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# 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 1000 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; 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.

**Key words:** Mexico; Brazil; drug utilization; antibiotics; non-prescription drugs; analgesics

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### Key messages

- While the policy reinforcement pushed down the over-the-counter (OTC) use of antibiotics, the use of antibiotics was substituted with the use of NSAIDs and analgesics in both countries
- In Mexico, the use of antibiotics was substituted to a smaller extent with cough and cold medicines
- 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.
- Given the large size of the pharmaceutical markets of Mexico and Brazil this analysis is relevant not only for the Latin American region but also for other countries which are currently implementing policies to promote appropriate use of antibiotics.

## 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; *Weintraub et al. (1991)*, 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. *Ross-Degnan et al. (1993)* 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. *Signorovitch et al. (2011)* 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.

In the previous 15 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 (*ANVISA 2010, 2013; Diario Oficial de la Federación 2010*). This implementation was carried out during 1999 in Chile, during 2005 in Colombia, during 2006 in Venezuela and during 2010 in Mexico and Brazil (*Bavestrello et al. 2002; Rivas and Alonso 2011; Santa-Ana-Tellez et al. 2013; Vacca et al. 2011*). The consequences in case of non-compliance that the owners of pharmacies face are closure of the pharmacy and high fines (*Diario Oficial de la Federación 2010*). After the policy reinforcement, the level of use of antibiotics decreased approximately by 1 defined daily dose per 1000 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 (*Rivas and Alonso 2011; Santa-Ana-Tellez et al. 2013; Wirtz et al. 2013*). 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 (*Santa-Ana-Tellez et al. 2015*).

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 the use of medicines for symptoms relief after the regulation of antibiotics sales in Mexico and Brazil in 2010.

## Materials and methods

### Data source and setting

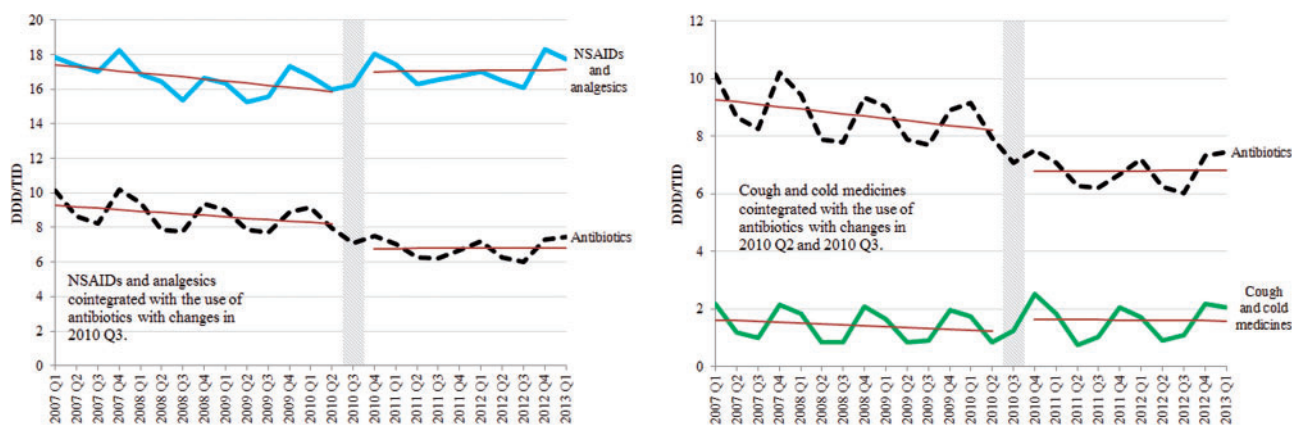
IMS Health provided retail quarterly sales data from the private sectors in Mexico and Brazil from the first quarter of 2007 to the first quarter of 2013. The data were obtained by submitting a research protocol to the IMS Health Global Health Research program. IMS Health constructed the database with 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 (*IMS Health 2008a,b*). 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 (*Van Boeckel et al. 2014*).

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 DDD/TID according to the Anatomical Therapeutic Chemical (ATC) classification system proposed by the World Health Organization (*WHO et al. 2003*). 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 (*Pan American Health Organization 2015*).

### Data analysis

For each group we conducted interrupted time series analyses (*Wagner et al. 2002*) 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 25 August 2010 and in Brazil on 29 November 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



**Figure 1.** Trends of use of NSAIDs-analgesics and cough and cold medicines in comparison with the use of antibiotics in Mexico. (a) Trends of use of antibiotics and NSAIDs-analgesics in Mexico (b) Trends of use of antibiotics and cough and cold medicines in Mexico. Bars positioned in the third quarter of 2010 indicate when the OTC antibiotic sales restriction started in Mexico. Cointegration was assessed using the Gregory-Hansen test, for further details of the results of the cointegration test see [Supplementary Table S2](#)

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 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 ([Santa-Ana-Tellez et al. 2013](#)). 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) ([Gregory and Hansen 1996, 2009](#)).

The GH cointegration test can only be conducted on non-stationary series with identical order of integration ([Gregory and Hansen 1996](#)). Therefore, as a prior test for cointegration, we used the Zivot-Andrews test for stationarity ([Zivot and Andrews 2002](#)). Results from the Zivot-Andrews test can be found in the [Supplementary Table S1](#). 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

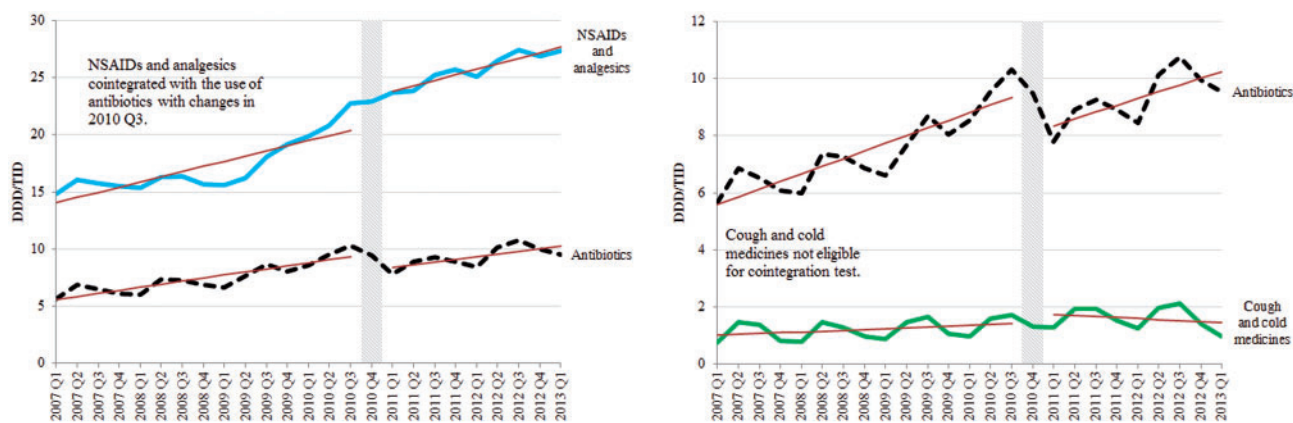
We summarize the interrupted time series results for Mexico in [Table 1](#) and for Brazil in [Table 2](#). In Mexico the reinforcement of the OTC sales restriction of antibiotics led to a decrease in the level of use of antibiotics of 1.5 DDD/TID at the intervention point but an increase in the level 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.

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

The results from the 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 [Supplementary Table S2](#)).

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 b](#)). In Brazil the use and change in level of use of NSAIDs-analgesics was related with the use of antibiotics but the



**Figure 2.** Trends of use of NSAIDs-analgesics and cough and cold medicines in comparison with the use of antibiotics in Brazil. (a) Trends of use of antibiotics and NSAIDs-analgesics in Brazil. (b) Trends of use of antibiotics and cough and cold medicines in Brazil. Bars positioned in the fourth quarter of 2010 indicate when the OTC antibiotic sales restriction started in Brazil. Cointegration was assessed using the Gregory-Hansen test, for further details of the results of the cointegration test see [Supplementary Table S2](#)

**Table 1.** Interrupted time series results for Mexico

	Change in level <sup>a</sup> (95% CI)	Change in slope <sup>b</sup> (95% CI)
Antibiotics	-1.53** (-2.11 to -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 to 0.06)

<sup>a</sup>Change in level measure as DDD/TID.

<sup>b</sup>Change in slope measure as DDD/TID per quarter.

<sup>c</sup>Number of denotes significance: \*95 and \*\*99%.

use of cough and cold medicines was not eligible to test for cointegration with antibiotics (Figure 2a and b). 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

**Table 2.** Interrupted time series results for Brazil

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

<sup>a</sup>Change in level measure as DDD/TID.

<sup>b</sup>Change in slope measure as DDD/TID per quarter.

<sup>c</sup>Number of \* denotes significance: \*95 and \*\*99%.

not recommended particularly in children because of the potential toxicities (Norazida *et al.* 2014). Some years ago several countries, such as the UK, USA and Australia rescheduled cough and cold medicines for under two years of age as prescription-only medicines following reports on adverse effects and lack of evidence on their effectiveness in children (Sung and Cranswick 2009).

Although some NSAIDs and analgesics (e.g. ibuprofen and paracetamol) are recommended to relief symptoms of viral infections in children and adults (CDC 2015), 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 (Arboleya *et al.* 2003; Lanza *et al.* 2009). In patients at risk of gastro-intestinal bleeding it is recommended to use a non-selective NSAID together with a gastro-protective agent such as a proton pump inhibitor (Arboleya *et al.* 2003).

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 (Cham *et al.* 2002). 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 (Kroeger *et al.* 2001; González Pier and Barraza Lloréns 2011). 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 allow sales of non OTC medications without the requirement of a medical prescription (Wirtz *et al.* 2009). Other studies have found that the self-medication in Latin American countries is a common practice (Villegas *et al.* 1987; Haak 1988; Price 1989) and Latin Americans living abroad also incur in self-medication (Mainous *et al.* 2008; González-López *et al.* 2012; Sánchez 2014).

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 (Pérez Cuevas *et al.* 2013, 2014). Even though nearly 80% of the Mexican population and Brazilian population is affiliated to a public insurance (Castro Hoyos 2012; Instituto Nacional de Salud Publica 2012), 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 (Sauceda-Valenzuela *et al.* 2010).

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 (Enriquez Rubio *et al.* 2005). 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 a result 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 users substituted 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.

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*Conflict of interest statement.* None declared.

## Supplementary Data

Supplementary data are available at *HEAPOL* online

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