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Effectiveness of different local actions to control vitamin D prescription in Italy

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Abstract

Introduction. In the last decade, the significant expenditure and consumption increase of vitamin D in Italy led some regions to adopt strategies to improve prescribing appropriateness and contain expenditure.

Materials and methods. Using the statistical analysis method of interrupted time series for consumption and expenditure of cholecalciferol, different types of interventions adopted in four Italian regions and their efficacy were evaluated.

Results. Molise achieved the best results by adopting a health professionals' education program in addition to a prescriber-sanction system. Emilia-Romagna also opted for a medical education strategy, but the results were less relevant due to the lack of penalties. Lazio obtained a slowdown in consumption growth by targeting on the utilization of lower-cost per defined daily dose (DDD) packs and adopting a therapeutic plan. Sardinia showed a decrease in expenditure by adopting a target threshold of lower-cost formulation.

Conclusion. The reimbursement of the lowest-cost packs within the National Health Service (NHS) undoubtedly influences spending trend, but it does not solve prescriptive inappropriateness.

Key words

- cholecalciferol
- expenditure
- intervention
- prescriptive appropriateness
- interrupted time series

INTRODUCTION

Vitamin D's role in bone tissue physiology has long been known, specifically in promoting formation and mineralization processes [1].

In the clinical context, there is a general agreement that vitamin D contributes to bone health and, when combined with calcium, if indicated, protects against bone demineralization, especially in the elderly [2-5]. Several observational studies on cardiomyopathy, neoplasms, and degenerative diseases found a worse health status in people with low 25-OH vitamin D levels. These findings prompted the development of randomized clinical trials (RCTs) to evaluate the potential extra-skeletal effects of vitamin D supplementation. However, the results of numerous RCTs did not confirm these assumptions but outlined ineffectiveness areas of vitamin D supplementation, especially in oncology and cardiology. In these studies, despite the use of relatively high doses (2,000 IU/day and 100,000 IU/month), the treated people did not have advantages in preventing events compared to the placebo group [6-10]. Furthermore, the absence of unique indications for defining the vitamin D dose to be prescribed and the lack of a shared results' interpretation of the 25-hydroxyvitamin D blood assay have raised important critical issues related to vitamin D [11-18]. There is an ongoing debate in the scientific community regarding which serum level of 25-OH-cholecalciferol should define vitamin D deficiency and whether to carry out a preventive supplementation. Normal levels of 25-OH vitamin D also do not have univocal values in the different international guidelines, generating further confusion [19, 20].

In Italy, since 2005, vitamin D and analogues have been subject to medical prescription and reimbursed by the NHS for treating and preventing vitamin D deficiency.

However, in the last few years, vitamin D consumption has steadily increased to the point that the Italian Medicines Agency (AIFA) has assessed vitamin D as a

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drug that requires extra oversight in terms of expenditure, consumption and clinical evidence in 2014. The observed increase in prescriptions suggested inappropriate prescriptive phenomena, primarily associated with its use in extra-skeletal diseases [21-23].

Therefore, between 2015 and 2017, targeted measures were adopted in some Italian regions to promote appropriate use and/or to control cholecalciferol's expenditure, the most prescribed drug. These implemented interventions can be classified into three main categories: 1) healthcare professional education program, 2) prescriptive appropriateness intervention, and 3) expenditure control and rationalization measures.

The first group includes information campaigns aimed at general practitioners to improve the appropriateness of medicines prescriptions, such as audits, dissemination of fact sheets about how medicines are used in clinical practice, or in-depth courses. The second group includes the compilation of treatment data sheets or the presence of a regional committee authorizing the therapy. The third category includes measures of expenditure control and rationalization to promote greater use of lower-cost packs.

This analysis aims to describe the different types of intervention implemented to regulate cholecalciferol prescription in four Italian regions (Lazio, Molise, Emilia-Romagna, and Sardinia) at different times and to verify whether their adoption was associated with a statistically significant change in the trend of consumption and expenditure. The analysis also provides an overview of spending and prescribing vitamin D and analogues in Italy from 2013 to 2019.

MATERIALS AND METHODS

Data

The data analyzed were retrieved from the Medicines Utilization Monitoring Centre (OsMed) flow for the regions of Lazio, Molise, Emilia-Romagna, and Sardinia. OsMed is an information flow of pharmaceutical prescriptions, established according to Italian Law 448/1998 and provided through pharmacies affiliated with the National Health Service (NHS), records the number of packs, the total expenditure, and consumption of reimbursed drugs in Italy stratified by region and month.

The active substances considered for this analysis were selected using the Anatomical Therapeutic Chemical classification at the fifth level (ATC V) in the pharmacological class of vitamin D and analogues of the marketed compounds commonly used in clinical practice: ergocalciferol (ATC A11CC01), dihydrotachysterol (A11CC02), alfacalcidol (A11CC03), calcitriol (A11CC04), cholecalciferol (A11CC05), calcifediol (A11CC06). Cholecalciferol is also available in fixed-dose combinations with calcium (A12AX). The consumption was expressed by defined daily dose (DDD) which represents the maintenance dose per day of therapy, in adult subjects, related to the main therapeutic indication of the substance (therefore it is a standard unit and not the recommended dose for the single patient). The DDD used to calculate cholecalciferol consumption is 20 mcg, according to the one chosen by WHO [24].

Expenditure and consumption data stratified by region, month, and active substance were analyzed for the period 2013-2019.

Statistical method

Monthly data about cholecalciferol expenditure and consumption, expressed as DDDs per 1,000 inhabitants/day, have been extracted and analyzed using the Interrupted Time Series (ITS) statistical method [25-29]. Segmented regression models were used, assuming a linear relationship between the dependent variable, (i.e., drug use or expenditure) and the explanatory variable, which was always time. To evaluate the adopted interventions that were implemented, the focus was mainly on consumption data, while outlay data were also analyzed by considering monthly per capita expenditure as a dependent variable.

The method evaluates several parameters before and after the regional actions.

The following model was used to estimate the parameters:

$$y_t = b_0 + b_1 time + b_2 dummy + b_3 time_{post} + b_4 seasonality + v_t \quad (1)$$

y_t represents the dependent variable of monthly cholecalciferol consumption (expressed as DDDs per 1,000 inhabitants/day) or per capita expenditure; b_0 is the value at the beginning of the period; b_1 is the parameter associated with time and measures the overall trend over the period considered (how much the dependent variable average increases, if $b_1 > 0$ or decreases if $b_1 < 0$ each month). The parameter b_2 is associated with a dichotomic variable that is equal to zero before the regional actions and equals to one in the following months, measuring the immediate impact of the intervention on the average consumption level (it indicates how far the line is moved up or down because of the resolution introduction). The parameter b_3 is associated with time starting from regional resolution introduction and measures the effect of these actions, or rather, the trend-changing produced (b_3 value indicates trend changing of the dependent variable as a result of provision introduction. Therefore, the value of $b_1 + b_3$ measures how much the dependent variable each month grows, if $b_1 + b_3 > 0$ or decreases if $b_1 + b_3 < 0$ dependent on the resolution introduction). Finally, the parameter b_4 is associated with the seasonal component and v_t represents the residual component.

A preliminary analysis was performed on the observed data for each region to assess:

- whether it was correct to assume a linear trend as suggested by equation (1) in Model 1, which implies a linear relationship between dependent variable y and explanatory variable t (time);
- whether it was necessary to incorporate a parameter to account for the seasonal component in the model. In all the regions, a systematic decrease in consumption data was observed in August, and hence the parameter b_4 associated with the $dummy=1$ was considered for this month, while it was set to zero for all other months.

To verify the effect of introducing the regional provisions through the evaluation of ITS models, successive steps were carried out, and the parameters of alternative models were estimated.

The AUTOREG procedure of SAS software was used for estimate the parameters, test and control for autocorrelation on the y_t residues that could distort the parameters estimate. The choice of the most suitable model (among A, B, C, D, E, F, G) to explain consumption or expenditure data was based on the Akaike Information Criteria (AIC) index *(see Supplementary Material "Mathematical formulas of statistical models" available online)*.

Every region represents a specific case, both for the type of resolution adopted and for the time of its introduction, therefore separate models for each region were developed and analyzed. Particularly for Emilia-Romagna, Lazio, and Molise, where the resolutions were aimed at improving prescription appropriateness, the analysis focused on consumption data, and the statistical models have been formulated taking into consideration as dependent variable y_t = DDDs per 1,000 inhabitants/day. A second set of models was estimated to assess whether, in addition to an eventual impact on consumption, the regional decisions also led to a reduction in spending, with monthly expenditure per capita as a dependent variable. The dependent variables' logarithmic transformations resulted in a better choice in the model specification. In contrast, for Sardinia, where the resolution aimed at reducing vitamin D medicines outlay, monthly per capita expenditure was considered as the dependent variable, and then consumption data were analyzed. The characteristics of the actions adopted by each region are summarized in *Table 1*.

RESULTS

Overview of expenditure, consumption and prescription of vitamin D and analogues in Italy for the period 2013-2019

The context analysis of NHS prescription of medicines containing vitamin D and analogues showed that in the last years, cholecalciferol, as a single component, was the most prescribed active ingredient in the analyzed period. Its expenditure and consumption also grew exponentially over time. In 2013, cholecalciferol expenditure amounted to 73.1 million euros (1.22 euros per capita) representing 57.1% of all medicines containing vitamin D and analogues outlay. In 2019, this value increased to 281.3 million euros (4.70 euros per capita), representing more than 80% of the expenditure. Its use also steadily grew, from 51.8 DDDs per 1,000 inhabitants/day in 2013 to 159.9 DDDs in 2019, recording a Compound Annual Growth Rate (CAGR) of about 20.7% (see *Table S1* and *Figure S1 in the Supplementary Material available online)*.

The international comparison of the outpatient expenditure of the first ten active substances, published in the National Report on Medicine Use in Italy of 2019 [21], outlined how cholecalciferol is the first drug in Italy. In other European countries analyzed, this drug was ranked between the 37th in Belgium and the 151st in France [21].

In Italy, cholecalciferol is available in three formulations (oral drops, vials for both injection or oral consumption, and oral solution bottle), each with different costs per pack. In 2019, the two bottles pack of 50,000 IU oral solution was the most expensive (14.3 euros), followed by the single bottle pack of 50,000 IU (8.1 euros per pack), the two bottles pack of 25,000 IU (7.8 euros per pack) and by the oral drops pack with dosing syringe (5.4 euros per pack). The analysis of the average cost per 1,000 IU, stratified by formulation and dosage, confirms this trend. However, the 25,000 IU single bottle pack (oral solution) represents the most expensive (0.205 euros per 1,000 IU; see *Table S2* and *Figure S2 in the Supplementary Material available online*).

In 2019, the total number of cholecalciferol packs prescribed was almost 35 million, with bottle packages accounting for about 80% of total expenditure, drop formulations represented 17.3%, and injectable solutions were only 2.9%. Thus, consumption was mainly directed towards packages with a higher average cost per 1,000 IU. Compared to the previous year, this annual regional expenditure and consumption trends of cholecalciferol showed remarkable growth in almost all Italian regions. Campania recorded the highest prescription increase (+34.5%), compared to the national average of +16.2%. Molise was the only region with a reversed trend, showing a decrease in consumption of about 3.4% between 2017 and 2018 and 9% between

Table 1
Intervention adopted by Lazio, Molise, Emilia Romagna and Sardinia in the period 2015-2017

Region	Date of action	Action adopted	Type of intervention
Lazio	July 2017	Prescriptive appropriateness indicator for cholecalciferol with the goal of increasing the prescription of lowest-cost packs to 70% of the total. Introduction of therapeutic plan for prescription in adults and assessment of prescribing appropriateness by a commission for the first prescription.	Appropriateness control and expenditure rationalization.
Molise	December 2017	Introduction of prescribing treatment form for cholecalciferol prescription. Healthcare professionals' education. Sanctioning actions to prescribers.	Appropriateness control and education of healthcare.
Emilia-Romagna	March 2016	Adoption of an information kit.	Education of healthcare professionals.
Sardinia	November 2015	Expenditure indicator with the goal of achieving a target of 70% calculated as a ratio between oral/intramuscular DDDs of 100-300,000 IU formulations and total DDDs.	Expenditure rationalization.

2018 and 2019, probably linked to the effect of the adopted resolution *(see Figure S3 e S4 in the Supplementary Material available online)*

TYPE AND EFFECTS OF REGIONAL INTERVENTIONS

Lazio

In July 2017, the authorities of the Lazio region introduced a prescriptive appropriateness indicator for cholecalciferol, with the goal of increasing the use of lowest-cost packs per DDD. The regional objective was to increase the prescription of lowest-cost packs to 70% of the total. Moreover, a therapeutic plan was implemented for cholecalciferol prescription in adults to optimize its use in this population group [30]. The therapeutic plan had to be drawn up by clinicians, and a special commission had to evaluate each patient's first prescription appropriateness. This provision can be defined as based on both appropriateness control and expenditure rationalization.

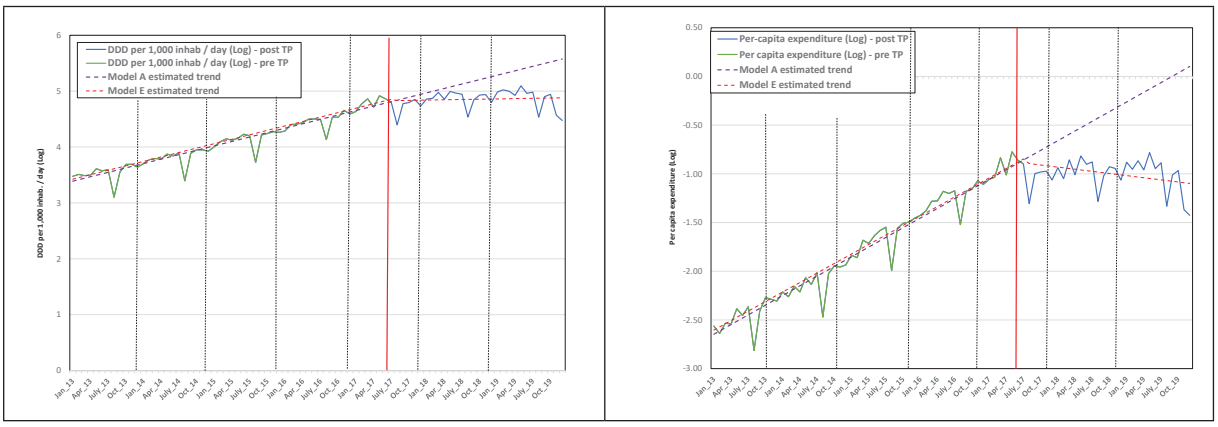
For the period 2013-2019, the monthly consumption data expressed as logarithms follow an approximately linear trend. Based on the AIC index, E is the best model explaining real consumption data. It shows a reduction in use and a stabilization trend compared to the data observed before the provision *(Figure 1)*. The monthly data of per capita expenditure, expressed in logarithm, were used to conduct the same analysis. Evaluating the expenditure trend and the AIC index, model E best represents the data after the intervention. The expenditure model also underlined a positive effect of the Lazio measure, which caused a decreasing trend. The results highlight a slowdown in consumption growth, moving from a monthly increase of 2.6%, expressed as DDDs per 1,000 inhabitants/day before the regional action, to about +0.03 after it. This trend corresponds to a monthly expenditure stabilization from +3.3% to -0.7%, respectively, before and after the regional provision.

Molise

In December 2017, Molise transposed the guidelines about vitamin D supplementation, integrating those of the Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMS) regarding the prevention and treatment of vitamin D deficiency. The region also introduced a prescribing treatment form for cholecalciferol prescription [31] with the aim of regulating, decreasing, and optimizing cholecalciferol use, combining a healthcare professionals' educational program with a prescriptive appropriateness control intervention. The added value of Molise's intervention is the provision of sanctioning actions committed by the director of the regional health government against non-compliant prescribers. Using the logarithmic transformation of the variable under study (DDDs per 1,000 inhabitants/day), the exponential curve becomes almost linear. Based on the AIC index, model G best explained the consumption data, showing not only a decrease in the use average level, but also a change in the direction of drug consumption which decreases *(Figure 2)*. The same analysis was carried out on per capita expenditure monthly data for the period 2013-2019, expressed as a logarithm. By comparing the various models, model E was found to be the best fit for the data, and all variables included in the model are statistically significant. This model underlines the positive effect of the regional intervention, which caused a lowering of the average level and a reversal trend after the introduction of guidelines and the regional form. It also highlights a marked effect on consumption, going from a +3% monthly use increase, expressed as DDDs per 1,000 inhabitants/day before the regional measure, to a negative value of about -1.1%. Similarly, the monthly per capita expenditure trend moves from +3.6% to -2.7%, respectively, before and after the regional resolution.

Emilia-Romagna

In March 2016, Emilia-Romagna adopted and disseminated an information kit about the role of vitamin

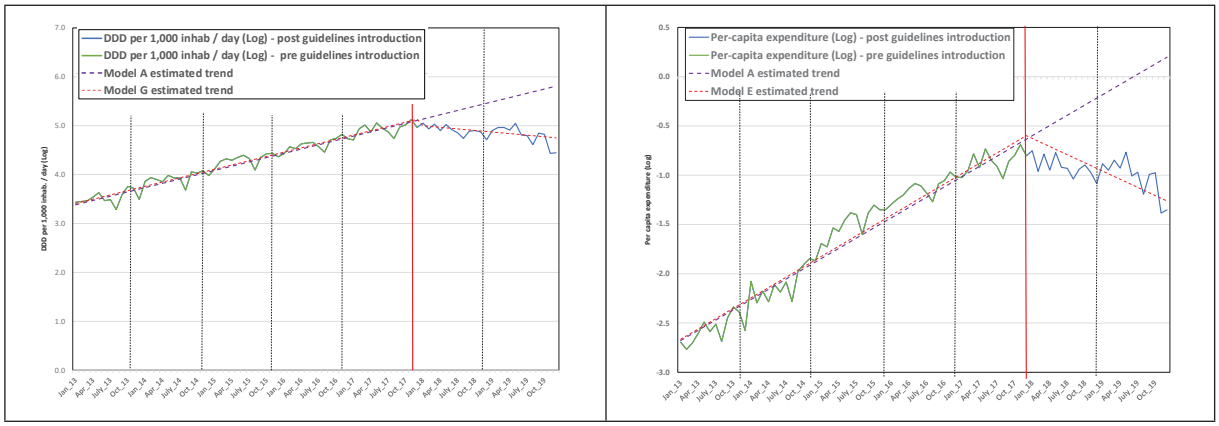


(a) (b)

Figure 1

Lazio - Comparison between real data and trend estimated by models on consumption (DDD per 1,000 inhabitants/day) and per capita expenditure.

The green and the blue line show the real tendency of DDDs per 1,000 inhabitants/day (a) or per capita expenditure (b) for the period between 2013-2019. The red vertical line indicates the timing of the introduction of therapeutic plan (TP) in July 2017. The dashed lines show the trends according to statistical models before (purple line) and after (red line) the regional action.



(a) (b)

Figure 2

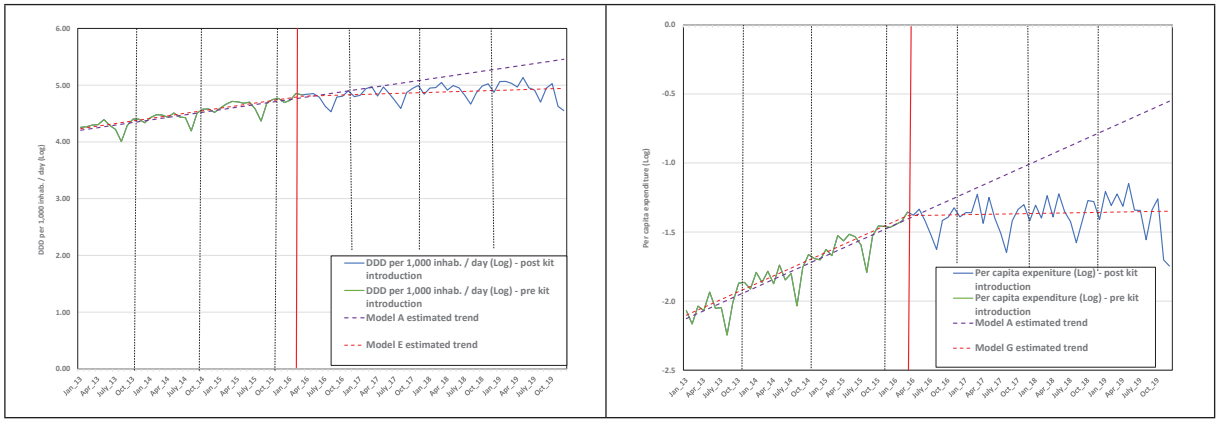
Molise - Comparison between real data and trend estimated by models on consumption (DDD per 1,000 inhabitants/day) and per capita expenditure.

The green and the blue line show the real tendency of DDDs per 1,000 inhabitants/day (a) or per capita expenditure (b) for the period between 2013-2019. The red vertical line indicates the timing of the introduction of guidelines form for cholecalciferol prescription in December 2017. The dashed lines show the trends according to statistical models before (purple line) and after (red line) the regional action.

D in clinical practice, aiming to evaluate and compare available effectiveness evidence. The topics of clinical interest addressed particularly the best behavioral advice to give clinicians, when to use blood assays are necessary and how they should be, at what levels should be started, which kind of medicines should be used, and what treatment patterns are most appropriate. Through the diffusion of the information kit, the region intended to provide some useful indications based on scientific evidence for a better vitamin D and analogues prescription, with the objective to reduce and optimize consumption [32]. This measure was focused on educating healthcare professionals. Using the logarithmic transformation of the variable under study (DDDs per 1,000 inhabitants/day), the exponential curve becomes almost linear. Based on the AIC index, the most suitable model for explaining consumption data is E. It underlines that after the information kit diffusion, the cholecalciferol use has been reduced and shows a stabilization trend. Monthly per capita expenditure data were converted into logarithms and used for the same analysis. Model E is the best data set model, where all the evaluated variables are statistically significant. It shows how, after the information kit introduction, there is a similar effect on consumption trend *(Figure 3)*. The results show a stabilization of consumption and expenditure. In fact, the growth moved from an increase of about +1.5% DDDs every month, before the information kit's diffusion, to a value of about +0.3% monthly after the intervention. Furthermore, the per capita expenditure trend changed from an increase (+1.9%) to a constant value (+0.1).

Sardinia

In November 2015, Sardinia approved a regional intervention defining specific actions to rationalize and contain pharmaceutical expenditure and improve pre-



(a) (b)

Figure 3

Emilia-Romagna - Comparison between real data and trend estimated by models on consumption (DDD per 1,000 inhabitants/day) and per capita expenditure.

The green and the blue line show the real tendency of DDDs per 1,000 inhabitants/day (a) or per capita expenditure (b) for the period between 2013-2019. The red vertical line indicates the timing of the adoption of the information kit in March 2016. The dashed lines show the trends according to statistical models before (purple line) and after (red line) the regional action.

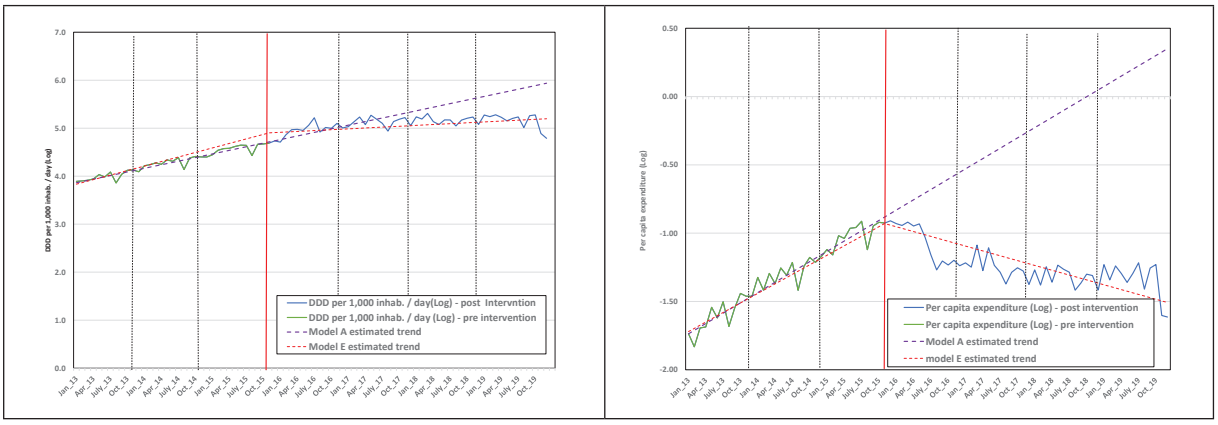
scribing appropriateness of vitamin D. The resolution established that each Local Health Unit should achieve a specific target value higher than 70% by the end of 2016, calculated as a ratio between oral/intramuscular DDDs of 100-300,000 IU formulations and total DDDs [33]. The provision clarifies that "the goal aimed to limit inappropriate use of cholecalciferol is to contain the user level of formulations different from the intramuscular or oral vials of 100/300,000 IU, within 30% of total dispensed doses". The lower annual gross expenditure was estimated at 1.5 million euros, corresponding to about 1.2 million of NHS net expenditure. The intervention aimed to reduce the higher unit price prescription of cholecalciferol and promote the use of lower-cost packs. Aggregate expenditure data indicated an effect of the intervention, showing an increasing trend until 2015 and then a marked decrease from 2016.

Unlike other regions, the Sardinia model was primarily based on cholecalciferol's per capita expenditure data, as the measure was exclusively geared towards reducing outlay. Using the logarithmic transformation of the variable under study (monthly per capita expenditure), the curve from exponential becomes almost linear. Once the linearity was verified through the data series graphic representation, the most suitable model based on the value of the AIC index was chosen. Model E is the best data set model and highlights a reduction in usage trend after the regional resolution approval. The same analysis for consumption data was carried out. Data, expressed as the log transformation of DDDs per 1,000 inhabitants/day, shows an evident impact on use reduction, even if there are fluctuations challenging to explain, particularly since 2016, the period after the intervention approval *(Figure 4a)*.

In summary, the results highlight a remarkable decrease in expenditure due to the regional intervention adopted *(Figure 4b)*. Per capita expenditure moved from a monthly increase of about 2.4% to a reduction of about 1.2%. Instead, consumption values increased from 100.2 DDDs per 1,000 inhabitants/day in 2015 to 175.0 in 2019. However, in the last year, there was a reduction of about 0.7% *(see Table S3 in the Supplementary Material available online)*. Probably, there was a gradual transition to the cheaper formulations (increasing use of oral or intramuscular formulation of 100,000 IU and a great reduction of formulation of 25,000 IU). The consumption analysis *(Figure 5)* shows that since the measure's introduction, there has been a fall in total packs, particularly of 25,000 IU oral solution single bottle packs. The consumption, expressed as total DDDs/1,000 inhabitants per day and stratified by formulation, shows an important growth of 100,000 IU packs (6 vials of injectable/oral solution) and 50,000 IU (oral solution two bottles' packs). Finally, different dosages determine different therapy days (five days for 25,000 packs, ten days for 50,000, and 60 days for 100,000), which could explain the fluctuations recorded.

DISCUSSION

The increase in expenditure and consumption of medicines containing vitamin D and analogues, reimbursed by the NHS, between 2013 and 2019, urged some regional interventions aimed at reducing the observed trends. However, the approach taken by each region was very different and resulting in highly variable outcomes. The analysis shows how Molise achieved the best results. Its educational program for health professionals has reduced both expenditure and consumption of cholecalciferol, although penalty-type regional control may have played a key role. Emilia-Romagna also approved an intervention based on medical education, but the results were less notable, likely due to the lack of penalties. In fact, in this region, there is a stabilization in consumption and expenditure trends, but not a decrease. Lazio introduced a prescriptive appropriateness indicator, targeting the use of lower-cost/DDD packs, and adopted a therapeutic plan for cholecalciferol prescription in adults. This action showed positive results

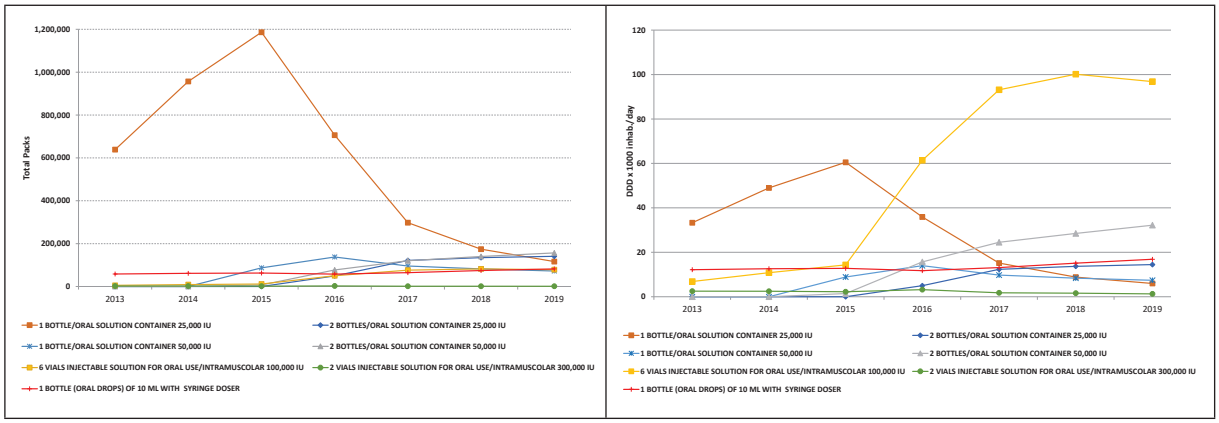


(a) (b)

Figure 4

Sardinia - Comparison between real data and trend estimated by models on consumption (DDD per 1,000 inhabitants/day) and per capita expenditure.

The green and the blue line show the real tendency of DDDs per 1,000 inhabitants/day (a) or per capita expenditure (b) for the period between 2013-2019. The red vertical line indicates the timing of the intervention in November 2015. The dashed lines show the trends according to statistical models before (purple line) and after (red line) the regional action.



(a) (b)

Figure 5
Sardinia - Comparison between consumption and expenditure trend stratified by different formulation (packs DDD x 1,000 inhabitants/day and Total expenditure per pack).
The figure shows the usage trend, expressed as number of packs (a) or DDD per 1,000 inhabitants/day (b), of different formulations of cholecalciferol for the period 2013-2019.

in containing the exponential growth of consumption and stabilizing per capita expenditure. The Sardinia resolution also showed that choosing the lowest cost packages could undoubtedly influence the spending trend, as highlighted by the change in the time course. However, it remains unclear whether this strategy could influence the appropriateness of vitamin D use. In general, there seems to be little mutual learning between regions, and the outcomes do not appear to be conclusive. Therefore, in October 2019, AIFA established the 96 Note to be applied throughout the national territory [34]. The AIFA Notes are a regulatory instrument that defines the drug's therapeutic indications reimbursed by the NHS based on the best evidence of literature efficacy and guarantees appropriateness of use by directing doctors' prescriptions [21].

According to Note 96, the NHS can reimburse medicinal products containing cholecalciferol, cholecalciferol/calcium salts, and calcifediol in two different cases. The first includes institutionalized persons, pregnant or breastfeeding women, and subjects with osteoporosis or osteopathy not eligible for remineralizing therapy, regardless of the 25-OH vitamin D serum levels determination. The second involves patients who need to be identified by a flow chart (Annex 1 of Note 96) to perform 25-OH-cholecalciferol serum assay and then identify the most appropriate drug dose [21, 34]. The Note 96 has been updated based on emerging scientific evidence regarding the lack of effect of vitamin D supplementation in healthy individuals without risk factors for osteoporosis and in the treatment of COVID-19. Some modifications suggested by clinicians and scientific societies have also been included [35]. Moreover, there are certainly persisting issues regarding the appropriate and evidence-based use of vitamin D. It should be noted that the trends analyzed in this study do not consider either supplementation through vitamin supplements or private purchases. It has been estimated that the share of privately purchased medication by citizens reached 20 million in 2019 [22].

CONCLUSION

The article discusses the importance of monitoring the effects of the measures adopted by different regions in Italy (Lazio, Molise, Emilia Romagna and Sardinia) in order to evaluate their effectiveness in inducing important changes in the prescription and expenditure of medicines containing cholecalciferol and understanding which type of action could be the most effective. The findings clearly indicate that the most effective approach involves educating and monitoring prescribers. It is necessary to consider that the costs associated with the various dosages of cholecalciferol are very different, and promoting the use of lower-cost packs could be the milestone to reduce medicines expenditure without compromising patient care, but ensuring the prescriptive appropriateness remains the most important issue to be considered, as showed by Sardinia intervention. Therefore, the prescription appropriateness should be implemented not only to avoid therapeutic abuse and economic waste, but also because prescriber monitoring seems to be a suitable governance mechanism.

The outcomes of regional measures for a single drug class are important in guiding regulatory action nationwide. However, when there is a problem of excess expenditure and consumption involves most of the regions, and only some of them take corrective actions, a central-level intervention is necessary. The AIFA notes have always been an instrument capable of promoting prescribing appropriateness based on the most recent scientific evidence.

Further detailed studies are required to evaluate which types of interventions (regional or national) produce the best results.

Conflict of interest statement

The Authors declare no conflict of interest.

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