Italian Public Health Expenditure for Vitamin D is still high: New Outlook to Saving From a Consumption Analysis in the Liguria Region

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Abstract

Purpose: Italian expenditure for vitamin D greatly increased in the last few years, reaching €314 million ($376.8 million) in 2019. In Italy, the main cause of the increase in public spending for vitamin D is the marketing of high-cost medicines. At national and regional levels, some interventions have been performed to reduce expenditure, but spending has continued to increase. The aim of this work is to propose a new saving strategy determined by an analysis of a significant sample of the market.

Methods: Data on the use of vitamin D formula- tions, including data for the different active substances that represent its pharmaceutical analogue and compo- sition of groups of equivalence, were extrapolated from the Italian Medicines Agency transparency lists and from the Farmadati database. Data on pharmaceutical expenditure were obtained from the Data Warehouse of Liguria Region; the composition of this expenditure was analyzed in detail, focusing on the characteristics of the pharmaceutical preparations and their cost (price per defined daily dose).

Findings: Vitamin D expenditure paralleled that of cholecalciferol, the most used active ingredient, which in Liguria increased from €643,352 ($772,022.4) in 2010 to €8,006,574 ($9,607,888.8) in 2019 (increase of 1144%). Spending focused on high-cost formulations, exceeding 90% of total cholecalciferol cost in 2019. We simulated a possible optimization of the expense for cholecalciferol by applying a revised price to all the cholecalciferol consumptions in high-cost products because these formulations do not have an added therapeutic value, finding that the saving would be at least 60%. National data on the detailed expenditure composition for vitamin D are not available, but we found a strong resemblance between total cholecalciferol expenditure time series in Italy and the Liguria Region.

Implications: The expense of cholecalciferol and consequently the expense of vitamin D could be optimized by modifying the reimbursement of high-cost formulations. At a national level, savings should be proportional to that estimated for Liguria Region. On the basis of the 2019 data, Italian savings with respect to total cholecalciferol expenditure should be € 170.65 million ($ 204.78 millions); per capita cholecalciferol expenditure would shift from € 4.66 ($ 5.59) to € 1.84 ($ 2.21).

Keywords: cholecalciferol, health expenditure, high-cost formulations, Liguria Region, vitamin D.

Introduction

Vitamin D deficiency (VDD) affects millions of people worldwide and its prevention and treatment represent challenges for public health administrators in every country because of its clinical and economic issues. The First International Conference on Controversies of Vitamin D [1], held in 2017, established that 25-hydroxyvitamin D [25(OH)D] concentrations below 12 ng/ml (30 nmol/l) are associated with an increased risk of rickets/osteomalacia, whereas 25(OH)D concentrations between 20 and 50 ng/ml (50–125 nmol/l) appear to be safe and sufficient in the general population for skeletal health. In many countries, including Italy, the previous reference value for the sufficient concentration was 30 ng/ml, leading to an over-estimation of VDD prevalence and consequent overtreatment.

In the EU the prevalence of VDD is high as shown in the summary outcomes of the ODIN Project [2]: 13% of EU residents from 35° N to 69° N (Italy is located between latitudes 37° N and 47° N) had serum 25(OH)D below 12 ng/mL, while 40% had levels below 20 ng/mL. In Italy, VDD prevention and treatment are based on pharmacological supplementation.

Medicines reimbursed by the Italian National Health Service (NHS) are included in a list called "Class A", which is regularly updated by AIFA (The Italian Medicines Agency). Drugs reimbursed by the NHS include essential medicinal products, such as chronic diseases treatments. Reimbursement includes all authorized therapeutic indications, except for the drugs with an AIFA Note. These are the regulatory tool that defines the therapeutic indications for which a certain medicinal product can be charged to the NHS. AIFA Notes can be introduced in three cases: when a medicinal product is authorized for different clinical indications, of which only some are for relevant pathologies; when a medicinal product is aimed at preventing a risk that is significant only for one or more population groups; when a medicinal product is suitable not only for uses of documented efficacy, but also for improper uses. In these cases, through the Notes, AIFA identifies, among all the indications for which a medicinal product is authorized, those to be charged to the NHS from a public health perspective, thus orienting therapeutic choices towards better efficacy and greater safety of use that limits reimbursement only to some indications [3,4].

In Italy, the physician (general practitioner or specialist) may prescribe a formulation of vitamin D to a patient according to prescription notes and recommendation by AIFA. The formulation is selected referring to guidelines and clinical evidence for vitamin D deficiency treatment and prevention. The Italian NHS reimburses a defined reference price for each drug formulation found in a list called 'Transparency list' that is regularly updated by AIFA. A specific formulation may be present in 'Transparency list' as branded or generic product; the two products may have different final prices (usually the branded product has a higher price) but the reference price is the same for

each specific formulation. Through co-payment, the patient can choose a branded product instead of a generic, but the patient cannot choose a formulation different from the prescribed one.

On the basis of on WHO's definition, defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults [5] DDD for Vitamin D corresponds to 20 µg (800 IU - International Units) [6]. Prescription medications differ by active substance, concentration, and price/DDD. Price/DDD allows the distinction between the more or less expensive products.

Public health expenditure in Italy for VDD prevention and treatment has drastically increased in the last few years, reaching up to € 314 million ($ 376.8) in 2019.

New reference values for the definition of VDD have been applied in Italy since October 2019, along with the introduction of prescriptive Note 96 by AIFA [7].

The prescribing Note 96 has defined limits to the prescription (charged to the NHS) of the drugs indicated for the prevention and treatment of VDD in adults. The limitations introduced by the Note 96 are described in the following clinical scenarios. Irrespective of the determination of 25(OH) D, Vitamin D can be prescribed to institutionalised people, pregnant or breastfeeding women and people suffering from osteoporosis from any established cause or osteopathies not candidate for remineralizing therapy. Conversely, after determination of 25(OH) D, Vitamin D can be prescribed to people with serum levels < 20 ng/ml of 25OHD and symptoms attributable to hypovitaminosis (asthenia, myalgia, diffuse or localized pain, frequent falls without motivation), people diagnosed with hyperparathyroidism secondary to hypovitaminosis D, people suffering from osteoporosis of any established cause or osteopathy, candidates for remineralising therapy for which the hypovitaminosis correction should be a prerequisite for the onset of therapy, long-term therapy with medications that interfere with vitamin D metabolism and diseases that can cause malabsorption in adults. The Note 96 is applied to cholecalciferol and calcifediol, the main pharmaceutical analogue of vitamin D.

As part of its monitoring activities, AIFA reported that in the first fifteen months (until January 2021) of the application of Note 96 there was a decrease in consumption and expenditure of drugs of about 30% compared to previous periods both in terms of packages supplied and expenditure incurred by the NHS. The most important effect in economic terms was in the first 12 months with an average saving of 9.1 million/month; currently, there is a residual effect of the Note (months 13-15) estimated in a reduction of about 2.1 million/month [8]. Initial signs were encouraging, but COVID-19 pandemic and its consequences must be considered, including access to health care, especially in 2020.

The effects of the introduction of Note 96 on the reduction of expenditure for Vitamin D are

consequent to the reduction in the number of treatments to be provided. Public expenditure for Vitamin D is the result of the product between number of pieces sold and piece price. The expenditure depends on the number of treatments required, or on the prevalence of the condition, which varies according to the criteria established to define the state of deficiency, and the cost for which the individual treatment is provided. With the same number of treatments provided, the use of more expensive products leads to an increase in expenditure.

Regional and local public health administrators engaged in several enforcement actions against Vitamin D expenditure. These actions were aimed to move toward the prescription of less expensive products [9–11].

Sanò et al. [12] evaluated whether a shift of vitamin D3 prescriptions toward 100000 IU formulation, less costly, could allow savings. Their scheme has been applied in a local health authority in Piedmont Region (Italy) since 2015. They concluded that a shift of vitamin D3 prescriptions toward 100000 IU formulations would allow reducing costs from the payer's perspective. Despite all these efforts Italian public health expenditure for Vitamin D continues to increase.

In 2011's National Report on the Use of Drugs in Italy (OsMed Report)[13], about vitamin D expenditure it is stated that "the disproportion between the percentage increase in expenditure and the increase in DDD prescribed was explained by the commercial push to the preference of oral preparations in single-dose vials for monthly administration with a cost 4 times higher, per delivered dose, compared to other oral preparations".

The present study focused on the cost of the treatments provided, by examining the pharmaceutical preparations on the market and their NHS reference prices. We hypothesize that in Italy the main cause of the increase in public spending for Vitamin D is due to the presence on the market of high-cost formulations in Class A (reimbursed by the NHS) for the treatment of VDD. We are particularly interested in comparing oral single-dose preparations for every two weeks, monthly and every two months administration and oral drop preparation for daily administration. All oral single-dose preparations have comparable prices, which are up to 4 times higher than that of daily oral drops as reported in the OsMed report. In this work, oral single-dose preparations have been called "high-cost products".

Most of VDD treatment and prevention recommendations occur in the field of osteoporosis, which represents a major risk factor for bone fractures in elderly populations. In Italy the prevalence of osteoporosis in the population aged $\geq$50 is 30.3% (77.2% in women), whereas the prevalence in the general population is 6.3% [14]. Liguria represents 2.56% of the Italian population and has the highest percentage of elderly people (population aged 65 or over) [15]; therefore Liguria represents

a paradigm for Vitamin D consumption. Our aim is to suggest strategies for reducing Vitamin D expenditure stemming from observations related to our paradigmatic region.

MATERIALS AND METHODS

Medicinal product data

An analysis of Vitamin D expenditure in Italy was carried out by extrapolating the data from the "National Report on the Use of Drugs in Italy (OsMed Report)" [13].

The OsMed Reports are released annually by AIFA, they make available medicine consumption and expenditure data for the general population in Italy.

We detected the following characteristics of Vitamin D expenditure: allocation, expense expenditure time series (period 2005-2019), 'mix effect' time series (period 2006-2019), and expenditure composition by its pharmaceutical analogue.

The comparison between cholecalciferol-based products currently on the market was made using data extracted from the AIFA Drug Database.

The database reports for each medicinal product the pharmaceutical form, the dosage, the status (authorized or revoked), the package leaflet and the summary of the product characteristics.

The NHS reference prices and the retail prices of the products covered by the paper were extracted from the AIFA transparency lists (list by active ingredient) and from the Farmadati database which is accessible through the identification of the enabled operator.

The information flow

The health consultation Data Warehouse (DWH) service is accessible from the Portale Ligure Socio Sanitario [16] through the identification of the enabled operator.

The analysis on quantitative and economic consumption was carried out using the flow data of the territorial pharmaceutical agreement and of the direct distribution limited to the channel of the distribution on behalf only. The DWH was interrogated for the extraction of all ATC (Anatomical Therapeutic Chemical classification system) of cholecalciferol preparations (A11CC05) for the reporting period 2010-2019. The formulations included the following dosages: 10000 IU/ml 10 ml, 25000 IU (packs of 1, 2, 4 vials), 25000 IU/2.5ml 10 ml, 50000 IU (packs of 1, 2 vials), 100000 IU/ml 6 vials and 300000 IU/ml 2 vials. These data are sent from the five Local Health Units (LHUs) to the Liguria Region and are the result of all the prescriptions issued by community pharmacies affiliated with the Region. The LHUs supply the essential levels of assistance established by the Government within each province. Every LHU is equipped with public legal status and entrepreneurial autonomy under the national and regional legislative dispositions in force. In Liguria, there are five LHUs. In regard to "community pharmacies", we mean regular

pharmacies located outside hospitals and accessible to all citizens. Community pharmacies are assigned to a municipality or indirectly to private persons with a degree in pharmacy. In Liguria, all community pharmacies are affiliated with the Regional health system.

All data are sent to the Liguria Healthcare Authority (A.Li.Sa.) and are the result of all the prescriptions issued by affiliated community pharmacies. The data of the activity are consolidated within the 10th of March of the following year with respect to the reference.

Estimation of optimized expense and potential saving

Optimized expense has been estimated by applying a revised price to all the consumptions of cholecalciferol's high cost products. The revised price has been considered equivalent to the price (per DDD) of the 10000 IU/ml 10 ml formulation (oral drops); the motivation lies in the fact that, at the moment, this is the less costly formulation among those for maintenance therapy. The revised price therefore corresponds to the ideal amount to maximize NHS saving.

The calculation of cholecalciferol optimized spending in Liguria region was based on the following data:

A = Cholecalciferol recognised expense: actual annual expenditure on cholecalciferol (all products);

B = Cost avoidance: zeroing of recognised expenditure for high-cost products;

C = Additional costs: sum of new expenditure deriving from the application of the revised price (RP) to the consumption (U) recorded for each high-cost product of cholecalciferol. For each high-cost product, the following formula was applied: RP x U, where U = consumption (DDD), consisting in (n x C)/800 where n = number of pieces sold per product and C = content (IU per pack), considering that for cholecalciferol 1 DDD = 800 IU.

Data regarding actual annual expense and number of pieces sold per product were derived from DWH of Liguria region.

Cholecalciferol optimized spending was calculated as: A – B + C. Part of actual annual expenditure, derived from the consumption of other cholecalciferol's products (with respect to high-cost products), remains unchanged. Potential saving arises from the difference between cost avoidance and additional costs.

The team of the authors includes prescribing physicians, which supported the setting used for the choice of revised price. However, this approach has not yet been discussed outside the working group.

RESULTS

Vitamin D expense: allocation, time series, composition

In Italy, in 2019, € 5.19 ($ 6,23) of every € 5.62 ($ 6.74) of the total per capita expense for vitamin

D was determined by agreed expenditure (92%). Total per capita expense refers to total public expenditure on pharmaceuticals, looking at drugs purchased by each citizen. Data refer to the entire population. Total public expenditure on pharmaceuticals was determined including gross agreed expenditure and expenditure on medicines purchased directly from public health establishments (hospitals). [13]**.**

Time series for per capita Vitamin D agreed expenditure started in 2007, whereas the annual rate of increase started in 2006. The annual rate of increase makes it possible to extend the per capita expense time series up to 2005 (Table 1).

In the period 2005-2019, per capita expenditure had a rate of increase of 1,302.7% with a compound annual rate of increase of 20.8%. Mix effect refers to prescription of more expensive products (positive mix effect) or less expensive products (negative mix effect) referring to cost per DDD. Time series for mix effects started in 2006. A positive mix effect was found during the entire time series with highly positive values (around 20%) from 2010 to 2014; in 2019 mix effect was -2% (Table 1).

Table 1. Time series of vitamin D expense by analogous (ATC) and 'mix effect' in Italy

	2005	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*	*2016*	*2017*	*2018*	*2019*
Vitamin D (ATC A11CC) per capita expense (agreed expenditure)	0.37*	0.38*	0.4	0.5	0.5	0.7	0.9	1.2	1.6	2.0	2.7	3.5	4.3	5.0	5.2
Cholecalciferol (ATC A11CC05) per capita expense								0.8* (68%)	1.2 (75%)	1.6 (80%)	2.3 (85%)	3.1 (88%)	3.9 (90%)	4.5 (90%)	4.7 (90%)
Other analogous aggregated (calculated)								0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5
Vitamin D per capita expense increase over previous year		3.0%	4.1%	12.3%	11.4%	32.5%	30.8%	30.5%	37.6%	28.1%	32.2%	30.3%	23.3%	16.2%	3.9%
Vitamin D 'mix effect' increase over previous year		4.9%	7.1%	7.4%	7.4%	19.9%	21.1%	18.6%	17.5%	20.4%	5.1%	1.7%	1.6%	1.1%	-2.0%

*Source: OsMed Report 2005-2019. All non-percentage data are reported in € (*calculated data).*
ATC = Anatomical Therapeutic Chemical classification system.

Vitamin D (ATC A11CC) expenditure results from the sum of the expenses for different active substances representing its pharmaceutical analogue: alfacalcidol (ATC A11CC03), calcitriol (ATC A11CC04), cholecalciferol (ATC A11CC05), calcifediol (ATC A11CC06); referring to

pharmaceutical analogue, the composition of Vitamin D expenditure is available from the year 2012. In Italy, in the last few years, the public spending for Vitamin D (ATC A11CC) has increased with a direct proportion to the expenditure for cholecalciferol (ATC A11CC05), one of its analogues (Table 1).

In 2012 cholecalciferol accounted for 68% of Vitamin D expenditure, has progressively come firmly to represent 90% of Vitamin D expenditure. In 2018, in Italy cholecalciferol ranked first among most expensive active substances, looking for agreed pharmaceutical expenditure, resulting € 273 ($ 327.6) million; in 2019 confirmed a first place resulting of € 281 ($ 337.2) million [13].

Cholecalciferol based products

Sixty-five cholecalciferol preparations were available in NHS Class-A up in 2019. These preparations were divided into 8 groups of equivalence (Table 2). Oral drops preparations (10,000 IU/ml 10 ml) have a price per DDD 2.55 to 4 times less compared to single-dose products for 'every two weeks', 'monthly', 'every two months' use. The whole of single-dose products for 'every two weeks', 'monthly', 'every two months' use represents cholecalciferol high-cost products group and corresponds to the following groups of equivalence: 25,000 IU (packs of 1, 2, 4 vials), 50,000 IU (packs of 1, 2 vials), 25,000 IU/2.5ml 10 ml.

Table 2. Characteristics of cholecalciferol preparations (ordered by date of marketing)

Group of equivalence[1]	Way of use	Date of marketing[2]	Denominations[1] (n. of commercial preparations)	IU per pack	Reference price per pack[3] (€)	Therapy cost (€/DDD[4])	Use in VDD maintenance treatment[5]
300000 IU/ml 2 vials	oral/IM vials	1/2006	2	600000	3.50	0.0047	unspecified
100000 IU/ml 6 vials	oral/IM vials	1/2006	2	600000	4.00	0.0053	unspecified
10000 IU/ml 10 ml	oral drops	1/2006	14	100000	4.50	0.0360	daily /weekly
25000 IU/2.5 ml	oral single dose	9/2009	14	25000	4.50	0.1440	every two weeks /monthly
50000 IU 1 vial	oral single dose	11/2014	8	50000	6.90	0.1100	monthly /every two month
50000 IU 2 vials	oral single dose	7/2015	8	100000	12.00	0.0960	monthly /every two month
25000 IU 2 vials	oral single dose	4/2016	14	50000	7.00	0.1120	every two weeks /monthly
25000 IU/2.5 ml 10 ml	oral dosing syringe	9/2016	3	100000	11.50	0.092	every two weeks/monthly

[1] AIFA transparency lists; group of equivalence '25.000 IU 4 vials' entered the market in December 2013 but currently is not present in AIFA transparency lists and in list of Class A and Class H medicinal products.
[2] Farmadati site
[3] AIFA list of Class A and Class H medicinal products.
[4] For cholecalciferol, DDD corresponds to 20 µg (800 IU). [6]
[5] vitamin D supplementation is supported among older adults age 65 years and older at risk of vitamin D deficiency and fractures if given in daily or equivalent weekly or monthly doses of 800 to 1000 IU and with good adherence [21]
IU = International Units, IM = intramuscular, VDD = Vitamin D Deficiency.

The marketing of these products determined a steep increase in per capita expense for Vitamin D in Italy (Figure 1).

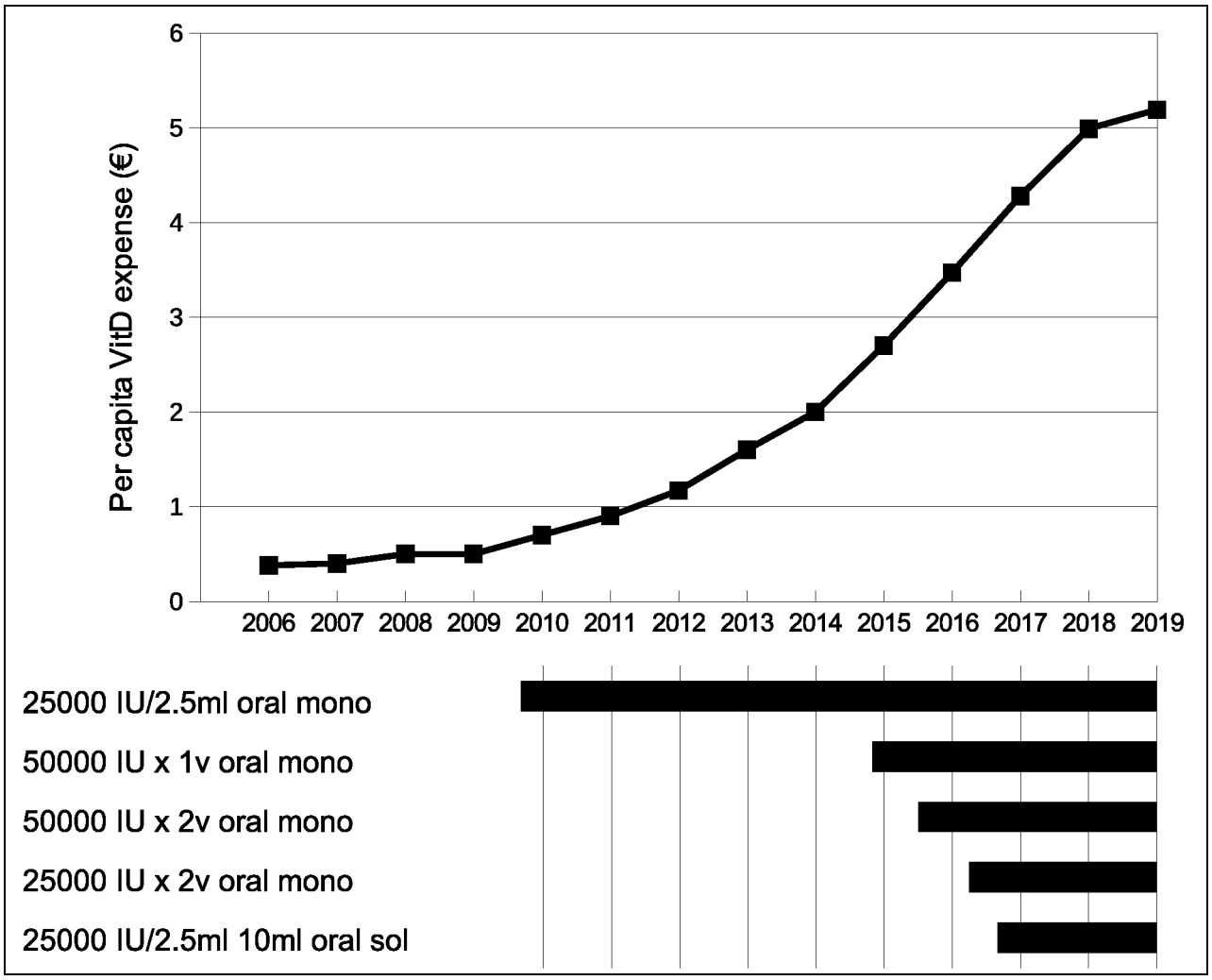

Figure 1: Relation between time series for Vitamin D expenditure and date of marketing of cholecalciferol high-cost products in Italy

Introduction of the five high-cost cholecalciferol formulations determined a significant increase of Vitamin D per capita expense curve slope during years 2009-2018. v = vial; mono = single dose; sol = solution. Horizontal bars represent the moment when each high-cost formulation came to the market.

Cholecalciferol expenditure composition by groups of equivalence in Liguria

Cholecalciferol expenditure composition by year and by group of equivalence is reported (Table 3). In the examined period cholecalciferol expenditure in Liguria region has grown from € 643,352 ($ 772,022.4) (2010) to € 8,006,574 ($ 9,607,888.8) (2019) with a rate of increase of 1,144%. The aggregated representation of cholecalciferol high-cost products expenditure (Table 3) reports the increase from 22.22% to 90.85% of the total cholecalciferol expenditure.

National data are available for total cholecalciferol expenditure (disaggregated data by group of equivalence are not available). Time series data for total cholecalciferol expenditure in Italy are similar to that of the Liguria Region (Figure 2).

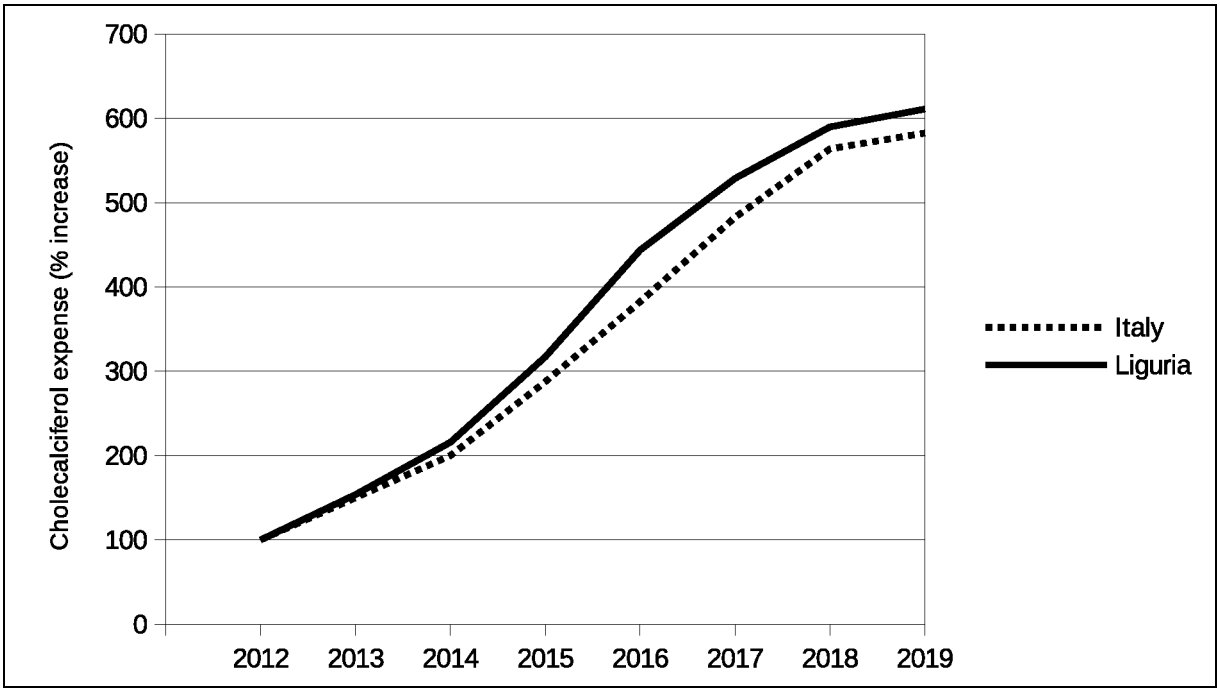

Figure 2: Percentage increase of Italy and Liguria expenditure for cholecalciferol in the 2012-2019 period
Increase of cholecalciferol expenditure in Liguria consistently increases over the years (2012-2019).

Table 3. Cholecalciferol expenditure composition by groups of equivalence. Regione Liguria, period 2010-2019.

	2010		2011		2012		2013		2014		2015		2016		2017		2018		2019	
Group of equivalence	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**	**€**	**%**
300.000 IU/ml 2 vials	9,061	*1.4*	12,565	*1.3*	14,178	*1.1*	15,634	*0.8*	15,904	*0.6*	14,479	*0.3*	14,143	*0.2*	12,618	*0.2*	9,387	*0.1*	7,441	*0.1*
100.000 IU/ml 6 vials	10,460	*1.6*	13,200	*1.4*	16,056	*112*	20,992	*1.0*	30,416	*1.1*	47,200	*1.1*	51,812	*0.9*	61,112	*0.9*	74.412	*1.0*	82,424	*1.0*
10.000 IU/ml 10 ml	480,858	*74.7*	546,610	*57.6*	607,683	*45.3*	689,968	*33.7*	751,979	*26.2*	769,781	*18.3*	734,534	*12.5*	751,117	*10.8*	699,091	*9.0*	642,683	*8.0*
25.000 IU/2.5 ml	142,973	*22.2*	376,970	*39.7*	702,918	*52.4*	1,324,076	*64.6*	2,075,841	*72.2*	3,046,791	*72.2*	3,227,533	*54.9*	3,002,647	*43.3*	2,478,498	*32.1*	1,045,167	*13.1*
25.000 IU 4 vials											41	*0,0*	109	*0.0*	16	*0.0*	0	*0.0*	0	*0.0*
50.000 IU 1 vials											292,498	*6.9*	714,832	*12.2*	986,343	*14.2*	1,164,480	*15.1*	399,236	*5.0*
50.000 IU 2 vials											46,813	*1.1*	719,276	*12.2*	992,606	*14,.3*	1,342,372	*17.4*	2,385,414	*29.8*
25.000 IU 2 vials													415,324	*7.1*	1,113,275	*16.1*	1,946,457	*25.2*	3,419,841	*42.7*
25.000 IU/2.5 ml 10 ml													2,495	*0.0*	9,326	*0.1*	14,651	*0.2*	24,368	*0.3*
Colecalciferol high cost products	**142,973**	***22.2***	**376,970**	***39.7***	**702,918**	***52.4***	**1,324,076**	***64.6***	**2,075,841**	***72.2***	**3,386,143**	***80.3***	**5,079,569**	***86.4***	**6,104,213**	***88.1***	**6,946,458**	***89.9***	**7,274,026**	***90.9***
total	**643,352**	**100**	**949,345**	**100**	**1,340,835**	**100**	**2,050,670**	**100**	**2,874,140**	**100**	**4,217,603**	**100**	**5,880,058**	**100**	**6,929,060**	**100**	**7,729,348**	**100**	**8,006,574**	**100**

IU = International Units.

Source: Datawarehouse Liguria Region.

The introduction of the Prescriptive AIFA Note 96

The AIFA Note 96 was approved in October 2019 and its effects can be assessed from November 2019. It has defined limits to the prescription, charged to the NHS, of the drugs indicated for the prevention and treatment of VDD in adults. As part of its monitoring activities, AIFA reported that in the first fifteen months (until January 2021) of the application of Note 96 there was a decrease in consumption and expenditure of drugs of approximately 30% compared to previous periods in terms of packages supplied and expenditure incurred by the NHS. The most important effect in economic terms was in the first 12 months with an average saving of € 9.1 million per month; currently, there is a residual effect of Note 96 (in months 13-15) estimated at a reduction of approximately € 2.1 million per month [8].

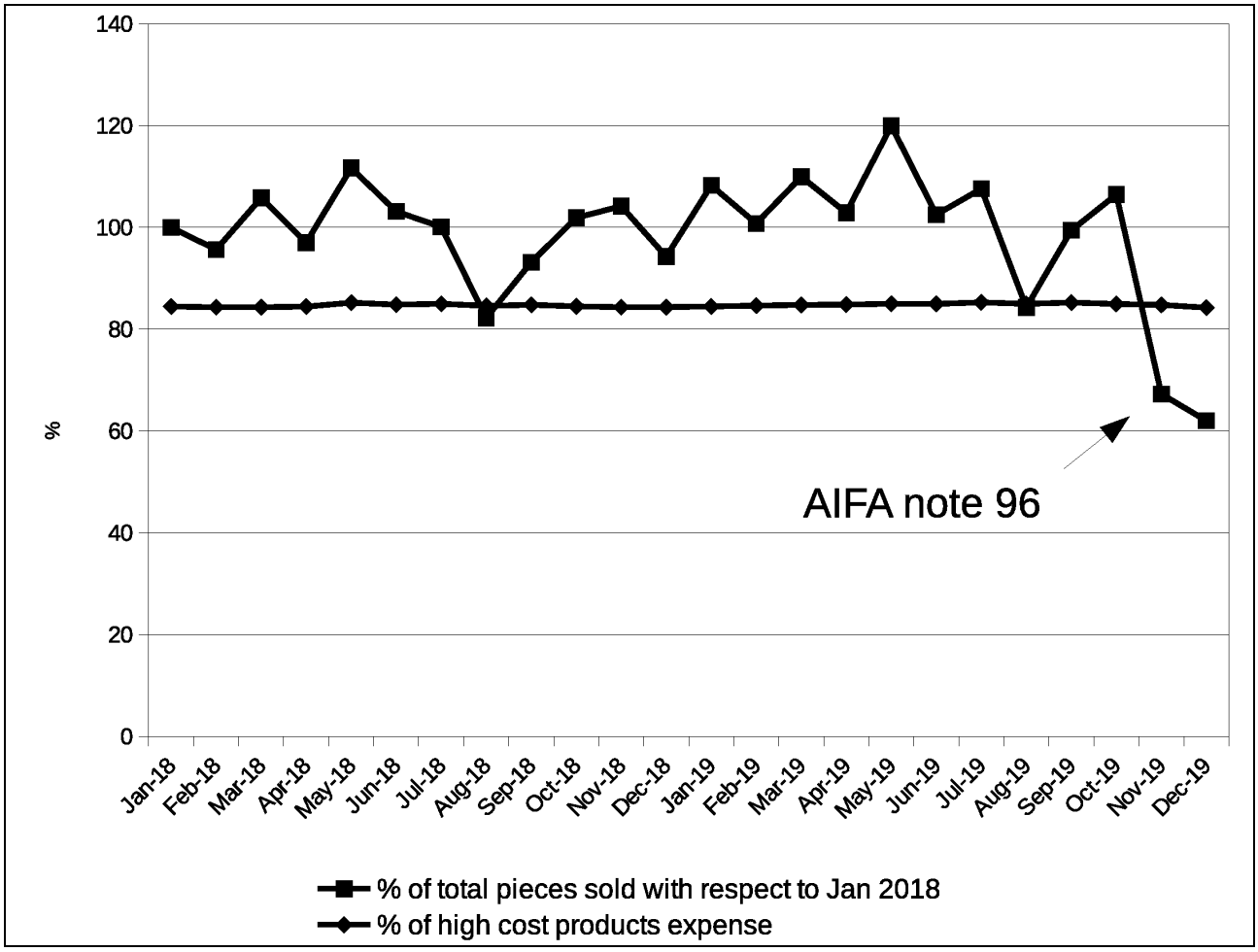

Figure 3: Consequences of AIFA Note 96

The application of AIFA Note 96 in November 2019 determined a drop in the total cholecalciferol pieces sold per month in Liguria (in the figure the monthly trend is plotted as % of total pieces sold in January 2018, solid squares), however, expense for high-cost cholecalciferol remains above 84% (solid diamonds).

Liguria data (available up to December 2019 included, at moment of submission) confirm a decrease in consumption of cholecalciferol compared to previous periods (November-December

2019 vs November-December 2018) (Figure 3); however over 84% of cholecalciferol consumptions remain determined by high-cost products. The assumptions for savings, deriving from the application of a revised price to all the consumptions of cholecalciferol's high cost products, are confirmed.

Cholecalciferol optimized spending estimation

Regarding Liguria Region data for 2019, potential savings have been calculated by application of a revised price to all the consumptions of cholecalciferol high-cost products.

With high-cost product expenditure set at zero (cost avoidance), new expenditure derives from the application of a revised price to the consumptions above mentioned (additional costs) with savings arising from the difference between cost avoidance and additional costs.

Additional costs sum a part of expenditure, derived from other cholecalciferol products consumptions, that remains unchanged and results in optimized expenditure.

Total cholecalciferol expenditure in Liguria in 2019 was € 8,006,574 ($ 9,607,888.8); optimized expenditure would be € 3,143,808 ($ 3,772,569.6). The potential savings would be € 4,862,766 ($ 5,835,319.2) (60.73%).

Extension of the assessment at national level

Data contained in the annual Federfarma report [17], show that in 2019 cholecalciferol ranks 1st or 2nd among the most expensive active substances in almost all the regions. The analysis of these data allows the creation of a time series of cholecalciferol expenditure in all the Italian regions for the period from 2016 to 2019.

In the period 2016-2019 cholecalciferol expenditure increase rate has positive value in all Italian regions, except Tuscany (-4.44%) and Sardinia (-20.43%). Data adjustment by population [18] shows that in 2019 per capita cholecalciferol expenditure ranges from 2.55 (Tuscany) to 7.24 (Campania) (Figure 4).

Considering the regional data and considering the strong resemblance between cholecalciferol expenditure time series in Italy and Liguria Region (Figure 2), savings deriving from the application of a revised price to all the cholecalciferol consumptions in high-cost products at a national level should be about proportional to that estimated for Liguria Region in 2019 (60.73%). In that event Italian NHS cholecalciferol expenditure savings should be € 170.65 ($ 204.78) million (total cholecalciferol expenditure in Italy in 2019 was € 281 [$ 337.2] million); per capita cholecalciferol expenditure would shift from € 4.66 ($ 5.6) to € 1.84 ($ 2.2).

It is desirable that, based on its composition by group of equivalence, an analysis of cholecalciferol expenditure be performed at a national level to confirm the results obtained for the Liguria Region and to promote centralised actions.

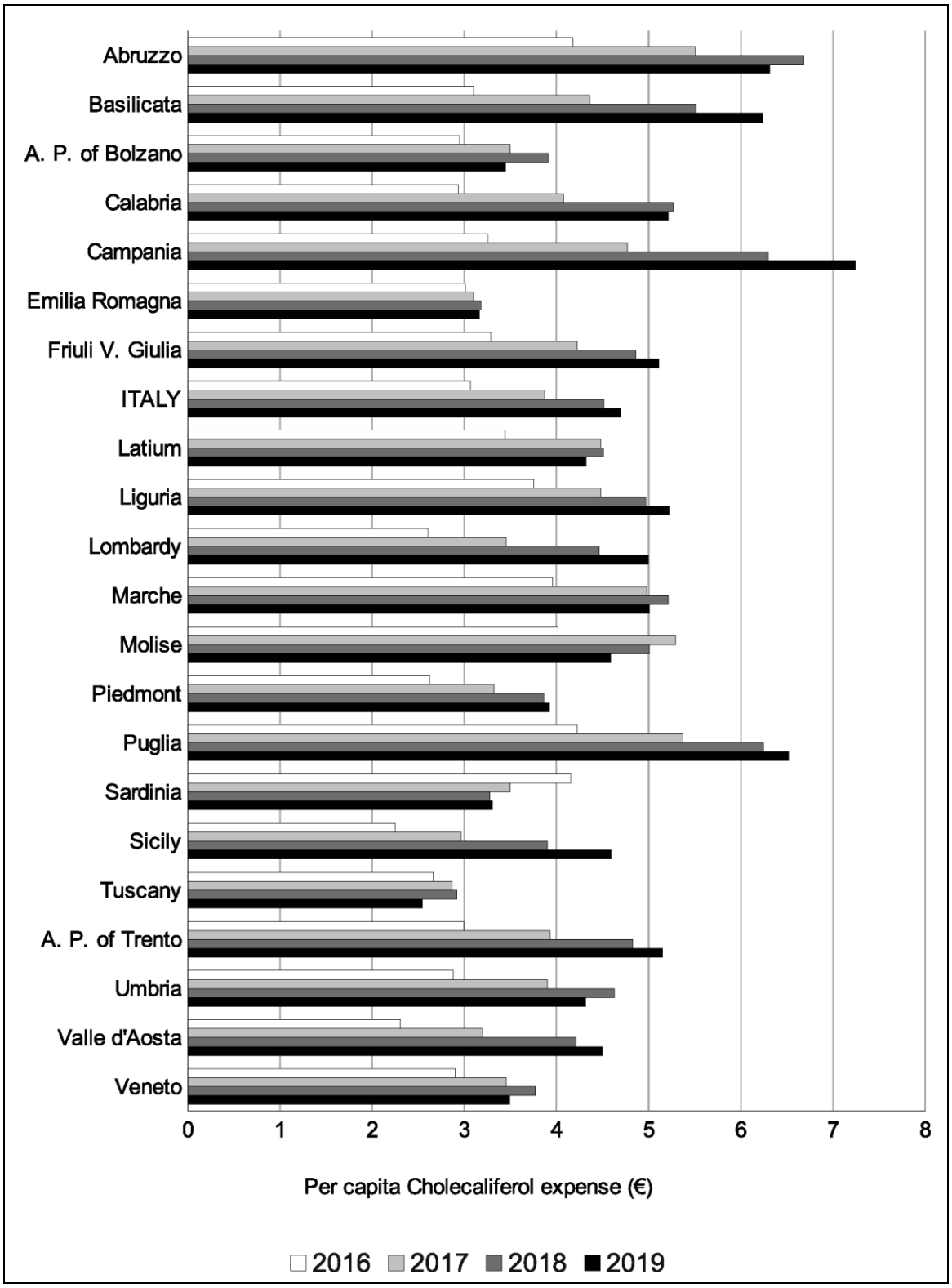

Figure 4: Per capita cholecalciferol expense in Italian Regions
Per capita cholecalciferol expense (€) is reported for each Italian region in the period 2016-2019. Percentage values represent expense variation from 206 to 2019. Regions are sorted by ISTAT codes (coarsely reflecting a north-south order).

DISCUSSION

In Italy, in the reference period (2005-2019), per capita expenditure for Vitamin D had a total rate of increase of 1302.7% with an mean increase rate of 20.8%. The analysis of the composition of vitamin D consumption found that 90% of the expenditure for Vitamin D was determined by the expenditure for cholecalciferol, one of its analogues, which therefore appears to be the most used for the prevention and treatment of hypovitaminosis D. Regarding data from the Liguria Region, a specific group of products, which can be defined as "high-cost formulations" based on reference price per DDD, determines over 90% of the expense for cholecalciferol.

These products share the characteristic of allowing drug administration every two weeks, monthly and every two months. Binkley et al. [19] evaluated the effect of daily and once monthly dosing of ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) on circulating 25(OH)D. Sixty-four community dwelling adults age 65+ were enrolled for a one-year study and the main outcome measure was serum 25(OH)D. They observed that total 25(OH)D increased from baseline to the 12-month follow-up with all regimens and similar increases were seen for both dosing frequencies; subjects receiving D3 (cholecalciferol) had significantly greater increases in 25(OH)D compared with those receiving D2 (ergocalciferol). Adherence with study preparation was as follows: daily D2, 95.4%; daily D3, 91.6%; monthly D2, 99.4%; and monthly D3, 98.9%. Delle Carbonare et al. [20] realized a short review on dosing regimens among children and elderly. They observed that in elderly subjects, in order to improve adherence of patients to treatment, a deferred regimen is proposed as a valid alternative to daily treatment, even though infrequent high-dose vitamin D supplements might be less effective or even harmful. They concluded that the best approach to correct a vitamin D deficiency is still debated and could be specific for different age groups.

The optimal regimen of vitamin D supplementation for maintaining normal levels has yet to be defined.

According to scientific evidence [21], the use of monthly single-dose formulations is considered equivalent to daily administration. However, daily administration can be guaranteed with much lower cost formulations and monthly single-dose do not seem to have an added therapeutic value. Since cholecalciferol accounts for 90% of Vitamin D spending, we think that high-cost formulations of Cholecalciferol are the main responsible for Vitamin D expense.

Sanò et al. [12] evaluated whether a shift of vitamin D3 prescriptions toward 100000 IU formulation, less costly, could allow savings. Their approach has been applied in a local health authority (ASL CN2) in Piedmont Region (Italy) starting from 2015. The introduction of the new formulation enabled the local health authority to save approximately € 280000 in 2017. They concluded that a shift of vitamin D3 prescriptions toward 100000 IU formulations would allow

reducing costs from the payer perspective.

Despite the good result of their approach, these measures were not adopted by the other LHAs of the Piedmont region. The regional expenditure in Piedmont for Vitamin D and Cholecalciferol subsequently increased. A possible explanation lies in finding that the use of 100000 IU and 300000 IU cholecalciferol vials (high concentration and low cost) is not included in the evidence-based clinical recommendations for maintenance therapy for hypovitaminosis D. It is likely that for this reason, the savings strategies based on the orientation of the prescription towards these products do not produce the desired effects on a large scale.

Hypovitaminosis D seems to have a predisposing or triggering role in various pathologies. Correction of Vitamin D deficiency appears to have a protective role in neurological diseases such as multiple sclerosis [22] and cerebrovascular diseases [23]. A recent meta-analysis confirmed that VDD is associated with a higher risk of COVID-19 infection as well as increased risk of complications and mortality, probably because of Vitamin D modulation of inflammatory cascade [24]. For this reason, recognition and treatment will be of increasing importance in our society.

To estimate a possible expense optimization in Liguria, we hypothesized that if the price of high-cost products became comparable to that of lower cost cholecalciferol formulations, 60.73% savings would have been achieved in Liguria based on 2019 data. We highlight that the savings estimated in this work are a theoretical maximum, whereas the real savings are likely to be smaller.

However, reflected on a national basis, such savings on Vitamin D expenses would sum up to € 170.65 ($ 204.78) million. This amount corresponds to a 1.7% saving on total expense for refunded drugs in Italy, consisting of € 10,070 ($ 12,084) million for 2019 [25]. For example, such savings would exceed 2019 expenditure for non-steroidal anti-inflammatory drugs in Italy [13].

For all the reasons, the expense for cholecalciferol and consequently the expense for Vitamin D, could be optimized, by modifying the reimbursement of high-cost formulations acting on the price of the single treatment. Since these formulations do not have an added therapeutic value that justifies a higher price, it could be proposed: 1) revision of the reference price in AIFA Transparency list by applying a “revised price” (eg, applying the reference price of the multi-dose bottle with dropper) or 2) passage of these formulations in class C (not reimbursed by the NHS).

As a limitation of the study, we did not take into account the time between the reference price is published (by AIFA) and the time it can be applied at the regional level (eg, the need of tenders in drug purchase). Indeed, most of the cholecalciferol-based formulations are purchased by community pharmacies affiliated with the regional Health service [13] not hospitals through tenders.

Our analysis is focused on Liguria region data assuming that award prices of cholecalciferol-based

formulations are comparable across regions. Data from this single Italian region, albeit representative of national picture, need to be reproduced by collecting data from other Italian regions.

CONCLUSIONS

The analysis of the expenditure for cholecalciferol through the Liguria Region data shows that the group of high-cost formulations has a preponderant and decisive role in the total expenditure for this active ingredient and therefore in determining the total expenditure for Vitamin D.

Since these formulations do not have an added therapeutic value that justifies a higher price, the expense for Vitamin D could be significantly reduced by acting on the expense for the single treatment delivered with high-cost formulations of cholecalciferol. To this aim, it should be necessary to align the reference price in AIFA Transparency list of these formulations with other existing ones and with a much lower cost, or moving these formulations to class C (not reimbursed).

To support any centralized actions, an analysis of cholecalciferol expenditure should be perfprmed at a national level to confirm the results obtained for the Liguria Region. The possibility of achieving saving through a policy that endorses the spending optimization could allow for the re-allocate resources representing a future benefit for the public community.

DISCLOSURE

The authors have no conflict of interest to disclose.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Michele Moretti: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing –original draft, Writing –review & editing, Supervision. Laura Paleari: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing –original draft, Writing –review & editing, Supervision. Fabrizio Figallo: Methodology, Formal analysis, Investigation, Data curation. Chiara Garbarini: Investigation, Writing –review & editing. Elisa Ponti: Writing –review & editing. Francesca Schena: Investigation. Lucio Marinelli: Conceptualization, Methodology, Investigation, Writing –original draft, Writing –review & editing, Supervision, Funding acquisition.

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