1	Database name 1	Cross-sectional
	Country 2	Database name 2	Longitudinal dynamic / open cohort
	Country 3	Database name 3	Longitudinal close cohort
	Country 4	Database name 4	Cohort study with outcome
	Country 4	Database name 5	Intervention study
	Country 5	Database name 6	Other
	Country 5	Database name 7	

Table 2 b. Study design section (continuation)

PMID article	Name of Countries involved (Add one country per line)	Database name or provider name	Age of the population (range)	Gender of population
Combination of numbers	Country 1	Database name 1	[Free text]	All
	Country 2	Database name 2	[Free text]	Only female
	Country 3	Database name 3	[Free text]	Only male
	Country 4	Database name 4	[Free text]	
	Country 4	Database name 5	[Free text]	
	Country 5	Database name 6	[Free text]	
	Country 5	Database name 7	[Free text]	

Name of the Countries involved (Add one country per line)	Database name or provider name	At which level the data was generated?	Primary purpose of data collection	Data origin based on the healthcare setting	Additional comments (optional)
Country 1	Database name 1	Wholesaler	Administrative	Ambulatory care	[Free text]
Country 2	Database name 2	Pharmacy records	Clinical record	Hospital care	[Free text]
Country 3	Database name 3	Pharmacy claims	Other	Both (possible to separate)	[Free text]
Country 4	Database name 4	Patient records		Both (not possible to separate)	[Free text]
Country 4	Database name 5	Patient		Other	[Free text]
Country 5	Database name 6	Other		n/available	[Free text]
Country 5	Database name 7				[Free text]

In case of longitudinal data, data coverage number of years	In case of longitudinal. Is the accuracy of the data coverage consistent through the years?	Description of time frame (Start year - End year)
1	Yes	2000
13	Yes	(2003 - 2007)
8	No	(2005 - 2012)
>20	n/determinable	[Free text]
		[Free text]
		[Free text]
		[Free text]

In case of "Special population" describe	Level of geographical analysis	Which method of comparison was used in this study?	If statistics used for comparison: Is the method appropriate?	Additional comments (optional)
[Free text]	Country	Statistical test	Yes	[Free text]
[Free text]	Region			[Free text]
[Free text]	City			[Free text]
[Free text]	Small health area			[Free text]
[Free text]	Other			[Free text]
[Free text]				[Free text]
[Free text]				[Free text]

Table 3. Drugs terminology and units section

PMID article	Name of Countries involved (Add one country per line)	Database name or provider name	Terminology	Expression of exposure measurement
Combination of numbers	Country 1	Database name 1	ATC	Persons exposed
	Country 2	Database name 2	EPhMRA	Volume
	Country 3	Database name 3	Therapeutic group name	Expenditure
	Country 4	Database name 4	Drug name	Combination of measures
	Country 4	Database name 5	Snomed	
	Country 5	Database name 6	National Drug Code	
	Country 5	Database name 7	Other	

Table 4. Population coverage section

PMID article	Name of the Countries involved (Add one country per line)	Database name or provider name	Coverage	If selected population specify
Combination of numbers	Country 1	Database name 1	Census	Not_applicable
	Country 2	Database name 2	Selected_population	Geographical
	Country 3	Database name 3	Random_sample	Not_applicable
	Country 4	Database name 4	Pragmatic_sample	Not_applicable
	Country 4	Database name 5	Other	Not_applicable
	Country 5	Database name 6		
	Country 5	Database name 7		

If volume involved, specify	Standardization of units of measurement	Potential comparability problems due to terminology and measurement assignment	Additional comments (optional)
DDD	Standardization by population and time	No	[Free text]
PDD	Standardization by population	Yes, towards under estimation	[Free text]
Packages	Standardization by time	Yes, towards over estimation	[Free text]
Units	No standardization	Yes, but undeterminable direction	[Free text]
Other	Other normalization	Not determinable	[Free text]
		Not applicable	[Free text]
			[Free text]

If sample Is the sample representative for the population studied?	If census, specify data coverage (in percentage of total population)	Is it possible ambulatory / hospital mix influence the data?	Is it possible that parallel import/ export influence the data?	Potential comparability problems due to data coverage?	Additional comments (optional)
Not applicable	[Free text]	No	No	Not applicable	[Free text]
Yes	[Free text]	Yes, towards under estimation	Yes, towards under estimation	Yes, towards under estimation	[Free text]
Not applicable	[Free text]	Yes, towards over estimation	Yes, towards over estimation	Yes, towards over estimation	[Free text]
Not applicable	[Free text]	Yes, but undeterminable direction	Yes, but undeterminable direction	Yes, but undeterminable direction	[Free text]
Not applicable	[Free text]	Not determinable	Not determinable	Not determinable	[Free text]
	[Free text]	Not applicable			[Free text]
	[Free text]				[Free text]

Table 5. Drug coverage section

PMID article	Name of the Countries involved (Add one country per line)	Database name or provider name	If the measurement of drug utilization is based on reimbursement data: is there differential reimbursement ?
Combination of numbers	Country 1	Database name 1	Exclusion of particular patient groups
	Country 2	Database name 2	Exclusion by payment caps (initial payments)
	Country 3	Database name 3	Exclusion by particular drug groups
	Country 4	Database name 4	Limited by the use of essential medicine list
	Country 4	Database name 5	More than one exclusion
	Country 5	Database name 6	Other
	Country 5	Database name 7	n/determinable

Table 6. Evaluation section

PMID article	Name of the Countries involved (Add one country per line)	Database name or provider name	Are the data sources well described?	Do the limitations acknowledge comparability problems?	Conclusion in balance with limitations
Combination of numbers	Country 1	Database name 1	Yes	Yes	Yes
	Country 2	Database name 2		No	
	Country 3	Database name 3		Not determinable	
	Country 4	Database name 4			
	Country 4	Database name 5			
	Country 5	Database name 6			
	Country 5	Database name 7			

Is it possible that market status of drugs studied influence the data?	Is it possible tha public / private mix influence the data?	Potential comparability problems due to drug coverage	Additional comments (optional)
No	Not applicable	No	[Free text]
Yes, towards under estimation	Yes, towards under estimation	Yes, towards under estimation	[Free text]
Yes, towards over estimation	Yes, towards over estimation	Yes, towards over estimation	[Free text]
Yes, but undeterminable direction	Yes, but undeterminable direction	Yes, but undeterminable direction	[Free text]
Not determinable	Not determinable	Not determinable	[Free text]
Not applicable		Not applicable	[Free text]
			[Free text]

Potential comparability problems due to terminology and measurement assignment	Potential comparability problems due to data coverage?	Potential comparability problems due to drug coverage	Reliability of drug utilization estimation per data source	How many data sources are trustworthy to be compared? (reliability >3)	Overall risk of bias of the study	Additional comments (optional)
No	Not applicable	No	1 (not reliable)	3	Low risk of bias	[Free text]
Yes, towards under estimation	Yes, towards under estimation	Yes, towards under estimation	1 (not reliable)			
Yes, towards over estimation	Yes, towards over estimation	Yes, towards over estimation	6 (very reliable)			
Yes, but undeterminable direction	Yes, but undeterminable direction	Yes, but undeterminable direction	3			
Not determinable	Not determinable	Not determinable	5			
Not applicable	0	Not applicable	2			
0	0	0	1 (not reliable)			

DISCUSSION

The checklist described above was developed to identify the data reliability and identify potential comparability problems that might affect the validity of the comparison between countries. The list can serve as a guide to review and assess CNC DU studies. Following a checklist when publishing CNC results could enhance transparency in data reporting. Also, this could facilitate their peer review and correct interpretation, with the final goal to improve the translation of this research into pharmaceutical policy decision-making.

The quality of CNC DU studies highly depends on the quality of the data sources, the use of adequate methodology, sufficient reporting of potential comparability problems, and a comprehensive assessment of data limitations and methodologies used. Most of the CNC of DU studies use routinely collected data for administrative health care purposes and can be designed and conducted with different elements that depend on the data source type, therapeutic groups analyzed, and existent reimbursement policies in the country studied, between other characteristics[1,3]. By assessing domains that could affect the CNC results in terms of reliability and validity, the checklist aims to provide guidance in the evaluation, development and reporting of this type of studies. These domains include terminology and measurement units, population coverage, and drug coverage. The resultant checklist includes items for a better detail of data sources stressing on population representativeness, population type, and reimbursement characteristics, to mention some items; thus facilitating the understanding on population and drug coverage of each data source. The instructions to fill in the checklist with a glossary included may help to understand concepts commonly used in drug utilization research, specifically in CNCs. The glossary includes terms such as: defined daily doses, differential reimbursement, essential medicine list, hospital pharmacy dispensing to outpatients, etc. The understanding on some of the terms might also improve the assessment of CNC DU studies.

This checklist differs from previous works by adding a categorization of potential comparability problems as an intermediate step for bias and validity assessment of the comparison between countries. The checklist was designed taking into account previous checklists to assess CNC studies and was modified after a series of discussions and testing phases by experts in the drug utilization field, however these previous checklists were not validated. Therefore, external reviewers are currently validating this checklist using it to review two CNC articles. With this step we can be sure that the checklist can be used as a tool for revision and assessment of CNC DU articles.

Although experts in drug utilization research developed the checklist, the heterogeneity of experts' experience and background enriched the discussion and importance of each item contained in the checklist. Previous guidelines in other fields have been developed as a joint effort from experts highlighting and discussing recommendations to improve research practices, for example, in conceptualizing, validating and reporting models transparently for pharmacoeconomics and outcomes research [6,7].

It has been recognized that with the increasing availability of routinely collected data for health care purposes a standardized results reporting is needed. This led to the design and publication of statements to improve the report of research carried out using health care administrative databases. The STROBE (Strengthening the Reporting of Observational Studies

in Epidemiology) and the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statements aim to improve the transparency of reporting of observational research and address specific reporting issues when using routinely collected health data for research purposes [8]. After the STROBE statement was published, suggestions for the statement improvement and research that comply with the guidelines have been published [9–12]. Likewise, some studies have used the RECORD statement for reporting results [13,14], and some other studies have emphasized that these statements do not cover specific areas and more guidance should be conducted [13,15].

Another essential initiative has been carried out by the European Innovative Medicines Initiative (IMI) which launched the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project. One of the outcomes of this project was the compilation and publication of yearly updated information on nationwide administrative databases that collect drug consumption data to strengthen the monitoring of the benefit-risk of medicines in Europe [16]. Although a high level of detail is needed to increase the validity and reliability of CNCs, this not always is feasible. General description of data sources such as the description provided by PROTECT can be referred during the reporting of CNCs or be taken as an example to describe the data sources used to compare the use of medicines between countries.

Although, criticism on the increasing developing of good practice guidelines and checklist arises, it has been recognized that checklists are useful on organizing and structuring methods and results on a systematic manner, therefore it is necessary to move forward from post-writing checklist to authoring tools to improve research reporting [17].

CONCLUSION

The developed checklist can be helpful for researchers who conduct cross-national comparisons by listing the basic information needed for an appropriate comparison of drug utilization within and between countries. Following the checklist can enhance the validity and reliability of comparison of drug utilization between countries, and facilitate their peer review and correct interpretation.

REFERENCES

1. Elseviers M, Wettermark B, Almarsdottir AB, Andersen M, Benko R, Bennie M, et al. Drug Utilization Research: Methods and Applications. Wiley-Blackwell; 2016. 568 p.
2. Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. Br J Clin Pharmacol. 2004 Oct;58(4):419–28.
3. Santa-Ana-Téllez Y, Duran C, Vander Stichele RR, Ibanez L, Sabate M, Ballarin E, et al. Cross national comparisons of drug utilization - an analysis of data and methods used. Unplublised. 2016;
4. Durán CE, Christiaens T, Acosta Á, Vander Stichele RH, Acosta A, Vander Stichele RH. Systematic review of Cross-National Drug Utilization Studies in Latin America: methods and comparability. PDS. 2015 Jan;25(1):16–25.
5. Gillström A, Wettermark B. Literature Review Cross-national comparison of DU activities [Internet]. 2011. Available from: http://www.pharmacoepi.org/pub/1c094bf0-2354-d714-513c-1bcc98255a3c
6. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling Good Research Practices—Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value Heal. 2012 Sep;15(6):796–803.
7. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force-2. Value Heal. 2012;
8. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLOS Med. Public Library of Science; 2015 Oct 6;12(10):e1001885.
9. Raja SG, Rochon M, Jarman JWE. Brompton Harefield Infection Score (BHIS): Development and validation of a stratification tool for predicting risk of surgical site infection after coronary artery bypass grafting. Int J Surg. 2015;16:69–73.
10. Hsiao C-Y, Lu H-L, Tsai Y-F. Factors influencing mental health nurses' attitudes towards people with mental illness. Int J Ment Health Nurs. 2015 Jun;24(3):272–80.
11. Mannocci A, Masala D, Mipatrini D, Rizzo J, Meggiolaro S, DI Thiene D, et al. The relationship between physical activity and quality of life in prisoners: a pilot study. J Prev Med Hyg. Pacini Editore; 2015;56(4):E172–5.
12. Kuller LH, Goldstein BD. Suggestions for STROBE Recommendations. Epidemiology [Internet]. 2007 Nov [cited 2016 Jul 13];18(6):792–3. Available from: http://content. wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001648-200711000-00024
13. Jung B, Daurat A, De Jong A, Chanques G, Mahul M, Monnin M, et al. Rapid response team and hospital mortality in hospitalized patients. Intensive Care Med. Springer Berlin Heidelberg; 2016 Apr 22;42(4):494–504.
14. Gregersen R, Andresen K, Burcharth J, Pommergaard H-C, Rosenberg J. Short-term mortality, readmission, and recurrence in treatment of acute diverticulitis with abscess formation: a nationwide register-based cohort study. Int J Colorectal Dis. 2016 May 31;31(5):983–90.
15. Tayjasanant S, Bruera E, Hui D. How far along the disease trajectory? An examination of the time-related patient characteristics in the palliative oncology literature. Support Care Cancer. 2016 Apr;1–8.
16. Ferrer P, Ballarín E, Sabaté M, Rottenkolber M, Amelio J, Hasford J, et al. Drug Consumption Databases in Europe. Available from: http://www.imi-protect.eu/documents/DUinventoryFeb2015.pdf
17. Editors TPM, Glasziou P, Altman D, Bossuyt P, Boutron I, Clarke M, et al. From Checklists to Tools: Lowering the Barrier to Better Research Reporting. PLOS Med. Public Library of Science; 2015 Nov 24;12(11):e1001910.

SUPPLEMENTARY MATERIALS

Table A. Checklist modified from Durán et al.

I. General data
*PMID
Author
Year
Reference
Number of countries involved
Number of European countries involved
Name of the Countries involved
*Kind of products
II. Study design and population
Study design
*In case of analytical study, name the methods used
Study type based on the number of observations
In case of longitudinal data, number of years
*Description of time frame
Population
In case of "Special population", description
Level of geographical analysis
III. Database description & data validity
Data description
Data Source
Database classification
Database owner
Data origin based on the healthcare setting
Data validity
Population coverage
Sample or census
Data Coverage
Extrapolation
Risk of data collection bias
Risk of extrapolation bias
Risk of Under/over detection bias by parallel import/export
Risk of ambulatory / hospital mix bias
Drug Coverage
Risk of under/over detection bias by OTC sales
Risk of under-detection bias by (use of) selected drug list.
Risk of terminology and measurement assignment bias
Other potential bias detected

Table A. (continued)

IV. Drugs terminology & units of measure
Terminology
Group(s) compared (ATC II)
Measure Units
V. Limitations
Limitation 1
Limitation 2

* Added items.

Table B. Research articles used for pilot 1 of the checklist

PMID	Author	Year	Title	Journal
15708101	Goossens H, et al.	2005	Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.	Lancet. 2005 Feb 12-18;365(9459):579-87.
18160392	Rosman S, et al.	2007	Prescribing patterns for upper respiratory tract infections in general practice in France and in the Netherlands.	Eur J Public Health. 2008 Jun;18(3):312-6. Epub 2007 Dec 26.
20860726	Zoëga H et al.	2010	Use of ADHD drugs in the Nordic countries: a population-based comparison study.	Acta Psychiatr Scand. 2011 May;123(5):360-7.
21564162	Sen EF et al.	2011	Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age.	Br J Clin Pharmacol. 2011 Jun;71(6):943-50.
21466569	Hudec R et al.	2012	Consumption of three most widely used analgesics in six European countries.	J Clin Pharm Ther. 2012 Feb;37(1):78-80.

Table C. Research articles used for pilot 2 of the checklist

PMID	Author	Year	Title	Journal
16236045	Walley T et al.	2005	Trends in prescribing and utilization of statins and other lipid lowering drugs across Europe 1997-2003.	Br J Clin Pharmacol. 2005 Nov;60(5):543-51.
19453723	Eurap Study Group.	2009	Utilization of antiepileptic drugs during pregnancy: comparative patterns in 38 countries based on data from the EURAP registry.	Epilepsia. 2009 Oct;50(10):2305-9.
20691035	Zahl PH et al.	2010	The relationship between sales of SSRI, TCA and suicide rates in the Nordic countries.	BMC Psychiatry. 2010 Aug 6;10:62.
20860726	Zoëga H et al.	2010	Use of ADHD drugs in the Nordic countries: a population-based comparison study.	Acta Psychiatr Scand. 2011 May;123(5):360-7.
20938914	Sabo A et al.	2011	Consumption of serum lipid-reducing drugs in Serbia compared with Scandinavian countries: a population-based study, 2004-2008.	Pharmacoepidemiol Drug Saf. 2011 Jan;20(1):45-9.
21466569	Hudec R et al.	2012	Consumption of three most widely used analgesics in six European countries.	J Clin Pharm Ther. 2012 Feb;37(1):78-80.
21564162	Sen EF et al.	2011	Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age.	Br J Clin Pharmacol. 2011 Jun;71(6):943-50.
21682002	De Natale R et al.	2011	Efficiency of glaucoma drug regulation in 5 European countries: a 1995-2006 longitudinal prescription analysis.	J Glaucoma. 2011 Apr-May;20(4):234-9.
21792563	Ponizovsky AM et al.	2012	Differences in the consumption rates and regulatory barriers to the accessibility of strong opioid analgesics in Israel and St. Petersburg.	Eur J Clin Pharmacol. 2012 Jan;68(1):89-95.
21923448	Parkin L et al.	2011	Comprehensive comparison of drug prescribing in the United States and United Kingdom.	Pharmacotherapy. 2011 Jul;31(7):623-9.
22079753	Hoebert JM et al.	2012	Do rheumatoid arthritis patients have equal access to treatment with new medicines?: tumour necrosis factor-alpha inhibitors use in four European countries.	Health Policy. 2012 Jan;104(1):76-83.
23018106	Benchimol EI et al.	2013	International variation in medication prescription rates among elderly patients with inflammatory bowel disease.	J Crohns Colitis. 2013 Dec;7(11):878-89..

Table C. (continued)

PMID	Author	Year	Title	Journal
23114457	Clay E et al.	2013	Contribution of prolonged-release melatonin and anti-benzodiazepine campaigns to the reduction of benzodiazepine and Z-drugs consumption in nine European countries.	Eur J Clin Pharmacol. 2013 Apr;69(4):1-10.
23608219	Kostev K et al.	2013	Changes in time to insulin initiation in type 2 diabetes patients: a retrospective database analysis in Germany and UK (2005-2010).	Prim Care Diabetes. 2013 Oct;7(3):229-33.
23775052	Wilby KJ et al.	2013	Cross-national comparison of antidepressant utilization in North America and Europe.	J Clin Psychopharmacol. 2013 Aug;33(4):585-7.
24252465	Valkhoff VE et al.	2013	Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries in the SOS project: what size of data platforms and which study designs do we need to assess safety issues?	BMC Pediatr. 2013 Nov 19;13:192.
24575970	de Groot MC et al.	2014	Antiepileptic drug use in seven electronic health record databases in Europe: a methodologic comparison.	Epilepsia. 2014 May;55(5):666-73.
24657114	Versporten A et al.	2014	Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe.	Lancet Infect Dis. 2014 May;14(5):381-7.
24997585	Holstiege J et al.	2014	Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study.	BMC Pediatr. 2014 Jul 5;14:174.
25022435	Van Boeckel et al.	2014	Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data.	Lancet Infect Dis. 2014 Aug;14(8):742-50.
18162422	Hamunen K et al.	2008	What do different databases tell about the use of opioids in seven European countries in 2002?	Eur J Pain. 2008 Aug;12(6):705-15.
19091608	Hamunen K et al.	2009	Trends in opioid consumption in the Nordic countries 2002-2006.	Eur J Pain. 2009 Oct;13(9):954-62.

Table D shows the percentage of peer agreement from the second pilot conducted. In this pilot at least two reviewers scored each research article. Each researcher scored from three to four research articles and the percentage of agreement per section was calculated. The domain with highest agreement was study design and population description with an agreement average of 75%, while drug coverage was the domain with the lowest agreement percentage (37%).

Table D. Percentage of peer agreement per article in pilot 2.

			Percentage of agreement by domain			
PMID	**Author**	**Year**	**Study design and population**	**Data description**	**Population Coverage**	**Drug coverage**
16236045	Walley T et al.	2005	100%	0%	29%	33%
19453723	Eurap Study Group.	2009	63%	50%	57%	33%
20691035	Zahl PH et al.	2010	50%	75%	29%	0%
20860726	Zoëga H et al.	2010	75%	50%	71%	67%
20938914	Sabo A et al.	2011	50%	50%	57%	33%
21466569	Hudec R et al.	2012	100%	0%	71%	67%
21564162	Sen EF et al.	2011	75%	75%	86%	33%
21682002	De Natale R et al.	2011	25%	25%	29%	0%
21792563	Ponizovsky AM et al.	2012	75%	25%	57%	33%
21923448	Parkin L et al.	2011	88%	100%	57%	33%
22079753	Hoebert JM et al.	2012	75%	75%	14%	100%
23018106	Benchimol EI et al.	2013	69%	25%	14%	0%
23114457	Clay E et al.	2013	75%	50%	43%	33%
23608219	Kostev K et al.	2013	38%	50%	43%	0%
23775052	Wilby KJ et al.	2013	75%	75%	0%	0%
24252465	Valkhoff VE et al.	2013	50%	50%	0%	33%
24575970	de Groot MC et al.	2014	92%	42%	76%	83%
24657114	Versporten A et al.	2014	75%	50%	29%	67%
24997585	Holstiege J et al.	2014	75%	50%	43%	0%
25022435	Van Boeckel et al.	2014	100%	100%	100%	67%
18162422	Hamunen K et al.	2008	100%	100%	86%	96%
19091608	Hamunen K et al.	2009	100%	50%	29%	0%

Table E. Research articles used for pilot 3 of the checklist

PMID	First author	Year	Title	Journal
17086563	Arellano FM, et al.	2006	Use of cyclo-oxygenase 2 inhibitors (COX-2) and prescription non-steroidal anti-inflammatory drugs (NSAIDS) in UK and USA populations. Implications for COX-2 cardiovascular profile.	Pharmacoepidemiol Drug Saf. 2006;15: 861–72.
19029175	Sturkenboom MCJM, et al.	2008	Drug use in children: cohort study in three European countries.	BMJ. 2008;337: a2245.
24252465	Valkhoff VE et al.	2013	Population-based analysis of non-steroidal anti-inflammatory drug use among children in four European countries in the SOS project: what size of data platforms and which study designs do we need to assess safety issues?	BMC Pediatr. 2013 Nov 19;13:192.
24793010	Abbing-Karahagopian V, et al.	2014	Antidepressant prescribing in five European countries: Application of common definitions to assess the prevalence, clinical observations, and methodological implications.	Eur J Clin Pharmacol. 2014;70: 849–857.
24657114	Versporten A, et al.	2014	Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe.	Lancet Infect Dis. 2014 May;14(5):381-7.

Table F1. Percentage of agreement from the third pilot for general data section

	General data			
PMID	**Data level**	**Data setting**	**Data provider**	**Data origin**
17086563	60%	60%	50%	60%
19029175	100%	94%	44%	78%
24252465	55%	50%	50%	71%
24657114	44%	62%	48%	48%
24793010	62%	57%	33%	83%

Table F2. Percentage of agreement from the third pilot for study design section

	Study design								
PMID	Study design	Temporal aspect	Number of years	Data consistency	Time frame description	Age	Gender	Socio-economic	Geographical level
17086563	60%	60%	40%	40%	80%	40%	100%	50%	100%
19029175	83%	67%	67%	50%	72%	33%	89%	89%	100%
24252465	67%	67%	17%	50%	19%	57%	83%	48%	57%
24657114	100%	75%	6%	6%	61%	31%	81%	66%	81%
24793010	100%	83%	60%	50%	69%	64%	100%	76%	71%

Table F3. Percentage of agreement from the third pilot for study design section

	Drugs terminology				
PMID	Terminology	Focus of measurement	Units	Normalization of units	Risk of bias due terminology
17086563	70%	80%	20%	80%	80%
19029175	78%	67%	100%	33%	44%
24252465	83%	83%		50%	83%
24657114	81%	61%	61%	31%	46%
24793010	33%	100%		83%	50%

Table F4. Percentage of agreement from the third pilot for drugs terminology section

	Population coverage									
PMID	Data Classi-fication	National registries	Sample percentage	Sample represen-tativeness	Census coverage	Info nursing homes	Parallel import export	Bias data coverage	Bias ambulatory mix	Bias parallel import export
17086563	60%	80%	20%	50%		60%	100%	30%	60%	100%
19029175	94%	83%	17%	72%		56%	50%	50%	50%	100%
24252465	50%	57%	2%	57%	2%	79%	79%	57%	67%	83%
24657114	47%	65%			58%	53%	68%	59%	48%	46%
24793010	57%	57%	33%	71%		48%	67%	52%	40%	67%

Table F5. Percentage of agreement from the third pilot for drugs terminology section

	Drug coverage			
	Differential reimbursement	**Bias reimbursement**	**POM or OTC**	**Bias POM or OTC**
17086563	60%	50%	60%	40%
19029175		33%	50%	83%
24252465	45%	40%	43%	62%
24657114	471%	45%	66%	66%
24793010	50%	52%	100%	86%

Table F6. Percentage of agreement from the third pilot for drugs terminology section

	Evaluation			
	Data reliability	**Number of trustworthy data**	**Comparison method**	**Overall bias**
17086563	50%	80%	40%	40%
19029175	92%	83%	40%	40%
24252465	57%	83%	50%	50%
24657114	62%	40%	100%	50%
24793010	45%	50%	60%	67%

CHAPTER 2.3

UPTAKE AND MARKET SHARE OF INSULIN ANALOGUES IN FIVE EUROPEAN COUNTRIES: DENMARK, FINLAND, NORWAY, SWEDEN, AND THE UNITED KINGDOM

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Manuscript in preparation

ABSTRACT

Background

The development and introduction of insulin analogues in the early 2000s represented a step forward towards the treatment of diabetes. Insulin analogues offer a balance between glycemic control and the risks associated with hypoglycaemia. However, their uptake might depend on the policy context and clinical recommendations of each country.

Objective

This study compares the uptake and market share of insulin analogues in five European countries, namely Denmark, Finland, Norway, Sweden, and the United Kingdom (UK), in the context of changes in their reimbursement and clinical guidelines.

Methods

We calculated the uptake and market share of different types of insulin (ATC code A10A) between January 2000 and June 2013 in Denmark, Finland, Norway, and Sweden using national pharmacy dispensing records. For the UK, we used the Clinical Practice Research Datalink (CPRD). Depending on data availability, the study period varied between countries. The monthly market share was calculated by dividing the monthly consumption of each insulin type (in defined daily doses (DDDs)) by the monthly consumption of all the insulin, taking into account the population growth. Time series regressions were used to estimate the uptake per insulin type as absolute percentage change in market share. Structural changes in the market share were explored using the Quandt-likelihood-ratio (QLR) test. We examined if structural changes were related to changes in policies, such as the entry of a new product in the market, changes in reimbursement, or the updates of clinical guidelines.

Results

The absolute increase in market share of insulin glargine in Norway was 0.1% per month, in Denmark and in the UK was 0.2%, and in Finland 0.3%. The uptake of insulin detemir in Norway and the UK were 0.1% per month, in Denmark 0.2%, and in Finland 0.3%. In Sweden, the uptake of both insulin analogues was minimal: 0.02% for insulin glargine and 0.05% for insulin detemir. At the beginning of the study period, human insulin was the most used insulin in all the countries except Sweden, where insulin aspart was predominantly used. We did not find sudden changes in the market share of insulin that could be related to the market approval of insulin, changes in diabetes treatment guidelines, and reimbursement policies.

Conclusions

We found that the uptake of the new insulin was similar among countries. Independent of the uptake, the market share of insulin was different in each country and changes in the market share occurred gradually over time. Variations in the market share might be explained by unobserved factors such as clinician prescribing behaviors and patient preferences.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic diseases in the world affecting approximately 415 million persons worldwide [1], and causing a number of disabling and life-threatening health problems such as an increasing risk of cardiovascular disease, kidney failure, blindness, and lower-limb amputation [2]. The objective of the treatment of diabetes mellitus is to lower the risk of complications associated with hyperglycaemia [3]. The recommended treatment varies between patients with diabetes mellitus type 1 and those with diabetes mellitus type 2. Patients with diabetes mellitus type 1 can only be treated with insulin injections, while treatment of diabetes mellitus type 2 usually starts with lifestyle changes such as exercise, diet, and weight control. If lifestyle changes are not sufficient to control the disease, oral blood glucose lowering drugs and/or insulin therapy is/are added to control blood glucose levels. In the long run, the majority of patients with diabetes mellitus type 2 require insulin therapy [4].

Insulin itself is a heterogeneous group of preparations that differ clinically, e.g. in terms of their half-life and the duration of effect. Short-acting insulin is used to mimic the response of endogenous insulin to food intake (bolus insulin) and to correct pre- or between-meal hyperglycemia. Intermediate and long-acting insulin are primarily used to provide a continuous supply of small amounts of insulin independent of food intake over a longer period of time (basal insulin). Long-acting human insulin preparations are obtained by crystallization with either protamine (Neutral Protamine Hagedorn—NPH insulin) or zinc (lente) [5]. However, the NPH insulin is associated with a pronounced insulin peak after injection and variable absorption [5,6]. Therefore, insulin analogues have been developed to provide insulin with a more physiological time course of action: insulin glargine (commercial name Lantus/Optinsulin, EU marketing authorization 9 June 2000) [7], insulin detemir (commercial name Levemir, EU marketing authorization 1 June 2004) [8], and insulin degludec (commercial name Tresiba, EU marketing authorization 21 January 2013) [9].

Over time, different factors might influence the market share of insulins. These factors include changes in pharmaceutical policies such as reimbursement policies, updates of clinical guidelines, or the approval of new treatments. The comparison of the uptake of new treatments and the market share of insulin between countries might help to identify those factors with major influence in the uptake of new medicines to treat diabetes, as well as to identify areas where more research or a guide for pharmaceutical policies to improve the use of insulin is needed.

This study aims to compare the uptake of insulin analogues and market share of insulins in five European countries: Denmark, Finland, Norway, Sweden and the UK in the context of changes in reimbursement policies and clinical guidelines.

METHODOLOGY

Data sources

To estimate the insulin uptake, we used large prescription databases for each country: the Danish, Finnish, Norwegian, and Swedish National Healthcare Registries and the Clinical Practice Research Datalink (CPRD) for the UK.

The Nordic nationwide prescription registers hold data on all prescribed drugs dispensed from pharmacies to patients in ambulatory care [10]. They cover the entire population of Denmark (5.6 million), Finland (5.4 million), Norway (5.1 million), and Sweden (9.6 million). The data recorded include patients' identity number (encrypted), gender and age, defined daily doses (DDD) and the ATC code of dispensed medicinal products [11]. Within each country, all the registers can be linked to other national databases through a specific code that is unique for each inhabitant. More information on the data coverage of each data source can be found in Table 1. The CPRD, a large computerized database established in 1987, comprises anonymized medical records from British general practitioners. During the mid-year of 2013, 4.4 million patients (6.9% of the UK population) met quality criteria for research based on data [12]. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provisions, specialist referrals, laboratory results, hospital admissions, and deaths.

For each country, the study period was defined based on the period of valid data collection (Table 1). We chose to use January 2000 as a start in cases when data were available for a longer period of time since the approval of insulin glargine occurred in June 2000. The end date was determined by the availability of data in each country, ranging from 2011–2013.

Outcome measures and data analysis

For each database we extracted the prescriptions of all insulins (ATC code A10A), and classified each insulin type by their own ATC code [13]. The volume of insulin prescribed in each database was expressed in DDDs. We estimated the market volume defined as the number of DDDs per 1000 inhabitants per month. One DDD of insulin (any type) is equivalent to 40 International Units. To control population changes over time, we estimated the monthly population for each country using information from the World Bank and used it as a denominator [14].

To evaluate how much of a type of insulin was used in relation to other insulins on the market, we calculated the percentage market share by dividing the monthly consumption of each insulin

Table 1. Data coverage and information included for each country

	CPRD (UK)	Denmark	Finland	Norway	Sweden
Start of data collection	Start CPRD in 1986	1996	1996	2004	2005
Study period	2000-2013	2000-2012	2000-2011	2004-2012	2005-2013
Data level	Patient	Patient	Patient	Patient	Patient
Healthcare setting	Ambulatory	Ambulatory	Ambulatory	Ambulatory	Ambulatory
Drug terminology and units	CPRD product codes	ATC (DDD)	ATC (DDD)	ATC (DDD)	ATC (DDD)
Data coverage	Representative sample 6.9%	Nationwide 100%	Nationwide 100%	Nationwide 100%	Nationwide 100%
Potential comparability problems due to data coverage?	Yes	No	No	No	No

ATC: Anatomical Therapeutic Chemical classification. DDD: Defined daily doses [11].

type (in DDD per 1000 population) by the monthly consumption of all insulins. With these percentages, we calculated the uptake of different types of insulin, defined as the absolute increase in percentage market share, in each country with time series regressions. Autocorrelation and stationarity were tested and corrected with autoregressive integrated moving average models.

To explore changes in the market uptake of insulin, we used the Quandt-Likelihood Ratio (QLR) test to look for structural changes in the series, specifically changes in the levels or the slopes at different time points [15]. The QLR test consists of calculating Chow breakpoint tests at every observation, except for observations that are too near the end points of the sample. We examined if the structural changes found (if any) were related to changes in policies, such as entry of a new product on the market, changes in the reimbursement, or the changes in clinical guidelines. In case of finding changes in policies that may have a direct impact on the use of (a certain) insulin, we used interrupted time series analysis [16] to measure the changes in the level and the slope of the use of insulin after changes in policies or entry of new types of insulin. STATA Software version 12 Stata Corp LP Texas 1996-2013 was used to conduct all the analyses [17].

Regulatory changes and clinical guidelines

We searched in different health institutions of each country for documents published between 1999 and 2013 related to changes in reimbursement decisions and clinical guidelines after the market approval for insulin analogues at the European and country level. Additionally, we looked for information on reimbursement agreements for these types of insulin in each country. Government websites and other relevant sites that include information about clinical guidelines for treatment of diabetes mellitus types 1 and 2 were also reviewed.

RESULTS

Market share and uptake of insulin analogues

The market share of the insulins was represented in the percentage of use per country (Figure 1). In the beginning of the study period, human insulin (ATC: A10AB01) dominated the market in most of the countries except for Sweden, and decreased over time while the absolute increase in percentage market share (uptake) of other types of insulin took place at different rates. The market share of human insulin decreased in all countries. Sweden had the lowest decrease rate (-0.1% per month), and Finland the highest decrease rate (-0.6% per month).

The market share of insulin glargine (ATC: A10AE04) increased in Norway by 0.1% per month, in Denmark and the UK by 0.2%, and in Finland by 0.3%. The uptake of insulin detemir (ATC: A10AE05) in Norway and the UK were 0.1% per month, in Denmark 0.2%, and in Finland 0.3%. In Sweden, the uptake of both insulin analogues was minimal, 0.02% for insulin glargine, and 0.05% for insulin detemir.

We also estimated the uptake of insulin aspart fast acting (AATC: A10AB05) and interemediate acting combined with fast acting (ATC: A10AD05). In the UK, the market share for insulin aspart intermediate combined with fast acting increased by 0.3% per month. In Denmark, both types of insulin aspart increased by 0.2% per month; in Norway, aspart intermediate

with fast acting increased by 0.2% and in Finland 0.1%. Table 2 shows the estimated uptake of the different insulins.

Figure 1a

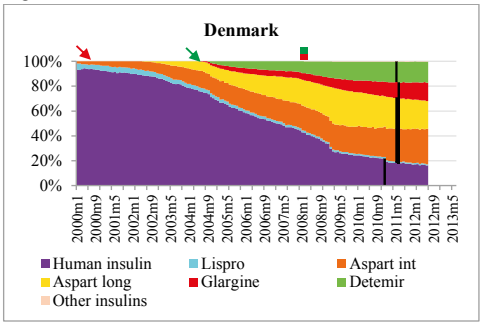

Figure 1b

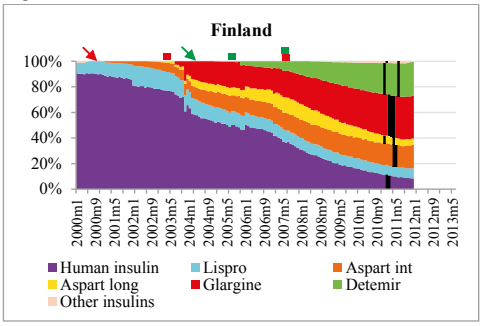

Figure 1c

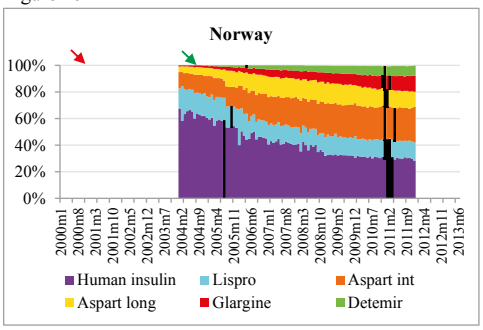

Figure 1d

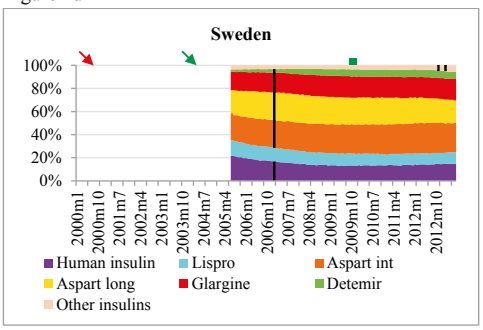

Figure 1e

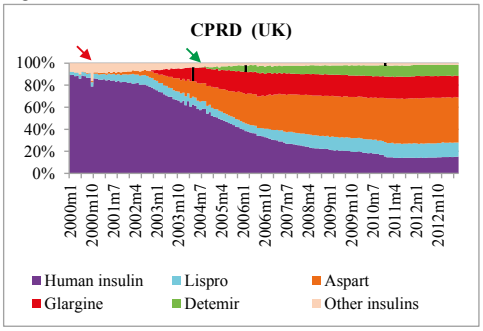

Figure 1. Market share among different insulins and insulin analogues in the 5 study countries. Market share of different insulins types in each country. Dark bars indicate structural breaks found with QLR test. More information can be found in the supplementary material table A. Market approval in the European Union of insulin analogues are indicated with arrows, red arrows for insulin glargine and green arrows for insulin detemir. Squares on top of the graphs indicate reimbursement approval, red for insulin glargine and green for insulin detemir.

Table 2. Prevalence of insulin users by country per month

	Denmark	Finland	Norway	Sweden	United Kingdom
Human insulin*	-0.52%	-0.63%	-0.40%	-0.07%	-0.47% (-0.62% - -0.32%)
Insulin Glargine A10AE04	0.15%	0.26%	0.12%	0.02%	0.15% (0.06% - 0.24%)
Insulin Detemir A10AE05	0.18%	0.34%	0.09%	0.05%	0.09% (0.05% - 0.13%)
Lispro A10AB04	-0.03%	-0.01%	-0.05%	-0.04%	0.06% (0.04% - 0.08%)
Aspart fast acting A10AB05	0.18%	0.13%	0.15%	0.03%	0.25%‡ (0.19% - 0.32%)
Aspart fast acting with intermediate acting A10AD05	0.18%	0.04%	0.08%	-0.01%	

Confidence intervals between parentheses. ‡In the United Kingdom the classification of insulin Aspart includes both intermediate and long acting. *Human insulin ATC codes: A10AB01, A10AC01, A10AD01, A10AE01, A10AF01.

Clinical guidelines for diabetes mellitus type 2 and reimbursement changes

Clinical guidelines are similar across countries. In diabetes mellitus type 2, patients are usually prescribed with insulin in combination with metformin or a sulfonylurea based on HbA1c levels. Countries have similar HbA1c targets: 6.5% of HbA1c in the UK (NICE-UK), 7% in Finland, Norway and Sweden, and 7.5% in Denmark. No changes in the clinical guidelines were related to the insulin treatment were found.

Recommendations to start insulin treatment are based on the insulin effect duration, and treatment may vary between patients. Clinical guidelines emphasize on tailoring the treatment based on HbA1c levels and patient needs. We summarized the initial recommended therapy for diabetes mellitus type 2 patients in Table 3.

In Norway and Sweden there were changes in reimbursement schemes that were implemented in 2010. However, this change did not affect the reimbursement status of insulin in Sweden and no drastic changes in the market share of insulin were found.

With the QLR test, we did not find significant structural changes in the market share of insulin that occurred at the same time of the market approval of insulin analogues. The majority of the structural changes in Denmark were found between May and June of 2011, in Finland most of these changes were found at the beginning and end of 2011, in Norway most of the changes were found at the end of 2010, in Sweden these changes occurred during the first month of 2007 and in the UK only few structural changes were found. None of the identified structural changes was related to changes in diabetes treatment guidelines and reimbursement policies. Results from the QLR test can be consulted in Table A in the supplementary material. Health system structures, and the reimbursement policies are summarized in Table 3.

DISCUSSION

This study showed that the uptake of new insulins was similar among the countries studied. However, the market share of insulins was different between countries. We did not observe any structural changes in the market share related to the introduction of the insulin analogues; on the contrary, the changes in the market share occurred gradually. During the study period, there were no apparent drastic changes in the clinical guidelines or in the reimbursement regulations that might have influenced changes in the uptake of insulin analogues and the overall market share of insulins. This could be due to the fact that the four Nordic countries have similar pharmaceutical policies and health system structures.

Recently, Lu et al, evaluated the uptake of newer pharmaceutical products for diabetes treatment (insulin analogues and thiazolidinediones) in three countries: Brazil, China and Thailand [19]. They found differences in the uptake of insulin analogues between these countries and suggested that factors related to characteristics of each country could have been related to the differences in the uptake. Even though these three countries are considered emerging markets they have numerous differences in government policies, health systems, industry strategies, to mention some. Those differences make it difficult to identify the main factors associated to differences in the uptake of insulins.

Table 3. Reimbursement regulations and clinical guidelines related to insulin analogues and diabetes treatment in each country

Country	United Kingdom	Denmark	Finland	Norway	Sweden
Reimbursement approval glargine	-	6-Feb-2008	2003 DM1 2007 DM2	2010+	-
First month when the prescription register of glargine is available	Sep-2009	May-2005	Jul-2003	January-2004*	July-2005*
Reimbursement approval detemir		6-Feb-2008	2005 DM1 2007 DM 2	2010+	1-Mar-2010
First month when the prescription register of detemir is available	Jul-2004	Aug-2008	Dec-2004	Sep-2004	Jul-2005
Reimbursement: Insulin and oral blood glucose lowering drugs	Free	Partially reimbursed	Free	Fully or partially reimbursed	Fully or partially reimbursed
Reimbursement:Medication for hypoglycaemia	Some categories of patients can get them free of charge; otherwise, not covered	Partially reimbursed	Free	Fully or partially reimbursed	Free or partially reimbursed
Reimbursement: Syringes, needles, pens and related supplies	Free	Pens are free Needles are free or partially reimbursed.	Free or subsidized, depending on the municipality	Fully or partially reimbursed	Free or partially reimbursed
First line therapy for DM2 [22,24]	Lifestyle changes + metformin	Lifestyle changes + metformin	Lifestyle changes + metformin	Lifestyle changes + metformin	Lifestyle changes + metformin
Second line therapy for DM2 [22,24]	-	DPP4 inhibitor GLP 1 analogue Insulin	DPP4 inhibitor GLP 1 analogue Insulin	NPH insulin Sulfonylurea	Insulin repaginide Sulfonylurea
Recommended initial insulin [24,25]	NPH	Basal insulin (analogue or NPH)	Basal insulin (analogue or NPH)	NPH	NPH Mealtime Premix

Note: The information presented in the table was obtained from grey literature and peer review. DM1: Diabetes mellitus type 1, DM2: Diabetes mellitus type 2. *For Norway the start of study period was January 2004, for Sweden the start of study period was July 2005. +For Norway the reimbursement approval for insulin glargine and detemir took place during 2010 just for DM1 and the first packages of insulin glargine were sold to pharmacies in June 2003 [26].

Consequently, it is feasible to hypothesize that the comparison between similar countries might lead to similar outcomes. Nevertheless, this hypothesis does not hold when comparing the use of medicines. Ten years ago, in 2006, Melander et al reported cross-national differences in the use of hypoglycaemic agents stratifying the analysis between insulin and oral antidiabetic drugs in ten European countries [20]. This research team also found cross-national differences that were difficult to be explained by the prevalence of diabetes mellitus [21] and suggested that different habits and attitudes towards screening and management of type 2 diabetes could play a role in the observed differences.

In the present study, it is difficult to explain the differences in uptake of insulin analogues between countries. Finland had the biggest uptake of both insulin analogues, and the highest decrease in human insulin. The earlier introduction of insulin glargine in the Finnish market might partially explain its larger uptake. The introduction of insulin detemir into the market followed with a bigger uptake than the first insulin analogue. This might be explained by prescribers' preferences towards insulin analogues.

The UK had a similar uptake of insulin glargine as Denmark with a lower uptake of insulin detemir, and lower decrease of human insulin. However, the uptake of insulin aspart was the highest among all the countries studied. In Sweden and the UK it is recommended that insulin glargine should be considered only for those people with type 2 diabetes who (1) require assistance from a health professional to administer their insulin injections, (2) find their lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes or (3) would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs [22]. The lower uptake rate of insulin glargine might be related to these recommendations.

In the UK, Norway had a bigger uptake of insulin glargine than insulin detemir and decrease of human insulin. The uptake of insulin aspart fast acting with intermediate acting was bigger than the insulin glargine uptake. The European Commission granted a marketing authorization valid throughout the European Union for insulin aspart on September 1999, approximately one year before the marketing authorization of insulin glargine. The earlier adoption of insulin aspart together with prescriber preferences could explain the uptake and market share of these insulins in the UK.

From all the countries studied, Sweden had the lowest uptake for all the insulins; in consequence, the market share had minimal changes in the time period studied. Since data availability only allowed us to evaluate the uptake and market share from July 2005 onwards, it was not possible to identify if changes in the uptake of these insulins occurred before 2005. The stability of the insulins' market share did not change after the changes in reimbursement schemes in 2010 [18].

Another factor that might explain the cross-national differences in the uptake and market share of insulins can be the different healthcare reimbursement rules for devices for insulin administration such as pens and needles. These devices are either free or partially reimbursed depending on the municipality and the country [4]. In addition, some factors related to the regulatory framework in each country can also play a role in the uptake and market share differences. These factors can be, for example, product register fees and registration process, which may present barriers to manufacturers that attempt to register their products [23].

For all the countries studied, except Denmark, the market share of insulin glargine was higher than the market share of insulin detemir. However, the consumption of insulin glargine might be underestimated because the treatment with insulin glargine requires a lower volume of insulin than the treatment with other insulins. Since a lower volume of insulin glargine is required for the treatment of diabetes, those low volumes might have been translated to a lower market share.

These findings suggest that factors such as diabetes prevalence, early adoption of insulins, and other unobserved factors such as patient and physician preferences might contribute to a different uptake and market share of insulins.

CONCLUSIONS

This study compared the uptake of different insulin between five Western European countries, the difference found cannot be explained by changes in reimbursement policies or changes in clinical guidelines The market share of these countries differed from each other probably due to differences in unobserved factors such as clinician prescribing behavior and patient preferences between others.

ACKNOWLEDGEMENTS

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REFERENCES

1. International Diabetes Federation. IDF Atlas [Internet]. 2015. Available from: http://www.diabetesatlas.org/
2. Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med. 2004 Oct 25;164(19):2147–55.
3. Azoulay L, Schneider-Lindner V, Dell'aniello S, Schiffrin A, Suissa S. Combination therapy with sulfonylureas and metformin and the prevention of death in type 2 diabetes: a nested case-control study. Pharmacoepidemiol Drug Saf. England; 2010 Apr;19(4):335–42.
4. Insulin | International Diabetes Federation [Internet]. Available from: http://www.idf.org/worlddiabetesday/toolkit/pwd/insulin
5. Hilgenfeld R, Seipke G, Berchtold H, Owens DR. The Evolution of Insulin Glargine and its Continuing Contribution to Diabetes Care. Drugs. Springer International Publishing; 2014;74(8):911–27.
6. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care. 2000 May;23(5):644–9.
7. European Medicines Agency - Lantus [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000284/human_med_000882.jsp&mid=WC0b01ac058001d124
8. European Medicines Agency - Levemir [Internet]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000528/human_med_000884.jsp&mid=WC0b01ac058001d124
9. European Medicines Agency - Tresiba [Internet]. 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002498/WC500138964.pdf
10. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, SÃ¸rensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. Basic Clin Pharmacol Toxicol [Internet]. 2010 Feb [cited 2015 Apr 19];106(2):86–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19961477
11. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment [Internet]. Oslo, Norway; 2016. Available from: http://www.whocc.no/atc_ddd_publications/guidelines/
12. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun;44(3):827–36.
13. World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD Index [Internet]. 2012. 2012. Available from: http://www.whocc.no/atc_ddd_index/
14. World Bank. World DataBank [Internet]. 2016 [cited 2016 May 16]. Available from: http://databank.worldbank.org/data/home.aspx
15. Quandt RE. Tests of the hypothesis that a linear regression system obeys two separate regimes. J Am Stat Assoc. 1960;55:320–30.
16. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.
17. StataCorp. 2011. Stata Statistical Software: Release 12. 2011.
18. Pettersson B, Hoffmann M, Andersson D, Wändell P, Levin L-Å. Utilization and costs of glucose lowering therapies following health technology assessment for the new reimbursement scheme in Sweden. Health Policy (New York). 2012;108(2):207–15.
19. Lu CY, Emmerick ICM, Stephens P, Ross-Degnan D, Wagner AK. Uptake of new antidiabetic medications in three emerging markets: a comparison between Brazil, China and Thailand. J Pharm policy Pract. 2015;8(1):7.
20. Neubert A, Hsia Y, de Jong-van den Berg LTW, Janhsen K, Glaeske G, Furu K, et al. Comparison of anti-diabetic drug prescribing in children and adolescents in seven European countries. Br J Clin Pharmacol. 2011;72(6):969–77.

21. Melander A, Folino-Gallo P, Walley T, Schwabe U, Groop P., Klaukka T, et al. Utilisation of antihyperglycaemic drugs in ten European countries: Different developments and different levels. Diabetologia. A. Melander, NEPI Foundation, Department of Clinical Sciences, Malmo University Hospital, S-205 02 Malmo, Sweden; 2006;49(9):2024–9.

22. National Institute for Health and Care Excellence. Insulin therapy in type 2 diabetes [Internet]. 2016. Available from: http://cks.nice.org.uk/insulin-therapy-in-type-2-diabetes#!scenario

23. Wirtz VJ, Knox R, Cao C, Mehrtash H, Posner NW, McClenathan J. Insulin Market Profile [Internet]. Boston; 2016. Available from: http://haiweb.org/wp-content/uploads/2016/04/ACCISS_Insulin-Market-Profile_FINAL.pdf

24. Järvinen S, Laine MK, Eriksson JG. Comparison of use of diabetic medication and clinical guidelines in four Nordic countries. Ann Med. Taylor & Francis; 2016;48(3):162–8.

25. NICE. Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. NICE; 2015.

26. Norwegian Institute of Public Health. Drug Consumption in Norway 2003-2007. 2008.

SUPPLEMENTARY MATERIALS

Table A: Structural breaks found with QLR test

	CPRD	Denmark	Finland	Norway	Sweden
Human insulin*		2010m12	2011m1, 2011m2	2005m7, 2010m11-2011m3	2007m1
Insulin Glargine A10AE04	2004m3	2011m6	2011m1-2011m4	2010m11, 2010m12 2011m2	2007m1
Insulin Detemir A10AE05	2006m1	2011m5	2010m11-2011m5	2006m3 2010m11	2007m1
Lispro A10AB04	-	2011m5 2011m6		2005m7 2010m12 - 2011m2	
Aspart fast acting A10AB05	-	2011m5 2011m6	2011m3 20011m4	2010m12 - 2011m4	2007m1
Aspart fast acting with intermediate acting A10AD05	-	2011m5 2011m6	2010m11-2011m4	2010m12 - 2011m1	2007m1
Other insulins	2010m12	2011m5 2011m6	2010m11-2011m5	2010m12	2012m11 2013m1 2013m2

QLR test show the maximum F-statistic from the Chow test over the time period studied. The critical value of the QLR statistic at the 95-percent significance level with one restriction is 8.68 (Stock and Watson, 2003, p. 471)

CHAPTER 3

INTERRUPTED TIME SERIES ANALYSIS AS A TOOL TO ASSESS PHARMACEUTICAL POLICY CHANGES

CHAPTER 3.1

THE EFFECT OF CHANGES IN THE DATA COLLECTION METHODS OF IMS HEALTH SALES DATA IN BRAZIL BETWEEN 2007 AND 2013

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Technical note for IMS Health

OBJECTIVE

The objective of this technical note is to explore the effects of changes in the data collection of IMS Health sales data in Brazil on the trend and level breaks by selected therapeutic groups.

Background

Alongside the M1209 Quantum update 10 wholesalers were included into the PMB panel design thus enhancing IMS Health's measurement of the Brazilian pharmaceutical market. A total of 96 new wholesalers were included into the panel design throughout 2009.

In January 2010, the change in number of units (UN) and local currency (LC) was compared by IMS. This comparison was done using the data from new wholesalers and the data from the wholesalers that were already part of the panel. The results from this comparison are shown in table 1 for the four quarters of 2009. It was found that on average there was an increase of 8.26% in the number of units sold between the old panel and the new panel of wholesalers. The change in number of units by therapeutic group was diverse as shown in table 1.

For all the groups there was an increase in the percentage change after the addition of wholesalers. The biggest change was observed in the fourth quarter of 2009. The therapeutic group that had the biggest change on the number of units was the group P (parisitology), and the lowest change was reflected in the group V (various) followed by group L (antineoplastic and immunomodulating agents).

The group C (cardiovascular system) was the group that had a change closest to the average change of all the groups.

This gradual incorporation of new wholesalers through 2009 might create a trend break from this point, as there is no back data incorporated. The trend break can affect estimations on evaluation of policies that affect the consumption of different therapeutic groups.

METHODOLOGY

Data

To assess the changes of number of wholesalers during 2009, we used quarterly data from IMS Health from the third quarter of 2007 to the first quarter of 2013. We examined the following groups, C (Cardiovascular System), J (Systemic Anti-Infectives), L (Antineoplastics), M (Musculo-Skeletal System), N (Nervous System), P (Parasitology) and R (Respiratory system).

Analysis

It is common to use the Defined Daily Dose per 1000 inhabitants day as a unit of measure to assess changes in consumption in time [1]. However, there are medicines in some therapeutic groups, especially the group of anti-neoplastic medicines, that do not have DDD assigned [2], as a consequence they are usually excluded from the consumption studies. The exclusion of these medicines can bias the results sub-estimating the effect on the addition of new wholesalers in the database. Therefore, we decided to examine the changes in the consumption in kilograms. To standardize the analysis, we worked with ratios of consumption, this means that we took

Table 1. Percentage change in the number of units during 2009 after the addition of new wholesalers.

		2009			
Therapeutic groups		**QTR1**	**QTR2**	**QTR3**	**QTR4**
	Average	0.42	0.77	3.83	8.26
A	Alimentary Tract and Metabolism	0.36	0.74	3.23	7.35
B	Blood and Blood.Forming Organs	0.38	0.76	3.42	6.69
C	Cardiovascular System	0.34	0.65	3.79	8.52
D	Dermatologicals	0.31	0.72	3.03	6.07
G	GenitoUrinary System and Sex Hormones	0.29	0.62	2.54	5.30
H	Systemic Hormones	0.38	0.81	3.39	7.26
J	Systemic Anti-Infectives	0.31	0.74	5.32	14.28
K	Hospital Solutions	0.00	0.37	8.42	14.34
L	Antineoplastic and Immunomodulating Agents	0.39	0.81	1.54	2.39
M	Musculo-Skeletal System	0.36	0.86	5.62	12.28
N	Nervous System	0.86	0.99	3.72	7.04
P	Parasitology	0.34	1.05	8.20	18.39
R	Respiratory System	0.42	0.75	4.78	11.28
S	Sensory Organs	0.50	1.08	3.16	6.07
T	Diagnostic Agents	0.10	0.20	3.03	15.12
V	Various	0.13	0.28	0.63	1.07

Source: IMS Health

the oldest quarter available as baseline (third quarter of 2007) and divided the consumption of the following quarters by the baseline.

We conducted interrupted time series analyses to assess changes in trend and level before, during and after 2009. We chose different breaking points to assess in which quarter the addition of new wholesaler had a major effect in the trend and level of consumption. The breaking points that we took into account can be found in Table 2. Additionally, to this, we assessed the existence of gradual changes in the time series using the Clemente-Montañez-Reyes test using the innovational outliers option.

Table 2. Breaking points assessed with interrupted time series analysis.

Year	**Quarter**
2008	Fourth
2009	First
2009	Second
2009	Third
2009	Fourth
2010	First

We worked with two different Anatomical Therapeutic Classifications (ATC) codes. The European Marketing Research Association (EphMRA) ATC code used by IMS Health [3] , and the ATC code established by the World Health Organization [2]. For the first classification we used the raw data as obtained by IMS Health. For the second classification we just focused on the antibiotics, antihypertensives and cough and cold medications groups. In these groups we excluded non-systemic medicines and medicines without a DDD assigned.

We conducted the analysis by therapeutic subgroup in both databases. We corrected for stationarity and autocorrelation using Autoregresive Integrated Moving Average (ARIMA) models with robust regression coefficients. We took into account existing seasonality using dummy variables. All the analyses were conducted using the STATA Software version 12 Stata Corp LP Texas 1996-2013 [www.stata.com].

RESULTS

Clemente-Montañez-Reyes test results (gradual changes in the series)

For most of the groups we found the first gradual change in the series in the fourth quarter of 2008 or during 2009 (Table 3). The only group that did not have a gradual change during 2009 was the group J, for this group we found changes at the fourth quarter of 2010 and 2011. the first change is related to the regulation of over-the-counter sales restriction of antibiotics during the last quarter of 2010. This structural change in 2010 might have overlayed the effect of the addition of wholesalers during 2009. The second gradual change for this group was found around the fourth quarter of 2011.

In the WHO ATC dataset we found gradual changes in the fourth quarter of 2008 for systemic antibiotics and cough and cold medications and first quarter of 2009 for antihypertensives. As in the EphMRA ATC set we found a second gradual change during 2011.

Table 3. Results from the Clemente-Montañez-Reyes test. Gradual changes in the series.

Classification		Therapeutic group	Gradual change	
EphMRA ATC	C -	Cardiovascular System	2009q1	2011q2
	J -	Systemic Anti-Infectives	2010q4	2011q4
	L -	Antineoplastics	2008q4	2011q4
	M -	Musculo-Skeletal System	2009q1	2010q4
	N -	Nervous System	2009q1	2011q4
	P -	Parasitology	2008q4	2010q2
	R -	Respiratory System	2008q4	2011q4
WHO ATC*	C -	Antihypertensives	2009q1	2011q2
	J -	Systemic Antibiotics	2008q4	2010q4
	R -	Cough and cold medications	2008q4	2011q4

Interrupted time series results

In Table 4 and Figures 1 to 7, we show the results of the interrupted time series analysis, for the Emphra ATC.

In the group C (cardiovascular system) we found changes in trend and/or level in all the breaking points that we assessed, we found changes in level of 0.05 Consumption Ratio (CR) using the fourth quarter of 2008 as breaking point and -0.06 CR when we used the first quarter of 2009 as breaking point. On the other hand, we found that the selection of breaking points around 2009 has a similar effect on the change in trend during 2009 and the first quarter of 2010, having a change in trend of around 0.03 CR per quarter (Figure 1).

We found that for the group J (systemic anti-infectives) there was a significant change in level of 0.3 CR using the fourth quarter of 2009 as a breaking point (Figure 2).

For group L (antineoplastics), we estimated changes in level using the first and third quarter of 2009. We found changes in trend in this group using the fourth quarter of 2008, first and second quarter of 2009 as breaking points (Figure 3).

The group M (musculo-skeletal system) had a decrease in the level of CR by 0.06 CR and a consistent change in trend of 0.045 CR per quarter when we used the fourth quarter of 2008 and the first two quarters of 2009 as breaking points, the change in trend diminished when we used the third quarter of 2008 as breaking point (Figure 4).

For group N (nervous system) the change in level was significant when we used the first and second quarter of 2009 as breaking points, while the change in trend was the biggest taking as breaking point the fourth quarter of 2008 with an increase of 0.075 CR. During 2009 we found significant changes in trend using each of the quarters of 2009 as breaking points (Figure 5).

Group P (parasitology) had a decrease in level using the fourth quarter of 2008 and first quarter of 2010 as breaking points. We estimated that when using the first three quarters of 2009 as breaking points we have significant changes in trend of CR (Figure 6).

For the group R (respiratory system), we found that just the use of the fourth quarter of 2009 as breaking point and the use of the second quarter of 2009 as a breaking point reflected a change in trend of around 0.035 CR per quarter (Figure 7).

Each graph represents the consumption ratio per therapeutic group from the third quarter of 2007 until the first quarter of 2013.

Using the WHO ATC classification we found that for antibiotics a change in trend was estimated if we used the fourth quarter of 2009 as breaking point (Table5). For antihypertensive we found a decrease in the level of CR while using the first quarter of 2009 as breaking point. While we estimated that for each of the quarters of 2009 there was a significant change in trend of around 0.025 CR. For the group of cough and cold preparations we found that using the fourth quarter of 2008 and the first two quarters of 2009 there was a change in trend of around 0.03 CR.

SUMMARY

In this technical note we explored the effect in changes of trend and level as a consequence of the addition of wholesalers in the database of Brazilian sales of medicines in the private sector. Trend and level breaks in the series of data points could have an effect on future estimations of sales of medicines in Brazil.

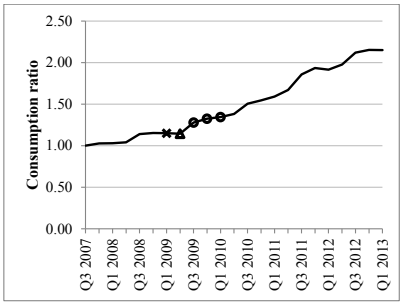

Figure 1. Consumption ratio of medicines in group C (cardiovascular System)

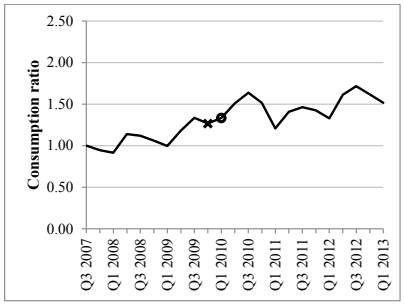

Figure 2. Consumption ratio of medicines in group J (Systemic Anti-Infectives)

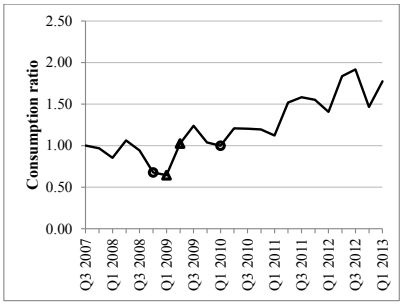

Figure 3 Consumption ratio of medicines in group L (Antineoplastics)

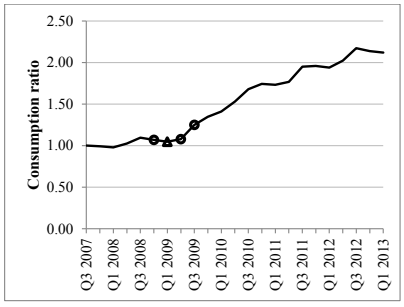

Figure 4 Consumption ratio of medicines in group M (Musculo-Skeletal System)

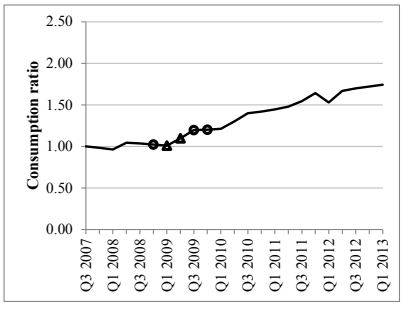

Figure 5 Consumption ratio of medicines in group N (Nervous System)

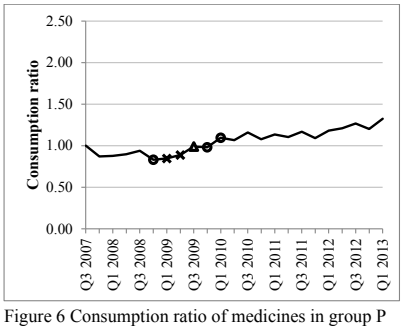

Figure 6 Consumption ratio of medicines in group P (Parasitology)

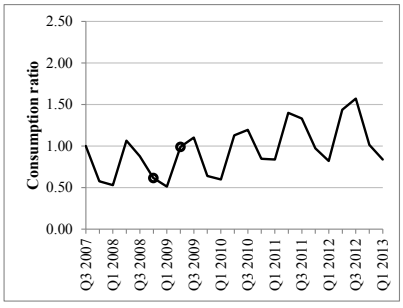

Figure 7 Consumption ratio of medicines in group R (Respiratory System)

Figures 1–7. Significant breaking points can be localized with three different signs: **X**: change in level of consumption; **O**: change in trend of consumption; : change in trend and level of consumption.

We examined the trend breaks with two methods; the first method was the Clemente-Montañez-Reyes test, which assessed the presence of gradual changes in the series. The second method was the use of interrupted time series analysis using different breaking points before, during and after 2009. We found (with both methods) changes in the series trend before and during 2009. The changes in trend were different between therapeutic groups.

The groups of J (anti-infectives), R (medicines for the respiratory system) and L (antineoplastic agents) showed seasonality in the consumption. We found one significant change in level in the fourth quarter of 2009 in the group of anti-infectives. In the contrary we found multiple changes in trend in the group of medicines for the respiratory system and the antineoplastic agents.

The groups M (musculo-skeletal system), N (nervous system), P (parasitology) and C (cardiovascular system), did not show evident seasonality in the consumption. We observed between these groups that the change in trend around 2009 was around 0.03 and 0.04 CR. The group M had the biggest changes in trend and starting at the fourth quarter of 2008, while the group P had the biggest changes at the fourth quarter of 2008 and first quarter of 2009.

It is important to explore solutions to reduce spurious estimations in the future. For instance, an analysis of policy change in 2009 could be polluted by effects in the trend and level caused by adding wholesalers to the established sample depending on the choice of the therapeutic reference group. The analysis presented above shows that the antihypertensives can be used as a reference group to adjust for the structural changes in the database because this group does not show any trend or level breaks. Although the group M can also be used as reference, the consumption of this group can be affected by other external changes because some of the active substances can be obtained OTC.

ACKNOWLEDGMENTS

The authors are very grateful to IMS Health for data provision.

Table 4. Results of interrupted time series analysis at different breaking points.

	Cardiovascular System (C)		Systemic Anti-Infectives (J)		Antineoplastic and Immunomodulating agents (L)		Musculo-Skeletal System (M)	
	Change in level	Change in trend	Change in level	Change in trend	Change in level	Change in trend	Change in level	Change in trend
2008q4	0.048**	0.007	0.065	0.046	-0.022	0.102***	-0.013	0.045**
	(0.025)	(0.713)	(0.673)	(0.482)	(0.641)	(0.003)	(0.604)	(0.035)
2009q1	-0.064***	0.030***	-0.100	0.068	0.194***	0.093***	-0.060***	0.045**
	(0.000)	(0.000)	(0.161)	(0.240)	(0.006)	(0.001)	(0.004)	(0.014)
2009q2	-0.002	0.038***	0.003	0.083	0.259***	0.076***	-0.022	0.045***
	(0.930)	(0.000)	(0.989)	(0.329)	(0.000)	(0.001)	(0.698)	(0.003)
2009q3	-0.009	0.031***	-0.039	0.082	0.016	0.041	0.064	0.032**
	(0.600)	(0.001)	(0.842)	(0.513)	(0.858)	(0.360)	(0.224)	(0.047)
2009q4	-0.001	0.029***	0.303***	-0.064	-0.091	0.038	0.028	0.012
	(0.958)	(0.008)	(0.000)	(0.191)	(0.250)	(0.358)	(0.634)	(0.566)
2010q1	-0.010	0.032***	0.048	-0.142*	-0.170***	0.048	0.048*	0.002
	(0.572)	(0.000)	(0.884)	(0.084)	(0.003)	(0.228)	(0.066)	(0.918)

Table 4. (continued)

	Nervous System (N)		Parasitology (P)		Respiratory System (R)	
	Change in level	**Change in trend**	**Change in level**	**Change in trend**	**Change in level**	**Change in trend**
2008q4	-0.016	0.075***	-0.079**	0.046	-0.012	0.038*
	(0.419)	(0.000)	(0.011)	(0.197)	(0.835)	(0.072)
2009q1	0.054**	0.041***	0.057	0.037***	-0.064	0.019
	(0.011)	(0.003)	(0.162)	(0.003)	(0.162)	(0.617)
2009q2	0.072***	0.030***	0.064	0.031***	0.081	0.036***
	(0.000)	(0.000)	(0.727)	(0.005)	(0.192)	(0.000)
2009q3	0.023	0.021**	0.083*	0.023**	-0.030	0.014
	(0.232)	(0.025)	(0.066)	(0.030)	(0.600)	(0.654)
2009q4	0.036	0.018*	0.047**	0.015	0.025	0.014
	(0.147)	(0.070)	(0.045)	(0.220)	(0.619)	(0.650)
2010q1	0.040	0.014	-0.102***	0.015	0.012	0.019
	(0.104)	(0.176)	(0.000)	(0.372)	(0.827)	(0.298)

p values in parentheses *** p<0.01, ** p<0.05, * p<0.1

Table 5. Shows the results of interrupted time series analysis at different breaking points using 3 groups of medicines categorized by the WHO ATC classification system.

	Antibiotics		Antihypertensives		Cough and cold preparations	
	Change in level	**Change in trend**	**Change in level**	**Change in trend**	**Change in level**	**Change in trend**
2008q4	0.032	0.001	0.016	0.016	-0.021	0.037*
	(0.552)	(0.986)	(0.578)	(0.471)	(0.707)	(0.067)
2009q1	-0.042	-0.002	-0.054***	0.021*	-0.000	0.034**
	(0.220)	(0.947)	(0.000)	(0.078)	(0.994)	(0.020)
2009q2	0.113	-0.000	-0.003	0.027**	0.050	0.031*
	(0.349)	(0.989)	(0.857)	(0.025)	(0.358)	(0.090)
2009q3	0.026	-0.011	-0.013	0.024**	-0.036	0.024
	(0.670)	(0.703)	(0.517)	(0.042)	(0.543)	(0.160)
2009q4	0.185***	-0.024	-0.005	0.024**	0.108*	0.021**
	(0.000)	(0.370)	(0.740)	(0.043)	(0.061)	(0.026)
2010q1	-0.059	-0.038	-0.008	0.019	0.004	0.020
	(0.323)	(0.265)	(0.628)	(0.145)	(0.937)	(0.253)

p values in parentheses *** p<0.01, ** p<0.05, * p<0.1

REFERENCES

1. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf
2. World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD Index [Internet]. 2012. 2012. Available from: http://www.whocc.no/atc_ddd_index/
3. IMS Health. IMS The Uniform System of Classification [Internet]. 2008 [cited 2014 Oct 3]. Available from: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Health Services Research Network/USC_Classiification_Process_2011.pdf

CHAPTER 3.2

IMPACT OF THE INTRODUCTION OF MANDATORY GENERIC SUBSTITUTION IN SOUTH AFRICA: PRIVATE SECTOR SALES OF GENERIC AND ORIGINATOR MEDICINES FOR CHRONIC DISEASES

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ABSTRACT

Purpose

To assess the impact of mandatory offer of generic substitution, introduced in South Africa in May 2003, on private sector sales of generic and originator medicines for chronic diseases.

Methods

Private sector sales data (June 2001 to May 2005) were obtained from IMS Health for proton pump inhibitors (PPIs; ATC code A02BC), HMG CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). Monthly sales were expressed as defined daily doses per 1000 insured population per month (DDD/TIM). Interrupted time series models were used to estimate the changes in slope and level of medicines use after the policy change. ARIMA models were used to correct for autocorrelation and stationarity.

Results

Only the SSRIs saw a significant increase in level of generic utilization (0.2 DDD/TIM; $p<0.001$) and a decrease in originator usage (-0.1 DDD/TIM; $p<0.001$) after the policy change. Utilization of generic PPIs decreased (level 0.06 DDD/TIM, $p=0.048$; slope 0.01 DDD/TIM, $p=0.043$), but utilization of originator products increased (level 0.05 DDD/TIM, $p<0.001$; slope 0.003, p=0,001). Generic calcium antagonists and ACE-I showed an increase in slope (0.01 DDD/TIM, $p=0.016$; 0.02 DDD/TIM, $p<0.001$), while the originators showed a decrease in slope (-0.003 DDD/TIM, $p=0.046$; -0.01 DDD/TIM, $p<0.001$). There were insufficient data on generic statin use before the policy change to allow for analysis.

Conclusion

Mandatory offer of generic substitution appeared to have had a quantifiable effect on utilization patterns in the 2 years after May 2003. Managed care interventions that were already in place before the intervention may have blunted the extent of the changes seen in this time period. Generic policies are an important enabling provision for a range of cost-containment efforts. However, decision taken outside of official policy may anticipate or differ from that policy, with important consequences.

INTRODUCTION

As is the case in many middle- and low-income countries, South Africa is engaged in a concerted effort to ensure universal health coverage (UHC), in the form of a National Health Insurance scheme [1]. Containing expenditure of medicines has been a consistent feature of South Africa's post-*apartheid* health policy since the democratic transition in 1994. A National Drug Policy (NDP) was issued in 1996, and then appended to the White Paper on the Transformation of the Health System in South Africa in 1997 [2,3].

The NDP largely followed the prescripts of the World Health Organization for such policies, last updated in 2003 [4], and committed to the use of interchangeable multi-source pharmaceutical products (IMPP; generics), using the international non-proprietary name (INN), or generic name, in order to contain expenditure. The policy expressed the intent to ultimately achieve generic prescribing in both the public and private sectors, but saw generic substitution as the first step.

The mandatory offer of generic substitution came into effect in May 2003 with a range of safeguards. In the event that a generic equivalent existed, it was mandatory that pharmacists offer the generic substitution that the patient could accept or refuse. In addition, the law, allowed the prescriber to indicate "no substitution" on the prescription. In such cases the pharmacist was prohibited from substituting the brand prescribed with a lower-priced version. Lastly, the South African national medicines regulatory authority (the Medicines Control Council (MCC)) was required to provide a "non-substitutable list". A second Amendment Act in 2002 added an obligation on the pharmacist to take reasonable steps to inform the prescriber that a substitution had occurred. This last change is not expected to have had any material impact on the practice of substitution.

South Africa has a fragmented health system, with the majority of patients catered for by the public sector. However, a well-resourced private sector provides healthcare services predominantly to those who have health insurance. There are currently approximately 8.8 million beneficiaries of the 87 medical schemes registered in South Africa [5]. The balance of the population (about 44.2 million) is catered for predominantly by the public sector, although some out of pocket purchasing by uninsured patients does occur in the private sector, including from medical practitioners who are licensed to dispense. The mandatory substitution law only targeted the private sector in South Africa. In the public sector, medicines were already largely generic. As only those medicines procured on tender are available in public sector facilities where substitution is not possible. The South African pharmaceuticals market was worth ZAR30 billion in 2011 (approximately US$1.9 billion at current exchange rates), of which the private market accounted for 25% by volume, but 65% by value [6]. In 2014, generic medicines were estimated to account for about 65% of all items dispensed in the private sector, and 40% of expenditure [7]. Data on generic utilization is only reported publicly by one of the medical scheme administrators, which provides services to medical schemes with a total of about 1 million beneficiaries. In 2014, generic medicines accounted for 55.6% of items claimed on behalf of these beneficiaries [8].

Only one assessment of the impact of the introduction of the new generic policy on utilization patterns in the South African private sector has been reported. Based on utilization of

only one beta-blocker (atenolol) in the largest medical scheme (Discovery Health), Deroukakis showed a significant change in claims patterns per 1000 beneficiaries between May 2002 and April 2004 [9]. However, visually, there appeared to be a premature change in claims in late 2002, "in anticipation of the implementation of the law". This study therefore aimed to assess the impact of the introduction of mandatory offer of generic substitution on private sector sales of generic and originator medicines, with a particular focus on medicines used for chronic non-communicable diseases. This study has wider implications in terms of the continued global efforts to sustain access to needed medicines, in particular to contain the effects on medicines expenditure of highly-priced medicines, many of which are biological medicines.

METHODS

Data source and setting

South African private sector monthly sales data from June 2001 to May 2005 were obtained from IMS Health for the following selected therapeutic groups: proton pump inhibitors (PPIs; ATC code A02BC), HMG CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). The choice of pharmacological groups was guided by the availability of generic equivalents, with none of the products tracked being included on the MCC's "non-substitutable" list [10]. Similar categories have been tracked in other markets [11].

Products were classified as originator or generic on the basis of registration with the South African medicines regulatory authority (MCC). For each active pharmaceutical ingredient, dosage form and strength, the first product obtaining market authorization was defined as the originator product. Generic equivalents were thus the subsequently authorized equivalents, registered on the basis of an abbreviated dossier and intended to be interchangeable. Monthly sales were converted to defined daily doses per 1000 insured population per month (DDD/TIM), using the information from the Anatomical Therapeutic Chemical (ATC)/defined daily dose (DDD) database maintained by the WHO Collaborating Centre for Drug Statistics Methodology [12]. The denominator was taken as the total number of medical scheme beneficiaries reported by the Council for Medical Schemes for each year [13].

Data analysis

Interrupted time series analyses were conducted at the therapeutic group level to estimate changes in the slope (long term changes) and level (short term changes) of use of originator and generic medicines after the introduction of mandatory offer of generic substitution [14]. Interrupted time series is the strongest quasi-experimental research design [15]. This method is appropriate for conducting impact evaluations when it is not possible to control the implementation of the intervention and repeated observations over time are available, in the form of time series data.

As the policy change was implemented on 2 May 2003, the six-month gap between February 2003 and July 2003 was used as the interruption in the series. To ensure unbiased estimation

it is important take into account stationarity and autocorrelation, as observations over time are correlated. Stationarity and autocorrelation. Autocorrelation and stationarity were therefore tested and corrected for, if present, using autoregressive moving average (ARIMA) models.

As a sensitivity analysis, the duration of the interruption in the series was varied between one and four months and assessed using Quandt Likelihod Ratio (QLR) statistics [16]. All analyses were conducted with STATA version 12 (StataCorp LP, College Station, Texas, USA).

RESULTS

The results of the interrupted time series analysis for four therapeutic groups (selective serotonin reuptake inhibitors, proton pump inhibitors, dihydropyridine calcium antagonists and angiotensin converting enzyme inhibitors) are shown in Table 1. Since there were insufficient data on statin usage before the policy intervention, this group was excluded from the analysis.

Only for the SSRI group was the change in level statistically significant and the changes in both level and slope in the expected direction, in that there was an increase in generic utilization (0.179 DDD/TIM; p<0.001) and a decrease in originator usage (-0.090 DDD/TIM; p<0.001). The trends over time are depicted in Figure 1.

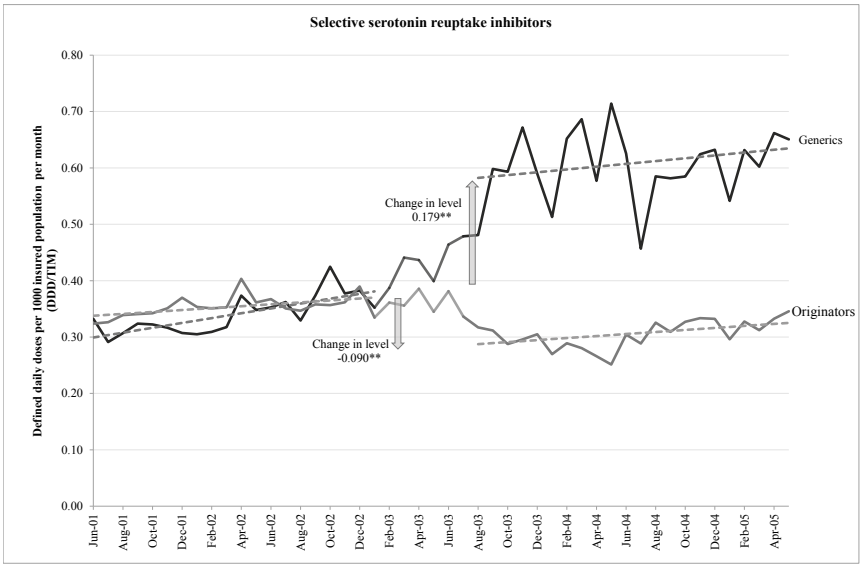

Figure 1. Change in level and slope: selective serotonin reuptake inhibitors.

Changes in the utilization of PPIs were more complex, as shown in Figure 2. Utilization of generic PPIs decreased by 0.063 DDD/TIM (p=0.048), with a slope increase of 0.005 DDD/TIM per month (p=0.043). However, the use of PPIs originator products also increased, as shown by a level change of 0.053 (p<0.001) and a slope change of 0.003 (p=0.001). A delayed increase in generic utilization was apparent from visual inspection.

Table 1. Interrupted time series analysis for 4 selected therapeutic groups, using February to July 2003 as the interruption in the series.

	Selective serotonin reuptake inhibitors		**Proton pump Inhibitors**		**Dihydropyridine calcium antagonists**		**Angiotensin converting enzyme inhibitors**	
	Generic	Originator	Generic	Originator	Generic	Originator	Generic	Originator
Trend	0.005	0.001	0.001	-0.001	0.001	0.001	0.002	-0.0002
(p value)	(0.036)	(0.249)	(0.602)	(0.228)	(0.605)	(0.198)	(0.515)	(0.901)
Change in level	0.179	-0.090	-0.063	0.053	-0.025	0.026	0.081	0.031
(p value)	(<0.001)	(<0.001)	(0.048)	(<0.001)	(0.548)	(0.228)	(0.157)	(0.231)
Change in slope	-0.004	-0.0004	0.005	0.003	0.006	-0.003	0.018	-0.009
(p value)	(0.120)	(0.814)	(0.043)	(0.001)	(0.016)	(0.046)	(<0.001)	(<0.001)
Constant	0.291	0.337	0.030	0.239	0.048	0.322	0.329	0.487
(p value)	(<0.001)	(<0.001)	(0.196)	(<0.001)	(0.154)	(<0.001)	(<0.001)	(<0.001)

Statistically significant values ($p<0.05$) are shown in bold

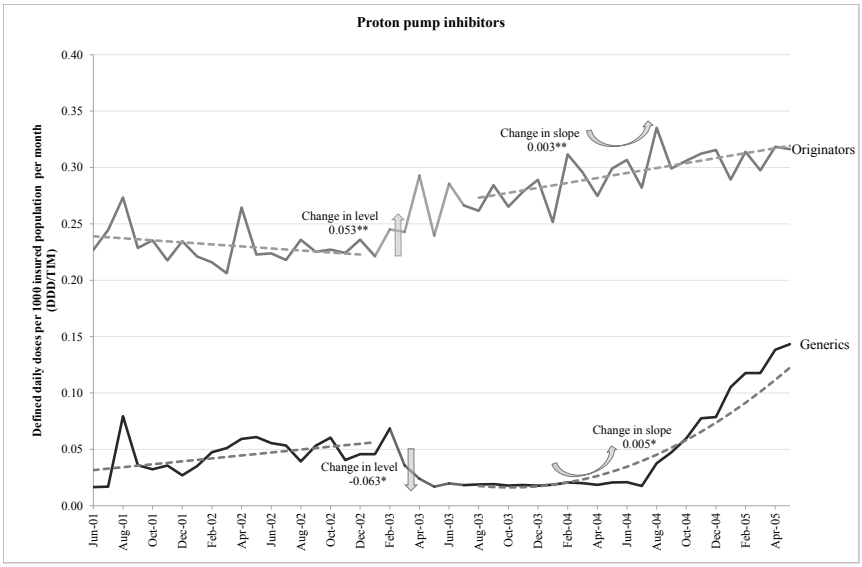

Figure 2. Change in level and slope: proton pump inhibitors.

Utilization of generic calcium antagonists did not show statistically significant changes in level, but a statistically significant 7-fold slope increase from 0.001 to 0.007 DDD/TIM (p=0.016). There was also a statistically significant slope decrease in utilization of the originator products (-0.003 DDD/TIM; p=0.046), as shown in Figure 3. Generic ACE-I utilization showed a 10-fold slope increase from 0.002 to 0.02 DDD/TIM (p<0.001), without a change in utilization level (Figure 4). The expected decrease in slope of utilization of originator ACE-I products was also significant (-0.01 DDD/TIM (p<0.001), with no significant changes in utilization level (Figure 3).

The sensitivity analyses, in which the interruption in the series was varied from one to four months, did not affect the overall results found (see supplementary data). Only for the PPIs and the SSRIs was an interruption at the end of April 2003 evident. However, an interruption in the series during April 2004 was shown for all therapeutic groups.

DISCUSSION

The results of this study provide evidence of a quantifiable effect of the introduction of mandatory offer of substitution, at least in respect of the four commonly used therapeutic groups for the treatment of chronic conditions in the South African private sector. To our knowledge this is the first study to have rigorously analyzed the impact of this policy change on several therapeutic groups in South Africa using interrupted time-series analysis. Whereas generic SSRIs replaced originator products after the implementation of the law in 2003, the effect on ACE-I and calcium channel blockers was less pronounced, but still statistically significant. For PPIs, the intended effect of the policy was not detected.

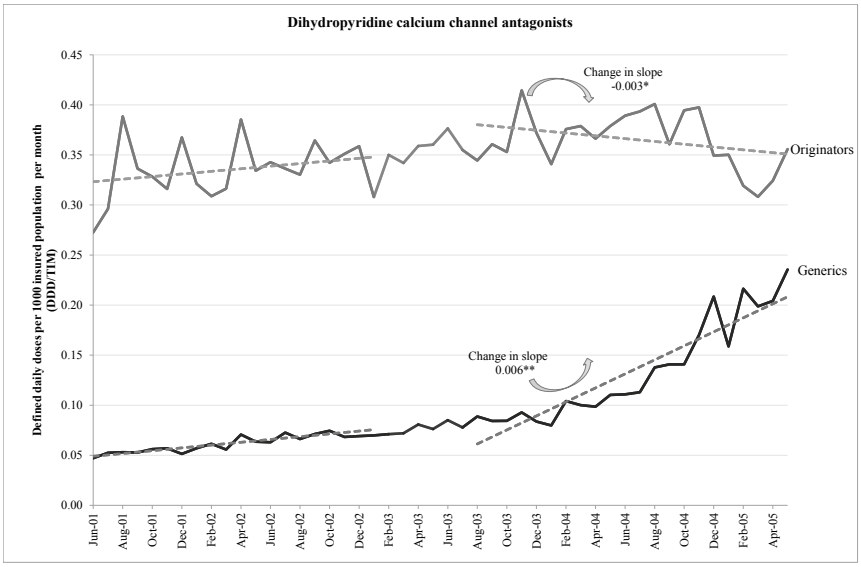

Figure 3. Change in level and slope: dihydropyridine calcium channel antagonists.

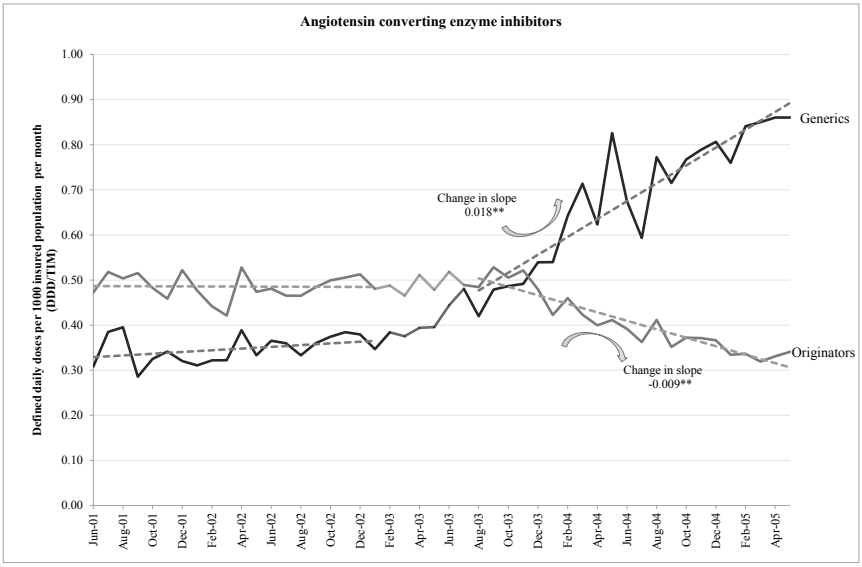

Figure 4. Change in level and slope: angiotensin converting enzyme inhibitors.

In order to interpret the results, it is important to take into consideration the context for this policy implementation process. The initial policy intent had been signaled in the 1996 National Drug Policy and included an amendment to medicines legislation in 1997. However, litigation (primarily aimed at the apparent change in intellectual property provisions in the law) had delayed the implementation of the law until 2003. Thus, although the pro-generic stance in the National Drug Policy was not the primary target, its implementation was nonetheless delayed. Within the private sector medical schemes environment, a range of managed care interventions aimed at increasing utilization of lower-priced generic medicines, had already been implemented prior to May 2003. For instance, a process of internal reference pricing, where a maximum medical aid price (MMAP) was set for particular molecules when generic equivalents were available, was first introduced in 1985 [17]a consideration of expenditure on medicines by medical schemes shows that this component of health care costs had grown to 26.1% in 1988, which is high by comparison with other Western economies. The use of generic medicines offers one possible solution to rising expenditure. For savings to be optimised, however, generics need to be used on a planned and structured basis. The maximum medical aid price (MMAP. Theoretically, this policy required the pharmacist making a substitution to obtain prior permission from the prescriber, at least in the form of a telephonic prescription. It is unknown to what extent this legal requirement was complied with, in the face of pressure from medical schemes in the form of the MMAP policy. It may well be that the "premature" changes described by Deroukakis [9] in relation to atenolol were also occurring with at least some of the therapeutic groups assessed in this study. Thus, although the change in law that came into effect on 2 May 2003 made substitution easier, the mandatory element in the system had already been introduced by managed care interventions such as MMAP. This may explain the lack of clear evidence for a dramatic substitution effect for ACE-I and dihydropyridine calcium antagonists.

In addition to the MMAP other factors may have contributed to the increase in generic consumption. Although South African law did not allow for therapeutic substitution before 2003, it is possible that, under pressure from medical schemes' cost-containment measures, or on request for a lower-priced alternative from patients to reduce out-of-pocket expenditure (in the form of co-payments demanded as a brand premium), prescribers may have chosen to change patients from a medicine for which no generic equivalent existed to one for which such an equivalent did exist. Within each of the pharmacological categories selected in this study, options for such substitutions existed. Conversely, options also existed where a product for which no generic equivalent was yet marketed was available. The launch of esomeprazole (first registered in South Africa in 2002) would have provided such an option, obviating the possibility of substitution if branded omeprazole was prescribed instead.

The results of our study are similar to the findings from an analysis of the effects of the introduction of mandatory offer of generic substitution in Sweden in 2002, where a "proportionally larger increase in sales of substitutable pharmaceuticals compared with sales of non-substitutable pharmaceuticals" was detected, at least for some therapeutic groups [18]. The same policy change had been shown to reduce patient co-payments and overall societal expenditure in Sweden, reversing a previous increase in the slope of both forms of pharmaceutical

expenditure [19]. In contrast, a reference pricing policy in Finland did not measurably add to the influence of previously implemented generic substitution in the medium to long term, based on a time series analysis of costs associated with antipsychotics[20].

There are a number of possible explanations for the increase in consumption of originator PPIs and the apparent lack of effect of mandatory offer of substitution in this therapeutic group. Increasingly, manufacturers of branded original medicines are competing in the market with their own variably priced equivalents (sometimes referred to as "clones"). The launch of chiral alternatives can also counter the loss of sales that follow patent expiry and generic entry. This has particularly been the case with the launch of esomeprazole, as an alternative to the heavily genericized omeprazole. This PPI was one of the products highlighted in an analysis of the impact of product "evergreening" in Swiss hospitals [18]. An overall increase in total PPI utilization, as was reported in Australia [21], may also have distorted the picture in South Africa. Overall generic market share has increased in South Africa's private sector between 2001 and 2011 [22]. However, as these authors point out, the situation is often complex and nuanced at the level of individual medicines".

The changes in generic policy also did not occur in isolation. In terms of the Medicines Amendment Act, a range of pricing interventions came into effect on 2 May 2004, a year after the generic substitution change [23]. The first stage involved the introduction of a non-discriminatory single exit price (factory-gate price) in 2004, which took into account the weighted average of all discounts and rebates offered to private sector purchasers in the preceding year. A ban on bonusing sampling and any form of incentive scheme was also introduced. However, due to legal challenges, the maximum dispensing fees for pharmacists and other licensed dispensing practitioners, and the maximum annual increase in the single exit price (SEP), was only implemented in 2007, after the period under review in this study. While the possibility cannot be ruled out, the impact of the cost-neutral introduction of the SEP in 2004 on generic utilization is expected to have been minimal. In other settings, the introduction of new pricing and co-payment schemes have had potentially deleterious effects on access to medicines. In South Korea, for example, such policies were estimated, on the basis of interrupted time series analysis, to have resulted in decreased numbers of prescriptions being filled for both branded and generic antihypertensive medicines [24] utilization and unit prices of overall pharmaceuticals; (2. Nonetheless, where a dominant single payer system is in place, costs savings can be achieved without negative health impacts. For example, a shift from branded originator to generic olanzapine was achieved in New Zealand, with 99.7% of patients switching and no measurable impacts on health service utilization or mortality [25].

This study has some limitations. The analysis is entirely dependent on the accuracy of the sales data collected and reported by IMS Health. However, this is an industry-standard process on which all manufacturers rely for data to guide marketing efforts. The denominator used was the total of all medical scheme beneficiaries reported by the Council for Medical Schemes. This figure ignores the possibility of purchases of prescription medicines in the private sector by non-beneficiaries, who pay out-of-pocket. However, this proportion was not expected to be large, nor was it expected to change markedly during the period under review. Although the choice of pharmacological groups assessed was guided by previous work [18], and captured

an important set of medicines used for chronic, non-communicable diseases, it remained a small sub-set of the entire market. It may be that other pharmacological groups showed different trends, or even a lack of effect of the change in generic policy. As with all such analyses, the lack of a control group cannot be avoided. Although the analysis has been conducted some years after the initial policy change, the policy question remains a valid one.

Beyond the national context, this study has important implications for global cost containment measures, in particular in relation to high-priced biological medicines. Increasingly, global markets will have access to biosimilars version of such biological medicines, authorized on the basis of comparability data, but not considered to be interchangeable. Much effort has been expended in deciding how best to name such products, with unique names rather than international non-proprietary names such as have been used for small molecule medicines [26]. Nonetheless, the possibility of data supporting interchangeability, and therefore substitution, has been identified as an important cost-saving measure [27]. It may well be that, as perhaps happened in South Africa with generic substitution, pressure from reimbursement bodies or insurers will drive changes in practice in advance of official policy or legal enablement. In the absence of sufficient data, such practices may put patients at risk, but also undermine confidence in biosimilars.

CONCLUSIONS

This study demonstrated a quantifiable change in generic utilization of medicines used for chronic non-communicable diseases following the introduction of a law requiring the mandatory offer of generic substitution by pharmacists and other dispensers in South Africa's private sector in 2003. Generic substitution policies are an important enabling provision for a range of cost-containment measures, including internal and external reference pricing, the use of limited lists (essential medicines lists), and standard treatment guidelines. Such policies are important enablers of the sustainability of UHC systems in all countries. The lessons learned from the introduction of generic substitution policies are also relevant to the debates about interchangeability of biological medicines, including biosimilars.

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REFERENCES

1. Minister of Health. White Paper on National Health Insurance in South Africa [Internet]. Government Notice No. 1230, Government Gazette No. 39506 2015. Available from: http://www.gov.za/sites/www.gov.za/files/39506_gon1230.pdf
2. Minister of Health. National Drug Policy for South Africa. National Department of Health [Internet]. South Africa; 1996. Available from: http://apps.who.int/medicinedocs/documents/s17744en/s17744en.pdf
3. Minister of Health. White Paper on the Transformation of the Health System in South Africa [Internet]. 1997. Available from: http://www.gov.za/sites/www.gov.za/files/17910_gen667_0.pdf
4. World Health Organization. How to Develop and Implement a National Drug Policy (Second Edition) [Internet]. Available from: http://apps.who.int/medicinedocs/en/d/Js2283e/4.1.2.html
5. Council for Medical Schemes. Annual Report. Pretoria; 2015.
6. Clark J. SA market: good fundamentals but some longer-term risks. Bank of America Merrill Lynch; 2012. 1-24 p.
7. Bateman C. Attacking "prejudice" against generics could save SA billions. South African Med J. Health & Medical Publishing Group; 2015 Nov 9;105(12):1004.
8. Mediscor. Medicines Review 2014. 2015.
9. Deroukakis M. Mandatory substitution successful. S Afr Med J. 2007 Jan;97(1):63–4.
10. Medicines Control Council. 2.10 Generic substitution. Pretoria; 2003.
11. Andersson KA, Petzold MG, Allebeck P, Carlsten A. Influence of mandatory generic substitution on pharmaceutical sales patterns: a national study over five years. BMC Health Serv Res. England; 2008;8:50.
12. World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD Index [Internet]. 2012. 2012. Available from: http://www.whocc.no/atc_ddd_index/
13. Council for Medical Schemes. Annual Reports for 2001 to 2005 [Internet]. Available from: http://www.medicalschemes.com/
14. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299–309.
15. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Houghton, Mifflin and Company; 2002.
16. Quandt RE. Tests of the hypothesis that a linear regression system obeys two separate regimes. J Am Stat Assoc. 1960;55:320–30.
17. Boyce D, Bartlett G. The maximum medical aid price programme. A review of the concept and of its ability to reduce expenditure on medicines. S Afr Med J. 1990 Aug 4;78(3):147–51.
18. Vernaz N, Haller G, Girardin F, Huttner B, Combescure C, Dayer P, et al. Patented Drug Extension Strategies on Healthcare Spending: A Cost-Evaluation Analysis. Schiff G, editor. PLoS Med. Public Library of Science; 2013 Jun 4;10(6):e1001460.
19. Andersson K, Bergström G, Petzold MG, Carlsten A. Impact of a generic substitution reform on patients' and society's expenditure for pharmaceuticals. Health Policy (New York). 2007;81(2):376–84.
20. Koskinen H, Mikkola H, Saastamoinen LK, Ahola E, Martikainen JE. Time Series Analysis on the Impact of Generic Substitution and Reference Pricing on Antipsychotic Costs in Finland. Value Heal. 2015;18(8):1105–12.
21. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. Pharmacoepidemiol Drug Saf. John Wiley & Sons, Ltd.; 2010 Jul 8;19(10):1019–24.
22. Kaplan WA, Wirtz VJ, Stephens P, Barra AG, Albuquerque I, Sooksriwong C, et al. The Market Dynamics of Generic Medicines in the Private Sector of 19 Low and Middle Income Countries between 2001 and 2011: A Descriptive Time Series Analysis. Lexchin J, editor. PLoS One. Public Library of Science; 2013 Sep;8(9):e74399.
23. Gray A, Suleman F. Pharmaceutical Pricing in South Africa. Pharmaceutical Prices in the 21st Century. Cham: Springer International Publishing; 2015. p. 251–65.
24. Lee I-H, Bloor K, Hewitt C, Maynard A. The effects of new pricing and copayment

schemes for pharmaceuticals in South Korea. Health Policy. 2012 Jan;104(1):40–9.

25. Lessing C, Ashton T, Davis PB. The impact on health outcome measures of switching to generic medicines consequent to reference pricing: the case of olanzapine in New Zealand. J Prim Health Care. 2015 Jun;7(2):94–101.

26. Food and Drug Administration. Labeling for biosimilar products: guidance for industry [Internet]. 2016 [cited 2016 Sep 5]. Available from: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf

27. Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: How Can Payers Get Long-Term Savings? Pharmacoeconomics. 2016 Jun;34(6):609–16.

Table 1: Results from the Quandt Likelihood Ratio statistic.

		Proton pump inhibitors		Dihydropyridine calcium antagonists		Angiotensin converting enzyme inhibitors		Selective serotonin reuptake inhibitors	
Year	Month	Originators	Generics	Originators	Generics	Originators	Generics	Originators	Generics
2003	1								
	2								
	3								
	4	X						X	X
	5	X						X	
	6	X	X	X			X		X
	7				X				
	8								
	9								
	10								
	11								
	12								
2004	1								
	2								
	3								
	4	X	X		X	X	X	X	X
	5	X	X			X		X	
	6	X				X	X	X	X
	7			X	X	X			
	8								X
	9								
	10								
	11								
	12								

The “X” denotes the structural breaks found in each of the series.

SENSITIVITY ANALYSES

Table 2a. Results of the time series analysis of South Africa for selective serotonin reuptake inhibitors

	Generics				Originator			
	Change in level		Change in slope		Change in level		Change in slope	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
April 2003.	0.111	(0.020)	0.001	(0.701)	-0.039	(0.177)	-0.002	(0.545)
April 2003 - May 2003	0.123	(0.015)	0.000	(0.925)	-0.045	(0.138)	-0.002	(0.544)
April 2003 - June 2003	0.152	(0.001)	-0.001	(0.782)	-0.084	(0.002)	-0.001	(0.702)
April 2003 - July 2003	0.176	(<0.001)	-0.003	(0.146)	-0.098	(0.000)	<0.001	(0.960)
March 2003 - April 2003	0.122	(0.058)	0.002	(0.626)	-0.039	(0.181)	-0.002	(0.538)
March 2003 - May 2003	0.156	(0.008)	0.001	(0.782)	-0.043	(0.128)	-0.002	(0.535)
March 2003 - June 2003	0.172	(<0.001)	-0.002	(0.404)	-0.083	(0.002)	-0.001	(0.679)

Table 2b. Results of the time series analysis of South Africa for proton pump inhibitors

	Generics				Originator			
	Change in level		Change in slope		Change in level		Change in slope	
Interruption in the series	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
April 2003.	-0.005	(0.833)	0.005	(0.242)	0.026	(0.206)	-0.002	(0.090)
April 2003 - May 2003	-0.003	(0.860)	0.005	(0.219)	0.027	(0.188)	-0.002	(0.063)
April 2003 - June 2003	-0.007	(0.787)	0.006	(0.145)	0.024	(0.279)	-0.002	(0.095)
April 2003 - July 2003	-0.011	(0.737)	0.006	(0.079)	0.025	(0.255)	-0.003	(0.067)
March 2003 - April 2003	-0.008	(0.744)	0.005	(0.238)	0.023	(0.325)	-0.002	(0.085)
March 2003 - May 2003	-0.007	(0.798)	0.005	(0.207)	0.024	(0.321)	-0.003	(0.067)
March 2003 - June 2003	-0.012	(0.729)	0.006	(0.123)	0.021	(0.368)	-0.003	(0.081)

Table 2c. Results of the time series analysis of South Africa for dihydropyridine calcium antagonists

	Generics				**Originator**			
	Change in level		**Change in slope**		**Change in level**		**Change in slope**	
Interruption in the series	**Coefficient**	**P value**	**Coefficient**	**P value**	**Coefficient**	**P value**	**Coefficient**	**P value**
April 2003.	-0.043	(0.188)	0.005	(0.103)	0.034	(<0.001)	0.003	(<0.001)
April 2003 - May 2003	-0.044	(0.060)	0.005	(0.081)	0.041	(<0.001)	0.002	(<0.001)
April 2003 - June 2003	-0.053	(0.014)	0.005	(0.028)	0.041	(<0.001)	0.003	(0.001)
April 2003 - July 2003	-0.060	(0.004)	0.005	(0.006)	0.044	(<0.001)	0.002	(0.002)
March 2003 - April 2003	-0.067	(0.002)	0.004	(0.160)	0.039	(<0.001)	0.003	(<0.001)
March 2003 - May 2003	-0.069	(0.003)	0.004	(0.110)	0.044	(<0.001)	0.003	(<0.001)
March 2003 - June 2003	-0.076	(0.002)	0.004	(0.069)	0.045	(<0.001)	0.003	(<0.001)

Table 2d. Results of the time series analysis of South Africa for angiotensin converting enzyme inhibitors

	Generics				Originator			
	Change in level		Change in slope		Change in level		Change in slope	
	Coefficient	P value	Coefficient	P value	Coefficient	P value	Coefficient	P value
April 2003.	0.023	(0.651)	0.018	(<0.001)	0.047	(0.018)	-0.008	(<0.001)
April 2003 - May 2003	0.044	(0.415)	0.018	(<0.001)	0.047	(0.018)	-0.009	(<0.001)
April 2003 - June 2003	0.059	(0.300)	0.018	(<0.001)	0.038	(0.067)	-0.009	(<0.001)
April 2003 - July 2003	0.071	(0.261)	0.018	(<0.001)	0.033	(0.136)	-0.009	(<0.001)
March 2003 - April 2003	0.023	(0.659)	0.018	(<0.001)	0.044	(0.053)	-0.009	(<0.001)
March 2003 - May 2003	0.044	(0.423)	0.018	(<0.001)	0.044	(0.055)	-0.009	(<0.001)
March 2003 - June 2003	0.062	(0.207)	0.018	(<0.001)	0.034	(0.151)	-0.009	(<0.001)

CHAPTER 4

PHARMACEUTICAL POLICY CHANGES IN MEXICO AND BRAZIL - THE CASE OF OTC SALES RESTRICTIONS

CHAPTER 4.1

IMPACT OF OVER-THE-COUNTER RESTRICTIONS ON ANTIBIOTIC CONSUMPTION IN BRAZIL AND MEXICO

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ABSTRACT

Background

In Latin American countries over-the-counter (OTC) dispensing of antibiotics is common. In 2010, both Mexico and Brazil implemented policies to enforce existing laws of restricting consumption of antibiotics only to patients presenting a prescription. The objective of the present study is therefore to evaluate the impact of OTC restrictions (2010) on antibiotics consumption in Brazil and Mexico.

Methods and Findings

Retail quarterly sales data in kilograms of oral and injectable antibiotics between January 2007 and June 2012 for Brazil and Mexico were obtained from IMS Health. The unit of analysis for antibiotics consumption was the defined daily dose per 1,000 inhabitants per day (DDD/TID) according to the WHO ATC classification system. Interrupted time series analysis was conducted using antihypertensives as reference group to account for changes occurring independently of the OTC restrictions directed at antibiotics. To reduce the effect of (a) seasonality and (b) autocorrelation, dummy variables and Prais-Winsten regression were used respectively.

Between 2007 and 2012 total antibiotic usage increased in Brazil (from 5.7 to 8.5 DDD/TID, +49.3%) and decreased in Mexico (10.5 to 7.5 DDD/TID, -29.2%). Interrupted time series analysis showed a change in level of consumption of -1.35 DDD/TID ($p<0.01$) for Brazil and -1.17 DDD/TID ($p<0.00$) for Mexico. In Brazil the penicillins, sulfonamides and macrolides consumption had a decrease in level after the intervention of 0.64 DDD/TID ($p=0.02$), 0.41 ($p=0.02$) and 0.47 ($p=0.01$) respectively. While in Mexico it was found that only penicillins and sulfonamides had significant changes in level of -0.86 DDD/TID ($p<0.00$) and -0.17 DDD/TID ($p=0.07$).

Conclusions

Despite different overall usage patterns of antibiotics in Brazil and Mexico, the effect of the OTC restrictions on antibiotics usage was similar. In Brazil the trend of increased usage of antibiotics was tempered after the OTC restrictions; in Mexico the trend of decreased usage was boosted.

INTRODUCTION

Inappropriate use of antibiotics enhances the development of antibacterial resistance, which is an important public health issue. It leads to treatment failures causing deaths and an increase in use of more costly antibiotics [1,2]. In many of the Latin American countries, prohibition of over the counter (OTC) sales of antibiotics in private pharmacies is not enforced, and self-prescription with antibiotics is common [3] because antibiotics are still requested and sold without prescription in private pharmacies. During previous years, various countries implemented policies to enforce prohibition of OTC antibiotic sales. Chile was one of the first countries in the region documenting the implementation of this type of policy that took place in September 1999, which resulted in a notable decrease in the short-term consumption [4], nevertheless it slowly increased from 2002 onwards [5].

Other Latin American countries have followed Chile's example over the past years. In 2005, Colombia started to regulate the OTC sales of antibiotics only in the capital city Bogota, while in Venezuela at the beginning of 2006, a similar policy was implemented but only applied to three therapeutic groups: macrolides, quinolones and third generation cephalosporins. The effect of these policies were evaluated recently, showing a decrease in level of consumption in Colombia, but no change in level or trend in Venezuela [6]. Ultimately, two of the largest countries in Latin America, Brazil and Mexico, implemented a similar policy during 2010 enforcing the prohibition of all systemic antibiotic sales without prescription.

For many years Mexico had the highest antibiotic consumption in the region [7]. The antibiotics as therapeutic group have occupied the second place in retail sales (40% without a prescription), but the first place with regards to reports on adverse reactions [8] [9]. The consequences of self-prescription were highlighted during the epidemic of influenza A (H1N1) in 2009. Indeed, the Mexican government justified the antibiotic regulation in 2010 [10] arguing that it would prevent harmful self-medication with antibiotics that had led to delayed medical diagnosis of life-threatening complications during the influenza epidemic [9]. This regulation requires prescriptions for antibiotics to be retained and registered in pharmacies, and imposes fines to the owners of the pharmacies for non-compliance.

Brazil has been catalogued by IMS Health as a *pharmemerging* country with a pharmaceutical growth over the last few years and an increased government investment in pharmaceutical manufactures [11]. Approximately 40% of the medicines consumed in Brazil are antibiotics and they are commonly self-medicated; in 2008 alone, the sale of these medicines had a revenue of 377 million USD, with over 70 million units sold [12]. The National Health Surveillance Agency in Brazil (ANVISA) has discussed the need to improve the control of sales of antibiotics since 2009; however, it was the spread of the multi-resistant KPC bacteria (*Klebsiella Pneumoniae Carbapenemase*) and related deaths from hospital infections during 2010 that speeded up the process of carrying out the regulation [9], which was implemented in November of 2010 [13]. After that, the regulation had some modifications detailing that the pharmacies should keep a copy of the prescriptions; from April 2013, the antibiotics were included into the National Controlled Substances Management System (SNGPC) to improve the supervision of their consumption [14]. None of the two countries carried out an information campaign to prevent

the inappropriate use of antibiotics, but Mexico did a campaign to inform the public about the regulatory changes.

Monitoring antibiotics consumption has been encouraged in order to design and evaluate interventions directed at optimizing the use of these medicines and prevent increasing resistance [15]. The evaluation of a policy implementation is relevant to identify its impact and take corrective actions if needed. Cross-national analysis can help to identify changes in trends of consumption in each country and understand the impact of similar measures in different settings. The aim of the present study is therefore to assess the impact of the antibiotics consumption restrictions introduced in 2010 in Mexico and Brazil and compare the effect of the measures in these two countries.

METHODS

Data source and setting

For this study, we obtained retail quarterly sales data in kilograms of oral and injectable antibiotics in the private sector from 2007 to the first two quarters of 2012 for Brazil and Mexico by submitting a research protocol to IMS Health under their Global Health Research program explaining the objectives and methodology to conduct the present study. The database was constructed with information of manufacturers and retail wholesalers. The kilograms sold of each antibiotic was converted into a defined daily dose per 1,000 inhabitants per day (DDD/TID) according to the Anatomical Therapeutic Chemical (ATC) classification system proposed by the World Health Organization [16]. Annual information on the population of Mexico and Brazil was obtained from the Pan American Health Organization records [17] and the population in each quarter was estimated using the growth rate per year.

The analysis was conducted in two stages: first, for the total amount of antibiotics consumption, and then for therapeutic sub-groups. In both countries, penicillins, tetracyclines, quinolones, macrolides and sulfonamides were the most frequently consumed therapeutic subgroups [7], and these were therefore included as separate classes. All other antibiotics were grouped as "others" for the analysis.

Data analysis

We first conducted a descriptive analysis calculating the average consumption in the period before and after the intervention taking the consumption of the quarters corresponding to the winter season for both countries. For Brazil this corresponded to the second and third quarter of each year, while for Mexico winter season occurs during the fourth and first quarter.

Subsequently, we used interrupted time-series analysis [18] to measure the impact of the policy implementation in each country estimating changes in level and trend in antibiotics consumption after the enforcement of the regulations. For Brazil we indicated the beginning of the regulated consumption at the first quarter of 2011 since the startup of the banning of OTC of antibiotics sales was on November 29th of 2010; while for Mexico we considered the beginning of the regulated consumption at the last quarter of 2010, since the regulation took place from August 25th of the same year. For this analysis we included all data points (quarters) from

the beginning of 2007 to the second quarter of 2012, except for the last quarter of 2010 for Brazil and the third quarter of 2010 for Mexico because these two periods were just partially affected by the restriction of OTC sales.

In the model, we included a reference group to account for changes in medicines consumption outside of the antibiotic regulation, such as changes in the economy and the health systems. We decided to use antihypertensive medicines since this group was not affected by the new policies and consumption does not present seasonal variation, but consumption would be affected by market growth or other external factors that we were interested in adjusting for.

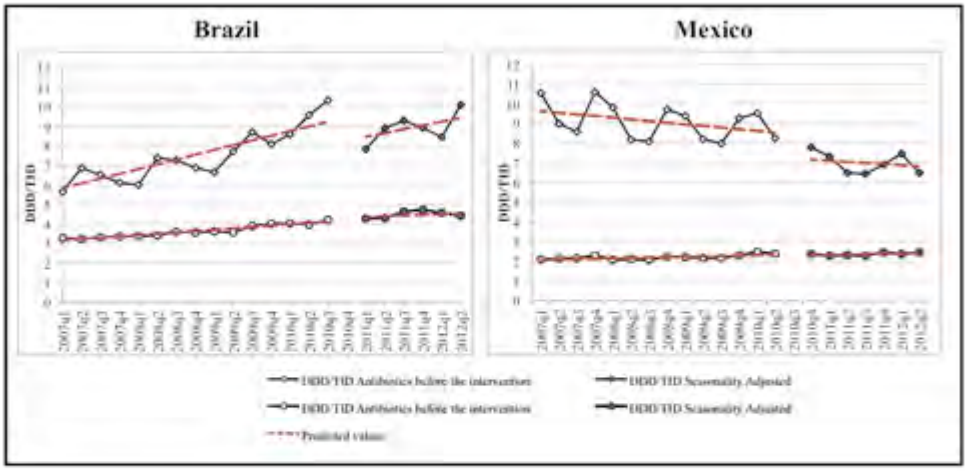
All models were adjusted for seasonality by using dummy variables. This was only applied for the antibiotics group and conducted separately in the segments before and after intervention, because it was observed graphically that the seasonality patterns changed after the intervention. Autocorrelation was corrected using Prais-Winsten regression [19] and the Durbin Watson test of all models showed that no autocorrelation persisted. All analysis were executed using the STATA Software version 12 [20].

RESULTS

Between January 2007 and June 2012 total antibiotics usage increased in Brazil (from 5.7 to 8.5 DDD/TID, +49.3%) and decreased in Mexico (10.5 to 7.5 DDD/TID, -29.2%) in the private sector. In each year, we observed that Brazil had the highest consumption during the second and third quarter while Mexico had the highest consumption between the fourth and first quarter. For both countries this corresponds to their respective winter seasons. Antihypertensive medicines did not show seasonality in consumption as was expected. In Brazil we observed that for both therapeutic groups, antihypertensives and antibiotics, the consumption increased during the study period. The slope for antihypertensives was 0.071 DDD/TID per quarter between 2007 and 2012 while the slope was 0.18 DDD/TID per quarter for antibiotics in the same period. In Mexico, the antihypertensives showed an *increase* in consumption (slope=0.016 DDD/TID per quarter) and the antibiotics had a negative trend of -0.15 DDD/TID per quarter (Figure 1). In addition to this, we observed a difference in seasonal patterns after intervention in both countries, the difference in consumption between summer and winter was smaller after the regulation started, particularly for Mexico (Figures 1 and 2).

Interrupted time series analysis adjusting for antihypertensive consumption showed a change in level of consumption of -1.35 DDD/TID ($p<0.01$) for Brazil (Table 1) and -1.17 DDD/TID ($p<0.00$) for Mexico (Table 2), without a significant change in the trend after the regulation was implemented (Figure 1). The change in level for Mexico was only significant after the adjustment for seasonality.

Penicillins were the most frequently consumed antibiotic in both countries (see Figures 2 and 3). Prior to the intervention, the average consumption of penicillins in Brazil was 3.1 DDD/TID (which represents 39% out of total antibiotics consumption). After the intervention in Brazil, the consumption had a significant decrease in level of -0.64 DDD/TID ($p<0.00$), a non-significant change in trend of 0.012 DDD/TID per quarter ($p=0.814$) and an average consumption of 3.8 DDD/TID, but this decrease did not have an impact in the proportional consumption (40% out of the total) since the total consumption trend



4.1

Figure 1. Trends in consumption in DDD/TID for Brazil and Mexico (2007-2012)

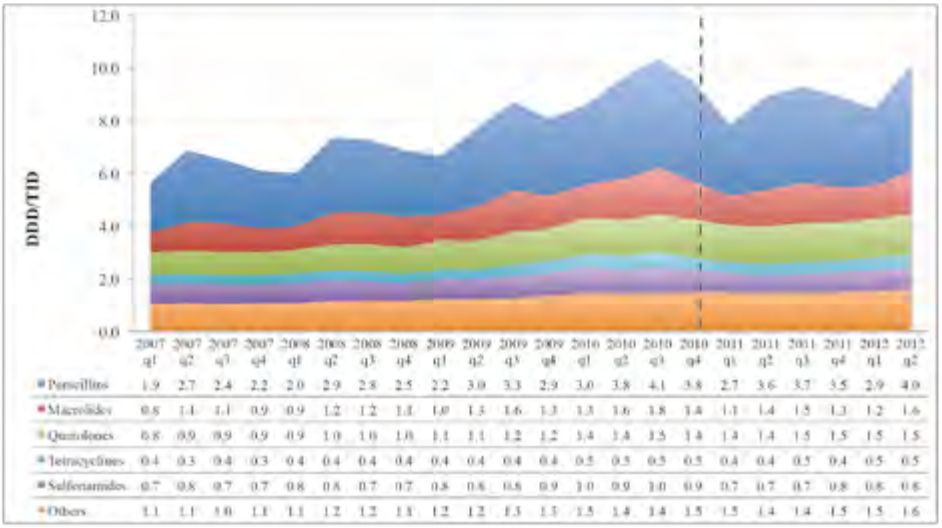


Figure 2. Consumption of AB therapeutic subgroups in Brazil.

remained increasing. In Mexico this therapeutic sub-group had a consumption of 4.0 DDD/TID (41% out of total) before the intervention with a significant decrease in level after the intervention of -0.86 DID/TID ($p<0.00$), with no change in trend (0.002 DDD/TID per quarter, $p=0.942$) and an average consumption of 2.7 DDD/TID corresponding to the 36% out of the total consumption after the policy intervention.

Quinolones had the same consumption in both countries before the regulations started, 1.1 DDD/TID (14% out of the total consumption in Brazil and 12% out of the consumption in

Table 1. Results of the time series analysis of Brazil for all antibiotics and by therapeutic sub-group

	All	Tetracyclines	Penicillins	Sulfonamides	Macrolides	Quinolones	Others
Intercept	5.604	0.314	2.033	0.667	0.852	0.745	0. 973
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Change in level after intervention DDD/TID¥	-1.348	-0.256	-0.635	**-0.414**	-0.465	-0.169	-0.163
	(0.005)	(0.113)	(0.018)	**(0.023)**	(0.010)	(0.328)	(0.348)
Change in trend after intervention DDD/TID per quarter¥	-0.018	0.036	0.012	0.326	0.023	0.006	0.022
	(0.798)	(0.375)	(0.814)	(0.430)	(0.568)	(0.885)	(0.596)
R^2	0.967	0.995	0.925	0.993	0.993	0.992	0.992

¥Adjusted for reference group, p values in parentheses. All: all therapeutic groups combined

Table 2. Results of the time series analysis of Mexico for all antibiotics and by therapeutic sub-group

	All	Tetracyclines	Penicillins	Sulfonamides	Macrolides	Quinolones	Others
Intercept	9.695	1.130	3.538	1.390	0.966	1.073	1.582
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Change in level after intervention DDD/TID¥	-1.172	0.008	**-0.857**	-0.174	0.049	-0.041	0.131
	(0.001)	(0.958)	**(0.000)**	(0.068)	(0.622)	(0.647)	(0.141)
Change in trend after intervention DDD/TID per quarter¥	0.026	0.015	0.002	0.022	-0.008	-0.006	0.005
	(0.663)	(0.477)	(0.942)	(0.145)	(0.662)	(0.687)	(0.722)
R^2	0.995	0.975	0.962	0.990	0.989	0.987	0.973

¥Adjusted for reference group, p values in parentheses. All: all therapeutic groups combined

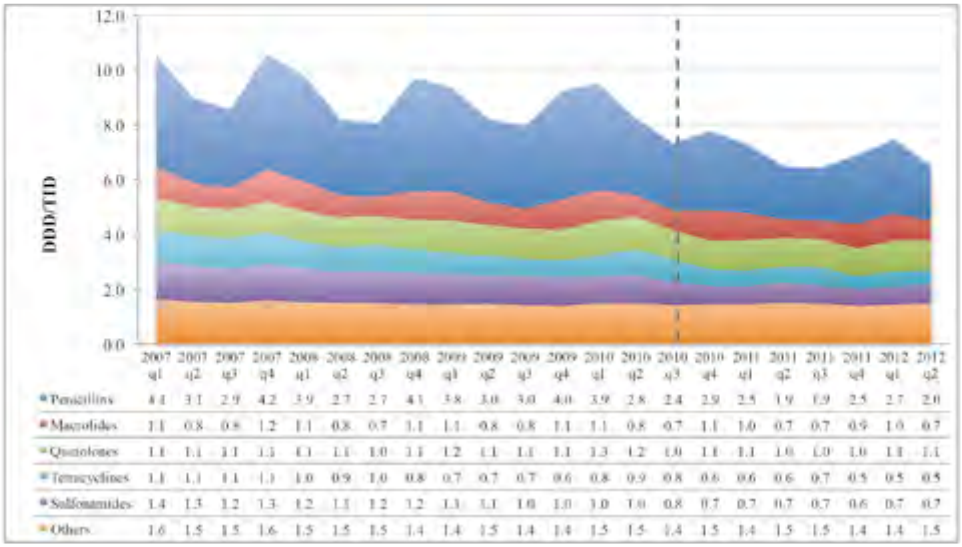


Figure 3. Consumption of AB therapeutic subgroups in Mexico

Mexico). The mean consumption in Brazil for this group increased by 0.4 DDD/TID meaning a 2% increase relative to the total consumption and did not change in absolute values with a no significant change in level of consumption of -0.17 DDD/TID (p=0.328) and a non-significant change in trend of 0.006 DDD/TID per quarter (p=0.885). For Mexico, even though the absolute consumption did not change, it increased relatively by 3% out of the total consumption; neither the change in level and trend were statistically significant -0.041 DDD/TID (p=0.647) and -0.006 DDD/TID per quarter (p=0.687) respectively.

Macrolides had an increase in the absolute consumption of 0.2 DDD/TID in Brazil with a consumption of 1.5 DDD/TID after the regulation, representing a relative reduction of 1%, with 16% out of the total consumption. A significant change in level for this group was -0.47 DDD/TID (p=0.010) and a non-significant change in trend of 0.02 DDD/TID per quarter (p=0.568). The absolute consumption in Mexico of this therapeutic group had a reduction of -0.1 DDD/TID having a consumption of 1 DDD/TID after the regulation and representing a relative increase of 2% out of the total consumption with a change in level of 0.049 DDD/TID (p=0.622) and a change in trend of -0.008 DDD/TID per quarter (p=0.662).

The mean consumption of sulfonamides in Brazil did not change in absolute numbers having a 0.8 DDD/TID of consumption before and after the regulation, but represented a relative decrease of 2% out of the total consumption during the time studied. The change in level was statistically significant with a decrease of 0.44 DDD/TID (p=0.023) and a no significant change in trend of 0.33 DDD/TID per quarter (p=0.430). Mexico had a reduction of consumption of 50% in the absolute consumption of this sub-group from 1.2 to 0.6 DDD/TID, and a relative reduction of 3% out of the total consumption with a significant reduction of the level of 0.17 DDD/TID (p=0.068) and a non-significant change in trend of 0.022 DDD/TID per quarter (p=0.145).

DISCUSSION

The main objective of this study was to estimate the impact of the OTC regulation on the antibiotics consumption in Brazil and Mexico in the private sector using retail data. We showed that after the regulations took place, an immediate and similar decrease of around 1 DDD/TID in the level of antibiotics consumption was seen in the private sector in both countries, despite the different consumption patterns before the implementation of these policies. We also tested whether the policy was associated with a reduction in the consumption of the therapeutic groups; a significant change in level of consumption by therapeutic group was only observed for the penicillins and sulfonamides in both countries, and macrolides just in Brazil. Unexpectedly, we did not find statistical significant changes in trend of the total consumption of any of the therapeutic subgroups.

A previous study assessing the trend in consumption for Mexico and Brazil between 1997 and 2007 showed a decrease in consumption in Mexico and a stable consumption in Brazil [7]. Our study shows that this decrease in antibiotics consumption in Mexico continued after 2007. However, we found that Brazil is having an increase in consumption in the private sector between 2007 and 2012, and the regulation did not affect this trend. Assuming a relatively stable prevalence of bacterial infections, one could assume that the antibiotics consumption in Brazil would also be constant or decreasing for those antibiotic groups that were the mostly demanded without prescription before the regulation. Further analysis is needed to explore the factors such as the economic growth that could be contributing to the increase in antibiotics sales in this country as well as to assess the effects of increased sales on antibacterial resistance. By including antihypertensives as a control group, we ruled out the potential effects of a general change in consumption in the private sector such as the shifting from the public to the private sector or changes in consumption of pharmaceuticals due to economic changes in both countries.

In this study we calculated the consumption using retail (private sector) data for two reasons. First, the change in regulation on OTC sales could have a greater repercussion in the private sector given that in the public sector a prescription was needed to get medicines even before the regulation. Therefore, self-medication with antibiotics is less common in that sector [6]. Second, there are no other sources of information to calculate and compare the antibiotics consumption between countries because of the inexistent uniform databases between countries to conduct a similar analysis. To enable better comparisons of total drug consumption, we calculated the DDD/TID using the whole population of each country as denominator. Therefore, actual use of antibiotics in the whole country (including the public sector) is higher than the consumption found in the present work. According to IMS Health reports, pharmaceutical volume coverage was 46% for Mexico and 72% for Brazil [21].

The effect of regulating OTC sales of antibiotics in Brazil and Mexico was smaller than the impact found in Chile (-5.56 DDD/TID) but similar to the effect reported in Colombia (-1 DDD/TID) [6]. However, it is important to mention that in Colombia the regulation only took place in the capital city, therefore we were expecting a bigger impact in Mexico and Brazil where the regulation took place throughout the country as in Chile. The differences observed between countries could be due to many factors, for example: the regulation implemented in Chile during 1999 was reinforced with an educational campaign and involvement of pharmacists. However these actions were not sustained and possibly because of this

the consumption started to increase since 2002 [5]. However, we found no description of a nationwide campaign to promote appropriate use of antibiotics at the time that both regulations took place for Brazil and Mexico. In Mexico the government informed the public about the regulatory changes. In addition, in Mexico physician offices were installed within or right next to pharmacies only separated by a wall; pharmacies' customers demanding antibiotics OTC are referred to these physicians' offices to get a prescription. There is not yet evidence about antibiotics prescribing patterns by these offices; but, since their installment was explicitly recommended by market consultancy groups in Mexico as a way "to avoid losses from antibiotics sales" [9], it is probable that prescriptions for antibiotics issued in these offices partly compensated for OTC sales of antibiotics. Although in Brazil a copy of the prescription for an antibiotic is required to be retained, there are anecdotal reports of problems in the verification of the prescription retention, and thus the policy might not be fully implemented. Therefore, from April 2013 onwards antibiotics are included into the National Controlled Substances Management (SNGPC) to improve the monitoring of their consumption. Pharmacies nationwide must submit information electronically concerning drugs subject to the reporting national system [14]. The SNGPC is an important regulatory tool for monitoring drug use nationally and played a key role in the removal of some appetite suppressant drugs from the Brazilian market when the data confirmed abuse [22]; thus, further changes in antibiotics consumption might be observed from 2013.

In the present study, in both countries, the therapeutic group of penicillins was the group with the major consumption and had the highest contribution to the seasonality patterns observed in the total consumption. High seasonal fluctuations in antibiotics consumption suggest inadequate use for viral acute respiratory tract infections (ARI) [23]. Graphically, we observed a change in the seasonality patterns after the policy started, particularly for Mexico, with less difference between consumption in winter and summer than before the regulations started. Penicillins has been reported to be the most common group for self-medication in Mexico [7]. The observed effect on seasonality may be due to the reduction of self-medication with antibiotics for acute respiratory infections. This seems to be confirmed by the fact that we found only a very small change in the overall percentage of consumption of each of the therapeutic groups. The reduction in the percentage of penicillins (5%) out of total antibiotic consumption was replaced by macrolides and quinolones.

More work is required to generate evidence on how to develop an appropriate and effective policy to reduce inappropriate antibiotics consumption in the context of health system reforms in Latin America, where barriers to access to medicines for the poor population, economic crisis, and inadequate prescription and self-medication practices place important challenges. Even though regulating sales of antibiotics is relevant to promote appropriate use, it is only one component of a more comprehensive strategy that is required; campaigns targeting public promoting appropriate use of antibiotics and interventions directed to medical staff are also important to ensure adequate antibiotics consumption. Implementing monitoring systems to track the implementation of the regulation in terms of consumption, antibiotic resistance and infections rates are also core components of a more comprehensive strategy.

CONCLUSIONS

Despite different overall usage patterns of antibiotics in Brazil and Mexico, the effect of the policy enforcing OTC restrictions on antibiotics usage was similar. In Brazil the trend of increase usage of antibiotics was tempered after the OTC restrictions, in Mexico the trend of decreased usage was boosted. The reinforcement of regulations banning the OTC sales of antibiotics need to be monitored together with the development of more comprehensive measures to promote adequate utilization of antibiotics in both countries.

REFERENCES

1. Diekema DJ, Brueggemann a B, Doern G V. Antimicrobial-drug use and changes in resistance in Streptococcus pneumoniae. Emerg Infect Dis. 2000;6(5):552–6.
2. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579–87.
3. Pan American Health Organization. Legislación sobre antibióticos en América Latina [Internet]. Washington, D.C.; 2004. Available from: http://www1.paho.org/spanish/ad/dpc/cd/amr-legis.pdf
4. Bavestrello L, Cabello A, Casanova D. [Impact of regulatory measures in the trends of community consumption of antibiotics in Chile]. Rev Med Chil. 2002 Nov;130(11):1265–72.
5. Bavestrello F L, Cabello M Á. Consumo comunitario de antimicrobianos en Chile, 2000-2008. Rev Chil infectología. 2011;28(2):107–12.
6. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. Trop Med Int Health. 2013 Mar;18(6):665–73.
7. Wirtz VJ, Dreser A, Gonzales R. Trends in antibiotic utilization in eight Latin American countries, 1997-2007. Rev Panam Salud Publica. 2010;27(3):219–25.
8. Dreser A, Wirtz VJ, Corbett KK, Echániz G. Uso de antibióticos en México: revisión de problemas y políticas. Salud Publica Mex. 2008;50:S480–7.
9. Dreser A, Vázquez-Vélez E, Treviño S, Wirtz VJ. Regulation of antibiotic sales in Mexico: an analysis of printed media coverage and stakeholder participation. BMC Public Health. 2012;12:1051.
10. Diario Oficial de la Federación. Acuerdo por el que se determinan los lineamientos a los que estará sujeta la venta y dispensación de antibióticos [Internet]. 2010. Available from: http://dof.gob.mx/nota_detalle.php?codigo=5144336&fecha=27/05/2010
11. IMS Health. Pharmerging shake-up [Internet]. 2006. Available from: http://www.imshealth.com/ims/Global/Content/Insights/Featured Topics/Emerging Markets/Pharma_Shake-up_Imperatives.pdf
12. Pfarma. Pfarma [Internet]. Available from: http://pfarma.com.br/noticia-setor-farmaceutico/legislacao-farmaceutica/387-rdc-44-2010-antibioticos.html
13. ANVISA. Resolução da Diretoria Colegiada – RDC Nº 44, de 26 de Outubro de 2010. [Internet]. 26/10/10. 2010. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0044_26_10_2010.html
14. ANVISA. Definida nova data para controle eletrônico de antibióticos [Internet]. 17/01/2013. 2013 [cited 2013 Apr 18]. Available from: http://portal.anvisa.gov.br/wps/content/anvisa+portal/ anvisa/sala+de+imprensa/ menu+-+noticias+anos/2013+noticias/definida+nova+data+para+controle+eletronico+de+antibioticos
15. Pan American Health Organization. Prevention and Control of Antimicrobial Resistance [Internet]. 1999. Available from: http://www1.paho.org/English/AD/DPC/CD/RegionalPlanParaguay.pdf
16. World Health Organization Collaborating Centre for Drug Statistics Methodology Norwegian Institute of Public Health. ATC/DDD Index [Internet]. 2012. 2012. Available from: http://www.whocc.no/atc_ddd_index/
17. Pan American Health Organization. Pan American Health Organization Data Tabulator [Internet]. 2015 [cited 2015 Feb 2]. Available from: http://www.paho.org/English/SHA/coredata/tabulator/newTabulator.htm
18. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.
19. Chipman JS. Efficiency of Least-Squares Estimation of Linear Trend when Residuals Are Autocorrelated. Econometrica. 1979;47(1):115–28.
20. StataCorp. 2011. Stata Statistical Software: Release 12. 2011.
21. IMS Health. Pharmaceutical Market, Mexico and Brazil. London; 2008.
22. ANVISA. Sistema de gerenciamento de produtos controlados completa cinco anos de funcionamento [Internet]. 30/03/2012. 2012. Available from: http://portal .anvisa.gov.br/ wps/content/ anvisa+portal/ anvisa/ sala+de+imprensa/ menu+-+noticias+anos/2012+noticias/sistema+de+gerenciamento+de+produtos+controlados+completa+ cinco+anos+de +funcionamento

23. Ferech M, Coenen S, Malhotra-Kumar S, Dvorakova K, Hendrickx E, Suetens C, et al. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. J Antimicrob Chemother. 2006 Aug;58(2):401–7.

CHAPTER 4.2

SEASONAL VARIATION IN PENICILLIN USE IN MEXICO AND BRAZIL: AN ANALYSIS OF THE IMPACT OF OVER-THE-COUNTER RESTRICTIONS

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ABSTRACT

Background

During 2010, Mexico and Brazil implemented policies to enforce existing laws of restricting over-the-counter sales of antibiotics. We determined if the enforcement led to more appropriate use by measuring changes in seasonal variation of penicillin use.

Methods

We used retail quarterly sales data in defined-daily-dose per 1000 inhabitants-day (DDD/TID) from IMS Health from the private sector in Mexico and Brazil from the first quarter of 2007 to the first quarter of 2013. This database contains information on volume of antibiotics sold in retail pharmacies using information from wholesalers. We used interrupted time-series models controlling for external factors with the use of antihypertensives with interaction terms to assess changes in trend, level and variation in use between quarters for total penicillin use and by active substance.

Results

The most used penicillin was amoxicillin, followed by amoxicillin-clavulanic acid, and ampicillin (minimal use in Brazil). Before the restrictions, the seasonal variation of penicillin use was 1.1 DDD/TID in Mexico and 0.8 DDD/TID in Brazil. In Mexico, we estimated a significant decrease in the seasonal variation of 0.4 DDD/TID after the restriction mainly due the changes in seasonal variation of amoxicillin and ampicillin. In Brazil, the seasonal variation did not change significantly, neither overall nor in the breakdown by individual active substances.

Conclusions

For Mexico inappropriate penicillin use may have diminished after the restrictions were enforced. For Brazil increasing use and no change in seasonal variation suggests that further efforts are needed to reduce inappropriate penicillin use.

INTRODUCTION

The inappropriate use of antibiotics by humans is one of the main drivers of antimicrobial resistance [1,2]. Antimicrobial resistance has been increasing worldwide but the development of new antibiotics has slowed down [3]. The combination of these two factors has important public health consequences such as long periods of treatment against resistant microbes, a switch to second line treatments with more adverse effects and longer duration of hospitalization, which are all associated with high costs and increased death rates [3,4].

Antibacterial resistance is an international problem; consequently, many countries have started taking action to contain it and reduce it. In the previous fifteen years, some Latin American countries such as Chile, Colombia, Venezuela, Brazil, and Mexico have implemented restrictions on the over-the-counter (OTC) sales of antibiotics, aiming to reduce their use and subsequently improve control of antimicrobial resistance. These OTC sales restrictions imply the requirement of a medical prescription to get antibiotics in private pharmacies and impose fines to the owners of pharmacies for noncompliance.

The impact of the earliest policies has been evaluated by Wirtz et al., who showed a decrease in the consumption of antibiotics after the OTC sales restriction by approximately 1 DDD/TID (defined daily dose per 1,000 inhabitants day) in Colombia, 5.5 DDD/TID in Chile and no decrease in Venezuela [5]. Similarly, we evaluated the impact of these restrictions in Mexico and Brazil, where the banning of OTC sales of antibiotics was reinforced during 2010. We found a direct decrease in the level of the overall consumption of antibiotics by about 1 DDD/TID in both countries without changes in the trends of consumption. In Mexico penicillin use decreased by 0.86 DDD/TID and sulfonamide use decreased by 0.17 DDD/TID. In Brazil penicillin use decreased by 0.64 DDD/TID, sulfonamide use by 0.41 DDD/TID, and macrolides by 0.47 DDD/TID [6]. In both countries, no shift towards use of other classes of antibiotics such as quinolones, macrolides and tetracyclines was observed. An interesting finding in the previous evaluation was that seasonal variation appeared to change after the restrictions took place, but this was not explored in more detail. Seasonal variation in antibiotic use has been associated with short-term lowering of resistance rates in the United States [7] and Israel [8]; moreover, low seasonal variation has been related to rational consumption profiles in Europe [9,10]. Furthermore, it has been suggested that a better understanding of seasonal variation of antibiotic prescribing can be useful in the design of interventions to reduce inappropriate use of antibiotics [11].

To determine if the OTC sales restrictions led to a more appropriate use of antibiotics in Mexico and Brazil, we measured the changes in the seasonal variation in penicillins use before and after the OTC sales restrictions. We focused on the consumption of penicillins because they are the most frequently used class of antibiotics in the selected countries. Additionally seasonal variation in their use and high rates of self-medication have been reported previously [6,12–14]

MATERIALS AND METHODS

Data source and setting

We used retail quarterly sales data from the private sectors in Mexico and Brazil provided by IMS Health. The data was obtained by submitting a research protocol to IMS Health under

their Global Health Research program explaining the objectives and methodology of the present study. IMS Health constructed the database with information of surveys done regularly at various stages of the pharmaceutical chain. The results of the surveys are projected by IMS Health to approximate total volume of sales per country. More information about IMS Health methodology can be found at

[http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS Institute for Healthcare Informatics/Global Health Research Program/Data_Sources_Global_Research.pdf,

http://www.pharmaceuticalpolicy.nl/Presentations/WinterMeeting2010/ Gieshoff, Andreas.pdf]

According to IMS Health reports, pharmaceutical volume coverage was 46% for Mexico and 72% for Brazil [15]. The data was received as kilograms per active substance of antibiotics (ATC code J01) and antihypertensives (ATC codes: C02 antihypertensives, C03 diuretics, C07 beta blocking agents, C08 calcium channel blockers, C09 agents acting on the renin-angiotensin system) as reference group, from the first quarter of 2007 to the first quarter of 2013.

We converted the kilograms sold of each antibiotic and antihypertensive into a daily defined dose per 1,000 inhabitants per day (DDD/TID) according to the Anatomical Therapeutic Chemical (ATC) classification system proposed by the World Health Organization [16]. We used as denominator the entire population of each country, which was estimated based on the growth rate per year using the annual information on the population of both countries from the Pan American Health Organization records [17].

Data analysis

To measure the impact of the policy implementation on the use of penicillins in each country, we used an interrupted time series analysis [18] with robust standard errors for each of the most used penicillins in both countries. The penicillins that are most commonly used were identified by calculating the percentage of use two years prior and two years after the introduction of the restrictions in both countries. In the interrupted time series analysis the antihypertensives group was used as a reference to account for external changes that may affect the consumption of medicines, such as economic growth, changes in coverage of IMS health data and modifications in the structure of health systems.

We estimated whether or not the difference in use between quarters (or seasons) changed after the restriction with a set of interaction terms with dummy variables with value of 1 for autumn, winter and spring seasons. We chose the quarter that corresponds to the summer season as a reference (dummy with value of zero) to evaluate the changes in seasonal variation (differences in the average use between autumn and winter compared to the average use during summer). The summer season takes place during the third quarter of each year in Mexico and during the first quarter of each year in Brazil.

The banning of OTC sales of antibiotics came into force in Mexico on August 25th of 2010 and in Brazil on November 29th of the same year; therefore, we marked the beginning of the regulated consumption for Mexico as the last quarter of 2010 and for Brazil as the first quarter of 2011. The data of the quarters when the restrictions started were not included in the analysis because these periods were only partially affected by the restriction of antibiotic sales. For each model, we examined the autocorrelation of residuals and corrected it, if present,

using autoregressive models. All the analyses were conducted using the STATA Software version 12 Stata Corp LP Texas 1996-2013 [19].

RESULTS

General trends in the use of penicillins

The proportion of the use of penicillins among all antibiotics was fairly similar between the two countries, being 33% to 38% of the total consumption of antibiotics (Figure 1). Overall amoxicillin and ampicillin were the most commonly used active substances, but the proportions of the use of these substances differed between both countries. In 2008, two years before the OTC restrictions, the use of amoxicillin alone represented 15% of overall antibiotic use in Mexico and 29% in Brazil; the use of amoxicillin in combination with clavulanic acid represented 8% in Mexico and 6% in Brazil. Ampicillin was only frequently used in Mexico (13%), but in Brazil the use was below 2%. In 2012, two years after the OTC restrictions, the proportion of the use of amoxicillin had decreased by 2%, while the use of amoxicillin with clavulanic acid had increased by 4% in both countries. The use of ampicillin had decreased by 5% in Mexico alone.

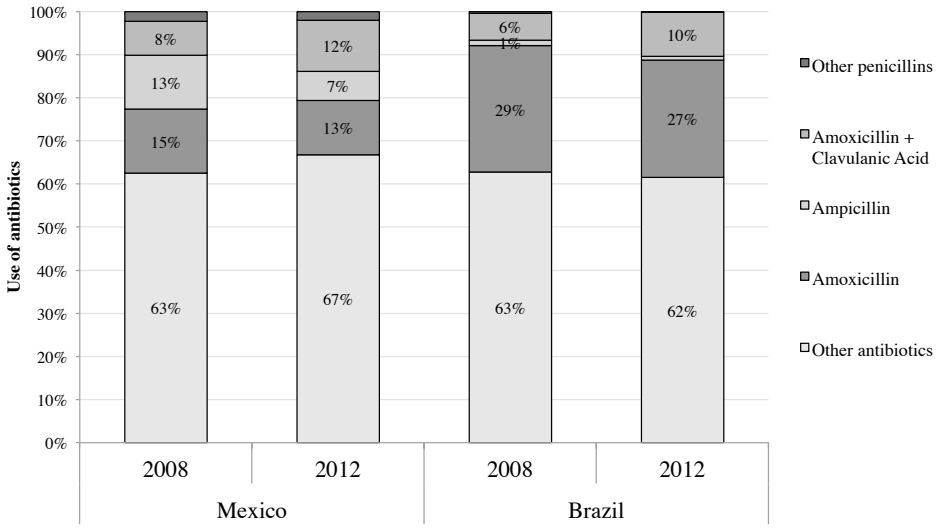

Figure 1. Percentage of use of antibiotics by active substance two years before and after the OTC restrictions took place.

A seasonal variation in the overall use of penicillins was clearly visible with higher use during winter and autumn seasons (Figures 2a and 2b). The time series analysis showed that before the OTC restriction, Mexico presented a seasonal variation (difference in the use between autumn-winter and summer) in the overall use of penicillins of 1.04 DDD/TID in winter and 1.23 DDD/TID in autumn; for Brazil this difference was only significant in autumn with 0.81 DDD/TID. (Table 1)

Table 1: Difference in the use of penicillins (expressed as DDD/TID) between autumn, winter and spring versus summer before the OTC restrictions

	Mexico			Brazil		
	Winter	**Spring**	**Autumn**	**Winter**	**Spring**	**Autumn**
All penicillins	1.039**	0.060	1.226**	0.880	0.265	0.809*
	(0.808 - 1.271)	(-0.210 - 0.33)	(0.981 - 1.472)	(-0.135 - 1.896)	(-0.462 - 0.993)	(0.017 - 1.601)
Amoxicillin	0.472**	0.021	0.589**	0.629	0.184	0.615*
	(0.303 - 0.641)	(-0.148 - 0.191)	(0.456 - 0.721)	(-0.106 - 1.363)	(-0.344 - 0.713)	(0.036 - 1.193)
Amoxicillin + Clavulanic Acid	0.293**	0.050	0.352**	0.251	0.085	0.196
	(0.200 - 0.386)	(-0.029 - 0.129)	(0.266 - 0.439)	(-0.027 - 0.528)	(-0.116 - 0.286)	(-0.025 - 0.416)
Ampicillin	0.255**	-0.004	0.259**	-0.001	-0.003	-0.003
	(0.180 - 0.331)	(-0.070 - 0.063)	(0.146 - 0.371)	(-0.012 - 0.011)	(-0.014 - 0.007)	(-0.013 - 0.008)
Other penicillins	0.019	-0.007	0.027	0.002*	-0.001	0.001
	(-0.012 - 0.049)	(-0.039 - 0.025)	(-0.011 - 0.064)	(0.000 - 0.004)	(-0.002 - 0.001)	(-0.001 - 0.003)

DDD/TID = defined daily dose per 1,000 inhabitants per day; * significant at 5%; ** significant at 1%; 95% CI = Robust 95% confidence intervals between parenthesis

Figure 2a: Mexico

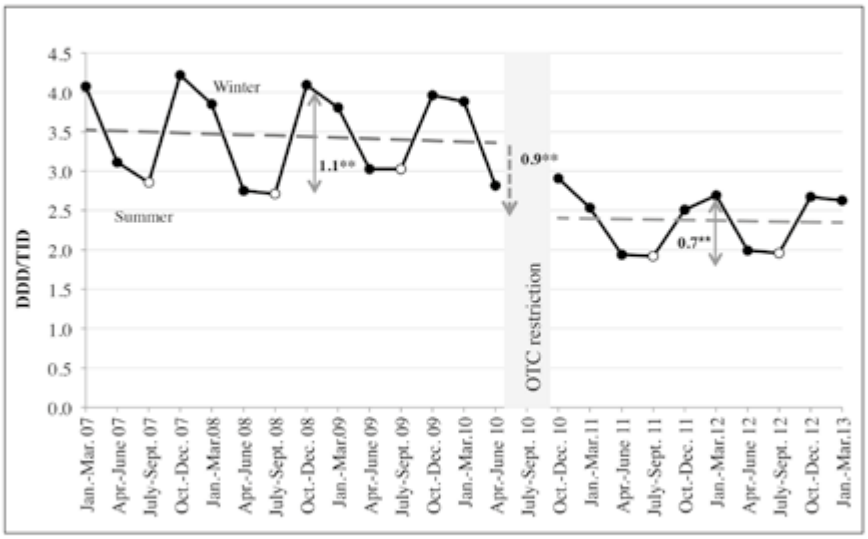

Figure 2b: Brazil

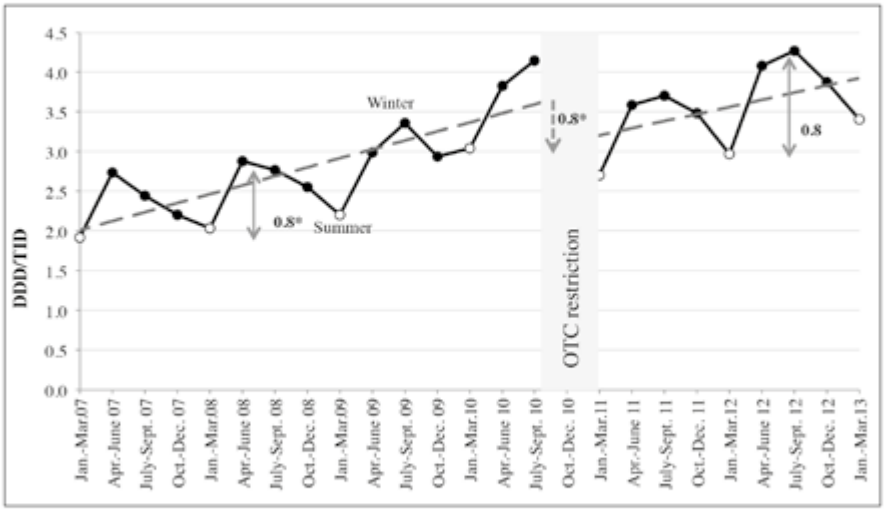

Figure 2. Overall penicillin use before and after the 2010 OTC restrictions indicating changes in level and trend of use and seasonal variation. No change in trend was observed (dotted line). Open dots indicate summer seasons, which were taken as reference to calculate seasonal variation.

After the OTC restriction, we estimated a significant reduction in the seasonal variation in Mexico of -0.36 DDD/TID in winter and -0.47 DDD/TID in autumn (see Table 2a), whereas in Brazil no significant change in the seasonal variation was observed (see Table 2b). In addition to this, the analyses showed a similar reduction in overall level of use, -0.94 DDD/TID in Mexico and -0.81 DDD/TID in Brazil without a change in trend in both countries.

Seasonal variation in individual penicillin use

Amoxicillin was the main driver of the seasonal variation in both countries. In Mexico the seasonal variation before the OTC restriction was significant for autumn with 0.47 DDD/TID and for winter 0.59 DDD/TID. In Brazil the seasonal variation was only significant for autumn with a 0.62 DDD/TID difference (see Table 1, Figure S1 and S2]. After the OTC restriction, Mexico showed a reduction of 33% (-0.17 DDD/TID) in the seasonal variation for the autumn season only (Table 2a). Brazil did not show a significant change in seasonal variation (Table 2b). Mexico showed a marginally significant reduction in the level of use of 0.44 DDD/TID (p=0.054). In contrast, Brazil had a significant reduction of 0.84 DDD/TID (p=0.010) in the level of use of amoxicillin.

In Mexico, amoxicillin in combination with clavulanic acid presented a significant seasonal variation before the OTC restriction with 0.35 DDD/TID higher use in autumn and 0.29 DDD/TID higher use in winter. In Brazil the seasonal variation was not significant. After the OTC restrictions in both countries this combination did not have a significant change in seasonal variation, level and trend of use (Table 2b).

The use of ampicillin was the highest in Mexico with a level of use of about 1.2 DDD/TID; in Brazil this was only 0.10 DDD/TID (Table 1, Figure S5 and S6). In Mexico, a seasonal variation in the use of this active substance was observed before the restriction, with a difference of almost 0.3 DDD/TID for both autumn and winter as compared with use in summer. The seasonal variation completely disappeared after the restriction together with a significant change in level of 0.47 DDD/TID. In Brazil, changes in the seasonal variation and level of use were not observed, but a significant change of 0.05 DDD/TID per quarter in the trend of use was estimated.

DISCUSSION

The objective of this study was to measure the changes in the seasonal variation of penicillin use before and after the OTC restrictions in Mexico and Brazil. The seasonal variation can be seen as a proxy of appropriate use of antibiotics. We showed that after the OTC restrictions, the seasonal variation in the use of penicillins in Mexico decreased by 63%, whereas the seasonal variation in Brazil did not show significant changes. In Mexico, significant decreases in seasonal variation in the use of both amoxicillin (-34%) and ampicillin (-93%) were the main drivers of the overall seasonal reduction. In Brazil, none of the active substances had a significant change in their seasonal variation.

A low seasonal variation together with a low use has been connected to appropriate use of antibiotics and low antimicrobial resistance rates [2,9,10]. In the present study, Mexico and Brazil showed seasonal variations in the use of penicillins with a higher use in autumn and winter than in summer. We estimated that the mean difference in use before the OTC restrictions was 1.1 DDD/TID for Mexico and 0.7 DDD/TID for Brazil, which corresponds with a 46% and 39% difference, respectively, between the mean consumption in summer compared to the mean consumption in winter. Previous studies have found that Northern European countries, where the irrational use of antibiotics is low, showed a mean difference of 23% in consumption of antibiotics between winter and summer. In contrast, Southern European countries, where

Table 2: Changes in the difference in the use of penicillins (expressed as DDD/TID) between autumn, winter and spring versus summer after the OTC restrictions and changes in level and trend of use

	Mexico: change in use of penicillins				
Table 2a	**Winter**	**Spring**	**Autumn**	**Level**	**Trend**
All penicillins	-0.359**	-0.032	-0.469*	-0.938*	0.027
	(-0.613 - -0.105)	(-0.309 - 0.245)	(-0.817 - -0.121)	(-1.825- -0.051)	(0.094 - 0.148)
Amoxicillin	-0.170	-0.009	-0.186*	-0.441	0.020
	(-0.352 - 0.011)	(-0.180 - 0.162)	(-0.361 - -0.011)	(-0.889 - 0.008)	(-0.042 - 0.082)
Amoxicillin + Clavulanic Acid	0.045	-0.052	-0.023	-0.001	0.027
	(-0.129 - 0.219)	(-0.139 - 0.035)	(-0.173 - 0.127)	(-0.371 - 0.369)	(-0.029 - 0.083)
Ampicillin	-0.229**	0.021	-0.247**	-0.474**	0.017
	(-0.364 - -0.095)	(-0.056 - 0.098)	(-0.398 - -0.096)	(-0.676 - -0.272)	(-0.010 - 0.044)
Other penicillins	-0.005	0.008	-0.013	-0.022	0.023*
	(-0.036 - 0.027)	(-0.024 - 0.040)	(-0.051 - 0.025)	(-0.164 - 0.120)	(0.004 - 0.043)
	Brazil: Changes in use of penicillins				
Table 2b	**Winter**	**Spring**	**Autumn**	**Level**	**Trend**
All penicillins	0.077	0.388	-0.000	-0.814	0.023
	(-1.142 - 1.297)	(-0.532 - 1.308)	(-1.009 - 1.008)	(-1.670 - -0.042)	(-0.114 - 0.160)
Amoxicillin	-0.012	0.267	-0.088	-0.843*	0.032
	(-0.883 - 0.858)	(-0.407 - 0.941)	(-0.808 - 0.631)	(-1.474 - -0.213)	(-0.066 - 0.130)
Amoxicillin + Clavulanic Acid	0.085	0.118	0.086	-0.147	0.034
	(-0.252 - 0.421)	(-0.117 - 0.352)	(-0.198 - 0.370)	(-0.519 - 0.224)	(-0.023 - 0.091)
Ampicillin	0.004	0.000	0.002	-0.254	0.049*
	(-0.021 - 0.029)	(-0.031 - 0.032)	(-0.025 - 0.029)	(-0.526 - 0.018)	(0.011 - 0.086)
Other penicillins	0.001	0.003	-0.000	-0.230	0.046*
	(-0.003 - 0.005)	(-0.001 - 0.006)	(-0.005 - 0.004)	(-0.502 - 0.042)	(0.009 - 0.084)

DDD/TID = defined daily dose per 1,000 inhabitants per day; * significant at 5%; ** significant at 1%; 95% CI = Robust 95% confidence intervals between parenthesis.

the irrational use of antibiotics is high, showed a mean difference of 38% of consumption of antibiotics between seasons [2,9]. If we follow the same method for our data from Mexico and Brazil, the inappropriateness of penicillin use was similar to Southern Europe two years before the OTC restrictions, but decreased by 9% in Mexico and increased 1% in Brazil after the OTC restrictions.

The limitation of using this method to assess seasonality is the impossibility to identify if the changes (if any) in the seasonal variation were significant after the OTC restrictions. Therefore, in the present work, we measured changes in the seasonal variation by adding interactions with dummy variables to an interrupted time series model. Following this method, we found that for Mexico the significant change in seasonal variation of overall use of penicillin from 1.1 DDD/TID to 0.7 DDD/TID, was mainly due the reduction in the seasonal variation of two active substances; amoxicillin with a decrease of 34% and ampicillin with a decrease of 93%, indicating a more appropriate use of these medicines after the OTC restriction. A key question is what might explain these findings. A possible explanation is that self-medication with antibiotics is expected to take place to solve upper-respiratory infections (URI). The use of amoxicillin in combination with clavulanic acid is recommended in international and national guidelines to treat URI caused by bacteria, in both children and adults [20,21] because this combination increases the coverage for both ampicillin-resistant *H. influenzae* and *M. catarrhalis* [20]. Therefore, the use of this combination would increase to some extent during autumn-winter seasons, when a high incidence of this type of infection occurs. Our analyses did not show changes in the level of use and seasonal variation in both countries, suggesting that this combination was not frequently sold OTC before the restriction of sales. Moreover, amoxicillin alone is also included in the clinical guidelines to treat URI [20], though it seemed that this active substance was consumed inappropriately before the OTC restriction in Mexico since this country presented a decrease in the seasonal variation (just for autumn) and a marginal reduction in the level of use. Contrarily, ampicillin – not widely recommended for URI because several bacteria such as *H. influenzae* are already resistant to it [20]– showed large seasonal variation before the restriction of antibiotic sales was enforced. The seasonal variation of this active substance vanished after the OTC restriction in Mexico, suggesting that this drop of use was mainly due to the reduction of self-medication and inappropriate use. This result is in line with previous reports of a high rate (78%) of self-medication in Mexico [22] and with the finding that ampicillin was one of the most consumed medicines in 2010 [http://www.eluniversal.com.mx/notas/668756.html] [23] as a consequence of which a high resistance rate to this active substance has been observed [24].

Contrary to our expectations, we did not find a significant difference in the overall use of penicillins between seasons in Brazil, nor by active substance. This unexpected result, together with the increasing trend in the use of pencillins in Brazil over time, may be due to the inclusion of the *Farmacia Popular* program, which has the objective to facilitate the access to medicines to all the population [25]. The effect of this program was partially controlled for by taking into account the trend of the use of antihypertensives. However, given that the program had differential subsides in medicines for chronic diseases this could cause a differential effect in the use between therapeutic groups. Therefore, more research is needed to evaluate the effect of

the *Farmacia Popular* program in Brazil in the use of different therapeutic groups. Furthermore, in 2013 Brazil has tightened its regulations of antibiotic sales by registering the sales of antibiotics on the controlled medicines electronic system indicating the difficulties of enforcing the OTC restriction between 2010 and 2013 [26]. Contrary to Brazil, there was not further enforcement such as this in Mexico.

In preliminary stages of this research we also explored seasonal variation in other frequently used therapeutic groups in both countries. We did not find seasonal variation in the use of tetracyclines, and sulfonamides in Mexico and tetracyclines, quinolones and sulfonamides in Brazil. The seasonal variation in quinolones in Mexico and macrolides in Brazil did not show significant changes after the restrictions took place. In Mexico macrolides had a decrease in the seasonal variation by 0.052 DDD/TID in the autumn season compared to summer season. We expected these results because these classes of antibiotics are less frequently used for self-medication [13,14].

A possible limitation of the data is the underestimation of antibiotic use in the whole country since we just focused in the private sector consumption. Nevertheless, the use of these data from the private sector allowed us to assess the changes in use of antibiotics in the sector where self-medication is relevant and where the policy was implemented; self-medication is less likely to happen in the public sector where pharmacies only dispense with demonstration of a prescription. Since we look at relative changes over time and because we correct for changes in the coverage by adjusting for antihypertensive use focusing only on the private sector, this limitation does not affect the overall results. The use of IMS Health data allowed us to make a comparison of the same type of sales restrictions between countries.

To the best of our knowledge, no previous work has estimated the impact of OTC restrictions on seasonal variation in the use of penicillins. This measure could be helpful to determine the impact of policy changes on the rational use of antibiotics, which could be reinforced using information campaigns to guide patients to seek treatment and avoid self-medication. Information campaigns have been a key factor in the success of the results of a similar policy in Chile [27,28] but there was no implementation of these campaigns in Mexico and Brazil. Our results have important policy implications because the evaluation of these policies can help decision makers to take corrective actions if needed as well to monitor the progress of this policy change. The main objective of OTC restrictions implemented in Mexico and Brazil was to reduce the use of antibiotics in the general population. The requirement of a medical prescription to get antibiotics in private pharmacies aimed to prevent self-medication with this therapeutic group and consequently to control antibacterial resistance. We suggest that, additional to the evaluation of changes in level and trend of use, it is important to examine changes in seasonal variation because this adds information on inappropriateness of use such as self-medication behaviour after an OTC sales restriction of antibiotics takes place.

The policies to restrict OTC sales of antibiotics led to a decrease in seasonal variation in Mexico but not in Brazil, which may indicate that inappropriate use of penicillins diminished after the restrictions were enforced in Mexico. For Brazil the increasing use of penicillins together with no change in seasonal variation suggests that further efforts have to be done to reduce their inappropriate use.

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REFERENCES

1. Austin DJ, Kristinssson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proc Natl Acad Sci. 1999;96(February):1152–6.
2. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579–87.
3. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013 Dec;13(12):1057–98.
4. Wise R, Hart T, Cars O, Streulens M, Helmuth R, Huovinen P, et al. Antimicrobial resistance. Is a major threat to public health. BMJ. 1998 Sep;317(7159):609–10.
5. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. Trop Med Int Health. 2013 Mar;18(6):665–73.
6. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HGM, Wirtz VJ. Impact of Over-the-Counter Restrictions on Antibiotic Consumption in Brazil and Mexico. PLoS One. 2013 Jan;8(10):e75550.
7. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. Clin Infect Dis. 2012 Sep;55(5):687–94.
8. Dagan R, Barkai G, Givon-Lavi N, Sharf AZ, Vardy D, Cohen T, et al. Seasonality of antibiotic-resistant streptococcus pneumoniae that causes acute otitis media: a clue for an antibiotic-restriction policy? J Infect Dis. 2008 Apr 15;197(8):1094–102.
9. Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf. 2007 Jan;16(1):115–23.
10. Achermann R, Suter K, Kronenberg A, Gyger P, Mühlemann K, Zimmerli W, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. Clin Microbiol Infect. 2011 Jun;17(6):855–61.
11. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010. Antimicrob Agents Chemother. 2014 May 3;58(5):2763–6.
12. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. Trop Med Int Health. 2013 Jun;18(6):665–73.
13. Grigoryan L, Monnet DL, Haaijer-Ruskamp FM, Bonten MJM, Lundborg S, Verheij TJM. Self-medication with antibiotics in Europe: a case for action. Curr Drug Saf. 2010;5(4):329–32.
14. Al-Azzam S, Al-Husein B, Alzoubi F, Masadeh M, Al-Horani "Mohammad Ali." Self-Medication with Antibiotics in Jordanian Population. Int J Occup Med Environ Health [Internet]. 2007 Jan 1 [cited 2014 Sep 15];20(4):373–80. Available from: http://www.degruyter.com/view/j/ijmh.2007.20.issue-4/v10001-007-0038-9/v10001-007-0038-9.xml
15. IMS Health. Pharmaceutical Market, Mexico and Brazil. London; 2008.
16. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf
17. Pan American Health Organization. Pan American Health Organization Data Tabulator [Internet]. 2015 [cited 2015 Feb 2]. Available from: http://www.paho.org/English/SHA/coredata/tabulator/newTabulator.htm
18. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.
19. StataCorp. 2011. Stata Statistical Software: Release 12. 2011.
20. Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJC, Hicks L a, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin

Infect Dis [Internet]. 2012 Apr [cited 2014 Jul 10];54(8):e72–112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22438350

21. CENETEC. Guía de Práctica Clinica - Infección Aguda de Vías Aéreas Superiores [Internet]. Mexico City; 2009 [cited 2014 Sep 12]. Available from: http://www.cenetec.salud.gob.mx/descargas/gpc/CatalogoMaestro/062_GPC__InfAgVASde3mesesa18a/INFECCION_VIAS_AEREAS_EVR_CENETEC.pdf

22. (Centro de Opinión Pública UVM). 78% de la población se automedica [78 % of the population self-medicate] [Internet]. Mexico City; 2013. Available from: http://opinionpublicauvm.mx/sites/default/files/presentaciones/Reporte de resultados automedicaci%C3%B3n 2013 v2.pdf

23. Wirtz VJ, Dreser A, Silva J, Echaniz G, Velazquez ME, Garza U, et al. Patrones de prescripción médica y de auto prescripción de antibióticos en Morelos 2006. Comisión Coordinadora de Institutos Nacionales de Salud y Hospitales de Alta Especialidad [Internet]. 2007 [cited 2014 Mar 3]. Available from: http://cid.oxfordjournals.org/content/46/2/155.full.pdf

24. Arredondo-García JL, Amábile-Cuevas CF. High resistance prevalence towards ampicillin, co-trimoxazole and ciprofloxacin, among uropathogenic Escherichia coli isolates in Mexico City. J Infect Dev Ctries. 2008;2(5):350–3.

25. Santos-Pinto CDB, do Rosário-Costa N, García Serpa Osorio-de-Castro C. Quem acessa o Programa Farmácia Popular do Brasil? Aspectos do fornecimento público de medicamentos The "Farmácia Popular do Brasil" Program and aspects of public provision of medicines in Brazil. Ciênc saúde coletiva. 2011;16(6):2963–73.

26. ANVISA. Definida nova data para controle eletrônico de antibióticos [Internet]. 17/01/2013. 2013 [cited 2013 Apr 18]. Available from: http://portal.anvisa.gov.br /wps/ content/ anvisa+portal/ anvisa/s ala+de+imprensa/menu+-+noticias+anos/ 2013+noticias/ definida+nova+data +para+ controle +eletronico+de +antibioticos

27. Bavestrello L, Cabello A, Casanova D. [Impact of regulatory measures in the trends of community consumption of antibiotics in Chile]. Rev Med Chil. 2002 Nov;130(11):1265–72.

28. Bavestrello F L, Cabello M Á. Consumo comunitario de antimicrobianos en Chile, 2000-2008. Rev Chil infectología. 2011;28(2):107–12.

SUPPLEMENTARY MATERIALS

Figure S1: Use of amoxicillin in Mexico

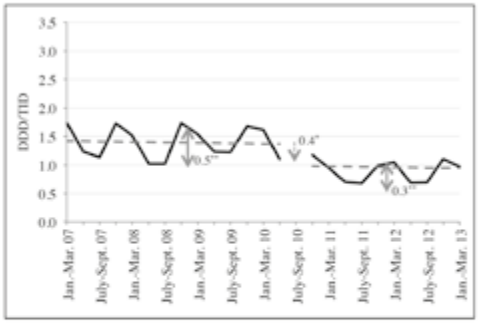

Figure S2: Use of amoxicillin in Brazil

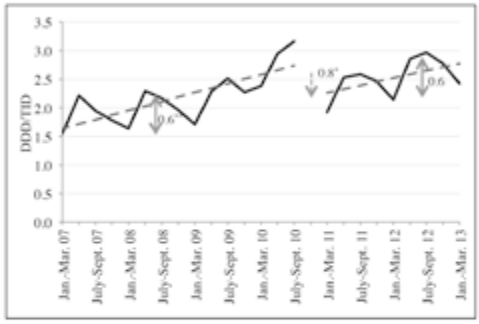

Figure S3: Use of amoxicillin with clavulanic acid in Mexico

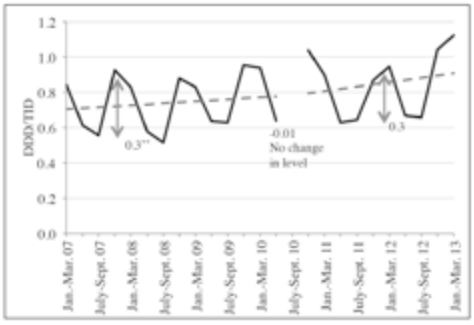

Figure S4: Use of amoxicillin with clavulanic acid in Brazil

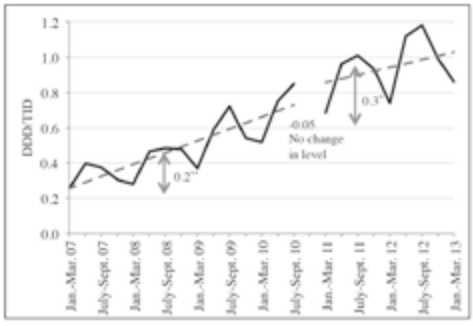

Figure S5: Use of ampicillin in Mexico

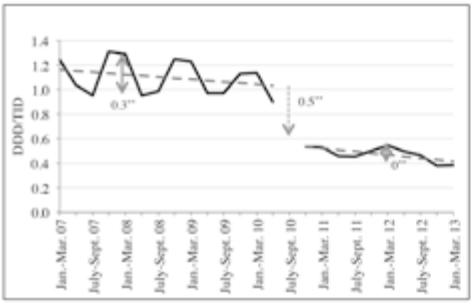

Figure S6: Use of ampicillin in Brazil

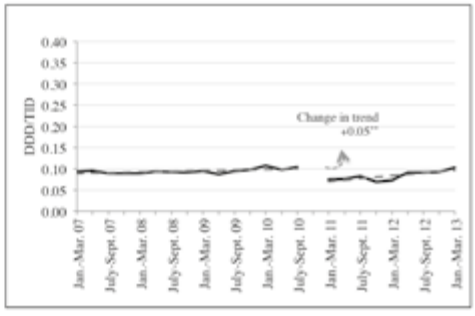

Figure A. Changes in trend, level and seasonality of use of active substances belonging to the therapeutic group of penicillins before and after the 2010 OTC restrictions in Mexico and Brazil.

CHAPTER 4.3

REPLY TO "DECREASE IN PENICILLIN SALES IN BRAZIL AFTER OVER-THE-COUNTER RESTRICTIONS"

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Antimicrob Agents Chemother. 2015; 59(9):5864

LETTER TO THE EDITOR

We thank Lopes-Júnior et al. [1] for their interest in our study and the opportunity to clarify a number of points from our work. We agree with Lopes-Júnior et al. that the over-the-counter sales restrictions of antibiotics had a positive effect on the use of antibiotics in Brazil by decreasing their use immediately after the implementation of the sales restrictions. In a previous study we reported these changes in the overall use of antibiotics and stratified by subgroups measured in defined-daily-doses per 1,000 inhabitants per day (DDD/TID) [2]. Brazil had an overall decrease in the level of use of antibiotics of 1.35 DDD/TID (13%) and significant decreases in level of use of the following therapeutic groups: sulfonamides (0.41 DDD/TID, 46%), macrolides (0.47 DDD/TID, 26%) and penicillins (0.64 DDD/TID, 15%), however, we found that the overall antibiotic use continued to grow after these immediate changes. Effects of external factors such as growth of the pharmaceutical market as a whole was adjusted for in this analysis by taking a control group (antihypertensives) into account.

Our study about seasonal variation of penicillins in Mexico and Brazil is a more detailed analysis of the effect of OTC sales restriction in these two countries [3], where we focused the analysis on the seasonal variation in penicillin use as a measure of change in self-medication patterns. The differences in results between our study and the study by Lopes-Júnior et al. [1] may be explained by differences in data sources and analysis techniques. Whereas Lopes-Júnior et al. [1] averaged the sales pre and post restriction of sales enforcement and compared the differences in percentages, we used interrupted time series analysis of longitudinal data to measure the impact of the policy on the use of antibiotics. This robust quasi-experimental method controls for most threats to internal validity by adjusting for pre-existing trends in study outcomes that are unrelated to the policy [4]. Nevertheless, we agree with Lopes-Júnior et al. [1] that the surveillance of antimicrobial prescription should be a common practice, not only in Brazil but in other Latin American countries. As recommended by international organizations [5] we also urge for nationally representative standardized data collection to accurately describe and compare utilization of medicines in Latin American countries.

REFERENCES

1. Lopes-Júnior R, de Sá Del Fiol F, Oliveira Araujo JL, de Toledo MI, Barberato-Filho S. Decrease in Penicillin Sales in Brazil after Over-The-Counter Restrictions. Antimicrob Agents Chemother. 2015;AAC01128-1.
2. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HGM, Wirtz VJ. Impact of Over-the-Counter Restrictions on Antibiotic Consumption in Brazil and Mexico. PLoS One. 2013 Jan;8(10):e75550.
3. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HGM, Wirtz VJ. Seasonal Variation in Penicillin Use in Mexico and Brazil: Analysis of the Impact of Over-the-Counter Restrictions. Antimicrob Agents Chemother. 2015 Jan;59(1):105–10.
4. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299–309.
5. World Health Organization. The evolving threat of antimicrobial resistance - Options for action [Internet]. Geneva, Switzerland; 2012. Available from: whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf

CHAPTER 4.4

EFFECTS OF OVER-THE-COUNTER SALES RESTRICTION OF ANTIBIOTICS ON SUBSTITUTION WITH MEDICINES FOR SYMPTOMS RELIEF OF COLD IN MEXICO AND BRAZIL: TIME SERIES ANALYSIS

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ABSTRACT

We evaluated changes in the use of non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics and cough and cold medicines and its relation with the use of antibiotics after the over-the-counter (OTC) antibiotic sales restrictions in Mexico and Brazil. IMS Health provided retail quarterly data from the private sectors in Mexico and Brazil from the first quarter of 2007 to the first quarter of 2013. Data of each active substance of antibiotics, easily accessible medicines perceived as antibiotics substitutes (cough and cold medicines, analgesics, and NSAIDs – the latter two being combined in the analyses), and medicines to control for external factors that can affect the medicines usage trend (antihypertensives) were converted from kilograms to defined-daily-doses per 1,000 inhabitants days (DDD/TID). Interrupted time series were used to estimate changes in level of medicines use at the intervention point and slope after the regulation. The Gregory-Hansen cointegration test was used to explore the relation between the use of antibiotics and perceived substitutes. After the regulation in Mexico NSAIDs-analgesics usage level increased by 1.1 DDD/TID with a slope increase of 0.2 DDD/TID per quarter and the cough and cold medicines usage level increased by 0.4 DDD/TID. In Brazil NSAIDs-analgesics usage level increased by 1.9 DDD/TID, and cough and cold medicines did not change. In the two countries, NSAIDs-analgesics usage changes were related with antibiotic usage changes, while only in Mexico cough and cold medicines usage changes had a relation with the antibiotics usage changes. These results showed a substitution effect on the use of other medicines, especially NSAIDs and analgesics, after reinforcement of OTC antibiotics sales restrictions. These regulations aimed to improve the antibiotics use and as a consequence reduce antimicrobial resistance, however, this type of policies should be comprehensive and take into account the potential substitution effects on the use of other medicines.

INTRODUCTION

Pharmaceutical policy amendments are created with the objective to improve the population well-being by improving the use, availability and accessibility of medicines. Nevertheless, even well planned policies can generate unintended consequences by creating incentives that can be harmful in the short or long term. Previous studies have investigated the unintended consequences of pharmaceutical policies; in 1991 Weintraub et al., evaluated the consequences of the triplicate benzodiazepine prescription regulation during 1989 in New York, finding an increase in the prescription of other psychotherapeutic drugs with higher habituation, tolerance and physical dependence [1]. In 1993 Ross-Degnan et al., reported a substitution effect towards different non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics after the withdrawal of Zomepirac in 1985, recommending the evaluation of perceived substitutes and implications after the withdrawal of drugs in the market [2]. In 2011, Signorovitch et al. documented that the temporary removal of olanzapine from the preferred drug list in Medicaid Florida had an unintended effect by disrupting the continuity of patients care with diagnosis of schizophrenia and bipolar disorder which led to an increase number of hospitalizations and emergency room visits in the months after the implementation [3].

In the previous fifteen years some Latin American countries have reinforced the regulation to prohibit over-the-counter (OTC) sales of antibiotics, with the aim to reduce their inappropriate use and antimicrobial resistance [4–6]. This implementation was carried out during 1999 in Chile, during 2005 in Colombia, during 2006 in Venezuela and during 2010 in Mexico and Brazil [7–10]. The consequences in case of non-compliance that the owners of pharmacies face are closure of the pharmacy and high fines [4]. After the policy reinforcement, the level of use of antibiotics decreased approximately by 1 defined daily dose per 1,000 inhabitants per day (DDD/TID) in Colombia, Brazil and Mexico and 5 DDD/TID in Chile, whereas no changes in level of use were found in Venezuela [9–11]. Additionally, the seasonal variation in the use of penicillins used as a proxy for self-medication decreased in Mexico after the policy reinforcement but did not change in Brazil [12].

After the banning of sales of antibiotics OTC, patients may have substituted the use of antibiotics with other type of medications to relief discomfort of perceived mild diseases. Since it was observed in Mexico that the self-medication with antibiotics mainly occurred with symptoms of cold, we hypothesized that the use of medications such as NSAIDs, analgesics and cough and cold medicines might have changed after the reinforcement of the regulations targeted only for antibiotics.

Therefore, in this work we evaluated if the use of medicines for symptoms relief changed after the regulation of antibiotics sales took place in Mexico and Brazil.

MATERIALS AND METHODS

Data source and setting

IMS Health provided retail quarterly sales data from the private sectors in Mexico and Brazil from the first quarter of 2007 to the first quarter of 2013. The data were obtained by submitting a research protocol to the IMS Health Global Health Research program. IMS Health

constructed the database with information from surveys conducted regularly at various stages of the pharmaceutical chain. The results of the surveys were projected to the approximate total volume of sales per country [13,14]. IMS Health data has been used for other cross-national comparisons of drug use and it has been recognized that this type of data can be considered as a good information source in cases where there is a weakness in surveillance networks [15].

The data were received as kilograms per active substance of antibiotics (ATC code J01), cough and cold medicines (ATC code R05), non-opioid analgesics (ATC code N02B), and NSAIDs (ATC code M01). NSAIDs and non-opioid analgesics were grouped together for the analysis. We used antihypertensives (ATC codes: C02 antihypertensives, C03 diuretics, C07 beta blocking agents, C08 calcium channel blockers, C09 agents acting on the renin-angiotensin system) as the reference group.

We converted the kilograms sold of each chemical substance into a defined daily dose per 1,000 inhabitants per day (DDD/TID) according to the Anatomical Therapeutic Chemical (ATC) classification system proposed by the World Health Organization [16]. We used the entire population of each country as the denominator, which was estimated with the growth rate per year using the annual population of both countries from the Pan American Health Organization records [17].

Data analysis

For each group we conducted interrupted time series analyses [18] to estimate changes in slope and level of use of each of the groups after the policy started. We used the beginning of the policies as an interruption of the series for each group. OTC sales of antibiotics were banned in Mexico on August 25th 2010 and in Brazil on November 29th of the same year. Therefore, the beginning of the regulated sales for Mexico was marked as the last quarter of 2010 and for Brazil as the first quarter of 2011, these quarters were excluded from each of the corresponding models for each group. The reference group was used to control for external changes that may affect the general trend of medicines consumption, such as economic growth and changes in coverage of IMS Health data, changes in access to medicines and modifications in the structure of health systems. Seasonal variation was assessed using dummy variables, autocorrelation and stationarity were tested and corrected for if present using autoregressive moving average (ARIMA) models.

To evaluate if the changes in the use of medicines were a consequence of the policy change we used the Gregory-Hansen (GH) cointegration test to evaluate if the use and changes in use of antibiotics and substitutes were related. We used this test because it is known that the use of antibiotics group in both countries had changes in level after the restriction started [10]. With the GH cointegration test we evaluated the relation of the use of antibiotics with the use of medicines for symptoms relief in four different scenarios: changes in level, changes in level and trend, changes in level and slope (also known as regime), and changes in level, slope and trend (also known as changes in regime-trend) [19,20].

The GH cointegration test can only be conducted on non-stationary series with identical order of integration[19].Therefore, as a prior test for cointegration, we used the Zivot-Andrews test for stationarity [21]. Results from the Zivot-Andrews test can be found in the supplemental

material eTable 1. Stationary therapeutic groups were not included in the cointegration test. All these analyses were conducted with STATA Software version 12 Stata Corp LP Texas.

RESULTS

In Mexico, a decreasing trend in the use of antibiotics was observed from 10 DDD/TID at the beginning of 2007 to 7.5 DDD/TID at the beginning of 2013. Moreover, seasonal variation was observed with higher use in the fourth and first quarter of each year corresponding to the winter seasons. The group of NSAIDs-analgesics had an average use of 17 DDD/TID with seasonal variation and fluctuations in slope along the series (figure 1a). The use of cough and cold medicines had a stable trend around 1.5 DDD/TID with similar seasonal variation as observed in the use of antibiotics (figure 1b).

In Brazil, an increasing trend in the use of antibiotics was observed from 5.6 DDD/TID at the beginning of 2007 to 9.5 at the beginning of 2013. Seasonal variation was observed with higher use in the second and third quarter of each year, also corresponding to the winter season. The highest increase in use was observed in the group of NSAIDs-analgesics with an increase in use from 15 DDD/TID at the beginning of 2007 to 27 DDD/TID at the beginning of 2013 without seasonal variation (figure 2a). The use of cough and cold medicines had a slight increasing trend with an average use of 1.4 DDD/TID and seasonal variation similar to what observed in the antibiotics group (figure 2b).

Effect of reinforcement of regulations on the use of medicines

We summarize the interrupted time series results for Mexico in Table 1 and for Brazil in Table 2. In Mexico the reinforcement of the OTC sales restriction of antibiotics led to a decrease in the level of use of antibiotics of 1.5 DDD/TID at the intervention point but an increase in the level of use at the intervention point of NSAIDs-analgesics (1.1 DDD/TID) and cough and cold medicines (0.4 DDD/TID). Additionally, an increase in the slope of use was estimated for antibiotics (0.1 DDD/per quarter) and NSAIDs-analgesics (0.2 DDD/TID per quarter).

Although the increasing slope of use of antibiotics in Brazil did not change after the policy reinforcement, the level of use at the intervention point decreased by 1.5 DDD/TID, we estimated after the policy reinforcement an increase in the level of use of NSAIDs-analgesics of 1.8 DDD/TID. The level of use of cough and cold medicines and the slope of use did not significantly change after the policy reinforcement.

Table 1. Interrupted time series results for Mexico

	Change in level [a] (95% CI)	**Change in slope [b] (95% CI)**
Antibiotics	-1.53** (-2.11 - -0.94)	0.11** (0.05 - 0.17)
NSAIDs and analgesics	1.08** (0.19 - 1.96)	0.19** (0.04 - 0.34)
Cough and cold medicines	0.42** (0.12 - 0.71)	0.01 (-0.04 - 0.06)

[a] Change in level measure as DDD/TID
[b] Change in slope measure as DDD/TID per quarter
[c] Number of * denotes significance: *95% and **99%

Table 2. Interrupted time series results for Brazil

	Change in level [a] (95% CI)	**Change in slope [b] (95% CI)**
Antibiotics	-1.54** (-2.48 - -0.61)	0.06 (-0.09 - 0.22)
NSAIDs and analgesics	1.88** (0.19 - 3.57)	0.26 (-0.02 - 0.54)
Cough and cold medicines	0.06 (-0.13 - 0.25)	0.01 (-0.02 - 0.04)

[a] Change in level measure as DDD/TID
[b] Change in slope measure as DDD/TID per quarter
[c] Number of * denotes significance: *95% and **99%

Relation between the use of antibiotics and the use of perceived substitutes

The results from the Gregory and Hansen (GH) cointegration test corroborated the relation between the use and changes in use of antibiotics, NSAIDs-analgesics, and cough and cold medicines. These results are summarized in Figure 1 for Mexico and Figure 2 for Brazil (for further details see eTable 2 in the supplemental material).

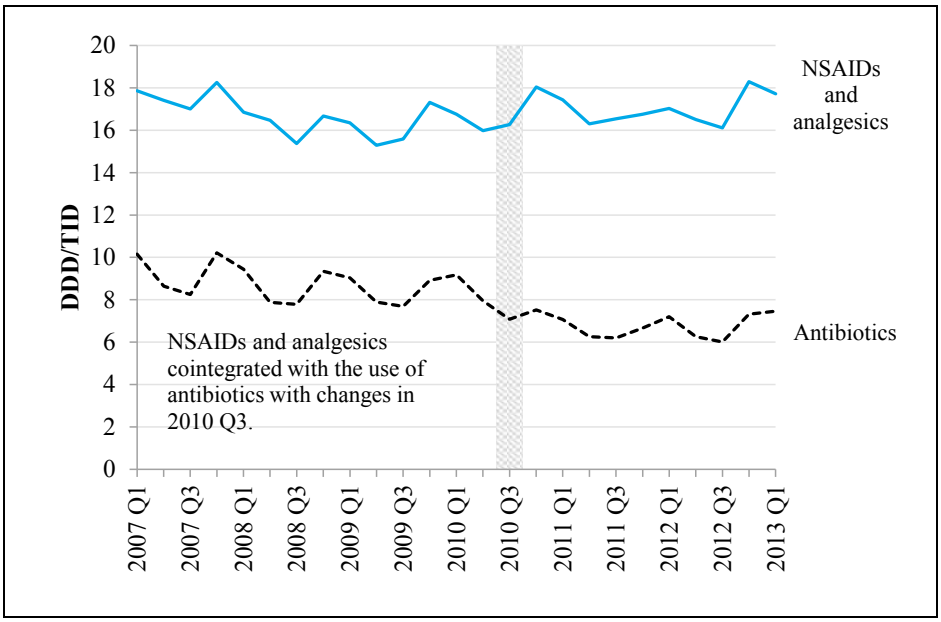
In Mexico, this test indicated that the use and change in level of use of NSAIDs-analgesics and cough and cold medicines were related with the use and change in level of use of antibiotics (figure 1a and 1b). In Brazil the use and change in level of use of NSAIDs-analgesics was related with the use of antibiotics but the use of cough and cold medicines was not eligible to test for cointegration with antibiotics (figure 2a and 2b). Therefore, the results suggest that in Mexico and Brazil the use of antibiotics was substituted with the use of NSAIDs-analgesics and only in Mexico the use of antibiotics was also substituted to a smaller extent with cough and cold medicines.

DISCUSSION

Using data from the private pharmaceutical sector in Mexico and Brazil we found that in Mexico the decrease in antibiotics usage level after the reinforcement of the policy was related with an increase in the level of use of NSAIDs-analgesics and a slight level increase in use of cough and cold medicines. In Brazil the decrease in antibiotics usage level was related with a level increase in the use of NSAIDs-analgesics. The cointegration tests confirmed for both countries that changes in use of NSAIDs-analgesics can be connected to changes in use of antibiotics as a result of the policy reinforcement.

To the best of our knowledge, this is the first study that has examined the effects of an antibiotic sales regulation on the use of other medicines as an unintended and potentially unwanted consequence of the policy reinforcement. As in previous studies on other policy implementations, we also observed such an effect in the present study: the relation of changes in use of antibiotics with changes in use of NSAIDs-analgesics in Mexico and Brazil and the relation of changes in use of antibiotics with changes in use of cough and cold medicines in Mexico. The use of cough and cold medicines is not recommended particularly in children because of the potential toxicities [22]. Some years ago several countries, such as the United Kingdom, United States of America and Australia rescheduled cough and cold medicines for

1a. Trends of use of antibiotics and NSAIDs-analgesics in Mexico



1b. Trends of use of antibiotics and cough and cold medicines in Mexico

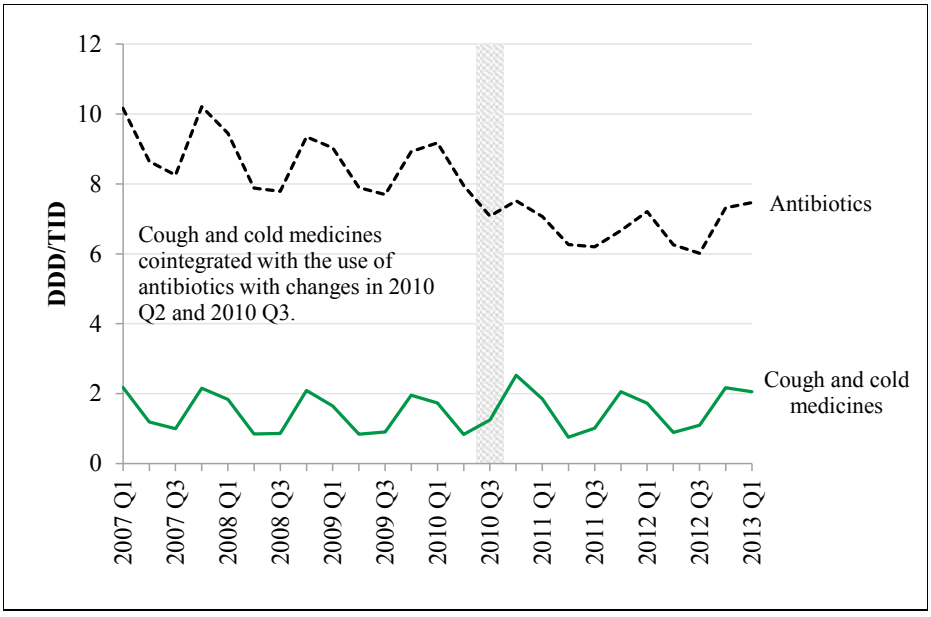
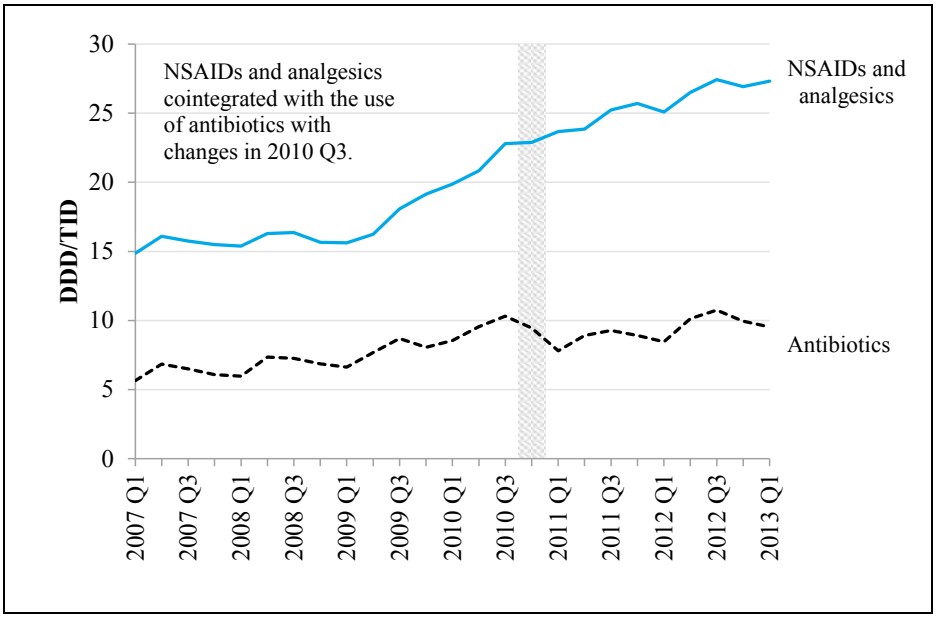


Figure 1. Trends of use of NSAIDs-analgesics and cough and cold medicines in comparison with the use of antibiotics in Mexico. Grey bars indicate when the OTC antibiotic sales restriction started in Mexico (third quarter of 2010). Cointegration was assessed using the Gregory-Hansen test, for further details of the results of the cointegration test see supplemental material eTable2.

2a. Trends of use of antibiotics and NSAIDs-analgesics in Brazil



2b. Trends of use of antibiotics and cough and cold medicines in Brazil

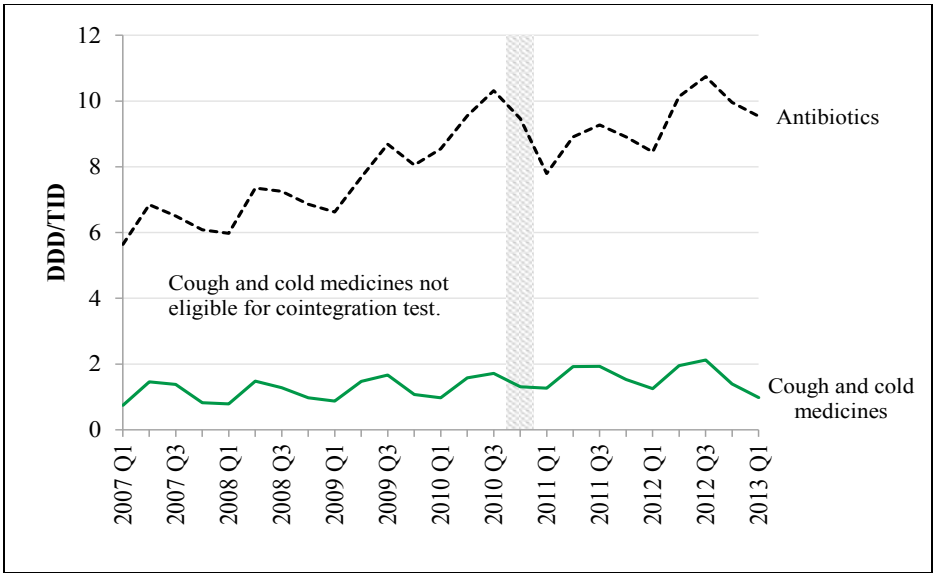


Figure 2. Trends of use of NSAIDs-analgesics and cough and cold medicines in comparison with the use of antibiotics in Brazil. Grey bars indicate when the OTC antibiotic sales restriction started in Brazil (fourth quarter of 2010). Cointegration was assessed using the Gregory-Hansen test, for further details of the results of the cointegration test see supplemental material etable2.

under two years of age as prescription-only medicines following reports on adverse effects and lack of evidence on their effectiveness in children [23].

Although some NSAIDs and analgesics (e.g. ibuprofen and paracetamol) are recommended to relief symptoms of viral infections in children and adults [24], it has been recommended that the use of NSAIDs should be at the lowest effective dose and that long-term use NSAIDs should be avoided if possible [25,26]. In patients at risk of gastro-intestinal bleeding it is recommended to use a nonselective NSAID together with a gastro-protective agent such as a proton pump inhibitor [26].

But patients in Mexico and Brazil who opted to self-medicate with NSAIDs-analgesics and patients in Mexico who opted to self-medicate with cough and cold medicines instead of antibiotics might not be aware of the appropriate use of these medications and their adverse effects [27]. Therefore, the increasing use of perceived substitutes of antibiotics and their potential consequences need to be taken into consideration to fully evaluate the benefit of the policy directed at OTC sales restrictions of antibiotics in these two countries since the main problem of responsible self-medication was not addressed by this policy. A comprehensive regulation to dispense medicines safely and efficiently in pharmacies should be enforced in both countries.

The effect on the use of NSAIDs and analgesics in Mexico and Brazil and cough and cold medicines in Mexico might be due to two different actions: changes in self-medication or changes in health seeking behaviours. Changes in self-medication behaviour might occur when patients unable to get antibiotics OTC ask for medication to relief their symptoms of disease thereby decreasing the use of antibiotics but increasing the use of NSAIDs-analgesics and cough and cold medicines. As in many Latin American countries, in Mexico and Brazil the majority of the personnel working in private pharmacies do not have the professional education to dispense medicines [28,29]. Therefore, the decision of the type of medicine needed relies on the patient or recommendations from non-health professional such as medicine sellers, family members or friends. Self-medication is common in Latin America, due to multiple reasons, one of them the regulatory deficiencies that allows sales of non OTC medications without the requirement of a medical prescription [30]. Other studies have found that the self-medication in Latin American countries is a common practice [31–33] and Latin Americans living abroad also incur in self-medication [34–36].

Changes in health seeking behaviours might occur when patients unable to obtain antibiotics OTC look for medical care. In absence of bacterial infection, healthcare professionals could prescribe NSAIDs and non-opioid analgesics resulting in a decrease of the prescription of antibiotics and increasing the prescription of these medicines. Previous studies have documented that in Mexico the number of physician offices next to pharmacies increased after the OTC sales restriction of antibiotics. Approximately 10% of the population who sought medical treatment received it at these medical offices instead of the social security services, public or other private services. As a consequence, the number of medicines (whether antibiotics or other medicines) prescribed by the physicians next to pharmacies was higher than the number of medicines prescribed to individuals who sought treatment elsewhere [37,38]. Even though nearly 80% of the Mexican population and Brazilian population is affiliated to a public insurance [39,40],

public health institutions have not been able to fulfil quality standards for access, capacity and quality of care and this might influence the decision of patients to self-medicate or to seek medical care in the private sector [41].

A possible limitation of this study is the underestimation of medicine use in the whole country since we just focused on the private sector consumption. With the use of the IMS Health data we were able to assess the changes in use of easily accessible medicines in the sector where self-medication is relevant; self-medication does not happen in the public sector where pharmacies only dispense to patients who show prescriptions from the same institution [42]. Additionally, with the analysis of these data we were able to make a comparison of the same type of sales restrictions between countries with a large time frame allowing the analysis with different tools for time series data.

Stationarity data properties for cough and cold medicines in Brazil did not enable us to test their cointegration with antibiotics. In Mexico the increase in the use of cough and cold medicines together with the observed relation with the use of antibiotics indicates that cough and cold medicines are used as substitutes. In both countries the non-stationarity properties of antibiotics and NSAIDs-analgesics enabled us to test for cointegration and finding a relation between the use and usage changes of antibiotics with the use and usage changes NSAIDs-analgesics. These results together with the usage level increase estimated with interrupted time series models confirm that while the use of antibiotics in Mexico and Brazil dropped the use of NSAIDs-analgesics went up as an unintended effect of the OTC antibiotic sales restriction policy. Further studies are needed to measure the health outcomes of the increase in use of NSAIDs in these two countries as well as the consequences of the increase in use of cough and cold medicines in Mexico.

CONCLUSION

An unintended effect of OTC antibiotic sales restrictions in Mexico and Brazil occurred when persons substituted the use of antibiotics with NSAIDs and analgesics in both countries and cough and cold medicines in Mexico. Hence, this type of policies should be comprehensive and should take into account the potential substitution effects on the use of other medicines. Therefore, sales regulations of any therapeutic group should be followed by an overall assessment of the use of other medicines that can be perceived as substitutes.

REFERENCES

1. Weintraub M, Singh S, Byrne L, Maharaj K, Guttmacher L. Consequences of the 1989 New York State triplicate benzodiazepine prescription regulations. JAMA. 1991;
2. Ross-Degnan D, Soumerai SB, Fortess EE, Gurwitz JH. Examining product risk in context. Market withdrawal of zomepirac as a case study. JAMA. 1993 Oct 27;270(16):1937–42.
3. Signorovitch J, Birnbaum H, Ben-Hamadi R, Yu AP, Kidolezi Y, Kelley D, et al. Increased olanzapine discontinuation and health care resource utilization following a Medicaid policy change. J Clin Psychiatry. 2011 Jun;72(6):787–94.
4. Diario Oficial de la Federación. Acuerdo por el que se determinan los lineamientos a los que estará sujeta la venta y dispensación de antibióticos [Internet]. 2010. Available from: http://dof.gob.mx/nota_detalle.php?codigo=5144336&fecha=27/05/2010
5. ANVISA. Resolução da Diretoria Colegiada – RDC No 44, de 26 de Outubro de 2010. [Internet]. 26/10/10. 2010. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2010/res0044_26_10_2010.html
6. ANVISA. Definida nova data para controle eletrônico de antibióticos [Internet]. 17/01/2013. 2013 [cited 2013 Apr 18]. Available from: http://portal.anvisa.gov.br/ wps /content /anvisa+portal /anvisa /sala+ de+ imprensa/menu+ -+noticias +anos/ 2013+noticias /definida+ nova+ data+ para+ controle+ eletronico+ de+ antibioticos
7. Bavestrello F L, Cabello M A, Casanova Z D. Impacto de medidas regulatorias en la tendencia de consumo comunitario de antibióticos en Chile. Rev Med Chil. Sociedad Médica de Santiago; 2002 Nov;130(11):1265–72.
8. Vacca CP, Niño CY, Reveiz L. Restriction of antibiotic sales in pharmacies in Bogotá, Colombia: a descriptive study. Rev Panam Salud Pública. Organización Panamericana de la Salud; 2011;30(6):586–91.
9. Rivas P, Alonso G. Regulations governing the dispensing of medications and their effect on antibiotic consumption in Venezuela. Rev Panam Salud Publica. 2011 Dec;30(6):592–7.
10. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HGM, Wirtz VJ. Impact of Over-the-Counter Restrictions on Antibiotic Consumption in Brazil and Mexico. PLoS One. 2013 Jan;8(10):e75550.
11. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. Trop Med Int Health. 2013 Mar;18(6):665–73.
12. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HGM, Wirtz VJ. Seasonal Variation in Penicillin Use in Mexico and Brazil: Analysis of the Impact of Over-the-Counter Restrictions. Antimicrob Agents Chemother. 2015 Jan;59(1):105–10.
13. IMS Health. IMS The Uniform System of Classification [Internet]. 2008 [cited 2014 Oct 3]. Available from: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Health Services Research Network/USC_Classiification_Process_2011.pdf
14. IMS Health. Pharmaceutical Market, Mexico and Brazil. London; 2008.
15. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014 Aug;14(8):742–50.
16. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf
17. Pan American Health Organization. Pan American Health Organization Data Tabulator [Internet]. 2015 [cited 2015 Feb 2]. Available from: http://www.paho.org/English/SHA/coredata/tabulator/newTabulator.htm
18. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.

19. Gregory AW, Hansen BE. Residual-based tests for cointegration in models with regime shifts. J Econom. 1996 Jan;70(1):99–126.

20. Gregory AW, Hansen BE. Tests for Cointegration in Models with Regime and Trend Shifts. Oxf Bull Econ Stat. 2009 May 1;58(3):555–60.

21. Zivot E, Andrews DWK. Further Evidence on the Great Crash, the Oil-Price Shock, and the Unit-Root Hypothesis. J Bus Econ Stat. Taylor & Francis; 2002 Jan 1;20(1):25–44.

22. Norazida AR, Sivasampu S, Teng CL. Cough and cold medication in children: a public health concern. Med J Malaysia. 2014 Oct;69(5):219–23.

23. Sung V, Cranswick N. Cough and cold remedies for children [Internet]. 2009. Available from: http://www.australianprescriber.com/magazine/32/5/122/4

24. CDC. Get Smart: Symptom Relief [Internet]. 2015. Available from: http://www.cdc.gov/getsmart/community/for-patients/symptom-relief.html

25. Lanza FL, Chan FKL, Quigley EMM. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728–38.

26. Arboleya LR, de la Figuera E, Garcia MS, Aragon B. Management pattern for patients with osteoarthritis treated with traditional nonsteroidal anti-inflammatory drugs in Spain prior to introduction of Coxibs. Curr Med Res Opin. L.R. Arboleya, Seccion de Reumatologia, Hospital de Cabuenes, Gijon, Asturias, Spain; 2003;19(4):278–87.

27. Cham E, Hall L, Ernst AA, Weiss SJ. Awareness and use of over-the-counter pain medications: a survey of emergency department patients. South Med J. 2002;95(5):529–35.

28. Kroeger A, Ochoa H, Arana B, Diaz A, Rizzo N, Flores W. Inadequate drug advice in the pharmacies of Guatemala and Mexico: the scale of the problem and explanatory factors. Ann Trop Med Parasitol. Routledge, part of the Taylor & Francis Group; 2001 Sep;95(6):605–16.

29. González Pier E, Barraza Lloréns M. Trabajando por la salud de la población: Propuestas de política para el sector farmacéutico. Versión para el diálogo. [Internet]. Funsalud. Ciudad de Mexico: Funsalud; 2011. Available from: http://www.funsalud.org.mx/eventos_2011/trabajando por la salud/Doc PolPublSFarm vFDigital 060511.pdf

30. Wirtz VJ, Dreser A, Leyva R. [The debate on self medication]. Salud Publica Mex. 2009 Jan;51(3):179–80.

31. Haak H. Pharmaceuticals in two Brazilian villages: lay practices and perceptions. Soc Sci Med. 1988 Jan;27(12):1415–27.

32. Villegas G, Brieva J, Danhier A. [Use of drugs on sale at private pharmacies]. Rev Med Chil. 1987 Oct;115(10):919–24.

33. Price LJ. In the shadow of biomedicine: self medication in two Ecuadorian pharmacies. Soc Sci Med. 1989 Jan;28(9):905–15.

34. González-López JR, Rodríguez-Gázquez M de los Á, Lomas-Campos M de las M. Self-medication in adult Latin American immigrants in Seville. Acta Paul Enferm. Escola Paulista de Enfermagem, Universidade Federal de São Paulo; 2012;25(spe2):75–81.

35. Mainous AG, Diaz VA, Carnemolla M. Factors affecting Latino adults' use of antibiotics for self-medication. J Am Board Fam Med. 2008 Jan;21(2):128–34.

36. Sánchez J. Self-medication practices among a sample of latino migrant workers in South Florida. Front public Heal. 2014 Jan;2:108.

37. Pérez-Cuevas R, Doubova S V, Wirtz VJ, Servan-Mori E, Dreser A, Hernández-Ávila M. Effects of the expansion of doctors' offices adjacent to private pharmacies in Mexico: secondary data analysis of a national survey. BMJ Open. 2014 Jan;4(5):e004669.

38. Pérez Cuevas R, Doubova S, Wirtz VJ, Dreser A, Serván Mori EE, Hernández Ávila M. Evidencia para la política pública en salud n Consultorios médicos en farmacias privadas: efectos inesperados en el uso de servicios de salud y el acceso a medicamentos [Internet]. 2013. Available from: http://ensanut.insp.mx/doctos/analiticos/UsoConsultorio.pdf

39. Insituto Nacional de Salud Publica. Encuesta Nacional de Salud y Nutricion 2012 [Internet]. 2012 [cited 2015 Jul 11]. Available from: http://ensanut.insp.mx/doctos/ENSANUT2012_Sint_Ejec-24oct.pdf

40. Castro Hoyos CE. Salud y seguridad social : un breve comparativo de cinco países de América Latina [Internet]. 2012 [cited 2015 Jul 12]. Available from: http://library.fes.de/pdf-files/bueros/kolumbien/09229.pdf

41. Sauceda-Valenzuela AL, Wirtz VJ, Santa-Ana-Téllez Y, De La Luz Kageyama-Escobar M.

Ambulatory health service users' experience of waiting time and expenditure and factors associated with the perception of low quality of care in Mexico. BMC Health Serv Res. BioMed Central; 2010;10(1):178.

42. Enriquez Rubio E, Frati Munari AC, González Pier E, Barraza Llórens M, Martínez Valdés E, Linares Luna Parra V. Hacia una política farmacéutica integral para México. Primera Ed. Secretaria de Salud; 2005.

SUPPLEMENTARY MATERIALS

eTable 1. Results from the Zivot-Andrews unit root test

	Intercept [a]	**Trend** [b]	**Intercept and trend** [c]
Mexico			
Antibiotics			
t statistic [d]	-3.3	-2.1	-3.4
Breaking date	2011-Q1	2012-Q1	2011-Q1
Lags [e]	2	2	2
NSAIDs and analgesics			
t statistic [d]	-4.0	-4.3	-4.3
Breaking date	2008-Q3	2008-Q4	2009-Q4
Lags [e]	2	2	2
Cough and cold medicines			
t statistic [d]	-4.1	-3.8	-4.2
Breaking date	2010-Q3	2008-Q4	2010-Q3
Lags [e]	1	1	1
Brazil			
Antibiotics			
t statistic [d]	-3.8	-2.9	-3.6**
Breaking date	2011-Q3	2010-Q4	2011-Q3
Lags [e]	2	2	2
NSAIDs and analgesics			
t statistic [d]	-2.7	-2.8	-3.2
Breaking date	2010-Q2	2008-Q1	2009-Q3
Lags [e]	0	0	0
Cough and cold medicines			
t statistic [d]	-13.0***	-12.0***	-13.9***
Breaking date	2011-Q1	2012-Q1	2011-Q2
Lags [e]	1	1	1

[a] Critical values of unit root with changes in intercept: 1%: -5.34 5%: -4.80 10%: -4.58
[b] Critical values of unit root with changes in trend: 1%: -4.93 5%: -4.42 10%: -4.11;
[c] Critical values of unit root with changes in both intercept and trend: 1%: -5.57 5%: -5.08 10%: -4.82.
[d] Number of * denotes rejection of the null hypothesis at different levels: * 10%, ** 5% and ***1%. Null Hypothesis: Unit root process with structural breaks.
[e] The lag length was selected using Akaike Information Criterion out of a maximum lag of 2.

eTable 2. Results from the Gregory and Hansen cointegration test

	ADF[a]	Breakpoint	Zt[b]	Za[b]	Breakpoint	Lags[c]
Mexico						
NSAIDs and analgesics						
Change in level	-5.02**	2010-Q1	-5.58***	-27.40	2010-Q2	1
Change in level trend	-5.29**	2010-Q1	-5.41**	-26.92	2010-Q2	1
Change in regime	-4.62**	2010-Q3	-5.20**	-26.01	2010-Q2	1
Change in regime trend	-5.16	2010-Q3	-5.40**	-27.07	2010-Q2	1
Cough and cold medicines						
Change in level	-4.97**	2010-Q2	-5.08**	-24.41	2010-Q2	0
Change in level trend	-5.93***	2010-Q4	-5.25**	-26.70	2010-Q2	0
Change in regime	-4.65	2010-Q3	-4.75*	-24.07	2010-Q3	0
Change in regime trend	-6.85***	2010-Q3	-5.69**	-28.88	2010-Q3	2
Brazil						
NSAIDs and analgesics						
Change in level	-4.83**	2010-Q3	-4.94**	-26.19	2010-Q3	0
Change in level trend	-8.67***	2010-Q4	-5.08**	-26.78	2010-Q4	1
Change in regime	-5.06**	2010-Q2	-5.16**	-26.10	2010-Q3	1
Change in regime trend	-9.36***	2010-Q4	-5.68**	-28.65	2010-Q3	1

[a] Number of * denotes rejection of the null hypothesis at different levels: * 10%, ** 5% and ***1%. Null Hypothesis: there is a unit root in the residuals and hence there is no cointegration. The null hypothesis is rejected if the statistic ADF* is smaller than the corresponding critical value.

[b] The test statistics can also be measured using the Philip test statistics that are denoted as Za and Zt. Critical values taken from Gregory and Hansen, 199626.

[c] The lag length was selected using Akaike Information Criterion out of a maximum lag of 2.

CHAPTER 5

DISCUSSION

INTRODUCTION

Among other objectives (e.g. drug development, regulation, production, marketing), pharmaceutical policies aim to promote the appropriate use of medicines in the population. The evaluation of these policies measures their effects and the degree to which these policies reached the targeted objectives. Furthermore, policy evaluations help to identify areas of improvement as well as unintended consequences. For example, in the 1990's, the consequences of the triplicate benzodiazepine prescription regulation during 1989 in New York was evaluated, finding a decrease in benzodiazepine prescribing but with an undesirable increase in prescribing of other psychotherapeutic drugs with higher habituation, tolerance and physical dependence [1]. Other evaluations have helped to identify how internal or external factors, such as an economic recession, also played a role in pricing and reimbursement of medicines [2]. Such evaluations are needed for evidence-based and effective policy-making. However, further development and improvement of the methodology used in such studies is of great importance to guarantee their proper assessment.

This thesis focuses on methodological aspects of drug utilization studies and their application to study diverse pharmaceutical policies implemented at the national level in multiple countries.

Drug utilization research has been useful in assessing the appropriate use of medicines and in evaluating the effect of pharmaceutical policies [1–4]. However, its usefulness in influencing pharmaceutical policies depends largely on robust data analyses [3–6]. In this thesis, different data sources have been analyzed with different methodologies to evaluate the effects of pharmaceutical policies on the use of medicines in countries with different income levels, focusing on cross-national comparisons (CNC) to study the impact of pharmaceutical policies on drug utilization. The data available to conduct these studies allowed the use of interrupted time series analysis to assess changes in medicine use [3]. Interrupted time series analysis has been one of the most used methodologies for pharmaceutical policy evaluation. However, other analyses with time series data, such as the assessment of structural changes and cointegration tests, can be conducted to study the use of medicines [7]. In this thesis, these methods are applied and evaluated for their future use in the evaluation of pharmaceutical policies.

CROSS-NATIONAL COMPARISONS IN DRUG UTILIZATION RESEARCH

Although drug utilization research has been around since the early 1960s, it has been in constant evolution. The quantity and quality of data used to conduct drug utilization studies have been increasing over the past years. Methodologies from other research fields such as economics, operation research or informatics, are now being widely applied in pharmacoepidemiology and drug utilization research. For example, propensity score matching and instrumental variables have been applied to reduce the effects of confounding and measurement errors in observational studies, and interrupted time series analysis has been implemented to evaluate changes in the use or pricing of medicines after a policy change [8–10].

The comparison of medicines' use between health care institutions, regions and countries has been facilitated as a consequence of improvement of both data and methods. However,

there is also a need for further standardization to conduct, to assess, and to evaluate cross-national comparisons (CNCs) of medicine use to increase validity and reliability of CNC studies. Other fields have developed good practice guidelines, such as guidelines for good pharmacoepidemiology practices by the International Society of Pharmacoepidemiology [11], guidelines on methodological standards in pharmacoepidemiology by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [12], and guidelines for systematic reviews and meta-analysis (PRISMA) [13], to mention some. These guidelines have set a precedent to improve the quality and comparability of research works with respect to those specific themes.

This thesis contributes in three ways to CNC of drug utilization research: 1) it identifies existing gaps in CNC of drug utilization; 2) it proposes a checklist to assess and report CNC of drug utilization as a first step in defining good practice standards; 3) it broadens drug utilization research to geographical regions where CNCs are not commonly conducted.

MAPPING THE FIELD OF DRUG UTILIZATION USING CROSS-NATIONAL COMPARISONS

With respect to mapping drug utilization research, this thesis found that existent CNCs of drug utilization have focused mainly on antibiotics, antihypertensives, opioids, antidepressants, and anti-psychotics (Chapter 2.1).

The growing concern about antimicrobial resistance around the world has been one of the fundamental reasons for studying the use of antibiotics in many countries. One of the most influential and game-changing CNC study resulted from the 2001 initiative to improve the use of antibiotics by the European Surveillance of Antimicrobial Consumption (ESAC), a consortium of European institutions funded by the European Union. The main objective of the ESAC project was to collect comparable and reliable data of antibiotic use in Europe from available public sources to assess the human exposure to antibiotics. The first results of the ESAC project were published in 2004 [14], reporting the methodologies used to collect the data, followed by the comparison of antibiotic use between 26 European countries in 2005 [15]. This project served as an example to develop similar studies that described the use of antibiotics in Eastern Europe [16] and Latin America [17].

Cardiovascular diseases (CVD) are one of the leading causes of death and disability worldwide [18]. The Euro-Med-Stat project, a similar initiative to the ESAC project, started in 2002 with the objective to establish an inventory of national medicine data sources and a survey of available data to assess data reliability and comparability between countries [19]. In the Euro-Med-Stat project, the use of statins and lipid-reducing agents were compared across several European countries such as Austria, Italy, France and Ireland. Data sources used were reimbursement databases and IMS Health data. Given the difficulty of comparing the results between data sources, the researchers in this project called for standardization of data collection and analysis for studies using administrative databases [20].

Other efforts of CNC have been undertaken by the IMI PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics) project [21], PROTECT was a five years project

funded by the Innovative Medicines Initiative (IMI) and started in 2009. In the PROTECT project, different data sources were used to develop methodological standards and innovative tools to strengthen the monitoring of the benefit/risk profile of medicines in Europe and to increase early detection and assessment of adverse drug reactions. The IMI-PROTECT group focused their research on the association between the use of antibiotics and acute liver injury; the association between the use of benzodiazepines and use of antidepressants and hip fracture; the association between use of inhaled long-acting beta2-agonists and acute myocardial infarction; the association between anti-epileptics and suicidality; and the association between calcium channel blockers and risk of cancer [22].

There is no doubt that the above described therapeutic groups are important; however, more insight in the way medicines for e.g. chronic obstructive pulmonary disease, mental diseases, diabetes, or cancer are prescribed and used, is also needed (see also chapter 2.1). Treatment of these diseases is costly and because of their high prevalence, the treatment is a burden for health systems [23,24]. This warrants further attention to these therapeutic groups.

Apart from the gaps in terms of therapeutic groups, other research gaps were found when comparing the use of medicines between countries. For example, the level of detail in the description of data sources used for CNCs, and information about population coverage and data coverage was minimal in the articles reviewed in chapter 2.1. These gaps in the reporting methodology of CNC studies served as a base for the development of an evaluation checklist to review CNC studies in chapter 2.2.

Reporting the results of a CNC of drug utilization is not a trivial task. The first objective of the evaluation checklist was to improve the assessment of CNCs of drug utilization studies. This can be done by focusing on the analysis of the comparability of data sources commonly used for drug utilization research, including assessment of the population and drug coverage as well as the type of codification and information included. It is equally important to take into account the primary objective of the database and the reimbursement status of each medicine studied. The checklist is a tool to systematically assess the collection and analysis of study data in a standardized way with the objective to simplify the identification of potential comparability problems between databases that affect the validity and reliability of the results.

Countries' characteristics such as health system structure, ethical and privacy legal systems, and reimbursement policies play an important role in the quantity and quality of data contained in each database. Databases that capture reimbursement information have been commonly used in drug utilization research [25], because they provide an approximation of the medicines used by the population. Even though this type of database has facilitated the study of medicine use, they have been built for administrative purposes, and their construction for research requires thoughtful maneuvering with all the inherent limitations. Other databases for clinical research such as electronic health records have also been used for drug utilization research [25], and this type of data collection system is still under development in many clinical settings across countries [26].

The checklist was pilot tested three times, during these testing phases users reported that the evaluation checklist was arduous to complete, mainly due to the frequent weaknesses in the reporting of CNC studies, which includes lack of a thorough description of databases

and health systems' context. In addition, the use of different units of measure can hamper the comparison across studies. Even with the perception of difficulty, the evaluation checklist can serve as a strategy to conduct and report CNC of drug utilization. The developed checklist is the first step to improve the assessment of CNC in a systematic way (see also chapter 2.2). This checklist can be useful not only for researchers who are interested and willing to conduct CNC of drug utilization studies, but also for decision-makers who wish to compare the use of medicines between countries to identify areas where more research is needed or guide pharmaceutical policies to improve the use of medicines.

The second objective of the evaluation checklist was to guide the report of CNC studies in the near future. The proposed checklist was developed and reviewed by a group of experts on drug utilization studies through numerous rounds of internal testing. External reviewers are currently testing this checklist as a process of validation. Still, the patterns of use of medicines and their comparisons between countries require further study. The literature review of CNCs, together with the checklist for evaluation, constitute the first step for the development of good practice guidelines for designing, conducting, analyzing and reporting CNC of drug utilization studies.

These guidelines will be discussed with members of the International Society of Pharmacoepidemiology, with the aim to ensure that the guidelines will enhance the validity and reliability of CNC of drug utilization studies, to facilitate their peer review, correct interpretation, and adequate translation into pharmaceutical policy decision-making. The final draft of the guidelines will be submitted to the International Society of Pharmacoepidemiology (ISPE) members for comments consistent with the ISPE Policy Manual and sent to the ISPE Board for action.

The results from the literature review and the development of the evaluation checklist for CNC of drug utilization studies were taken into account for the assessment of insulin uptake in Denmark, Finland, Norway, Sweden, and the United Kingdom (chapter 2.3). Although medicines to treat diabetes have been previously studied [27], this analysis identified differences in insulin use in each of these countries after the more recent market approval of several new insulin analogues. The data of the Cancer Risk and Insulin Analogues (CARING) project [28] was used to study the insulin uptake in relation to the implementation of different policies, such as market approval, reimbursement decisions, and clinical recommendations, which may be associated with insulin-prescribing practices.

The findings presented in this chapter 2.3 demonstrate that insulin analogues uptake was gradual in all the countries studied. The prescription of insulin analogues started before their inclusion in a reimbursement list, without the identification of any relation between reimbursement decisions and insulin analogues uptake. However, other factors might have influenced the insulin market uptake. These factors include campaigns for early detection of diabetes mellitus, marketing strategies, and insulin availability and accessibility [29]. The assessment of these factors on insulin usage was out of the scope of this study.

International and national guidelines to treat diabetes mellitus recommend the use of basal insulin as a first treatment approach when lifestyle changes and oral anti-diabetic treatment fail to reduce the HbA1c level [30]. Neutral Protamine Hagedorn (NPH) insulin is the most

commonly used insulin because it is available at a lower cost than other basal insulins, such as insulin glargine and insulin detemir [31]. Although various countries from different income levels have included insulin analogues in their positive lists [32], in the case of Brazil, the country has been advised to disinvest in insulin glargine given its high price without major health benefits in comparison with other basal insulins [33].

The analysis of medicine uptake for chronic diseases is important given the aging of the population. Scandinavian countries have been identified as being distinct from many other countries because of their comprehensive health coverage and reimbursement policies [34–38]. The analyses of the use of medicines in Denmark, Finland, Norway, and Sweden have been documented in the past [27]. One of the factors that have contributed to the frequent study of medicine use in these countries is the availability of centralized statistics on dispensed prescriptions [39,40]. However, one potential weakness of the Scandinavian prescription databases is their lack of information about diagnosis or the severity of the conditions treated; therefore, we were not able to distinguish between insulin treatments depending on the severity of the illness. Furthermore, medicines dispensed to individuals during a hospital stay and to individuals in nursing homes are not completely recorded, thus creating observation gaps; this leads to an underestimation of total medicine usage, especially in the elderly population. A general problem using dispensing data to assess medicine use is that it is not possible to know whether the dispensed medicines were actually taken by the patients or not. Nevertheless, the Scandinavian databases are the best approximation on the use of medicines in the population and can serve as an example to conduct drug utilization studies since their imperfections are minimal in comparison with other databases [40–42]. Therefore, the insulin uptake study provides important results on the comparison of the use of insulin in different countries, and the results can be used for future decision-making for the treatment of chronic diseases in this region or other regions of the world. Additionally, this study also can help to explain some of the results found in the CARING project, providing information on trends in use of the different insulin types together with the align of use with clinical guidelines and pharmaceutical policies. This information gave context to the outcomes found in the CARING project. The main objective of CARING project was to determine any link between the use of various insulins and cancer incidence. The results of the project showed no evidence of differences between human insulin and insulin analogues and risk of cancer [28].

STATISTICAL METHODS TO ANALYZE DRUG UTILIZATION IN CROSS-NATIONAL COMPARISONS

At present, there are various methodologies for pharmaceutical policy analysis. These methods can vary depending on the research questions and the data available to answer them. Qualitative and quantitative methods have been used alone or in combination to study drug utilization and the impact of pharmaceutical policies [43]. For comparing the use of medicines between countries and regions, most studies have focused on the evaluation of their use by reporting the number of defined daily doses (DDDs) or prescribed daily doses (PDDs), among other units of measure [25]. In addition to its contribution to CNC drug utilization research, this thesis broadens the knowledge on research methodology used in this field.

For the evaluation of pharmaceutical policies, up to now there has been a strong focus on segmented time series analyses following the publication of a seminal article describing this methodology in 2002 [10]. However, when evaluating pharmaceutical policies or other policies, it is important to take into account that the effect of the policy can be modified by other factors. In the case of pharmaceutical policies, the use of medicines can be affected by several factors. These factors can be setting-related, such as economic growth, changes in the health system structure, or changes in the medicines' reimbursement coverage; on the other hand, these factors can be related to changes in the method of the data collection.

Chapter 3.2 addresses the use of reference groups to control for external changes that might affect the use of medicines or the data analyzed. Brazil served as a case example to justify the importance of reference groups in the evaluation of policies. In the previous 25 years, Brazil has had economic and social changes in major social determinants of health and has re-organized the health system [44]. All these changes can affect the demand of medicines within and between health sectors. For the evaluation of changes on the dispensing policies of antibiotics, data from IMS Health was used. However, IMS Health updated the sample of Brazilian medicine sales by increasing the sample size over a period of time. This improved the data coverage in the country, with the drawback of affecting estimations occurring during the time period surrounding the sample update period and had a direct effect on the overall trend of the medicines studied in that specific time period.

Therefore, it is recommended, if possible, to document the changes in the data collection procedures and how this can affect the results.

5

CONDUCTING CROSS-NATIONAL COMPARISONS OF DRUG UTILIZATION OUTSIDE EUROPE

In this thesis, two regions of the world were explored in addition to the North of Europe, where most of the drug utilization studies have been conducted. We expanded the study of pharmaceutical policies using time series analysis to Latin American countries and South Africa. In these two regions, universal health coverage is evolving [45–47]. One of the main goals of universal health coverage is increasing the equity in access to medicines for the population while ensuring financial protection. The evaluation of pharmaceutical policies in these contexts is an important component to provide information on medicine utilization. This information could support policy decisions towards universal health care.

The study in chapter 3.2 focused on the evaluation of the use of generic medicines for chronic non-communicable diseases after the introduction of a law requiring the mandatory offer of generic substitution by pharmacists and other dispensers in South Africa during 2003. The mandatory offer of generic substitution appeared to have had minimal effect on utilization patterns in the two years after 2003. After the implementation of the policy, the use of generics of selective serotonin reuptake inhibitors (SSRIs) increased and the use of originator SSRI decreased, the effect on angiotensin-converting-enzyme inhibitors (ACE-I) and calcium channel blockers was less pronounced, but still statistically significant. For proton pump inhibitors (PPIs), the intended effect of the policy was not detected. These mixed results were

perhaps because other managed care interventions were already in place [48], but it remains an important enabling provision, to reduce the cost of medicines in many countries[49]. However, other elements still need to be addressed; for example, the selection of medicines in the private sector, an enforceable code of marketing practice, and a more transparent way of indicating which medicines can be substituted, based on suitable bioequivalence and other data [50], this information can be useful to identify prescription practices that are not complying with the substitution policy.

On the other side of the world, Latin American countries are also advancing towards strengthening existing systems with universal health coverage. In this thesis, Mexico and Brazil were studied in the context of reinforcement of OTC sales restriction of antibiotics as a measure to control antimicrobial resistance.

The study of the use of antibiotics in this region of the world is important given the burden of infectious diseases [18]. For the evaluation of the restriction of antibiotics' OTC sales, we measured the size of the effect of the policy in chapter 4.1. The evaluation of the impact of prohibiting OTC sales of antibiotics is important for informing policy-makers about the effectiveness of the measures taken, including undesired effects of interventions. The effect of this policy was studied analyzing IMS Health data from the private sector, and a decrease in the level of use of antibiotics in both countries was found; however, we did not find significant changes in the slope of the use of antibiotics after the policy implementation.

Previous analyses have studied policy changes in prohibiting OTC antibiotic sales in low and middle-income countries. Other countries have implemented these types of policies; for example, Chile's effort to prohibit OTC antibiotic sales in 1999 was accompanied by a public information campaign on the prudent use of antibiotics [51]. The set of these actions led to a reduction of antibiotics consumption by 30% in less than six months; however, this level of consumption was not maintained when the information campaign was suspended [52]. In Colombia, the sales restriction of antibiotics took effect in 2005 and was limited to the Capital District of Bogota; although this effect did not occur nationwide and resulted on a small effect of the regulation of 1 DDD/TID [53], it was comparable to the effect found in Mexico and Brazil in chapter 4.1. In Venezuela, the law enforcement to restrict the sales of OTC antibiotics focused on specific therapeutic groups (macrolides, quinolones and third generation cephalosporins), and no decrease in antibiotic consumption was found [53].

As mentioned in chapter 3.1, antihypertensives were used as a reference group to control for external factors. In Brazil, the use of a reference was of particular relevance, since the number of new wholesalers was included in the dataset from 2009 onwards. This created a trend break in consumption from this point onwards, making the slope more tilted. This structural break can affect the evaluation of policies. As a consequence, the use the antihypertensives as a reference group was important to show that although there was a decrease in the level of use of antibiotics in Brazil, the increasing slope of use did not change significantly after the restriction of OTC sales of antibiotics in 2010.

Without data that allows the quantification of total antibiotic consumption with high accuracy, retail sales data can be used to inform policy-making as long as the inherent limitations of these data sources are taken into account. These results should be complemented with other

data sets that allow a more complete quantification of the overall pharmaceutical consumption at the national level. For example, in Europe there are a number of ongoing activities to help countries in developing future policies to improve the use of antibiotics [54]. These activities include the surveillance network ESAC-Net that collects data of national consumption of antibiotics. Implementing regulatory enforcement has shown an impact in some countries, but a sustainable, concerted approach, including strategies to promote appropriate use, will be needed to address the problem in the future [54].

ADVANTAGES AND DISADVANTAGES OF USING SALES DATA TO STUDY DRUG UTILIZATION

Medicines' consumption can be measured using sales, prescription, dispensing or actual usage data. Access to national prescription or dispensing data on medicine consumption in the countries studied in this thesis is difficult to obtain because public and private sectors are fragmented and electronic records differ by country. However, sales data for the private sector is recorded for marketing study purposes at the national level to allow comparison between countries. One of the largest market intelligence data providers is IMS Health. A research protocol was submitted to the IMS Health Global Health Research program to obtain the data for the purpose of this thesis. IMS Health constructed the database with information from surveys conducted regularly at various stages of the pharmaceutical chain. The results of the surveys were projected to the approximate total volume of sales per country [55,56]. There has been collaboration with IMS Health on other CNCs of drug utilization, and it has been recognized that this type of data can be considered as a good information source in cases where there is a lack of high quality data from surveillance networks on antibiotic consumption such as the European Centre for Disease Prevention and Control [57].

Like other data sources, sales data from IMS Health have some advantages and disadvantages. IMS Health is an international healthcare information company, specializing in the collection and interpretation of anonymized health information, and it is often the only source of large electronic data on aspects of medicine utilization at a national level across the world. Like other sources of information, IMS Health data is generated for other purposes than research and data coverage depends on the country and sector. For example, it has been reported that the coverage for only the retail in Mexico is 69%, while in Brazil it is 100% [57]. IMS Health data is expensive for private parties; however, under certain conditions, data for academic or public health research purposes can be obtained from IMS Health at limited or no costs. In recent years several publications have used IMS Health data to evaluate the use of medicines in low and middle-income countries. For example, to examine gender differences in access to prescribed medicines [58], to compare the uptake of treatment for diabetes in China, Brazil and Thailand [59]; and to evaluate the impact of the universal health coverage on the use of medicines in Thailand [60].

In the evaluation of OTC sales restrictions of antibiotics in Mexico and Brazil, we faced some limitations: we were not able to demonstrate if the reduction of the consumption of antibiotics was entirely due to the OTC sales restriction. As the data provided for the study was sales data

from each country that was studied, it was not possible to stratify between medicines sold with prescription and without prescription. Therefore, the seasonal variation in the use of penicillin was used as a proxy to estimate the inappropriate use of antibiotics. The seasonal variation in antibiotic use has been associated with short-term lowering of resistance rates; moreover, low seasonal variation has been related to appropriate-use profiles in Europe [61,62].

Furthermore, it has been suggested that a better understanding of seasonal variation of antibiotic prescriptions can be useful in the design of interventions to reduce inappropriate use of antibiotics [63]. Unintended effects of these policies were also addressed by assessing the substitution of antibiotics with other therapeutic groups that, without supervision, can also cause harm to the patients. Previous studies have investigated the unintended consequences of pharmaceutical policies; for example, the temporary removal of olanzapine in 2005 from the preferred drug list in Medicaid Florida had an unintended effect by disrupting the continuity of patients care with diagnosis of schizophrenia and bipolar disorder which led to an increase number of hospitalizations and emergency room visits in the months after the implementation [64]. The evaluation of substitution effects of medicines can be studied using cointegration tests [65]. This test assesses the relation between two time series. Therefore, by using this test it was possible to evaluate if the changes of use of medicines perceived as substitutes of antibiotics: NSAIDs, analgesics and medicines to diminish symptoms of cold; were related to the changes of use of antibiotics after the OTC sales restrictions in Mexico and Brazil.

Cointegration tests have also been used to forecast the consequences of present actions, such as the deforestation of the Amazon rainforest in Brazil. With this test, it was forecasted the decline of the forest under various policy scenarios [7]. Drug utilization research could benefit by the use of different methods such as cointegration and forecasting of time series, that are commonly used in other research areas, for a better assessment of medicines use under different scenarios and improve the evidence based policy-making. The improvement of methodologies used in time series data can ensure a more valid evaluation of different pharmaceutical policies.

The analysis of data collected as part of the routine administration of healthcare has enabled the comparison of medicines use between countries, however this type of data is not always available and the use of other data sources can be helpful to evaluate the policies implemented. Public health authorities from different countries can use the results of CNC of drug utilization to benchmark the use of medicines in their own countries. This benchmarking can be useful for the evaluation of future decisions to improve the distribution, prescription and delivery of medicines to the general population. Initiatives to compare the use of medicines between countries and evaluations of pharmaceutical policies, have provided of great experience to the field of drug utilization research. In countries where data is available, data quality assessment and improvement of methods can be key to identify problems and evaluate solutions more accurately. Lessons learnt from these experiences may be of a great help to improve evidence based decision making in these countries and in countries with scarce systems of data collection.

Multi-country collaborations should help to improve and standardize tools for comprehensive regular data collection. Concurrently, countries that do not possess sufficient data to evaluate

the use of medicines and the effects of pharmaceutical policies, can seize those constraints to improve methodologies of data collection and analysis.

CONCLUSION

This thesis contributes to the field of drug utilization research and to the evaluation of pharmaceutical policies using CNC of drug utilization and time series analysis. Gaps in CNC of drug utilization studies were identified, and an evaluation checklist to assess these studies was proposed, setting further steps in the development of standards for the assessment and the report of CNCs. Moreover, methods in time series were described to extend their use in the drug utilization research and pharmaceutical policy analysis field. Of equal importance, this thesis includes the evaluation of pharmaceutical policies in geographical areas where this type of research is lacking, mainly because the data is scarce. Therefore, in this thesis, the use of sales data was highlighted as a valuable mean to evaluate the use of medicines and the effects of pharmaceutical policies in these countries. The studies in this thesis show that the effects of interventions in the pharmaceutical sector need to be adequately quantified, and provide new approaches to do so which strengthens evidence-based policy making.

REFERENCES

1. Weintraub M, Singh S, Byrne L, Maharaj K, Guttmacher L, Health NYSD of, et al. Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations. JAMA J Am Med Assoc. American Medical Association; 1991 Nov 6;266(17):2392.
2. Leopold C, Zhang F, Mantel-Teeuwisse AK, Vogler S, Valkova S, Ross-Degnan D, et al. Impact of pharmaceutical policy interventions on utilization of antipsychotic medicines in Finland and Portugal in times of economic recession: interrupted time series analyses. Int J Equity Health. 2014;13:53.
3. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299–309.
4. Lu CY, Emmerick ICM, Stephens P, Ross-Degnan D, Wagner AK. Uptake of new antidiabetic medications in three emerging markets: a comparison between Brazil, China and Thailand. J Pharm policy Pract. 2015;8(1):7.
5. Wettermark B. The intriguing future of pharmacoepidemiology. Eur J Clin Pharmacol. 2013 May 3;69(S1):43–51.
6. Almarsdóttir AB, Traulsen JM. Studying and evaluating pharmaceutical policy--becoming a part of the policy and consultative process. Pharm World Sci. 2006 Feb;28(1):6–12.
7. Granger CW. Time series analysis, cointegration and applications. Am Econ Rev. 2004;94(3):421–5.
8. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. Basic Clin Pharmacol Toxicol. 2006 Mar;98(3):253–9.
9. Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010 Jun;19(6):537–54.
10. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299–309.
11. International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2–10.
12. European Medicines Agency. Guide on Methodological Standards in Pharmacoepidemiology [Internet]. 2010. Available from: http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideMethStandardsPE_Rev3.pdf
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. American College of Physicians; 2015 Jun 2;162(11):777–84.
14. Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. Br J Clin Pharmacol. 2004 Oct;58(4):419–28.
15. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. England; 2005 Feb;365(9459):579–87.
16. Versporten A, Bolokhovets G, Ghazaryan L, Abilova V, Pyshnik G, Spasojevic T, et al. Antibiotic use in eastern Europe: a cross-national database study in coordination with the WHO Regional Office for Europe. Lancet Infect Dis. United States; 2014 May;14(5):381–7.
17. Wirtz VJ, Dreser A, Gonzales R. Trends in antibiotic utilization in eight Latin American countries, 1997-2007. Rev Panam Salud Publica. 2010;27(3):219–25.
18. Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. Elsevier; 2014 Dec 17;385(9963):117–71.
19. The EURO-MED-STAT Group. EURO-MED-STAT: monitoring expenditure and utilization of medicinal products in the European Union countries: a public health approach. Eur J Public Health. 2003 Sep;13(3 Suppl):95–100.
20. Walley T, Folino-Gallo P, Stephens P, Van Ganse E. Trends in prescribing and utilization of statins

and other lipid lowering drugs across Europe 1997-2003. Br J Clin Pharmacol. T. Walley, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3GF, United Kingdom; 2005;60(5):543–51.

21. IMI PROTECT. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium [Internet]. Available from: http://www.imi-protect.eu/

22. Klungel OH, Kurz X, de Groot MCH, Schlienger RG, Tcherny-Lessenot S, Grimaldi L, et al. Multi-centre, multi-database studies with common protocols: lessons learnt from the IMI PROTECT project. Pharmacoepidemiol Drug Saf. 2016 Mar;25(S1):156–65.

23. Mauldin PD, Salgado CD, Hansen IS, Durup DT, Bosso JA. Attributable hospital cost and length of stay associated with health care-associated infections caused by antibiotic-resistant gram-negative bacteria. Antimicrob Agents Chemother. 2010 Jan;54(1):109–15.

24. Tarride J-E, Lim M, DesMeules M, Luo W, Burke N, O'Reilly D, et al. A review of the cost of cardiovascular disease. Can J Cardiol. Pulsus Group; 2009 Jun;25(6):e195–202.

25. Elseviers M, Wettermark B, Almarsdottir AB, Andersen M, Benko R, Bennie M, et al. Drug Utilization Research: Methods and Applications. Wiley-Blackwell; 2016. 568 p.

26. World Health Organization. Atlas of eHealth country profiles: the use of eHealth in support of universal health coverage: based on the findings of the third global survey on eHealth 2015. [Internet]. 2015. Available from: http://apps.who.int/iris/bitstream/10665/204523/1/9789241565219_eng.pdf?ua=1

27. Melander A, Folino-Gallo P, Walley T, Schwabe U, Groop P-H, Klaukka T, et al. Utilisation of antihyperglycaemic drugs in ten European countries: different developments and different levels. Diabetologia. 2006 Sep;49(9):2024–9.

28. CARING. CARING (CAncer Risk and INsulin analoGues) project [Internet]. Available from: http://www.caring-diabetes.eu/

29. OECD, Danish Diabetes Association NN. The diabetes epidemic and its impact on Europe [Internet]. 2012. Available from: https://www.oecd.org/els/health-systems/50080632.pdf

30. Järvinen S, Laine MK, Eriksson JG. Comparison of use of diabetic medication and clinical guidelines in four Nordic countries. Ann Med. Taylor & Francis; 2016;48(3):162–8.

31. Drummond M, Jönsson B, Rutten F, Stargardt T. Reimbursement of pharmaceuticals: reference pricing versus health technology assessment. Eur J Health Econ. 2011 Jun;12(3):263–71.

32. Bazargani YT, de Boer A, Leufkens HGM, Mantel-Teeuwisse AK. Selection of essential medicines for diabetes in low and middle income countries: a survey of 32 national essential medicines lists. PLoS One. Public Library of Science; 2014;9(9):e106072.

33. Caires de Souza AL, de Assis Acurcio F, Guerra Júnior AA, Rezende Macedo do Nascimento RC, Godman B, Diniz LM. Insulin glargine in a Brazilian state: should the government disinvest? An assessment based on a systematic review. Appl Health Econ Health Policy. 2014 Feb;12(1):19–32.

34. Festøy H, Aanes T, Yu LM, Ognøy A, Gregersen T. PHIS Pharma Profile Norway [Internet]. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/PHIS Pharma Profile Norway Nov11.pdf

35. The Danish Medicines Agency, The Ministry of the Interior and Health. PHIS Pharma Profile - Denmark. 2011.

36. Närh U. PHIS Hospital Pharma Report [Internet]. 2009. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/PHIS Finland_Hospital Pharma_Report 2009.pdf

37. Svensson J. PHIS Hospital Pharma Report [Internet]. 2009. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/V5 PHIS Hospital Pharma report SE_final version.pdf

38. Norwegian Medicines Agency, Drug Procurement Cooperation. PPRI Pharma Profile - Norway [Internet]. 2015. Available from: http://whocc.goeg.at/Literaturliste/Dokumente/CountryInformationReports/PPRI_Pharma_Profile_Norway_20150626_final.pdf

39. Wettermark B, Zoega H, Furu K, Korhonen M, Hallas J, Norgaard M, et al. The Nordic prescription databases as a resource for pharmacoepidemiological

research--a literature review. Pharmacoepidemiol Drug Saf. England; 2013 Jul;22(7):691–9.

40. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. Denmark; 2010 Feb;106(2):86–94.

41. Avilés W, Ortega O, Kuan G, Coloma J, Harris E. Quantitative assessment of the benefits of specific information technologies applied to clinical studies in developing countries. Am J Trop Med Hyg. American Society of Tropical Medicine and Hygiene; 2008 Feb;78(2):311–5.

42. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HGM, Wirtz VJ. Reply to "decrease in penicillin sales in Brazil after over-the-counter restrictions". Antimicrob Agents Chemother. 2015 Sep;59(9):5864.

43. World Health Organization. Introduction to Drug Utilization Research [Internet]. World Health Organization; 2003. Available from: http://www.whocc.no/filearchive/publications/drug_utilization_research.pdf

44. Couttolenc B, Gragnolati M, Lindelow M. Twenty years of health system reform in Brazil : an assessment of the sistema unico de saude [Internet]. Washington, D.C.; 2013. Available from: http://www-wds.worldbank.org/ external/ default/ WDSContentServer/ WDSP/IB/2013/06/21/ 000442464_ 20130621122542 /Rendered/ PDF /786820 PUB0EPI10 Box 0377351 B00 PUBLIC0.pdf

45. Savedoff WD, de Ferranti D, Smith AL, Fan V. Political and economic aspects of the transition to universal health coverage. Lancet. 2012;380(9845):924–32.

46. World Bank. Universal Healthcare on the rise in Latin America [Internet]. 2013 [cited 2016 Jun 22]. Available from: www.worldbank.org/en/news/feature/2013/02/14/universal-healthcare-latin-america

47. Minister of Health. White Paper on National Health Insurance in South Africa [Internet]. Government Notice No. 1230, Government Gazette No. 39506 2015. Available from: http://www.gov.za/sites/www.gov.za/files/39506_gon1230.pdf

48. Boyce D, Bartlett G. The maximum medical aid price programme. A review of the concept and of its ability to reduce expenditure on medicines. S Afr Med J. 1990 Aug 4;78(3):147–51.

49. Posner J, Griffin JP. Generic substitution. Br J Clin Pharmacol. Wiley-Blackwell; 2011 Nov;72(5):731–2.

50. Gray AL. Medicine pricing interventions - the South African experience. South Med Rev. 2009;2(2):15.

51. Bavestrello F L, Cabello M A, Casanova Z D. Impacto de medidas regulatorias en la tendencia de consumo comunitario de antibióticos en Chile. Rev Med Chil. Sociedad Médica de Santiago; 2002 Nov;130(11):1265–72.

52. Bavestrello F L, Cabello M Á. Consumo comunitario de antimicrobianos en Chile, 2000-2008. Rev Chil infectología. Sociedad Chilena de Infectología; 2011 Apr;28(2):107–12.

53. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. Trop Med Int Health. 2013 Jun;18(6):665–73.

54. European Centre for Disease Prevention and Control. European Surveillance of Antimicrobial Consumption ESAC - Net [Internet]. 2016 [cited 2016 May 14]. Available from: http://ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx

55. IMS Health. IMS The Uniform System of Classification [Internet]. 2008 [cited 2014 Oct 3]. Available from: http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/Health Services Research Network/USC_Classiification_Process_2011.pdf

56. IMS Health. Pharmaceutical Market, Mexico and Brazil. London; 2008.

57. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014 Aug;14(8):742–50.

58. Stephens P, Ross-Degnan D, Wagner AK, Baghdadi G, Fikree F, Pasha O, et al. Does access to medicines differ by gender? Evidence from 15 low and middle income countries. Health Policy (New York). Elsevier; 2013 Apr;110(1):60–6.

59. Lu CY, Emmerick ICM, Stephens P, Ross-Degnan D, Wagner AK. Uptake of new antidiabetic medications in three emerging markets:

a comparison between Brazil, China and Thailand. J Pharm policy Pract. 2015 Jan;8(1):7.

60. Garabedian LF, Ross-Degnan D, Ratanawijitrasin S, Stephens P, Wagner AK. Impact of universal health insurance coverage in Thailand on sales and market share of medicines for non-communicable diseases: an interrupted time series study. BMJ Open. 2012;2(6).

61. Elseviers MM, Ferech M, Vander Stichele RH, Goossens H. Antibiotic use in ambulatory care in Europe (ESAC data 1997-2002): trends, regional differences and seasonal fluctuations. Pharmacoepidemiol Drug Saf. 2007 Jan;16(1):115–23.

62. Achermann R, Suter K, Kronenberg A, Gyger P, Mühlemann K, Zimmerli W, et al. Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests. Clin Microbiol Infect. 2011 Jun;17(6):855–61.

63. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. Trends and seasonal variation in outpatient antibiotic prescription rates in the United States, 2006 to 2010. Antimicrob Agents Chemother. 2014 May 3;58(5):2763–6.

64. Signorovitch J, Birnbaum H, Ben-Hamadi R, Yu AP, Kidolezi Y, Kelley D, et al. Increased olanzapine discontinuation and health care resource utilization following a Medicaid policy change. J Clin Psychiatry. 2011 Jun;72(6):787–94.

65. Gregory AW, Hansen BE. Tests for Cointegration in Models with Regime and Trend Shifts. Oxf Bull Econ Stat. 2009 May 1;58(3):555–60.

CHAPTER 6

SUMMARY, SAMENVATTING
AND RESUMEN

CHAPTER 6.1

SUMMARY

Pharmaceutical policies provide a framework to coordinate activities in the pharmaceutical sector, and regulate the interaction between the government, the pharmaceutical industry, wholesalers, retailers, health professionals and patients. To serve public health, pharmaceutical policies aim to promote equitable access to and appropriate use of medicines in the population. Pharmaceutical policies cover areas such as development, regulation, production, marketing, prescribing and dispensing of medicines. Evaluation of policies is needed to measure their effects and the degree to which these policies reach the targeted objectives. Furthermore, the evaluation of these policies helps to identify areas of improvement as well as unintended consequences.

Drug utilization studies can be used to evaluate pharmaceutical policies. These studies provide information on how medicines are used in daily practice and can describe the extent of the medicine use in a certain area, such as a specific region, country, city or hospital. This information can be used to compare patterns of prescribing, dispensing and utilization of medicines between countries, i.e. cross-national comparisons (CNC).

As outlined in **Chapter 1**, the aim of this thesis is to evaluate the effects of different pharmaceutical policies on the use of medicines. These policies were evaluated using diverse data sources from the public and private sector in countries in Africa, Latin America, and Western Europe. Although interrupted time series analysis has been one of the most used methodologies for the evaluation of pharmaceutical policies, further development and improvement of methodologies used in such studies is of great importance to guarantee their proper assessment to improve evidence-based and effective policy-making. Therefore its use in policy analysis is further examined in this thesis.

After the introduction, **Chapter 2.1** presents a literature review of CNC studies published between 2000 and 2015, summarizing their characteristics in terms of data and methodological approaches used to evaluate the use of medicines between countries in different geographical areas: Europe, Asia, Africa, Oceania and the Americas. For this review, 104 CNC studies were selected and for each of them the overall CNC characteristics were extracted. Examples of these characteristics were: number of countries involved in the comparison, therapeutic group(s) studied, number of years covered in the study and description of the time frame. We focused on the description of databases such as the data generation level (wholesaler, pharmacy records) and whether the primary objective of the data was administrative or not. We also reviewed the methodology used and the units of measure and terminology to describe exposure. All these characteristics were analyzed descriptively. Although, Europe was the continent where by far most of the CNC of drug utilization studies have been conducted (n=88), the lack of reporting of database characteristics might reduce the validity of the comparisons. In other continents, IMS Health data was the main information source (in 9 out of 16 studies) due to the lack of other available data sources to evaluate the use of medicines. Nearly half of the studies reviewed (n=56), based their analysis on only one type of database (e.g. dispensing, reimbursement), while the other half based their analysis on data combinations. Most of the studies (69%) were descriptive and the rest were analytical. The availability of administrative health care databases in Europe has facilitated the comparison of use of medicines between European countries, but the lack of reporting the characteristics of databases and settings decreases the reliability of these

comparisons. This review highlights the need for better guidance on conduct and reporting of CNCs to set a base for their correct assessment.

Chapter 2.2 presents the development of an evaluation checklist for CNC studies. This checklist is intended to assist in the evaluation of the strengths and limitations of CNC of drug utilization studies. The development of this checklist was conducted in conjunction with experts in drug utilization research and CNC. The checklist was pilot tested with different CNC of drug utilization studies obtained in the review in Chapter 2.1. The development of this checklist comprised six steps: 1) development of the first draft of the checklist based on similar checklists obtained from literature; 2) first pilot testing of the checklist where comments regarding ease of reading and flow of items were provided and minor changes to some items and the checklist layout were made to increase face validity; 3) second pilot testing where twenty randomly selected articles of CNC DU (from the literature review in chapter 2.1) were scored and the percentage of agreement between reviewers was calculated; 4) checklist adjustment to improve the clarity and facilitate the ability to score each data source contained in each research article; 5) third pilot and final revision where five research articles were scored and agreements on terminology were made during a face-to-face meeting; 6) test for external validity by sending the checklist to researchers in the drug utilization field to test the clarity and ease of this checklist.

The final version of the checklist is structured in six domains (general data, study design, terminology and units, population coverage, drug coverage and overall evaluation). The checklist addresses the main potential comparability problems in CNC of drug utilization studies in a systematic manner by facilitating the identification and extraction of relevant information related to data sources and methods from CNC of drug utilization studies. Hence, with the information extracted, the validity of the comparisons can be assessed taking into account the potential comparability problems in terminology, units of measure, population coverage and drug coverage between data sources used in a CNC of drug utilization study. The developed checklist will serve as a basis to develop good practice guidelines for designing, conducting, analyzing and reporting CNC of drug utilization studies.

In **Chapter 2.3**, time series regressions were used to assess cross-national differences in the uptake of insulin analogs in four Scandinavian countries (Denmark, Finland, Norway and Sweden), and the United Kingdom as an example of a cross-national comparative study. To conduct this comparison, the monthly market share was calculated by dividing the monthly consumption of the defined daily doses (DDD) of each insulin type by the monthly consumption of all insulins, taking into account the population growth of each country. Time series regressions were used to estimate the uptake rate per insulin type. Structural changes in the market share were explored using the Quandt-likelihood-ratio (QLR) test. Afterwards, we examined if structural changes were related to changes in policies, such as the entry of a new product in the market, changes in reimbursement, or updates of clinical guidelines.

We found that the uptake rates of the new insulins were similar among countries except Sweden. The uptake rate of insulin glargine increased 0.1% per month in Norway, 0.2% in Denmark and in the UK, and 0.3% in Finland. The uptake rate of insulin detemir increased 0.1% per month in Norway and the UK, 0.2% in Denmark, and 0.3% in Finland. In Sweden, the uptake rates of both insulin analogues was minimal, i.e. 0.02% for insulin glargine and 0.05% for insulin

detemir. At the beginning of the study period, human insulin was the most used insulin in all the countries except Sweden, with insulin aspart being predominantly used. We did not find sudden changes in the market share of insulin that could be related to the market approval of insulin, changes in diabetes treatment guidelines, or reimbursement policies. Therefore we concluded that variations in the market share might be explained by unobserved factors such as clinician prescribing behaviors and patient preferences.

Interrupted time series analysis is used in drug utilization studies, specifically in the evaluation of the effect of pharmaceutical policies. **Chapter 3** focuses on methodological aspects of this analytical technique when used for evaluating policies using interrupted time series analysis. **Chapter 3.1** presents an evaluation of changes in the collection of IMS Health sales data in Brazil on the trend and level of use of selected therapeutic groups. This evaluation was conducted because in Brazil IMS Health gradually incorporated new wholesalers through 2009 that might have created a trend break from this point onwards. Such a trend break could affect estimations on evaluation of policies changing the estimation of consumption of different therapeutic groups. We examined the trend breaks with two methods; the first method was the Clemente-Montañez-Reyes test, which assessed the presence of gradual changes in the series. The second method was an interrupted time series analysis using different breaking points before, during and after 2009. We found changes in the series trend before and during 2009 with both methods. The changes in trend were different between therapeutic groups. The analysis presented in this chapter shows that antihypertensives can be used as a reference group to adjust for the structural changes in the database because this group does not show any trend or level breaks.

Subsequently, in **Chapter 3.2** interrupted time series analysis was used to evaluate the effect of the introduction of the mandatory offer of generic substitution in the use of medicines for chronic diseases in South Africa in May 2003. South African private sector monthly sales data from June 2001 to May 2005 were obtained from IMS Health for the following selected therapeutic groups: proton pump inhibitors (PPIs; ATC code A02BC), HMG CoA reductase inhibitors (statins; C10AA), dihydropyridine calcium antagonists (C08CA), angiotensin converting enzyme inhibitors (ACE-I; C09AA) and selective serotonin reuptake inhibitors (SSRIs; N06AB). Only the SSRIs had a significant increase in level of generic utilization (0.2 defined daily doses per 1000 inhabitants per month (DDD/TIM); $p<0.001$) and a decrease in originator usage (-0.1 DDD/TIM; $p<0.001$) after the policy change. Utilization of generic PPIs decreased (level -0.06 DDD/TIM, $p=0.048$; slope -0.01 DDD/TIM, $p=0.043$), but utilization of originator products increased (level 0.05 DDD/TIM, $p<0.001$; slope 0.003, $p=0.001$). Generic calcium antagonists and ACE-I showed an increase in slope (0.01 DDD/TIM, $p=0.016$; 0.02 DDD/TIM, $p<0.001$), while the originators showed a decrease in slope (-0.003 DDD/TIM, $p=0.046$; -0.01 DDD/TIM, $p<0.001$). We concluded that this policy had a quantifiable effect on utilization patterns in the 2 years after May 2003, when the intervention started. However, managed care interventions that were already in place before the intervention may have blunted the extent of the changes seen in this time period.

On the other side of the world, in the Latin America region, Mexico and Brazil restricted the over-the-counter (OTC) sales of antibiotics in 2010. Firstly, we measured the size of the effect of the policy in **Chapter 4.1** by analyzing IMS Health data between January 2007 and June 2012

from the private sectors of Brazil and Mexico. We found that between 2007 and 2012 total antibiotic usage increased in Brazil (from 5.7 to 8.5 defined daily doses per 1,000 inhabitants per day (DDD/TID), +49.3%) and decreased in Mexico (10.5 to 7.5 DDD/TID, -29.2%). Interrupted time series analysis showed a change in level of consumption of -1.35 DDD/TID ($p<0.01$) for Brazil and -1.17 DDD/TID ($p<0.01$) for Mexico. In Brazil the penicillins, sulfonamides and macrolides consumption had a decrease in level after the intervention, while in Mexico we found that only penicillins and sulfonamides had significant changes in level. We concluded that despite different overall usage patterns of antibiotics in Brazil and Mexico, the direct effect of the OTC restrictions on antibiotics usage was similar. In Brazil the trend of an increased usage of antibiotics was tempered after the OTC restrictions; in Mexico the trend of a decreased usage was boosted.

Next, we determined if the enforcement led to more appropriate use by measuring changes in seasonal variation of penicillin use in the same dataset (**Chapter 4.2**). The most used penicillin was amoxicillin, followed by amoxicillin-clavulanic acid, and ampicillin (minimal use in Brazil). Before the restrictions, the seasonal variation of penicillin use was 1.1 DDD/TID in Mexico and 0.8 DDD/TID in Brazil. In Mexico, we estimated a significant decrease in the seasonal variation of 0.4 DDD/TID after the restriction mainly due the changes in seasonal variation of amoxicillin and ampicillin. In Brazil, the seasonal variation did not change significantly, neither overall nor in the breakdown by individual active substances. These results suggest that for Mexico inappropriate penicillin use may have diminished after the restrictions were enforced. For Brazil increasing use and no change in seasonal variation suggests that further efforts are needed to reduce inappropriate penicillin use.

In **Chapter 4.3**, an editorial letter describes the importance of the quality of databases and appropriate methodologies to better assess the effect of interventions such as OTC sales restriction of antibiotics in Brazil. We highlighted that differences in results between evaluations may be explained by differences in data sources and techniques of analysis, finalizing with a call for nationally representative standardized data collections to accurately describe and compare utilization of medicines in Latin American countries.

Then, **Chapter 4.4** assesses the unintended effects of the OTC sales restriction policy by measuring the changes in the use of therapeutic groups that can be perceived as substitutes of antibiotics to relieve cold symptoms. We evaluated changes in the use of non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics and cough and cold medicines and its relation with the use of antibiotics after the OTC antibiotic sales restrictions in Mexico and Brazil. Interrupted time series were used to estimate changes in level of medicines use at the intervention point and slope after the regulation. The Gregory-Hansen cointegration test was used to explore the relation between the use of antibiotics and perceived substitutes. After the regulation in Mexico, the use of NSAIDs-analgesics and cough and cold medicines increased by 1.1 DDD/TID and 0.4 DDD/TID respectively. In Brazil NSAIDs-analgesics usage level increased by 1.8 DDD/TID, and cough and cold medicines did not change. In the two countries, NSAIDs-analgesics usage changes were related with antibiotic usage changes, while only in Mexico cough and cold medicines usage changes had a relation with the antibiotics usage changes. These results showed a substitution effect on the use of other medicines, especially

NSAIDs and analgesics, after reinforcement of OTC antibiotics sales restrictions which might have unintended clinical consequences. These regulations aimed to improve the antibiotics use and as a consequence reduce antimicrobial resistance. However, this type of policies should be comprehensive and take into account the potential substitution effects on the use of other medicines.

In **Chapter 5**, the general discussion draws lessons from the studies conducted in this thesis. The importance of CNC studies is addressed together with the next steps to improve their reporting by adequate and detailed descriptions of data coverage and countries characteristics such as marketing status of medicines and reimbursement policies to increase the validity and reliability of comparisons. The use of interrupted time series analysis and the application of this method in the evaluation of pharmaceutical policies are discussed. Applying other statistical tests in time series such as cointegration and forecasting can improve the evaluation of policies by examining unintended effects and forecasting possible outcomes. The chapter concludes with the discussion of the evaluation of pharmaceutical policies outside of Europe, in settings where the data sources with information of drug utilization are scarce. The studies in this thesis show that the effects of interventions in the pharmaceutical sector need to be adequately quantified, and provide new approaches to do so which strengthens evidence-based policy making.

CHAPTER 6.2

SAMENVATTING

Geneesmiddelenbeleid stelt de kaders waarbinnen de activiteiten in de farmaceutische sector worden gecoördineerd. Het beleid reguleert daarbij de interactie tussen de overheid, de farmaceutische industrie, groothandels, medewerkers in de gezondheidszorg en patiënten. Tevens kan geneesmiddelenbeleid aan de algemene volksgezondheid bijdragen door te waarborgen dat er sprake is van een gelijkwaardige toegang tot en goed gebruik van geneesmiddelen. Het geneesmiddelenbeleid richt zich daarbij op zowel de ontwikkeling, regulering, productie, marketing, als het voorschrijven en het afleveren van geneesmiddelen. Het evalueren van het beleid is noodzakelijk om de effecten van de genomen maatregelen te meten en vast te stellen in welke mate de gestelde doelen worden behaald. Tevens kan een dergelijke evaluatie bijdragen aan het identificeren van mogelijkheden voor verbetering van beleidsmaatregelen en het in kaart brengen van onbedoelde consequenties van het beleid.

Onderzoek naar het gebruik van geneesmiddelen kan worden gebruikt voor de evaluatie van geneesmiddelenbeleid. Dergelijk onderzoek geeft inzicht in het gebruik van geneesmiddelen in de dagelijkse klinische praktijk en kan de mate van gebruik in een bepaalde setting, zoals een specifiek land, regio, stad of ziekenhuis, vaststellen. Dit soort informatie kan ook worden gebruikt om patronen van voorschrijven, afleveren of gebruik van geneesmiddelen tussen landen te vergelijken.

Zoals in **hoofdstuk 1** is weergegeven was het doel van dit proefschrift om de effecten van verschillende beleidsmaatregelen op het gebruik van geneesmiddelen te bepalen. Hiertoe werden diverse gegevensbronnen uit zowel de publieke als de private sector van landen in Afrika, Latijns Amerika en West-Europa gebruikt. Tijdreeksanalyses is een van de meest gebruikte methoden om geneesmiddelenbeleid te evalueren, maar het is van groot belang deze methode verder te ontwikkelen en verbeteren om zo een juiste toepassing te kunnen garanderen. Daarom werd de toepassing van tijdreeksanalyses in beleidsonderzoek nader bestudeerd in dit proefschrift.

Na de introductie wordt in **hoofdstuk 2.1** een literatuuroverzicht van vergelijkingen van gebruik van geneesmiddelen tussen landen gepresenteerd. De 104 geïncludeerde studies waren tussen 2000 en 2015 gepubliceerd en er is gekeken naar de gegevensbronnen en methoden die werden toegepast om geneesmiddelengebruik in verschillende landen en regio's (Europa, Azië, Afrika, Oceanië en Noord- en Zuid-Amerika) te evalueren. Voorbeelden van specifieke karakteristieken van het betreffende onderzoek die bestudeerd werden zijn het aantal landen dat in de vergelijking werd meegenomen, de geneesmiddelgroep(en) die werd(en) bestudeerd, het aantal jaar waarvoor gegevens beschikbaar waren en de tijdspanne die het betreffende onderzoek besloeg. Tevens richtten we ons op de karakteristieken van de gebruikte gegevensbestanden, waaronder een beschrijving van het niveau waarop de gegevens werden gegenereerd (groothandel of apotheek) en het primaire doel van de gegevensverzameling (voor administratieve doeleinden of niet). Tot slot bestudeerden we de voor de vergelijking gebruikte methoden inclusief de meeteenheden en terminologie om blootstelling aan geneesmiddelen uit te drukken. De beschrijvende resultaten lieten zien dat veruit de meeste landenvergelijkingen waren uitgevoerd in Europa (n=88), maar dat de validiteit van deze vergelijkingen mogelijk werd verminderd door een gebrek aan adequate beschrijving van de eerder genoemde karakteristieken. In andere regio's waren gegevens van IMS Health de belangrijkste informatiebron (in 9 van de 16 gevonden onderzoeken), doordat andere bronnen vaak afwezig zijn in dergelijke regio's. Bijna

de helft van de geïncludeerde onderzoeken (n=56) baseerde hun analyses op één type gegevens (bijvoorbeeld voorschrijf- of aflevergegevens), terwijl de andere helft meerdere bronnen combineerde. De meerderheid van de studies (69%) was beschrijvend van aard, de overige studies waren analytische studies. De beschikbaarheid van bestanden met administratieve patiëntengegevens heeft de vergelijking van geneesmiddelengebruik tussen landen in Europa vergemakkelijkt, maar het gebrek aan een adequate beschrijving van de karakteristieken van de gebruikte gegevensbestanden en bijbehorende setting vermindert de betrouwbaarheid van deze vergelijkingen. Dit literatuuroverzicht benadrukt de behoefte aan betere richtlijnen voor het doen en rapporteren van onderzoek naar geneesmiddelengebruik tussen landen als basis voor een goede beoordeling daarvan.

Hoofdstuk 2.2 bevat aansluitend een beschrijving van de ontwikkeling van een checklist voor de vergelijking van geneesmiddelengebruik tussen landen. Het doel van deze checklist is het ondersteunen van de beoordeling van de sterkte punten en beperkingen van een dergelijke vergelijking. Het opstellen van de checklist is in samenwerking met experts op het gebied van studies naar (vergelijkend) geneesmiddelengebruik gebeurd. In de testfase is een aantal van de in hoofdstuk 2.1 geïdentificeerde onderzoeken beoordeeld aan de hand van de checklist. Hierbij werden 6 stappen doorlopen: 1) ontwikkeling van een eerste versie van de checklist op basis van vergelijkbare checklists zoals die in de literatuur waren gevonden; 2) eerste testfase waarin aandachtspunten met betrekking tot leesbaarheid en structuur werden verwerkt en kleine aanpassingen aan sommige criteria werden gedaan om validiteit op zicht te vergroten; 3) tweede testfase waarin 20 willekeurig geselecteerde studies uit het literatuuroverzicht van hoofdstuk 2.1 werden beoordeeld en de mate van overeenkomst tussen de beoordelaars werd bepaald; 4) verdere aanpassingen om de duidelijkheid te vergroten en het beoordelen van meerdere gegevensbronnen binnen één studie te vergemakkelijken; 5) derde en laatste testfase waarin vijf nieuwe studies werden beoordeeld en overeenstemming over terminologie werd bereikt tijdens een fysieke bijeenkomst; 6) bepaling van de externe validiteit door onderzoekers met ervaring op het gebied van vergelijkend onderzoek naar geneesmiddelengebruik, waarbij ook duidelijkheid en gebruiksgemak worden beoordeeld.

De definitieve versie van de checklist is opgedeeld in 6 domeinen: algemene gegevens, onderzoeksopzet, terminologie en meeteenheden, dekking algemene bevolking, dekking geneesmiddelen en algemene beoordeling). De checklist besteedt op een gestructureerde manier aandacht aan de belangrijkste problemen die kunnen optreden bij vergelijkend onderzoek. Dit wordt gedaan door het identificeren en extraheren van de benodigde relevante informatie met betrekking tot gegevensbestanden en gebruikte onderzoeksmethoden. Deze informatie wordt vervolgens gebruikt om de validiteit van de vergelijking tussen landen te beoordelen, waarbij mogelijke problemen bij het vergelijken van terminologie, meeteenheden, dekking van de algemene bevolking en van geneesmiddelen tussen verschillende gegevensbronnen aan bod komen. De ontwikkelde checklist zal de basis vormen voor nog te ontwikkelen richtlijnen voor het ontwerp, uitvoeren, analyseren en rapporteren van vergelijkingen van geneesmiddelengebruik tussen landen.

In **hoofdstuk 2.3** zijn tijdreeksanalyses gebruikt om verschillen in opname en gebruik van insulineanaloga tussen vier Scandinavische landen (Denemarken, Finland, Noorwegen en Zweden) en het Verenigd Koninkrijk te bestuderen. Dit onderzoek is een typisch voorbeeld van

een vergelijking van de effecten van geneesmiddelenbeleid tussen landen. In dit onderzoek is het marktaandeel van elk type insuline per maand bepaald door de maandelijkse consumptie uitgedrukt in *defined daily doses* (DDD) van een individueel insuline te delen door de totale consumptie van insulines, waarbij tevens rekening is gehouden met de groei van de bevolking in ieder land. Tijdreeksanalyses werden gebruikt om de snelheid van opname per type insuline te bepalen. Structurele veranderingen in het marktaandeel werden onderzocht met behulp van de Quandt-likelihood-ratio (QLR) test. Vervolgens werd bepaald of structurele veranderingen waren gerelateerd aan veranderingen in geneesmiddelenbeleid, zoals het op de markt komen van een nieuw product, veranderingen in vergoeding of aanpassingen van behandelrichtlijnen.

Dit onderzoek liet zien dat de snelheid waarmee insulines werden opgenomen gelijk was in de verschillende landen met uitzondering van Zweden. De snelheid waarmee het marktaandeel van insuline glargine toenam bedroeg 0,1% per maand in Noorwegen, 0,2% in Denemarken en het Verenigd Koninkrijk en 0,3% in Finland. Voor insuline detemir was de snelheid waarmee het marktaandeel toenam 0,1% per maand in Noorwegen en het Verenigd Koninkrijk, 0,2% in Denemarken en 0,3% in Finland. In Zweden was deze snelheid minimaal voor beide insulines, namelijk 0,02% voor insuline glargine en 0,05% voor insuline detemir. Aan het begin van de onderzoeksperiode was humaan insuline het meest gebruikte insuline in alle landen met uitzondering van Zweden waar met name insuline aspart werd gebruikt. Er werden geen structurele veranderingen in het marktaandeel van verschillende insulines gevonden die samenhingen met de toelating tot de markt van nieuwe insulines, veranderingen in behandelrichtlijnen voor diabetes mellitus of veranderingen in de vergoeding van insulines. Daarom concludeerden we dat variatie in het marktaandeel van insulines mogelijk verklaard kan worden door factoren die niet werden bestudeerd, zoals voorschrijfgedrag van artsen of voorkeuren van patiënten.

Tijdreeksanalyses worden gebruikt in studies naar geneesmiddelengebruik, met name in studies waarin de effecten van beleidsmaatregelen worden geëvalueerd. **Hoofdstuk 3** richt zich op methodologische aspecten van deze analytische techniek daar waar deze gebruikt wordt binnen farmaceutisch beleidsonderzoek. **Hoofdstuk 3.1** bestudeert het effect van veranderingen in de verzameling van verkoopgegevens van geneesmiddelen door IMS Health in Brazilië op de trend en het niveau van geneesmiddelengebruik van geselecteerde geneesmiddelgroepen. In 2009 werden in Brazilië gegevens van nieuwe groothandels aan het bestand toegevoegd, wat tot een trendbreuk in geneesmiddelengebruik vanaf dit moment zou kunnen leiden. Een dergelijke trendbreuk kan schattingen van de consumptie van verschillende geneesmiddelgroepen, zoals die worden gebruikt om beleidsmaatregelen te evalueren, negatief beïnvloeden. In dit onderzoek werden trendbreuken op twee manieren onderzocht. De eerste methode was de Clemente-Montañes-Reyes test, die de aanwezigheid van graduele veranderingen in de series onderzoekt. De tweede methode betrof een tijdreeksanalyse met verschillende breekpunten voor, gedurende en na 2009. Beide testen lieten veranderingen in de trend van geneesmiddelengebruik zien voor en gedurende 2009. Deze veranderingen verschilden tussen geneesmiddelgroepen. De analyses in dit hoofdstuk laten zien dat antihypertensiva als referentiegroep kunnen worden gebruikt om voor structurele veranderingen te corrigeren, aangezien er geen breuk in de trend of het niveau van het gebruik van deze groep geneesmiddelen werd waargenomen.

Vervolgens werden tijdreeksanalyses in **hoofdstuk 3.2** gebruikt om het effect van het verplicht aanbieden van generieke substitutie op het gebruik van geneesmiddelen voor chronische aandoeningen in Zuid-Afrika te bestuderen. Deze beleidsmaatregel werd in mei 2003 van kracht. Gegevens over het maandelijks gebruik van geneesmiddelen in de private sector in Zuid-Afrika werden verkregen van IMS Health over de periode juni 2001 tot mei 2005 voor de volgende geneesmiddelgroepen: protonpompremmers (PPIs; ATC code A02BC), HMG CoA reductaseremmers (statines; C10AA), dihydropyridine calciumantagonisten (C08CA), angiotensine converterend enzymremmers (ACE-remmers; C09AA) en selectieve serotonine heropnameremmers (SSRIs; N06AB). Het gebruik van generieke varianten van een geneesmiddel nam door de beleidsmaatregel alleen significant toe bij de SSRIs (0,2 *defined daily doses* per 1000 inwoners per maand (DDD/DIM; p<0,001), waarbij het gebruik van merkgeneesmiddelen binnen deze groep afnam (-0,1 DDD/DIM; p<0,001). Het gebruik van generieke varianten van PPIs nam af (niveau -0,06 DDD/DIM, p=0,048; trend -0,01 DDD/DIM, p=0,043), maar het gebruik van merkgeneesmiddelen nam binnen deze groep juist toe (niveau 0,05 DDD/DIM, p<0,001; trend 0,003 DDD/DIM, p=0,001). De trend in het gebruik van generieke varianten van calciumantagonisten en ACE-remmers nam toe (respectievelijk met 0,01 DDD/DIM, p=0,016 en 0,02 DDD/DIM, p<0,001), terwijl die van de bijbehorende merkgeneesmiddelen afnam (respectievelijk -0,003 DDD/DIM, p=0,046 en -0,01 DDD/DIM, p<0,001). Er werd geconcludeerd dat de beleidsmaatregel een meetbaar effect had op gebruikspatronen van de onderzochte geneesmiddelgroepen in de twee jaar na introductie van de maatregel in mei 2003. Maatregelen die in de georganiseerde zorg zijn genomen vóór de introductie van deze beleidsmaatregel kunnen echter een afzwakkend effect hebben gehad op de in dit onderzoek waargenomen veranderingen.

Aan de andere kant van de wereld, in Latijns Amerika, hebben Mexico en Brazilië de verkoop van antibiotica zonder recept, de zogenaamde *over-the-counter* (OTC) verkoop, in 2010 beperkt. Als eerste hebben we in **hoofdstuk 4.1** de grootte van het effect van deze beleidsmaatregel bepaald door gegevens uit de private sector van IMS Health te analyseren voor de periode januari 2007 tot en met juni 2012. Dit onderzoek wees uit dat het totale gebruik van antibiotica gedurende de onderzoeksperiode steeg in Brazilië (van 5,7 naar 8,5 *defined daily doses* per 1000 inwoners per dag (DDD/DID, +49,3%) en daalde in Mexico (van 10,5 naar 7,5 DDD/DID, -29,2%). Tijdreeksanalyses lieten een verandering in het niveau van consumptie van antibiotica ten tijde van de beleidsmaatregel zien van -1,35 DDD/DID (p<0,01) in Brazilië en -1,17 DDD/DID (p<0,01) in Mexico. In Brazilië werd een afname van het niveau van gebruik van penicillines, sulfonamides en macroliden waargenomen, terwijl in Mexico alleen het niveau van gebruik van penicillines en sulfonamides significant verminderde. De conclusie was dat, ondanks het feit dat de patronen in antibioticagebruik verschilden tussen Brazilië en Mexico, het directe effect van het beperken van OTC-gebruik op het totale gebruik van antibiotica vergelijkbaar was. In Brazilië werd de trend van toegenomen antibioticagebruik getemperd door de beleidsmaatregel, terwijl de afname van het gebruik in Mexico werd versterkt.

Vervolgens werd bepaald of de handhaving van de beleidsmaatregel leidde tot beter gebruik van antibiotica door variatie in gebruik van penicillines tussen seizoenen te bestuderen in dezelfde set van gegevens (**hoofdstuk 4.2**). Het meest gebruikt penicilline was amoxicilline,

gevolgd door de combinatie van amoxicilline met clavulaanzuur en ampicilline (minimaal gebruik van ampicilline in Brazilië). Voor de beleidsmaatregel bedroeg de variatie in het gebruik van penicillines tussen seizoenen 1,1 DDD/DID in Mexico en 0,8 DDD/DID in Brazilië. Voor Mexico werd berekend dat deze variatie significant verminderde met 0,4 DDD/DID na de implementatie van de restricties, met name door minder seizoensgebonden variatie in het gebruik van amoxicilline en ampicilline. In Brazilië werd geen significant verschil gevonden tussen seizoensgebonden variatie in het totale gebruik van penicillines voor en na de beleidsmaatregel noch in het gebruik van individuele penicillines. Deze resultaten suggereren dat onjuist gebruik van penicillines in Mexico mogelijk is gedaald naar aanleiding van de genomen beleidsmaatregel. De stijging van het antibioticumgebruik in Brazilië geeft - in combinatie met de bevinding dat er geen verandering in seizoensgebonden variatie in antibioticagebruik is opgetreden – reden tot zorg. Verdere maatregelen zijn daarom nodig om onjuist gebruik van antibiotica terug te dringen.

In **hoofdstuk 4.3** beschrijft een ingezonden brief het belang van de kwaliteit van gegevensbestanden en de toegepaste methoden om de effecten van interventies, zoals het terugdringen van OTC-gebruik van antibiotica in Brazilië, te kunnen beoordelen. In deze brief wordt benadrukt dat verschillen in resultaten van vergelijkbare evaluaties kunnen worden verklaard door verschillen in onderliggende gegevens en gebruikte analysetechnieken. De brief eindigt daarom met een oproep om tot een gestandaardiseerde gegevensverzameling te komen die representatief is voor het nationale geneesmiddelengebruik. Hiermee kunnen vergelijkingen van geneesmiddelengebruik tussen landen in Latijns Amerika accurater worden uitgevoerd en beschreven.

Tot slot zijn in **hoofdstuk 4.4** de onbedoelde effecten van het beperken van OTC-gebruik van antibiotica onderzocht. Hierbij werd geanalyseerd of de beleidsmaatregel heeft geleid tot een verandering in het gebruik van geneesmiddelen die als mogelijke alternatieven voor antibiotica ter verlichting van symptomen van bij verkoudheid worden beschouwd. Veranderingen in het gebruik van niet-steroïde anti-inflammatoire geneesmiddelen (NSAIDs), niet-opioïde analgetica en hoestmiddelen en de relatie daarvan met het gebruik van antibiotica na de invoering van de beleidsmaatregel in Mexico en Brazilië werden bestudeerd. Tijdreeksanalyses werden gebruikt om veranderingen in het niveau van gebruik ten tijde van de interventie en in de trend na de interventie te schatten. De Gregory-Hansen co-integratietest werd gebruikt om de relatie tussen het gebruik van antibiotica en mogelijke alternatieven te bestuderen. Na invoering van de beleidsmaatregel nam het gezamenlijk gebruik van NSAIDs en niet-opioïde analgetica en van hoestmiddelen in Mexico met respectievelijk 1,1 DDD/DID en 0,4 DDD/DID toe. In Brazilië nam het gezamenlijk gebruik van NSAIDs en niet-opioïde analgetica wel toe met 1,8 DDD/DID, maar het gebruik van hoestmiddelen niet. In beide landen hingen de veranderingen het gezamenlijk gebruik van NSAIDs en niet-opioïde analgetica samen met veranderingen in het gebruik van antibiotica, terwijl er alleen in Mexico een samenhang tussen veranderingen in het gebruik van hoestmiddelen en antibioticagebruik werd waargenomen. Deze resultaten tonen dus een substitutie-effect van de beleidsmaatregel aan, met name in de richting van meer gebruik van NSAIDs en/of niet-opioïde analgetica, wat een ongewenst klinisch effect zou kunnen hebben. Het doel van de beperking van OTC-gebruik van antibiotica is het terugdringen van

onjuist gebruik en daarmee antibioticaresistentie. Dit soort grootscheepse beleidsmaatregelen moeten echter rekening houden met mogelijke ongewenste effecten op het gebruik van andere geneesmiddelen.

Hoofdstuk 5 is de algemene discussie die lessen trekt uit de verschillende onderzoeken in dit proefschrift. Het belang van vergelijkingen van geneesmiddelengebruik tussen landen wordt onderstreept, waarbij aanbevelingen worden gedaan voor vervolgstappen om de rapportage van dergelijke studies te verbeteren. Adequate en gedetailleerde beschrijvingen van de dekking van de onderliggende gegevens en specifieke informatie over toelating en vergoeding van geneesmiddelen zijn per land nodig om de validiteit en betrouwbaarheid van vergelijkingen te vergroten. Het gebruik en de toepassing van tijdreeksanalyses binnen farmaceutisch beleidsonderzoek wordt in dit hoofdstuk verder bediscussieerd. Het toepassen van additionele testen zoals co-integratie en voorspellende testen kunnen de evaluatie van de effecten van geneesmiddelenbeleid verder verbeteren, met name ten aanzien van het in kaart brengen van ongewenste effecten en het voorspellen van mogelijke uitkomsten. Het hoofdstuk eindigt met een discussie van de mogelijkheden voor het evalueren van beleidsmaatregelen buiten Europa, in omstandigheden waar gegevens over geneesmiddelengebruik schaars zijn. De lessen die uit de studies in dit proefschrift getrokken kunnen worden leiden tot de aanbeveling dat de effecten van interventies in de geneesmiddelensector goed gekwantificeerd moeten worden. Dit proefschrift laat zien dat dat kan en dat dit bijdraagt aan het versterken van *evidence based* geneesmiddelenbeleid.

CHAPTER 6.3

RESUMEN

Las políticas farmacéuticas proporcionan un marco para la coordinación de actividades en el sector farmacéutico y la regulación de la interacción entre el gobierno, la industria farmacéutica, vendedores, productores, distribuidores, profesionales de la salud y pacientes. Para mejorar la salud pública, las políticas farmacéuticas tienen como objetivo promover el acceso equitativo y el uso apropiado de medicamentos en la población. Las políticas farmacéuticas cubren áreas tales como el desarrollo, la regulación, la producción, la comercialización, la prescripción y la dispensación de medicamentos. La evaluación de estas políticas es necesaria para verificar tanto el cumplimiento de los objetivos establecidos y medir los efectos esperados o no esperados, así como como para identificar aspectos que requieren ser mejorados.

Los estudios de utilización de medicamentos se emplean para evaluar las políticas farmacéuticas, ya que proporcionan información sobre el uso de medicamentos en la práctica diaria a diferentes niveles (región, país, ciudad o en hospitales específicos). La información proveniente de estudios de utilización de medicamentos puede ser utilizada en comparaciones de patrones de prescripción, dispensación y utilización de medicamentos entre países.

Como se indica en el **capítulo 1,** el objetivo de esta tesis es evaluar los efectos de diferentes políticas farmacéuticas sobre el uso de medicamentos. Estas políticas fueron evaluadas utilizando diversas fuentes de datos del sector público y privado en distintos países de África, América Latina y Europa Occidental. A pesar de que el análisis de series de tiempo interrumpidas ha sido uno de los métodos más utilizados para la evaluación de las políticas farmacéuticas, es de gran importancia mejorar las metodologías utilizadas en este tipo de estudios para garantizar su correcta evaluación y para mejorar la toma de decisiones basadas en evidencia. Por lo tanto, el uso de series de tiempo interrumpidas en el análisis de políticas farmacéuticas se examina más adelante en esta tesis.

Después de la introducción, en el **capítulo 2.1** se presenta una revisión de literatura de estudios que comparan el uso de medicamentos entre países, publicados entre 2000 y 2015. En este capítulo se resumen características en términos de datos y enfoques metodológicos utilizados para evaluar el uso de los medicamentos entre países de Europa, Asia, África, Oceanía y América. Para esta revisión de literatura, se extrajeron las características principales de 104 estudios. Algunas de las características analizadas fueron: número de países considerados en la comparación, grupo(s) terapéutico(s) estudiados, y la descripción del marco temporal. Nos enfocamos en la descripción de las bases de datos considerando aspectos como el nivel de generación de datos (por ejemplo: productores, distribuidores, registros de farmacia y registros clínicos) y si el objetivo principal de los datos era administrativo o no. También se revisó el tipo de metodología, incluyendo unidades de medición y terminologías utilizadas. Todas estas características se analizaron de manera descriptiva. En esta revisión se encontró que a pesar de que Europa fue el continente en el que por ahora se han llevado a cabo la mayor parte de los estudios comparativos entre países en términos de uso de medicamentos (n = 88), la falta de información sobre las características de las bases de datos usadas en estos estudios, podría reducir la validez de las comparaciones. En otros continentes, los bases de datos de IMS Health fueron las principales fuentes de información (9 de 16 estudios), esto debido a la falta de disponibilidad de otras fuentes de datos para evaluar el uso de medicamentos. Casi en la mitad de los estudios analizados (n = 56) se utilizó un solo tipo de base de datos (por

ejemplo: bases de datos de dispensación y reembolso); mientras que, en la otra mitad de los estudios, el uso de medicamentos fue evaluado usando combinaciones de diferentes bases de datos. La mayoría de los estudios revisados (69%) eran descriptivos y el resto eran analíticos. En los estudios analíticos además de la descripción del uso de medicamentos, se estudió la asociación de uso de medicamentos con algún evento de salud establecido. La disponibilidad de datos administrativos que son capturados regularmente en la asistencia sanitaria en Europa ha facilitado la comparación del uso de los medicamentos en los países de esta región, pero la falta de descripción de las características de los países y de las bases de datos disminuye la fiabilidad de estas comparaciones. En esta revisión de literatura se destaca la necesidad de una mejor orientación de cómo realizar y reportar estudios que comparan el uso de medicamentos entre países con la finalidad de establecer una base para su correcta evaluación.

En el **capítulo 2.2** se presenta el desarrollo de una lista de verificación para evaluar los estudios que comparan el uso de medicamentos entre países. Esta lista de verificación tiene la intención de ayudar a la evaluación de las fortalezas y limitaciones de este tipo de estudios. El desarrollo de esta lista de verificación se llevó a cabo en colaboración con expertos en investigación de uso de medicamentos y tomando como base estudios comparativos entre países. La lista de verificación fue aplicada en diferentes pruebas piloto usando estudios que comparan el uso de medicamentos entre países incluidos en la revisión de literatura (Capítulo 2.1). El desarrollo de esta lista de verificación consistió en seis pasos: 1) Desarrollo de la primera versión de la lista de verificación tomando como punto de inicio las listas de verificación similares obtenidas a partir de la literatura. 2) Primera prueba piloto de la lista de verificación, donde se hicieron observaciones con respecto a la facilidad de lectura e integración de la información de los artículos, para posteriormente hacer cambios menores en el diseño para aumentar la validez aparente de la lista. 3) Segunda prueba piloto se utilizó la lista de verificación como herramienta para revisar veinte artículos que comparan el uso de medicamentos entre países, esta selección de artículos fue realizada al azar a partir de la revisión de la literatura descrita en el capítulo 2.1, posteriormente se calculó el porcentaje concordancia entre los revisores de los artículos. 4) Ajuste de la lista de verificación para mejorar la claridad y facilitar el llenado de la información de cada una de las bases de datos utilizadas en cada artículo de investigación. 5) Tercer prueba piloto y revisión final, en este paso se utilizó la lista de verificación para revisar cinco artículos de investigación, además en una reunión presencial se discutió y acordó la terminología utilizada en la lista de verificación. 6) Prueba de validez externa mediante el envío de la lista de verificación a investigadores en el campo de utilización de medicamentos con la finalidad de poner a prueba la claridad, facilidad de lectura y el llenado de la lista de verificación.

La versión final de la lista de verificación está estructurada en seis dominios (datos generales, diseño de estudio, terminología y unidades de medición, cobertura poblacional, cobertura de medicamentos y evaluación global). La lista de verificación aborda los principales problemas potenciales de comparabilidad de uso de medicamentos entre países en una manera sistemática, facilitando la identificación y extracción de información relevante y relacionada con las fuentes de datos y métodos comparativos en estudios de utilización de medicamentos. Por lo tanto, con la información extraída, la validez de las comparaciones puede ser evaluada teniendo en cuenta los posibles problemas de comparabilidad en terminología, unidades de medición, cobertura

poblacional y de medicamentos en las diferentes fuentes de datos utilizadas en estudios de utilización de medicamentos. La lista de verificación desarrollada servirá como base para desarrollar guías de buenas prácticas para el diseño, la realización, el análisis y el reporte de estudios que comparan el uso de medicamentos entre países.

En el **capítulo 2.3**, se utilizaron análisis de series de tiempo para evaluar la cuota de mercado de análogos de insulina en cuatro países escandinavos (Dinamarca, Finlandia, Noruega y Suecia), y el Reino Unido como un ejemplo de comparación de medicamentos entre países. Para llevar a cabo esta comparación, la cuota mensual del mercado fue calculada dividiendo el consumo mensual de las dosis diarias definidas (DDD) de cada tipo de insulina entre el consumo mensual de todas las insulinas, tomando en cuenta el crecimiento poblacional de cada país. En este capítulo, se utilizaron regresiones de series de tiempo para estimar el cambio porcentual en la cuota de mercado de cada tipo de insulina. Los cambios estructurales en la cuota de mercado se analizaron utilizando la prueba de razón de verosimilitud Quandt (QLR). Posteriormente, se analizó si los cambios estructurales estaban relacionados con cambios en las políticas, tales como la entrada de un nuevo producto en el mercado, los cambios en políticas de reembolso, o actualizaciones en las guías clínicas.

En este estudio se encontró que el porcentaje de cambio en las cuotas de mercado de las nuevas insulinas fueron similares entre los países, excepto en Suecia. El cambio porcentual de la insulina glargina fue de 0.1% mensual en Noruega, 0.2% en Dinamarca y en el Reino Unido, y 0.3% en Finlandia. El cambio porcentual de la insulina detemir fue del 0.1% mensual en Noruega y el Reino Unido, 0.2% en Dinamarca, y 0.3% en Finlandia. En Suecia, el cambio porcentual de ambos análogos de insulina fue mínimo, es decir, un 0.02% en insulina glargina y 0.05% en insulina detemir. Al comienzo del período de estudio, la insulina humana fue la insulina más utilizada en todos los países, excepto en Suecia, en donde se usa pronominadamente insulina aspart. En este estudio no encontramos cambios repentinos en la cuota de mercado de insulinas que podrían estar relacionados con la autorización de venta de nuevas insulinas, los cambios en las guías para el tratamiento de la diabetes, o cambios en las políticas de reembolso. Por lo tanto, llegamos a la conclusión de que las variaciones en la cuota de mercado podrían explicarse por factores no observados tales como las conductas de prescripción y las preferencias de los pacientes, entre otros.

Las regresiones de series de tiempo interrumpidas han sido usadas frecuentemente en la evaluación de políticas farmacéuticas, el **capítulo 3** se enfoca en los aspectos metodológicos de este tipo de análisis. En el **capítulo 3.1** se presenta una evaluación de los cambios en la recolección de datos de ventas de IMS Health en Brasil y su impacto en la tendencia y en el nivel de uso de diferentes grupos terapéuticos seleccionados. Esta evaluación se llevó a cabo debido a que IMS Health en Brasil incorporó gradualmente nuevos datos de mayoristas durante 2009. Este cambio en la muestra podría haber creado un cambio estructural en la pendiente de ventas de medicamentos a partir del 2009. Un cambio estructural en la pendiente de ventas de medicamentos podría afectar la evaluación de políticas farmacéuticas que se enfocan en el cambio de consumo de medicamentos. Por esta razón, examinamos los cambios de tendencia con dos métodos. El primer método fue la prueba Clemente-Montañez-Reyes, que evalúa la presencia de cambios graduales en las series de tiempo en diferentes grupos terapéuticos. El

segundo método consiste en un análisis de series de tiempo interrumpidas usando diferentes cortes en el tiempo durante y después del 2009. Con ambos métodos, encontramos cambios en la pendiente de las series antes y durante el año 2009. Los cambios en la pendiente fueron diferentes entre los grupos terapéuticos. El análisis presentado en este capítulo muestra que los antihipertensivos pueden utilizarse como grupo de referencia para ajustar los cambios estructurales en la base de datos, debido a que este grupo no mostró cambios estructurales, ni cambios en la pendiente.

Posteriormente en el **capítulo 3.2** se utilizó el análisis de series de tiempo interrumpidas para evaluar el efecto de la oferta obligatoria de sustitución de medicamentos innovadores por genéricos para el tratamiento de enfermedades crónicas en Sudáfrica. Esta política fue implementada en mayo de 2003. Para esta evaluación utilizamos datos de ventas mensuales del sector privado sudafricano a partir de junio de 2001 hasta mayo del 2005, estos datos se obtuvieron de IMS Health. En este capítulo se analizaron los siguientes grupos terapéuticos: inhibidores de la bomba de protones (IBP; código ATC A02BC), inhibidores de la HMG CoA reductasa (estatinas; C10AA), antagonistas del calcio dihidropiridínicos (C08CA), inhibidores de la enzima convertidora de la angiotensina (IECA; C09AA) e inhibidores de la recaptación de serotonina (ISRS; N06AB). Después del cambio en la política, sólo los ISRS tuvieron un aumento significativo en el nivel de uso de medicamentos genéricos (0.2 dosis diarias definidas por 1,000 habitantes al mes (DDD/TIM -por sus siglas en inglés-); $p < 0.001$) y una disminución en el uso del medicamento innovador (-0.1 DDD/TIM; $p < 0.001$). El uso de IBP genéricos disminuyó en nivel (-0.06 DDD/TIM, $p = 0.048$) y en tendencia (-0.01 DDD/TIM, $p = 0.043$), pero el uso de los productos innovadores aumentó en nivel (0.05 DDD/TIM, $p < 0.001$) y tendencia (0.003 DDD/TIM, $p=0.001$). Los antagonistas del calcio genéricos y los IECA mostraron un aumento en la pendiente (0.01 DDD/TIM, $p=0.016$; 0.02 DDD/TIM, $p < 0.001$), mientras que los innovadores mostraron una disminución en la pendiente (-0.003 DDD/TIM, $p=0.046$; -0.01 DDD/TIM, $p<0.001$). Concluimos que esta política tuvo un efecto cuantificable en los patrones de utilización de medicamentos durante los 2 años posteriores a su implementación en mayo del 2003. Sin embargo, otras intervenciones ya existentes en los servicios sanitarios pueden haber mitigado el alcance de los cambios observados en este período de tiempo.

Al otro lado del mundo, en la región de América Latina, México y Brasil restringieron la venta libre de antibióticos en 2010. En el **capítulo 4.1** se estimó la magnitud del efecto de esta política mediante el análisis los datos de los sectores privados de ambos países. Estos datos fueron obtenidos de IMS Health para el periodo entre enero de 2007 y junio de 2012. En esta evaluación, se encontró que entre 2007 y 2012 el uso total de antibióticos aumentó en Brasil (5.7 a 8.5 dosis diarias definidas por 1.000 habitantes día (DDD/TID), + 49.3%) y disminuyó en México (10.05 a 7.05 DDD/TID, -29.2 %). Los análisis de series de tiempo interrumpidas mostraron un cambio en el nivel de consumo de -1.35 DDD/TID ($p < 0.01$) para Brasil y -1.17 DDD/TID ($p < 0.001$) para México. En Brasil, el nivel de consumo de penicilinas, sulfonamidas y macrólidos tuvieron una disminución después de la intervención, mientras que en México se estimó que sólo las penicilinas y sulfonamidas tuvieron cambios significativos en el nivel de consumo. Por lo tanto, llegamos a la conclusión de que, a pesar de los diferentes patrones generales de uso de antibióticos en Brasil y México, el efecto directo de las restricciones sobre

el uso de antibióticos sin receta fue similar. En Brasil la pendiente en aumento en el uso de antibióticos se apaciguó después de las restricciones de venta libre; en México se incrementó la tendencia la pendiente a la baja en el consumo de antibióticos.

A continuación, se determinó si la restricción en la venta libre de antibióticos contribuyó a un uso más apropiado de estos medicamentos. Esto fue realizado mediante la medición de los cambios en la variación estacional de uso penicilinas con datos de IMS Health **(capítulo 4.2).** La penicilina más usada fue la amoxicilina, seguida por amoxicilina - ácido clavulánico y ampicilina (con un uso mínimo en Brasil). Antes de las restricciones, la variación estacional en el uso de penicilinas fue de 1.1 DDD/TID en México y 0.8 DDD/TID en Brasil. En México se estimó que después de la restricción hubo una disminución significativa en la variación estacional de 0.4 DDD/TID, debido principalmente a los cambios en la variación estacional de la amoxicilina y la ampicilina. En Brasil, la variación estacional no cambió significativamente en general, ni por desglose de sustancias activas individuales. Estos resultados sugieren que en México el uso no apropiado de penicilinas puede haber disminuido después de la implementación de las restricciones de venta libre. En Brasil, el aumento en el uso de antibióticos y la ausencia de cambios en la variación estacional sugiere la necesidad de más esfuerzos para reducir el uso no apropiado de penicilinas.

En el **capítulo 4.3,** en una carta editorial se describe la importancia de la calidad de las bases de datos y metodologías apropiadas para evaluar de una mejor manera el efecto de políticas farmacéuticas tales como la restricción de las ventas sin receta de antibióticos en Brasil. En esta carta destacamos que las diferencias en los resultados entre diferentes evaluaciones en el mismo país pueden ser consecuencia de diferencias en las fuentes y técnicas de análisis de datos. Esta carta finaliza con un llamado a la recolección de datos estandarizada y representativa a nivel nacional con la finalidad de describir y comparar con precisión el uso de medicamentos en los países de América Latina.

A continuación, en el **capítulo 4.4** se evalúan los efectos no deseados de la política de restricción de venta sin receta en México y Brasil mediante la medición de los cambios en el uso de grupos terapéuticos que pueden ser percibidos como sustitutos de antibióticos para aliviar síntomas de resfriado y su relación con el uso de antibióticos después de las restricciones de venta libre. Los substitutos percibidos evaluados fueron: anti-inflamatorios no esteroideos (AINE), analgésicos no opioides, antigripales y medicamentos para la tos. Se utilizaron series de tiempo interrumpidas para estimar los cambios en el nivel de uso de medicamentos y cambio en la tendencia de uso en el punto de intervención. Se utilizó la prueba de conteigracion de Gregory-Hansen para estimar la relación entre el uso de antibióticos y sustitutos percibidos. Después de la regulación en México, el uso del grupo de AINEs y analgésicos aumento en 1.1 DDD/TID, mientras que el nivel de uso de antigripales y medicamentos para la tos aumentó en 0.4 DDD/TID. En Brasil, el nivel de uso AINEs-analgésicos aumentó en 1.8 DDD/TID, y el uso de antigripales y medicamentos para la tos cambió. En ambos países, los cambios de uso de AINE-analgésicos estuvieron relacionados con los cambios de uso de antibióticos, mientras que sólo en México el cambio de uso de antigripales y medicamentos para la tos tuvieron una relación con los cambios en el uso de antibióticos. Estos resultados mostraron un efecto de sustitución de antibióticos con el uso de otros medicamentos, especialmente los AINEs y

analgésicos que pueden tener consecuencias clínicas no deseadas. En este capítulo concluimos que las políticas destinadas a mejorar el uso de antibióticos y reducir la resistencia a los antimicrobianos deben ser exhaustivas teniendo en cuenta los posibles efectos de sustitución en el uso de otros medicamentos.

En la discusión general (**capítulo 5**), se resumen las lecciones aprendidas de los estudios realizados en la presente tesis. Se enfatiza la importancia de los estudios que comparan el uso de medicamentos entre países, así como los próximos pasos para mejorar su reporte mediante descripciones adecuadas y detalladas de las características de los países en términos de sistemas de salud, cobertura de datos, y comercialización de los medicamentos para aumentar la validez y la fiabilidad de las comparaciones. Además, en este capítulo se discute el uso de análisis de series de tiempo interrumpidas y la aplicación de este método en la evaluación de las políticas farmacéuticas y se sugiere la aplicación de otras pruebas estadísticas en series de tiempo tales como pruebas de cointegración y pronóstico para mejorar la evaluación de las políticas mediante el examen de los efectos no deseados y la previsión de los posibles resultados. El capítulo concluye con la discusión de la evaluación de las políticas farmacéuticas fuera de Europa, donde las fuentes de datos con la información de utilización de medicamentos son escasas. Los estudios realizados en esta tesis demuestran que los efectos de las políticas farmacéuticas necesitan ser cuantificados adecuadamente, y también proporcionan nuevas perspectivas para la formulación de políticas farmacéuticas basadas en evidencia.

CHAPTER 7

ADDENDUM

CHAPTER 7.1

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CHAPTER 7.2

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CHAPTER 7.3

SCIENTIFIC PUBLICATIONS

SCIENTIFIC PUBLICATIONS INCLUDED IN THIS THESIS

Andrew L. Gray, **Yared Santa-Ana-Tellez**, Veronika J. Wirtz. *Impact of the introduction of mandatory generic substitution in South Africa: private sector sales of generic and originator medicines for chronic diseases.* Trop Med Int Health, 2016.

Yared Santa-Ana-Tellez, Aukje K. Mantel-Teeuwisse, Hubert G. Leufkens, Veronika J. Wirtz. *Effects of over-the-counter sales restriction of antibiotics on substitution with analgesics, non-steroidal anti-inflammatory products and cough and cold medicines in Mexico and Brazil: time series analysis.* Health Policy Plan 2016 [Epub ahead of print]

Yared Santa-Ana-Tellez, Aukje K. Mantel-Teeuwisse, Hubert G. Leufkens, Veronika J. Wirtz. *Reply to "Decrease in Penicillin Sales in Brazil after Over-the-Counter Restrictions".* Antimicrob Agents Chemother. 2015;59(9):5864

Yared Santa-Ana-Tellez, Aukje K. Mantel-Teeuwisse, Hubert G. Leufkens, Veronika J. Wirtz. *Seasonal Variation in Penicillin Use in Mexico and Brazil: Analysis of the Impact of Over-the-Counter Restrictions.* Antimicrob Agents Chemother. 2015 Jan;59(1):105-10

Yared Santa-Ana-Tellez, Aukje K. Mantel-Teeuwisse, Anahi Dreser, Hubert G. Leufkens, Veronika J. Wirtz. *Impact of over-the-counter restrictions on antibiotic consumption in Brazil and Mexico.* PLoS One. 2013 Oct 16;8(10): e75550.

Yared Santa-Ana-Tellez, Carlos Durán, Elena Ballarin, Monique Elseviers, Luisa Ibañez, Aukje K. Mantel-Teeuwisse, Monica Sabate, Björn Wettermark, Veronika J. Wirtz, Robert H. Vander Stichele. *Cross-national comparisons of drug utilization - an analysis of data and methodological approaches used.* Manuscript in preparation.

Yared Santa-Ana-Tellez, Carlos Durán, Elena Ballarin, Monique Elseviers, Luisa Ibañez, Aukje K. Mantel-Teeuwisse, Monica Sabate, Björn Wettermark, Veronika J. Wirtz, Robert H. Vander Stichele. *Development of a checklist to evaluate cross-national comparisons of drug utilization studies.* Manuscript in preparation.

Yared Santa-Ana-Tellez, Marloes T. Bazelier, Aukje K. Mantel-Teeuwisse, Nils Ekström, Morten Andersen, Kari Furu, Jari Haukka, Øystein Karlstad, Peter Vestergaard, Hubert G. M. Leufkens, Marie L. De Bruin. *Uptake and market share of insulin analogues in five European countries: Denmark, Finland, Norway, Sweden, and the United Kingdom.* Manuscript in preparation.

Yared Santa-Ana-Tellez, Aukje K. Mantel-Teeuwisse, Veronika J. Wirtz. *The effect of changes in the data collection methods of IMS Health sales data in Brazil between 2007 and 2013.*Technical note for IMS Health.

SCIENTIFIC PUBLICATIONS NOT INCLUDED IN THIS THESIS

Omar Galárraga, Veronika J. Wirtz, **Yared Santa-Ana-Tellez**, Eline Korenromp. *Domestic Contributions to HIV Programming in Low- and Middle-Income Countries.* PloS One. 2013 Jul 6: e67565.

Veronika J. Wirtz, Juan Jose Herrera-Patino, **Yared Santa-Ana-Tellez**, Anahi Dreser, Monique Elseviers, Robert H. Vander Stichele. *Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries.* Trop Med Int Health. 2013 Jun;18(6):665-73.

Veronika J. Wirtz, **Yared Santa-Ana-Tellez**, Clint H. Trout, Warren A. Kaplan. *Allocating scarce financial resources for HIV treatment: benchmarking prices of antiretroviral medicines in Latin America.* Health Policy Plan. 2012 Dec;27(8):638-48.

Veronika J. Wirtz, **Yared Santa-Ana-Tellez** Y, Edson Servan-Mori E, Leticia Avila-Burgos. *Heterogeneous effects of health insurance on out-of-pocket expenditure on medicines in Mexico.* Value Health. 2012 Jul-Aug;15(5):593-603.

Veronika J. Wirtz, Warren A. Kaplan, **Yared Santa-Ana-Tellez**, Ruy Lopez Ridaura. *Affordable, quality, long-term care and pharmacotherapy of chronic diseases: a framework for low and middle-income countries*. Report commissioned by The Alliance for Health Policy and System Research, World Health Organization, Geneva. 2011. Available at: http://www.who.int/alliance-hpsr/projects/alliancehpsr_atm_chronicdiseases_mexico_wirtz.pdf

Yared Santa-Ana-Tellez, Lisa M. DeMaria, Omar Galárraga. *Costs of Interventions for AIDS Orphans and Vulnerable Children: A Systematic Literature Review.* Trop Med Int Health. 2011 Nov;16(11):1417-26.

Omar Galárraga, Veronika J. Wirtz, Alejandro Figueroa-Lara, **Yared Santa-Ana-Tellez**, Ibrahima Coulibaly, Kirsi Viisainen, Antonieta Medina-Lara and Eline L. Korenromp. *Unit Costs for Delivery of Antiretroviral Treatment and Prevention of Mother-to-Child Transmission of HIV: A Systematic Review for Low- and Middle-Income Countries.* Pharmacoeconomics 2011; 29(7):579-599.

Miguel Angel Gonzalez-Block, Alma Lucila Sauceda-Valenzuela, **Yared Santa-Ana-Tellez**. *Factors associated with the demand for delivery care in Mexico.* Salud Publica Mex. 2010 Sep-Oct;52(5):416-23. Spanish.

Alma Lucila Sauceda-Valenzuela, Veronika J. Wirtz, **Yared Santa-Ana-Tellez**, Maria de Luz Kageyama Escobar. *Ambulatory health service users' experience of waiting time and expenditure and factors associated with the perception of low quality of care in Mexico*. BMC Health Services Research 2010, 10:178.

Veronika J. Wirtz, Steven Forsythe, Atanacio Valencia-Mendoza, Sergio Bautista-Arredondo, **Yared Santa-Ana-Tellez**. The *cost of antiretrovirals: maximizing value for money. AIDS 2031*. Results for Development 2010. Available at: http://www.resultsfordevelopment.org/sites/resultsfordevelopment.org/files/resources/The%20Cost%20of%20Antiretrovirals.pdf.

CHAPTER 7.4

ABOUT THE AUTHOR

Yared Santa-Ana-Téllez was born on May 14, 1981 in Mexico City, Mexico. In 2000, she started her studies in Experimental Biology at the Universidad Autonoma Metropolitana (UAM) in Mexico City and in 2002, she was awarded the Los Alamos Summer Stay Award to conduct research at Los Alamos National Laboratory in New Mexico, where she joined the Advance Measurement team to conduct elastic scattering spectroscopy in tissue models. In 2003, she returned to Los Alamos for a second internship with the same team. When she returned to Mexico to complete her bachelor's degree, she also joined the Nanotechnology and Chemical Engineering group at UAM as an intern. In her free time, she also joined the Biophysics department in the same university to continue her training in light scattering in tissues. However, being willing to try research outside of laboratories, she applied to and joined the master's program in Health Economics at the Institute of Public Health in Cuernavaca Morelos in Mexico in 2005, and during the second year of her master's, she joined the collaborative training program for evaluation and monitoring HIV/AIDS and TB interventions in the University of California, Berkeley. After completing her master's in 2008, she joined the Health Economics division of the Center for Health Systems Research at the National Institute of Public Health in Mexico (INSP) as a research assistant. In this capacity, she worked on various research projects focusing on the analysis of health interventions with an emphasis on HIV/AIDS and the use of medications. In November 2012, she joined the Department of Pharmacoepidemiology and Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences as a PhD student in the Faculty of Science at the Utrecht University in the Netherlands, under the aegis of which the work presented in this thesis was conducted.