Medication use in public pharmacies

Methodology and elements of interpretation

Selection of themes, elements of data interpretation and analysis method of the medication use in public pharmacies

NIHDI – Healthcare Service – Research, Development, Quality Promotion Directorate
Appropriate Care Unit
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1. Introduction

The Appropriate Care Unit was created within the Research-Development-Quality Directorate of the NIHDI's Healthcare Service as a result of the NIHDI's 2016-2018 Administration Contract[1]. In Article 35, this Contract refers to 'the setting up of an Appropriate Care Unit targeting, more specifically, an integrated approach to the rational use of resources'. The Appropriate Care Unit was set up since the second quarter 2017.

The concrete implementation of the Unit was formalised in the '2016-2017 Healthcare Monitoring Action Plan', published by the NIHDI on 18 July 2016[2]. This plan lists around thirty measures aimed at optimizing health-care efficiency by encouraging appropriate practices and by avoiding unnecessary cares.

The plan states that the tasks of the Appropriate Care Unit include analysing the 'relevance of care,' with the aim of identifying unexplained variations in consumption emerging after standardisation of the Belgian population. These variations are indeed potentially a sign of non-optimal use of resources.

The reports of 'variations in medication use' contain the analyses conducted in this context. Each report focuses on a particular topic. The purpose of this document is to set out the overall shared methodology followed in all these analyses.

[1] (National Institute for Health and Disability Insurance, 2016)
[2] (National Institute for Health and Disability Insurance, 2016)

2. CHOICE OF TOPICS

Each "Medication use in public pharmacies" report focuses on one group of drugs. This group of drugs covers several drug codes that are selected.

The choice of the selected analyses is made according to different criteria. These criteria, which are detailed below, are (in no particular order): availability of data, drug target and epidemiologic interest, existence of complementary documentation, actuality, potential benefits (priority public health) and the obsolescence of drugs.

1. Availability of data

Our unit can only conduct analyses when the necessary databases are available. Initially, the database used is the NIHDI's Pharmanet. The use of this database does not allow us to analyse the consumption of drugs that are not reimbursed by the health insurance.

2. Drug target

The groups of drugs chosen for analysis cover the ATC classification (Anatomical Therapeutic Chemical Classification System) and correspond to underlying diseases for which the epidemiology can be highlighted.

3. Existence of complementary documentation

Our analyses are consolidated by the existence of extra documentation on the group of drugs. This documentation may be internal (e.g., a report from the MEID[3], CRM-CTG[4],..), national (e.g., reports from insurance funds or the KCE[5]), or international (similar analyses conducted in other countries). The existence of this material undoubtedly strengthens our analysis through the different angles of approach and the comparability of the data that it allows.

4. Actuality

We may prioritise certain topics based on current concerns or specific requests from the authorities if data are available.

5. Potential benefits

We identified the most prescribed drugs over the past year. Given the frequency of consumption of these drugs, our analyses will be of greater benefit for the general public, in terms of accessibility and quality of care, if unexplained variations are indeed observed.

[3] Service d'évaluation et de contrôle médicaux de l'INAMI
[4] Commission de remboursement des médicaments / Commissie Tegemoetkoming Geneesmiddelen
[5] Centre fédéral d'expertise des soins de santé

6. Evolution of drug prescriptions

The consumption of drugs evolves rapidly in function of the introduction of new molecules on the market. The analysis of the evolution allows to observe the relative evolution of drug classes per theme.

3. ANALYSIS METHODOLOGY

A. Sources of data

Our analyses are primarily based on the NIHDI's Pharmanet documents.

The Pharmanet documents are data from public pharmacies communicated by the invoice offices within the framework of the health care insurance. These data show the information of the prescriptions issued, namely the identifier of the substance issued, the number of packages, the date of sale, an encrypted patient code and the prescriber code. These data concern drugs reimbursed under the health insurance scheme.

Packaging is converted into DDD (Defined Daily Dose) according to the references of the World Health Organization. This daily dose corresponds to the assumed average maintenance dose per day for a drug used for its main indication in adults. It considers the route of administration: for example, the DDD of morphine is 100 mg orally and 30 mg parenterally or rectally.

Low-cost drugs are identified based on their CNK code. The CNK code is a unique identification number per package, assigned to all drugs and parapharmaceuticals (medical devices, food supplements, cosmetics ...) delivered in pharmacies.

Pharmanet also provides the following information on patients: age, gender, reimbursement scheme and district of domicile.

Cross-referencing the prescriber code with NIHDI data allows the prescriber's specialty to be retrieved.

Finally, the comparison of Pharmanet with the database "LMPB - IQVIA" (the sales of wholesalers to public pharmacies) allows to estimate the approximate share of medicines delivered outside the insurance at the level of the ATC5-code (level of chemical subgroup).

Note that the data of the persons of 95 and more are grouped together.

B. Selection of analyses and extraction of raw data

The selections concern the codes of the drugs that are analysed as well as the population of insured persons considered in the analysis:

Selection of codes: Each analysis covers a number of drugs relating to the group analysed and that are considered in the analysis of the volume of consumption and in that of the expenditures.

Filter on the insured population or the specialty of the prescribers: Certain filters may be applied to the analyses in order to select only part of the population (selection based on the sex and/or age of insured persons) or prescribers (selection of one or more specialities).

However, this selection is not applicable to the IQVIA data.

By default, the period of analysis covers the last ten years of available data. This period may be shortened if the analysis over the ten-year period does not allow a sufficiently homogeneous analysis, because the existence or coverage of the codes has fluctuated during this time.

For each drug code, the following variables are extracted by district, gender, age[6] and reimbursement scheme:

- The **number of insured persons** for whom we know the district (of domicile), gender, age, and reimbursement scheme
- The **number of DDD** for the patients for whom we know the district (of domicile), gender, age, and reimbursement scheme
- **Expenditure** for patients with known district (of domicile), gender, age, and reimbursement scheme

Grouping of districts: Districts with fewer than 100,000 people insured are associated with a neighbouring district in the same province. In all our analyses, the following districts are therefore grouped together: Oostende/Veurne, Ieper/Diksmuide, Roeselare/Tielt, Gent/Eeklo, Charleroi/Thuin, Huy/Waremme, Namur/Philippeville, Neufchâteau/Marche-en-Famenne, Virton/Bastogne/Arlon. These groupings and labels apply to all measurements, maps and graphs produced by district. In all the analyses as well as in this document, the notion of grouped district is reflected in the use of the term "district*".

[6] Data on persons aged 95 and older are grouped together our analyses.

C. Standardisation of data

The published documents present data from five different standardisations. These standardisations of the number of DDD, number of DDD per patient, percentage of insured consumers and the expenses are based on:

i. the age, the gender, and the reimbursement scheme of the patient to obtain data per **domicile** (district*, province, or region)

ii. the age and the gender of the patient to obtain data per **domicile** (district*, province, or region) and **reimbursement scheme**

iii. the age and the reimbursement scheme of the patient to obtain data per **domicile** (district*, province, or region) and **gender**

iv. the patient's reimbursement scheme to obtain data per **domicile (of the insured)** (district*, province, or region), **age group**[7] and **gender**. Standardisation is adjusted by a factor considering the age share per age group and per gender.

v. the patient's reimbursement scheme to obtain data per **age group** and per **gender**. Standardisation is adjusted by a factor considering the age share per age group and per gender.

The standardisation consists of three steps, which are described in the paragraphs below (example of annual DDD):

1. Calculation of the non-standardised annual number of DDD
2. Calculation of the distribution in the total population of the last year of the analysis period
3. Calculation of the standardised annual number of DDD

1. Calculation of the non-standardised annual number of DDD

For standardisation used to obtain data per location (patient’s domicile) (standardisations i, ii, iii and iv), we calculate the annual number of DDD per 100 000 insured~~, and the expenditure per insured~~ per location (district*, province, or region), broken down by gender, age, and reimbursement scheme. For the standardisation where data should not be obtained based on the patient's domicile (standardisation v), these values are calculated by gender, age, and reimbursement scheme.

2. Calculation of the distribution in the total population

Different distributions are used for the different standardisations, and these are calculated based on the total Belgian population of the last year of the analysis period, i.e., all insured persons residing in Belgium for whom the district, the gender, age, and reimbursement scheme are known or estimated. The calculated distributions are as follows:

[7] Data on persons aged 95 and older are grouped together our analyses.

i. the **age-gender-reimbursement scheme** distribution, to standardise the data based on the age, the gender, and the reimbursement scheme of the insured

➢ The age-gender-reimbursement scheme distribution is calculated as the number of insured persons by age, gender, and reimbursement scheme relative to the total number of insured persons in the Belgian population.

ii. the **age-gender** distribution, to standardise the data based on the age and the gender of the insured person.

➢ The age-gender distribution is calculated as the number of insured persons by age and gender relative to the total number of insured persons in the Belgian population.

iii. the **age-reimbursement scheme** distribution, to standardise the data based on the age and the reimbursement scheme of the patient

➢ The age-reimbursement scheme distribution is calculated as the number of insured persons by age and reimbursement scheme relative to the total number of insured persons in the Belgian population.

iv. & v. the **reimbursement scheme** distribution, to standardise the data based on the patient's reimbursement scheme

➢ The distribution of the reimbursement scheme is calculated as the number of insured persons per reimbursement scheme compared to the total number of insured persons in the Belgian population.

➢ For data presented per age group and sex, the standardisation is adjusted by a factor considering the age share per age group and per sex.

3. Calculation of standardised annual number of DDD

The standardised annual number of DDD is calculated by multiplying the non-standardised DDD by the concerned distribution and adding them together on the basis of the insured person's domicile (standardisation i), the patient’s domicile and reimbursement scheme (standardisation ii), the patient’s domicile and gender (standardisation iii), the patient’s domicile, age group and gender (standardisation iv) and by age group and gender (standardisation v).

The standardised DDD per insured consumer is calculated by dividing the standardised DDD per insured by the standardised percentage of insured consumers.

D. Indicators: graphs and tables

Note 1: 2020 was indicated on the evolution graphs by a vertical dashed line, to draw the attention on the impact of the COVID-19 crisis.

Note 2: On January 1, 2019, several modifications were made to the geographical division of certain districts. The list of communes/districts impacted is available on https://statbel.fgov.be/fr/propos-de-statbel/methodologie/classifications/geographie. The same adjustments were applied to the earlier data to have consistency in the graphs and evolution trends over time.

Note 3: As explained above, districts with fewer than 100,000 insured persons are grouped together with a neighbouring district in the same province.

i. *Table: ATC codes (Anatomical Therapeutic Chemical Classification System) selected for this analysis*

The table « ATC codes (Anatomical Therapeutic Chemical Classification System) selected for this analysis » shows the ATC codes selected for the analysis, stating whether they were included in the analysis of prescriptions (‘Rates’) and expenditure (‘Expenses’), with their label. The ATC code groupings used in this report are indicated in the CodeGroup1 and CodeGroup2 columns. Drugs considered "low-cost" are listed on the NIHDI website.

1. Profile of insured consumers

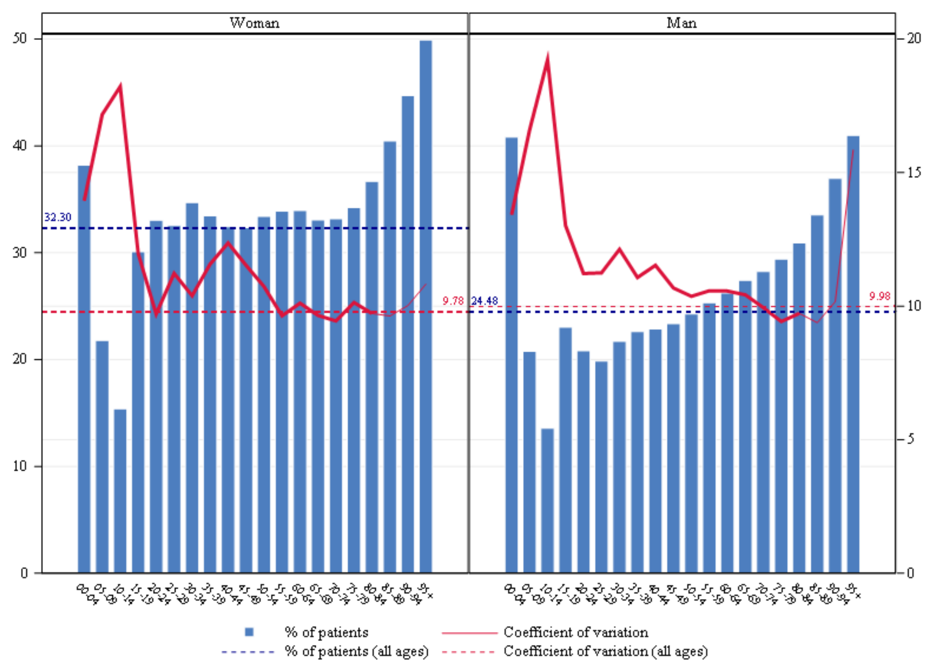
ii. Graph: Percentage of insured consumers and coefficient of variation by district, by age group and sex*

The percentage of insured consumers by age group is presented in a bar chart by gender. The associated coefficient of variation is shown by a red line on top of the bar chart. It is a relative measurement of variation. To calculate the coefficient of variation, the standard deviation is divided by the mean of the percentages per district*. The vertical axis on the left side of the graph shows the percentage of insured consumers and the right-hand vertical axis shows the coefficient of variation. The horizontal axis shows the age groups. The blue horizontal dashed lines represent the total percentage of insured consumers, and the red dashed lines show the overall coefficient of variation (i.e., all age groups combined).

The line of the coefficient of variation is thicker for those age groups for which the value of the coefficient can be validly interpreted, i.e., for age groups in which there are sufficient insured persons per district* to allow for a proper comparison.

If a selection is made by gender, only the graph relating to the selected gender is presented. If a selection is made by age, the value of the bars will be zero for groups that contain none of the selected ages.

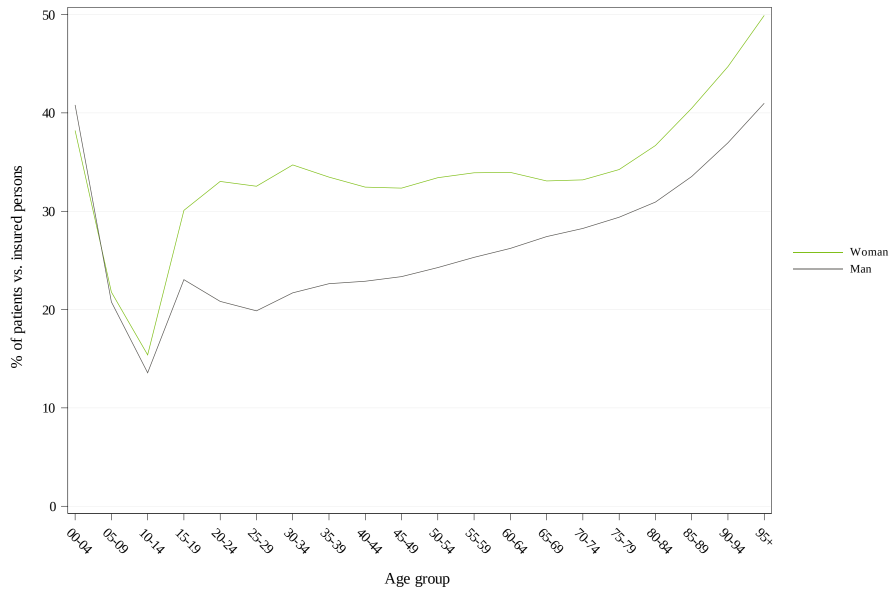
In all the graphs concerning the percentage of insured consumers, the values are non-standardised, except if mentioned otherwise.



Example: Percentage of insured consumers and coefficient of variation by district*, by age group and sex

iii. Graph: Comparison of the percentage of insured consumers by age group and sex

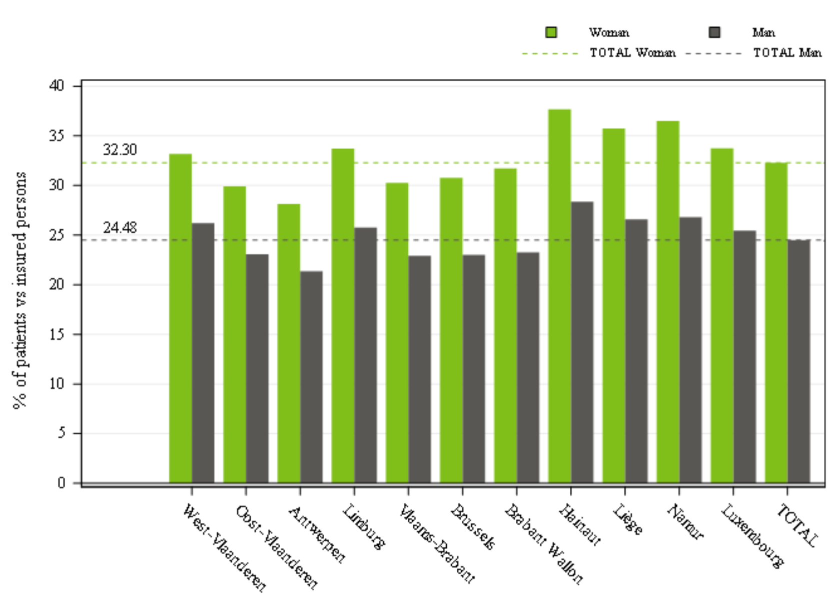
In this graph, the percentages of insured consumers are shown by age group and gender. A green line is used for the females and a grey line for the males.



Example: Comparison of the percentage of insured consumers by age group and sex

iv. Graph: Percentage of insured consumers by province

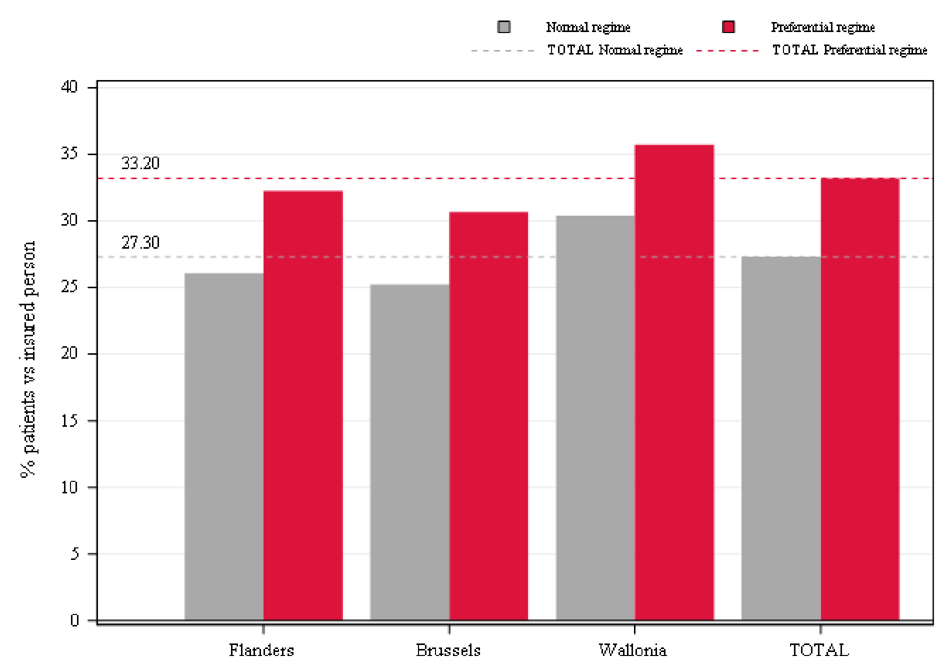
The percentage of insured consumers by province (based on the place of domicile of the patient) and by gender, are represented by a bar chart with double bars. The grey bars show the percentages for men, while the green bars show the percentages for women, for each province. The grey and green dashed lines show the total percentage of insured consumers according to the same color code. If a selection by gender is made on the population, this graph will not be displayed.



Example: Percentage of insured consumers by province

v. Graph: Percentage of insured consumers by reimbursement scheme and by region

The percentages of insured consumers by region of the patient's domicile and by applicable reimbursement scheme are shown by a bar chart. The red bars are percentages of insured consumers eligible for a preferential scheme. The grey bars are the percentages of insured consumers without a preferential scheme. The red dashed line shows the total percentage of insured consumers covered by a preferential scheme, while the grey dashed line shows the percentage of insured consumers not covered by a preferential scheme.



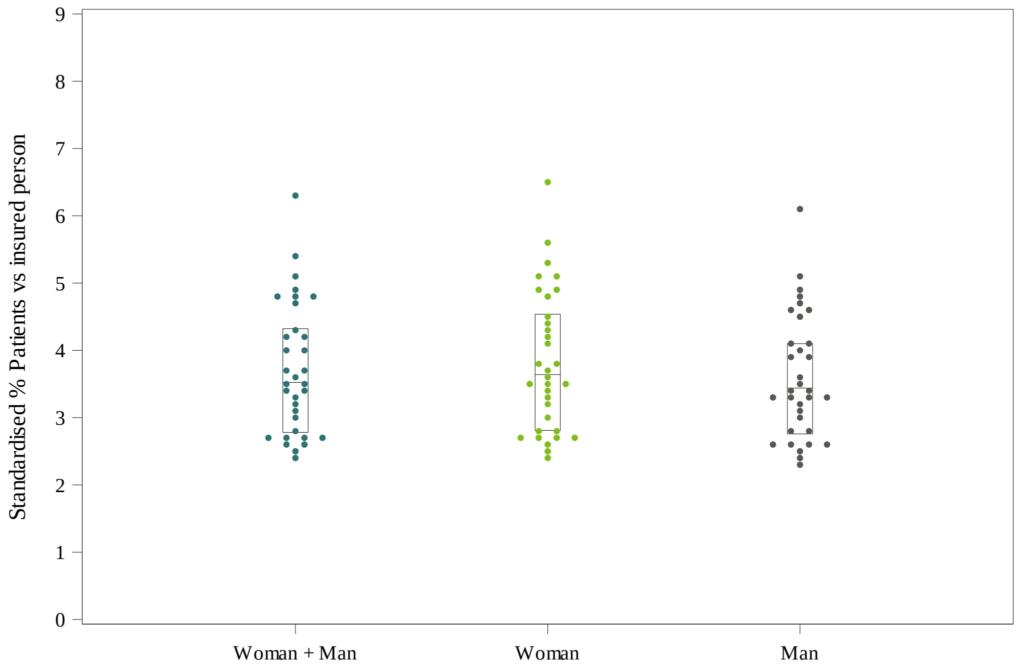
Example: Percentage of insured consumers by reimbursement scheme and by region

vi. Graph: 'Dot plot' showing percentages of insured consumers by district, by sex*

A dot plot is a scatter plot in which, for each observation, the points are plotted on a categorical scale. These simple graphs can be used to highlight groupings and gaps, as well as outliers. Here, the dot plot is used to present the distribution of the percentage of insured consumers by district*, with each dot representing a district*, first for all patients, and then by gender. If a selection is made based on gender, only the data for the selected gender are shown.

To convert the continuous data into categorical data, the percentages of insured consumers are rounded to the nearest multiple (tenth of %, unit, …), depending on the size of the maximum percentage.

The graph also shows boxes with the 25th, 50th and 75th percentile of the unrounded percentages of insured consumers, first for all patients, and then by gender. The 25th percentile is indicated by the bottom line of the box, the 75th percentile by the top line, and the 50th percentile by the middle line of the box.

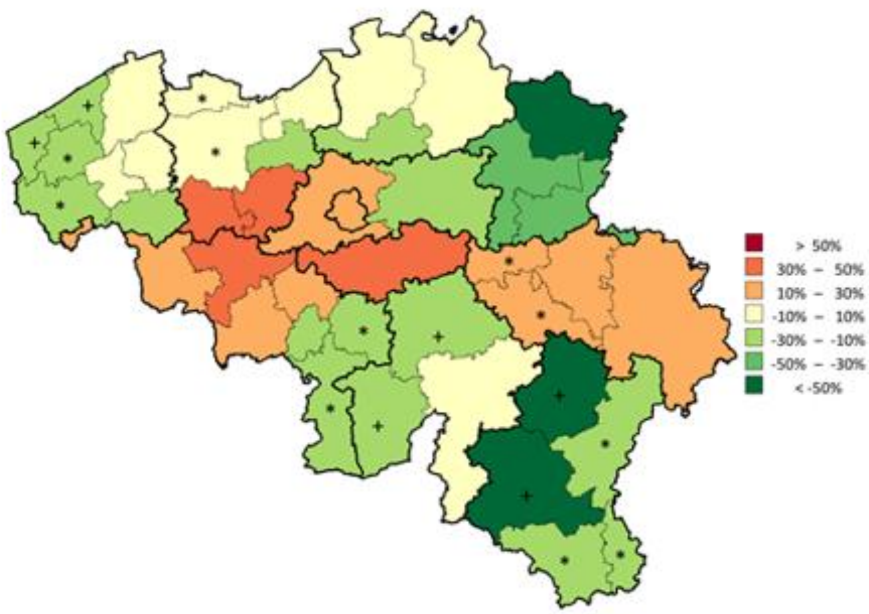


Example: 'Dot plot' showing percentages of insured consumers by district*, by sex

*vii. Graph: Map showing distribution of percentages of insured consumers, by district**

On a map of Belgium, where the district boundaries are represented by thin lines and the province boundaries by thick lines, the districts* are coloured according to a comparative scale with, firstly, the national percentage of insured consumers, and, secondly, the national expenditure. This comparative scale is expressed as a percentage of difference of the percentage of insured consumers or the expenses of the district* compared to the national value: between -10 and 10 %, the value for the district* is considered as equal to the national value; between 10 and 30 %, the value for the district* is considered as 20 % higher than the national value; between -10 and -30 %, the value for the district* is considered to be 20 % below the national value, etc. These differences are calculated based on the percentage of insured consumers for the last year of the analysis. They are divided into categories of 20 %. The following colours were defined for the distinct categories of the comparison scale (example for the percentage of insured consumers):

Colour	Category	Description
	More than 50%	The percentage of insured consumers per district* is minimally 50 % higher than the national percentage
	Between 30% and 50%	The percentage of insured consumers per district* is between 30 % and 50 % higher than the national percentage
	Between 10% and 30%	The percentage of insured consumers per district* is between 10 % and 30 % higher than the national percentage
	Between - 10% and 10%	The percentage of insured consumers per district* is maximally 10 % lower and maximally 10 % higher than the national percentage
	Between -30% and -10%	The percentage of insured consumers per district* is between 10 % and 30 % lower than the national percentage
	Between -50% and -30%	The percentage of insured consumers per district* is between 30 % and 50 % lower than the national percentage
	Less than -50%	The percentage of insured consumers per district* is minimally 50 % lower than the national percentage
	Not used	No insured consumers in this district*



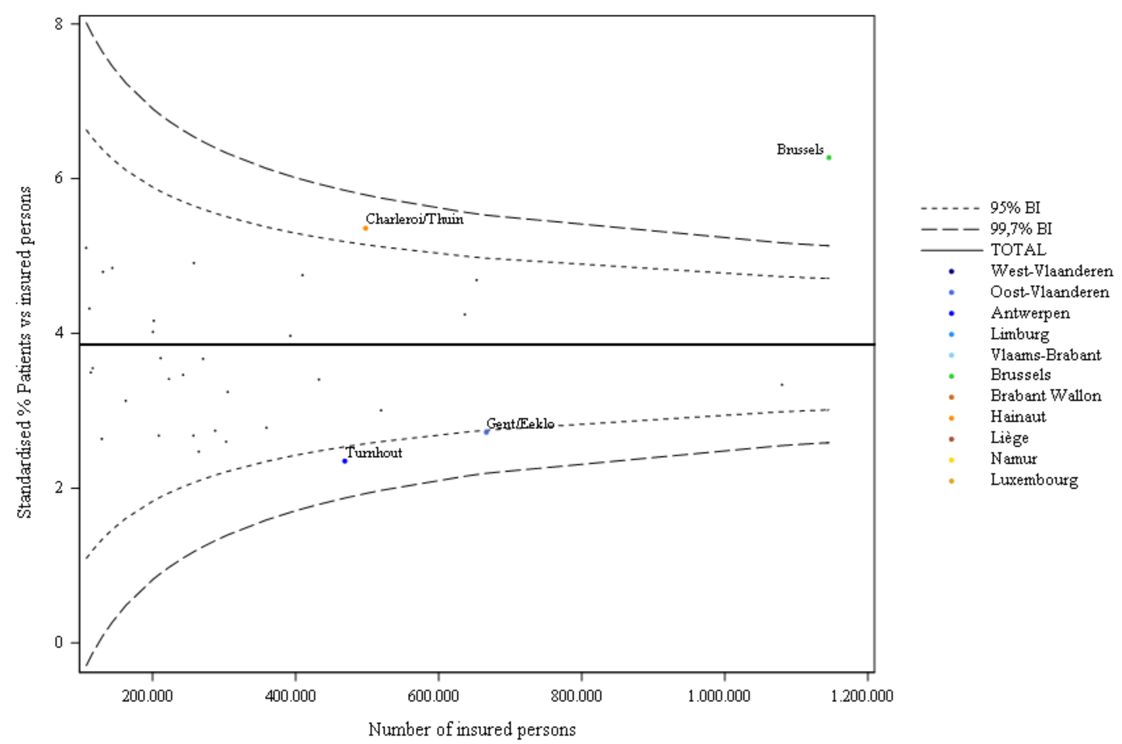
Example: Map showing distribution of percentages of insured consumers, by district*

Districts marked with * or + are grouped together within the same province.

*viii. Graph: 'Funnel plot' showing the percentages of insured consumers by district**

This funnel plot is a scatter plot which shows the percentage of insured consumers per district*, in relation to the size of the population of the district*. In addition to the dots per district*, 95% and 99.7% confidence limits are also displayed on the graph. The confidence intervals have a typical shape of a funnel: the smaller the population of a district*, the greater the expected variation, and vice versa.

The graph below is an example of a funnel plot showing the percentage of insured consumers per Belgian district*. The horizontal line represents the national percentage of insured consumers. The funnel-shaped lines show the 95% (two standard deviations from the national percentage) and the 99.7% (three standard deviations from the national percentage) confidence limits.



Example: 'Funnel plot' showing the percentages of insured consumers by district*

The districts* between the curves are considered to be 'average'. The districts* outside the upper and lower 99.7% confidence limits are considered outliers. The zone between the confidence limits at 95% and those at 99.7% is considered as a 'warning zone'. Only the titles of the districts* outside the 95% confidence limits are spelled out.

As we represent the percentage of insured consumers on the vertical axis, the confidence intervals are based on a Poisson distribution and are dependent on the national percentage and on the population size of the district*. The 95% and 99.7% confidence intervals for the 33 grouped districts are calculated as follows:

1. Calculation of the <u>percentage of insured consumers</u> per district* *i:*

$$Y_i = (percentage\ of\ insured\ consumers\ )_i$$

2. Calculation of the <u>national percentage of insured consumers:</u>

$$\theta = \frac{\sum_i (number\ of\ insured\ persons)_i * \ Y_i}{\sum_i (number\ of\ insured\ persons)_i}$$

3. Calculation of the <u>standard error</u> in district* *i* based on the aggregated data:

$$SE_i = \sqrt{\frac{\theta}{(number\ of\ insured\ persons)_i}}$$

4. Calculation of the <u>overdispersion</u>

When the confidence intervals are calculated based on the Poisson distribution, many districts* are outside the confidence intervals. This has to do with overdispersion (more variability in the percentage of insured consumers than what is expected based on a Poisson distribution). To remedy this issue, the overdispersion is calculated and considered in the confidence intervals.

For each district*, a z-score is calculated:

$$z_i = \frac{Y_i - \theta}{SE_i}$$

In order to avoid that the most aberrant districts* influence the calculation of the overdispersion too much, the 10% smallest z-scores are replaced by the P10, and the 10% largest z-scores are replaced by the P90 before the overdispersion is calculated as follows.

$$\rho = \frac{\sum_i {z_i}^2}{43}$$

5. Determination of <u>confidence intervals</u> by district* i:

$$\text{lower 95\% confidence interval}_{\ \mathrm{i}} = \theta - 2 * SE_i * \sqrt{\rho}$$

$$\text{upper 95\% confidence interval}_{\mathrm{i}} = \theta + 2 * SE_i * \sqrt{\rho}$$

$$\text{lower confidence interval 99.7\%}_{\ \mathrm{i}} = \theta - 3 * SE_i * \sqrt{\rho}$$

$$\text{upper confidence interval 99,7\%}_{\ \mathrm{i}} = \theta + 3 * SE_i * \sqrt{\rho}$$

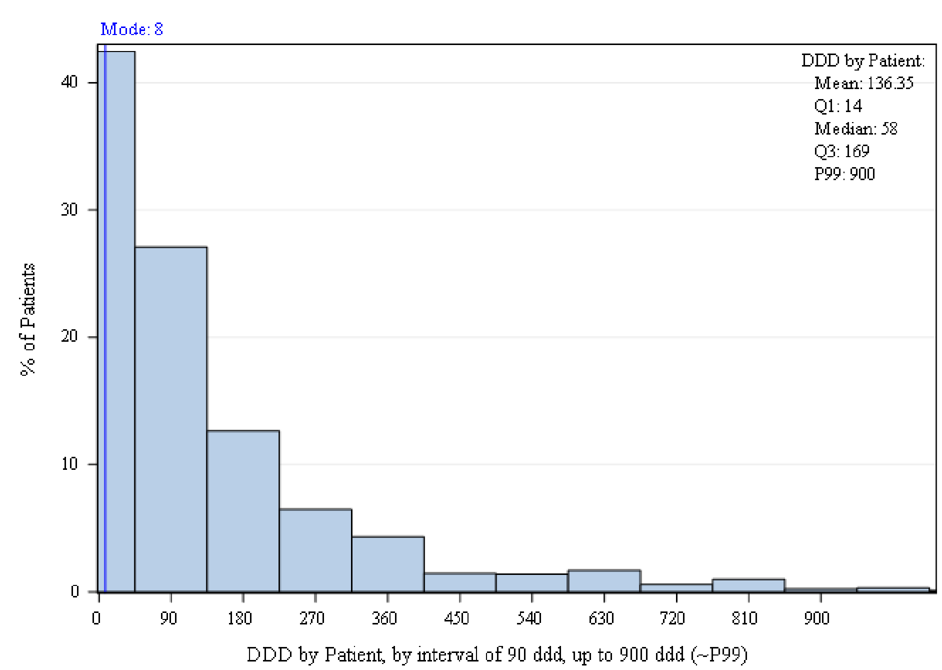
2. Consumption per insured consumer

ix. Table et graphs: Distribution of insured consumers in consumption classes and by annual average

In the first graph, the insured consumers are classified according to their annual consumption. In the table and following graph, the insured consumers are classified according to their consumption relative to the average national dose.

Variations in different classes may reflect differences in treatment duration or dosage (depending on the prescription, patient profile, pathology, compliance, …), but may also reflect other biases such as, among others, repetition of episodes over the year or the timing of initiation of chronic treatment.

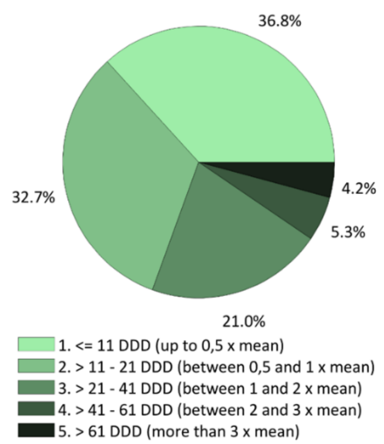
The first graph is a histogram of the insured consumers per class of annual consumption of DDD. The classes are shown up to P99. Some descriptive statistics are shown on the plot.



Example: Distribution of insured consumers into consumption classes

In the table and pie chart, the insured consumers are classified according to their consumption in relation to the national average dose. Five categories are defined, going from less than half of the average yearly consumption, to 0.5-1 times the average yearly consumption, 1-2 times the average yearly consumption, 2-3 times the average yearly consumption and more than three times the average yearly consumption.

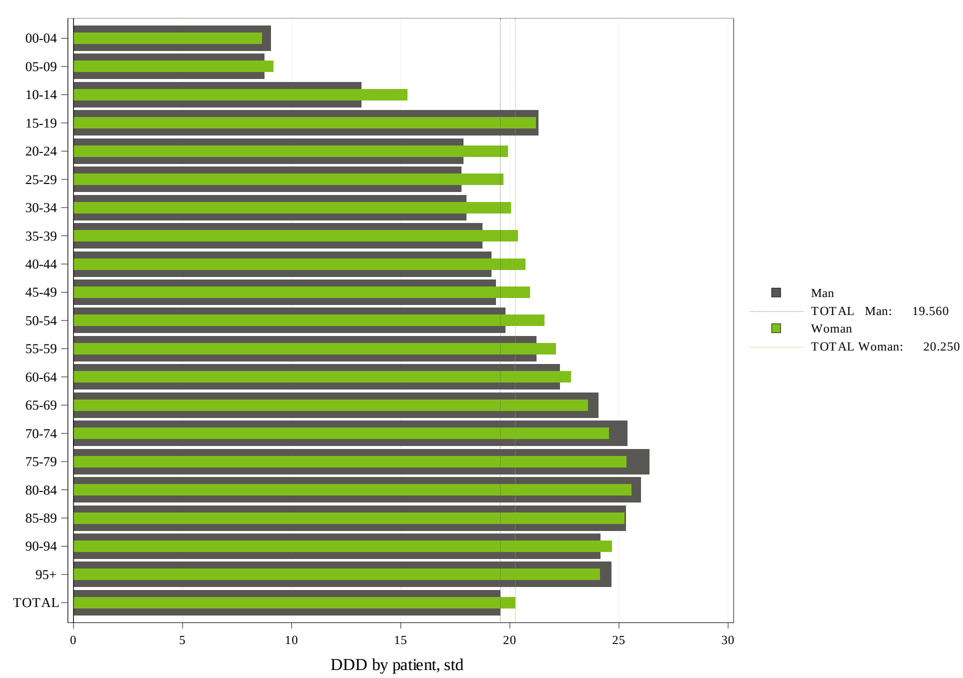
Frequency	Per year
≤ to ½ average annual consumption	36,8%
>0,5 and ≤1 times the average annual consumption	32,7%
>1 and ≤2 times the average consumption	21,0%
>2 and ≤ 3 times the average consumption	5,3%
>3 times the average annual consumption	4,2%



Example: Distribution of insured consumers by average annual dose delivered

x. Graph: Average quantity of medication consumed by sex and age per insured consumer

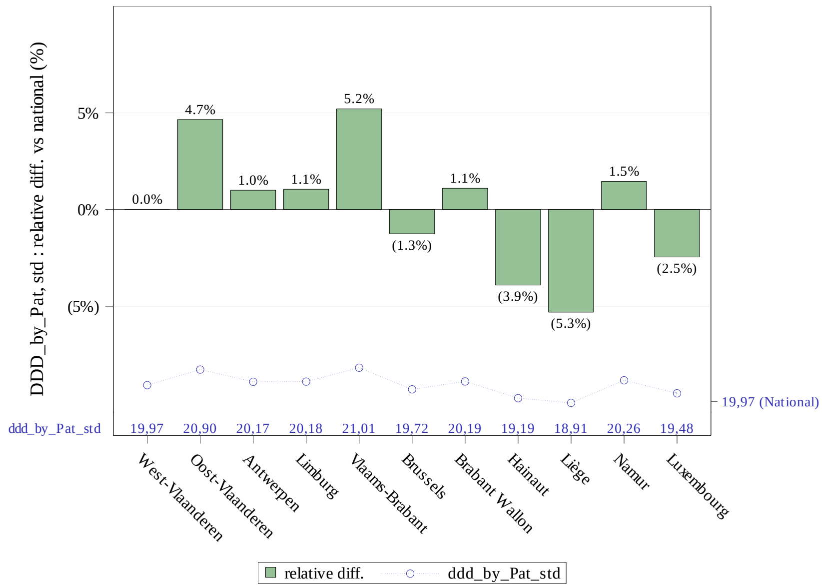
The histogram illustrates the average annual dose (in DDD) per age class and sex.



xi. Graph: Average quantity of medication consumed per insured consumer by province

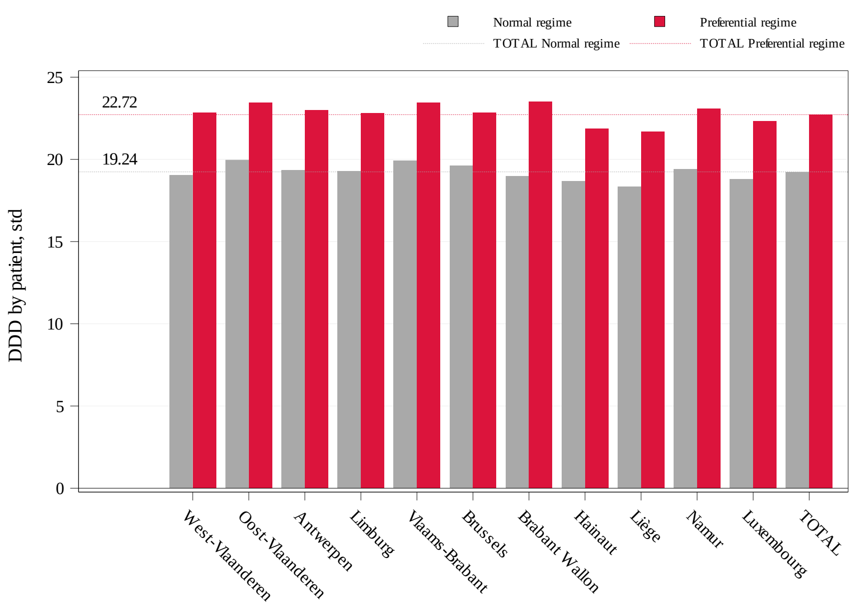
The histogram by province shows the difference in DDD consumption per insured consumer compared to the national average.

The dotted line shows the average DDD consumption per insured consumer, per province. The indicator is calculated by dividing the total DDD consumption by the number of insured to whom the drugs selected have been administered in the year.



Example: Consumption per insured consumer (DDD) by province and variation vs average national value

xii. Graph: Consumption per insured consumer (DDD) by province and by reimbursement scheme

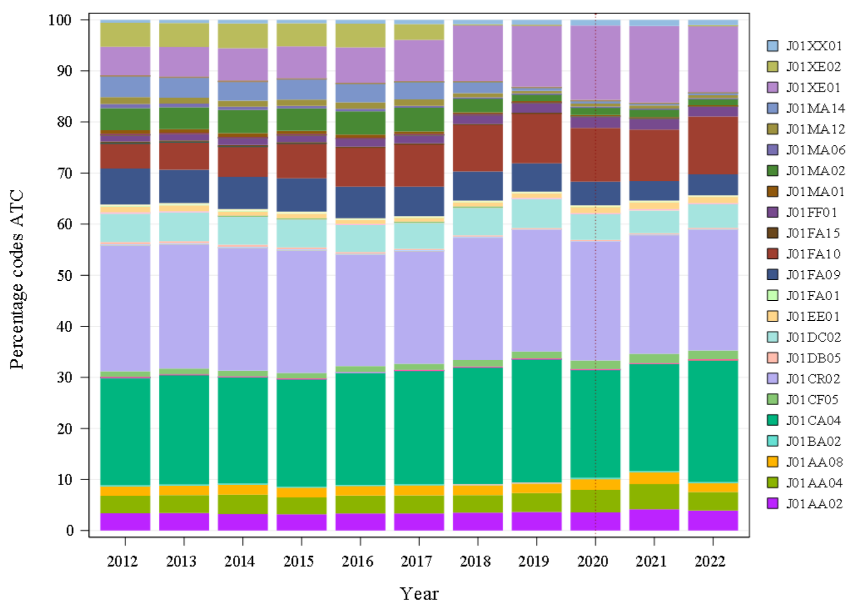


Example: Consumption per insured consumer (DDD) by province and by reimbursement scheme

3. Volume of prescribed medication

xiii. Graph: Volume distribution (DDD) of ATC codes delivered

This 100% stacked histogram shows the relative distribution of the percentages of ATC codes throughout the years. In this graph only the ATC codes used in volume are represented and not those that are only used for the expenses. For readability, the list is limited to the 23 most delivered ATC codes.



Example: Volume distribution (DDD) of ATC codes delivered

xiv. Table: Specialisation of prescribers

The *Specialisation of prescribers* table shows the following non-standardised data by medical specialty:

- Total prescribers: the number of prescribers who prescribed at least one medicine delivered
- Concerned prescribers: the number of prescribers who prescribe the ATC codes selected for this analysis
- % Prescribers: the percentage of prescribers prescribing these codes out of the number of providers who prescribed at least one medicine delivered
- Median of prescribed DDD: the median number of DDD per concerned prescriber
- Q3 of prescribed DDD, or third quartile, or P75: the value of the number of DDD that is larger than the number of DDD of 75% of the prescribers, but lower than the number of DDD of the 25% remaining prescribers
- Volume of prescribed DDD: the volume of DDD prescribed, i.e., the volume of sales of medicines converted into DDD broken down by prescriber's specialty

- % DDD: the percentage of medicines prescribed, i.e., the ratio of the number of medicines dispensed by this speciality to the total number of medicines prescribed among the ATC codes selected
- % Cheap DDD: the percentage of low-cost drugs, i.e., the ratio of the number of medicines identified as "low-cost" by national code number (CNK) to the total number of medicines dispensed among the selected ATC codes
- Expenses: the total costs borne by insurance (excluding patient share and non-insurance sales)
- % Expenses: the share of expenditure broken down by prescriber specialty in relation to the total expenditure

Specialties accounting for less than 1% of the total number of DDD prescribed or with fewer than five prescribers are grouped in the 'Other specialties' category. For reasons of confidentiality, this "Other speciality" category will only be reported if there are at least five prescribers in total.

xv. *Table: Evolution of DDD consumption per 100 000 insured persons*

	TOTAL	
Annual consumption (DDD)	***75.840.145***	
Trend (2012-2022)	**-2,92%**	***** (-3,82%)**
Trend (2012-2019)	-2,76%	***
Trend (2019-2022)	-3,31%	

This table shows on the national level:

- The average yearly growth percentage for the entire analysis period
- The average yearly growth percentage for the first period of analysis (that precedes the last three or four years)
- The average yearly growth percentage for the last three of four years of analysis
- The statistical significance of the trend test on the whole period of analysis, based on a regression model (if the model allows) and the corresponding average yearly growth (between brackets) as estimated by the regression model
- The statistical significance of the test for the change in trend based on a regression model (if the model allows)

To know whether the trend on the entire analysis period is significant, a linear mixed model is fitted on the log of the DDD per 100.000 insured. This model defines a regression line per province and calculates the slope. A significance test for the slope is done at the level of each province, region and at the national level. The test at the national level is shown in the table.

The test for the change in slope is described below in the section «*Table: Evolution of DDD consumption by province and by region* ».

The significance level is fixed at 5%. The significance of the tests is indicated by *** (P-value ⩽ 0.001) very significant, ** (P-value ⩽ 0.01), * (P-value ⩽ 0.05) or NS (P-value > 0.05) for a non-significant result. If the significance tests are not available, the significance is indicated as NA.

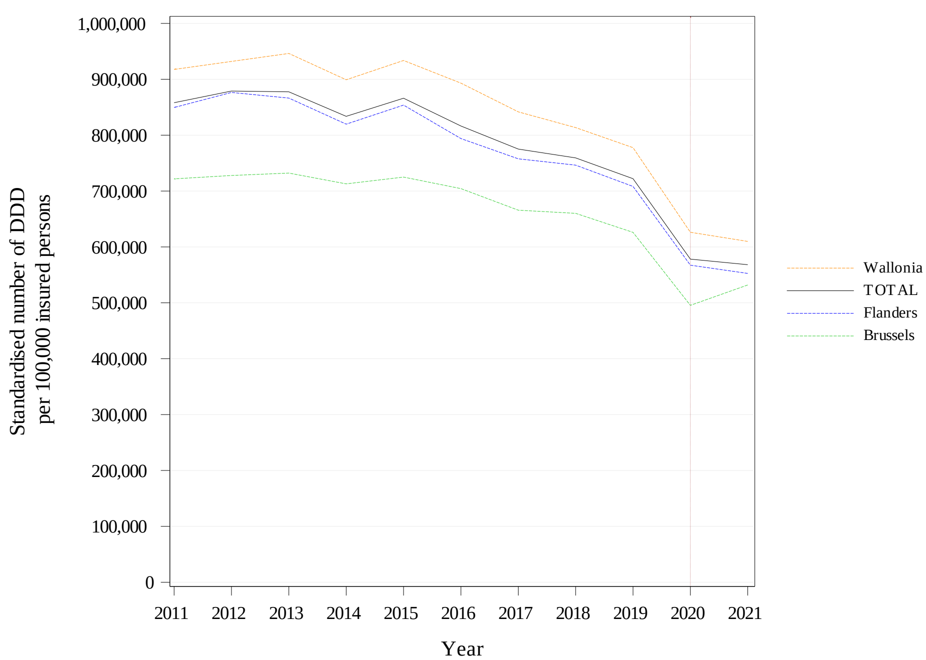
Note: the same table exists for the expenses by insured.

xvi. Graph: Evolution of DDD consumption per 100 000 insured persons

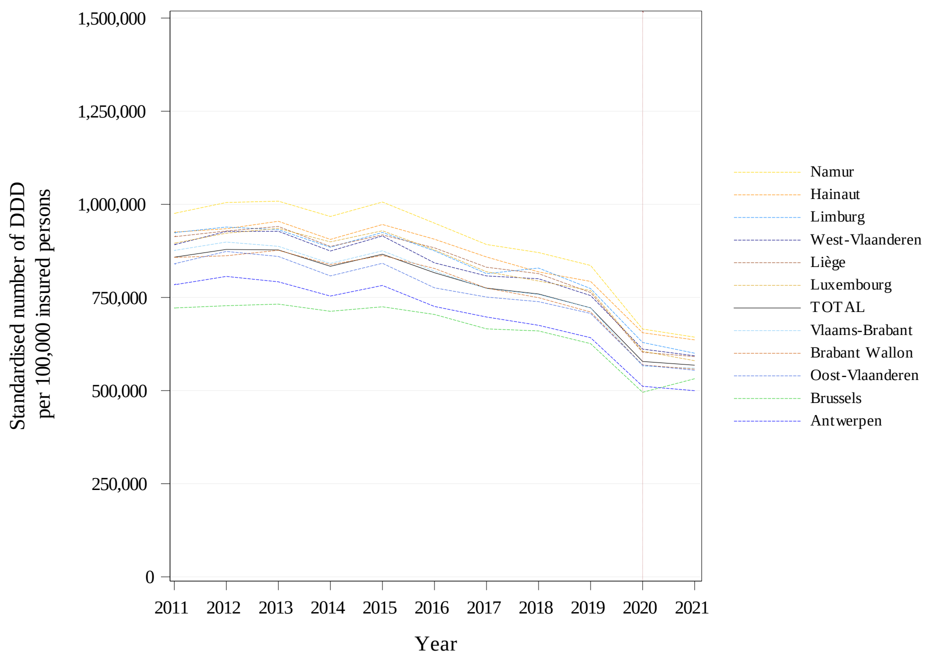
The evolution of the consumption of DDD per 100.000 insured is illustrated in two graphs, a first one by region and another one by province. The graphs show a coloured curve for each region and a black curve for Belgium. The x-axis shows the years, and the y-axis shows the standardised consumption of DDD per 100 000 insured persons. The colours are specific to each region: blue for Flanders, green for Brussels and ochre for Wallonia.

Note: The year 2020 was highlighted by a vertical dashed line, in order to draw the attention on the impact of the COVID-19 crisis.

Note: The evolution graph by region also exists for the expenses by insured.



Graph: Evolution of DDD consumption per 100 000 insured persons by region



Graph: Evolution of DDD consumption per 100 000 insured persons by province

xvii. Table: Evolution of DDD consumption by province and by region

The table '*Comparison of DDD per province and per region*' relates to the complete analysis period of ten years (if the data are available for each year). The title of each column indicates to which period the data refer. All the data (years, regions, and provinces) were standardised with respect to the structure of the population of insured persons of the last year (age, gender and scheme of reimbursement).

The table contains the following data per province and per region, as well as for the entire Belgian population for the standardised consumption of DDD per 100 000 insured persons:

- The standardised consumption of DDD for the last year
- The average yearly growth percentage for the entire analysis period
- The average yearly growth percentage for the first period of analysis (that precedes the last three or four years)
- The average yearly growth percentage for the last three of four years of analysis
- The significance of the test for change in slope from the regression analysis, where available

The average annual growth percentage is calculated using the following formula:

$$Average\ annual\ growth\ percentage = \left(\frac{standardised\ DDD_{last\ year}}{standardised\ DDD_{first\ year}}\right)^{\frac{1}{last\ year - first\ year}} - 1$$

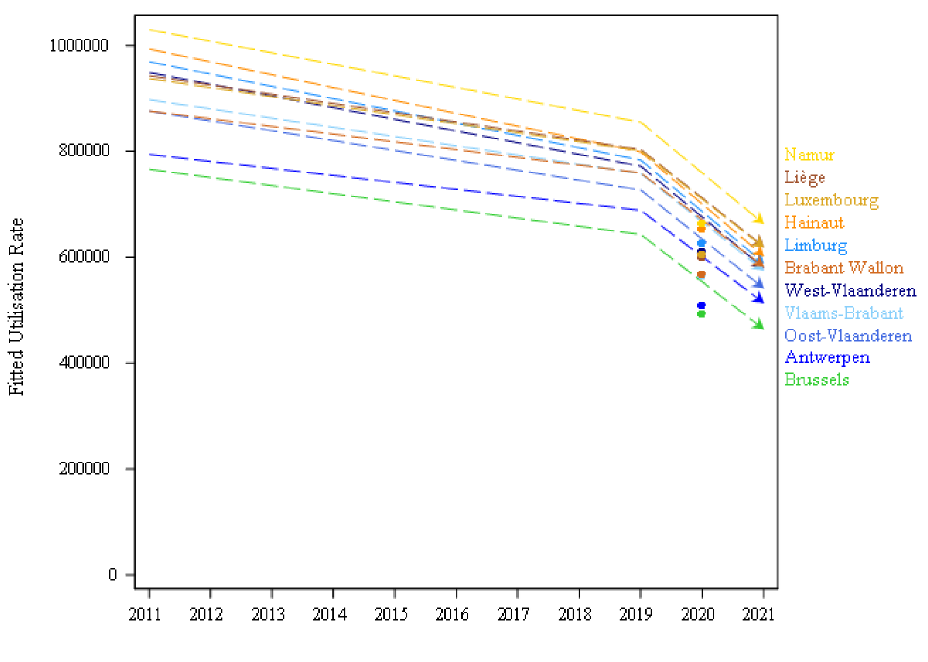
To find out whether the trend of the data in the last years has changed compared to the trend in the years before, a linear mixed model in two steps was used. On the one hand, each model fits a separate regression line per province and on the other hand it calculates the change in slope for the last years of the analysis period compared to the period before.

The first step tests whether the trend in the last years is different from the trend in the years before at the national level. If that change in slope is significant, a second model is fitted that allows the change in slope to vary by province. The report shows the results of the statistical tests for the change in slope. The first model shows the significance at the national level only. If the test at the national level is significant, the second model shows the significance at the level of the province, region and for Belgium.

The significance level is fixed at 5%. The significance of the tests is indicated by *** (P-value ≤ 0.001) very significant, ** (P-value ≤ 0.01), * (P-value ≤ 0.05) or NS (P-value > 0.05) for a non-significant result. If the significance tests are not available, the significance is indicated as NA.

The data of 2020 are excluded from these models.

As a visual illustration of the evolution of DDD consumption by province as it is estimated by the mixed regression model, a graph was added to the report. Although the data of 2020 were excluded from this analysis, they were indicated on the graph for information.



Example: Trend break assessment model by province – Regression lines

4. Expenditure borne by the health insurance and by the insured

xviii. Table: Evolution of expenditure per ATC code and per DDD

This table shows, for each year of the analysis period, the expenditure per ATC code per DDD, i.e., total expenditure divided by the total number of DDD, expressed by ATC code. For the sake of readability, the list is limited to the 23 most delivered ATC codes in the last year.

Code ATC	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Average annual growth rate
J01AA02	0,54	0,50	0,50	0,50	0,49	0,45	0,41	0,40	0,40	0,40	0,41	-2,83%
J01AA04	0,78	0,77	0,77	0,78	0,76	0,63	0,52	0,50	0,49	0,48	0,48	-4,78%
J01AA08	0,95	0,90	0,88	0,84	0,82	0,68	0,57	0,55	0,55	0,55	0,55	-5,39%
J01BA02	3,07	3,06	3,08	3,14	4,40	5,09	5,11	5,10	5,11	5,11	5,14	5,28%
J01CA04	1,06	1,00	0,99	0,96	0,96	0,83	0,71	0,66	0,66	0,68	0,67	-4,40%
J01CF05	2,86	2,85	2,82	2,85	2,86	2,33	1,97	1,95	1,90	1,73	1,51	-6,18%
J01CR02	1,09	1,04	1,03	1,00	1,09	0,91	0,71	0,70	0,73	0,73	0,73	-3,92%
J01DB01	2,45	2,46	2,47	2,48	2,50	2,11	1,77	1,71	1,53	1,54	1,57	-4,38%
J01DB05	2,03	2,02	2,01	1,96	1,88	1,60	1,57	1,67	1,47	1,43	1,50	-3,03%
J01DC02	0,70	0,70	0,69	0,67	0,66	0,56	0,45	0,43	0,44	0,44	0,44	-4,62%
J01EE01	0,97	0,95	1,28	1,22	1,13	1,08	1,03	1,02	1,03	1,04	1,06	0,97%
J01FA02	2,91	2,94	2,97	2,98	2,97	2,60	2,30	2,30	2,31	2,33	2,35	-2,09%
J01FA09	0,98	0,95	0,94	0,91	0,90	0,76	0,59	0,57	0,56	0,55	0,55	-5,63%
J01FA10	1,52	1,47	1,44	1,37	1,33	1,14	0,95	0,88	0,84	0,84	0,86	-5,47%
J01FF01	2,62	2,36	2,32	2,29	2,15	1,77	1,46	1,38	1,37	1,33	1,30	-6,73%
J01GB01	14,25	16,29	26,09	23,25	21,16	23,14	21,81	19,66	22,37	24,45	24,97	5,77%
J01MA01	1,29	1,19	1,18	1,14	1,11	0,92	0,76	0,69	0,90	0,73	0,74	-5,44%
J01MA02	1,67	1,47	1,45	1,41	1,38	1,13	0,93	0,86	0,86	0,85	0,84	-6,58%
J01MA12	1,88	1,67	1,57	1,56	1,44	1,20	1,02	1,01	1,01	1,00	0,99	-6,18%
J01MA14	3,34	3,27	2,88	2,04	1,86	1,53	1,18	1,12	1,10	1,09	1,09	-10,59%
J01XB01	49,35	46,75	44,64	45,00	45,36	45,22	44,93	44,95	44,10	43,46	42,80	-1,41%
J01XE01	0,34	0,34	0,34	0,34	0,33	0,28	0,25	0,25	0,25	0,25	0,26	-2,87%
J01XX01	7,85	7,86	7,89	7,80	7,48	6,49	5,80	5,85	5,90	5,92	6,03	-2,61%

Example: Evolution of expenditure per ATC code and per DDD in euros

In this table, the average annual growth rate is calculated using the following formula:

$$Average\ annual\ growth\ percentage = \left(\frac{Expenditure\ per\ DDD_{last\ year}}{Expenditure\ per\ DDD_{first\ year}}\right)^{\frac{1}{last\ year - first\ year}} - 1$$

This growth percentage is therefore calculated by considering only the values for the first and last year of the analysis period, without considering the intermediate variations.

xix. Table : Key data summary

The 'Summary of Key Data' table contains the following data for the Belgian population (data which can be found in the different chapters of the report and whose methodological details are given in the relevant paragraphs of this document):

- Main prescribers:
  - The specialty identified as prescribing predominantly for the group of drugs being analysed, with the percentage of total volume prescribed.
- Percentage of sales not covered by the health insurance (NIHDI):
  - Approximate value estimated from the difference between the declarations of the sales of wholesalers to the pharmacies converted in DDD and what is paid by the health insurance and the patient contribution, for the drugs with the relevant ATC5 codes for the analysis. This is a contextual indicator.
- Profile of insured consumers:
  - Percentage of insured consumers
  - Median age of the patient
  - Max/min ratio of the median age of the patient (based on the districts*, excluding outliers[8])
  - Percentage of women amongst the insured consumers
  - Ratio of the insured consumers benefiting a preferential rate and that of those without preferential rate
  - Coefficient of variation of the percentage of insured consumers per district*. The coefficient of variation is a relative measure of variability, and it is calculated as the standard deviation divided by the mean
  - Max/min ratio of percentage of insured consumers (based on the districts*, excluding outliers)
- Consumption
  - Annual consumption in DDD
  - Consumption of DDD per 100 000 insured persons
  - Average annual consumption per insured consumer (in DDD)
  - Percentage insured consumers with more than three times the average consumption
  - On the one hand, the coefficient of variation (of the consumption in standardised DDD per district*) calculated for the first three years of the analysis period and, on the other hand, this coefficient of variation for the last three years of the analysis period.

    The coefficients of variation of the first three and the last three years of analysis are compared based on a test using a Bootstrap procedure. The difference between the coefficients of variation is considered as significant if the P-value is lower than or equal to 0,05.

[8] The outliers were determined using the default method that is used with boxplots, i.e. values below Q1 – 1.5*IQR or above Q3 + 1.5*IQR, with Q1 the first quartile, Q3 the third quartile and IQR = Q3 – Q1.

    - The average yearly growth percentage of the consumption in DDD for the entire analysis period
    - The average yearly growth percentage for the years preceding the last three or four years of the analysis period
    - The average yearly growth percentage for the last three or four years of the analysis period
    - Statistical significance of the slope over all the years of the analysis period
    - Statistical significance of the change in slope in the last three or four years of analysis compared to the years before
- Direct expenditure (based on DDD)
    - Annual expenditure at the expense of the health insurance
    - Average annual expenditure per insured
    - Average patient share per insured consumer
    - Max/Min Ratio of expenditure per insured (based on the districts*, excluding outliers)
    - Percentage low-cost drugs
    - Average yearly growth percentage of expenses for the entire analysis period
    - Average yearly growth percentage of expenses for the last three of four years of the analysis period

If the max/min ratio cannot be calculated because the minimum is zero, it is indicated NA (not available) in the table.

If the period between the base year (i.e., the first year of the analysis period) and the last year is less than three years, NA (not available) is indicated for the trend.

The degree of statistical significance is symbolised by one to three asterisks, in increasing order of significance: * P-value ≤ 0.05 / ** P-value ≤ 0.01 / *** P-value ≤ 0.001. Otherwise, NS is displayed ("not significant").

E. Statistical analysis

To ensure the comparability of the consumption rate and the level of expenditure, all the data were standardised on the basis of age, gender and reimbursement scheme for the Belgian population of the last year of the analysis period.

All the data presented in this document are based on the entire population of insured, and are summarised by descriptive statistics (mean, median). Nevertheless, some statistical analyses may be relevant to perform on these data. The following hypotheses were tested in this report :

1) To what extent does a criterion explain differences in the consumption of DDD?
   A linear mixed model ANOVA was used based on the standardised data with respect to age for each district*, region, gender and reimbursement scheme. Region, gender and reimbursement scheme were taken into account in the model as fixed effects as well as all two-way interactions and the 3-way interaction. Type III significance tests were used to find out which effects have a significant influence on the consumption of DDD. For a correct interpretation of the analysis, first the significance of the 3-way interaction should be checked, followed by the two-way interactions and then by the main effects. If the 3-way interaction is significant, the interpretation of differences should be done on this level and two-way interactions and main effects should not be interpreted. If the 3-way interaction is not significant, the 2-way interactions can be checked for significance. Each effect that is part of a significant interaction should be interpreted at the level of the interaction and not at the level of the main effect. Only if an effect is not part of a significant interaction, the main effect can be interpreted directly. This analysis only covers the last year of the data presented in the report and only used data from Flanders and Wallonia.

2) To what extent do the trends observed differ from one period to another?
   To check whether there is a break in trend for the three or four most recent years of the analysis period compared to the years before (for the whole country, by province and by region), a linear mixed model was fitted on the data of all provinces and a significance test was done to find out whether the change in slope for the last three or four years was significant.

3) To what extent does the geographical variation differ from one period to another?
   The coefficient of variation for the first three years of the analysis and that of the three most recent years were compared using a test based on a Bootstrap procedure.

4. APPENDIXES

1. Analysis of variance (ANOVA), excluding Brussels (based on insured consumers)

To evaluate the significance of different effects, a linear mixed ANOVA model was fitted on the data of the districts* of Flanders and Wallonia, after standardisation with respect to age. The model includes the factors region, sex, and reimbursement scheme as main effects and all 2-way interactions and the 3-way interaction.

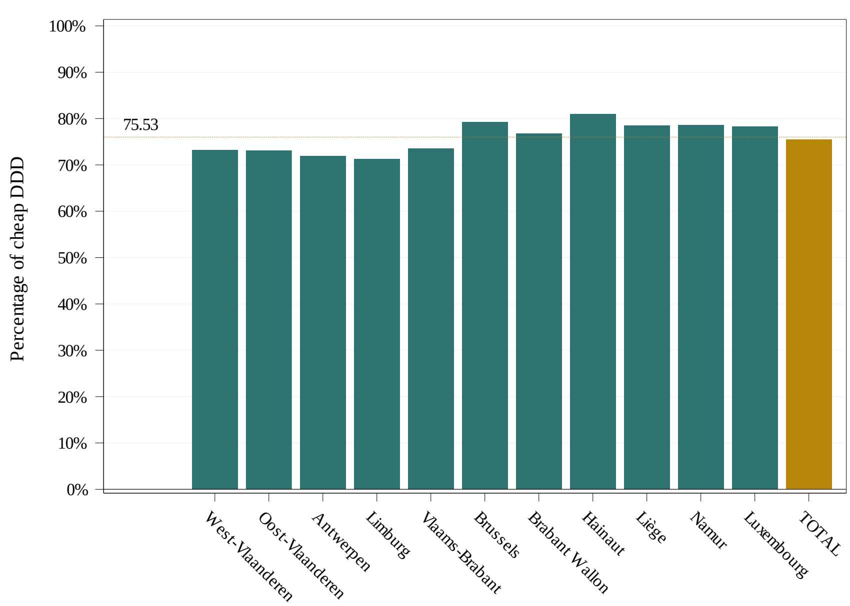
For a correct interpretation of the analysis, the 3-way interaction should be interpreted first (last line in table), next the 2-way interactions and finally the main effects. If the 3-way interaction is significant, all interpretations should be done at the level of that interaction, while the 2-way interactions and main effects should not be interpreted. If the 3-way interaction is not significant, the significance of the 2-way interactions should be checked. Every effect that is part of a significant interaction should be interpreted at the level of the interaction and not at the level of the main effect. Only when a main effect is no part of a significant interaction the interpretation can be done directly at the level of the main effect.

The asterisks indicate the level of significance of the statistical tests: * P-value ⩽ 0,05 / **P-value ⩽ 0,01 / *** P-value ⩽ 0,001 and NS for a non-significant result.

2. Percentage of low-cost medication

xx. Graph: Percentage of 'low-cost' medication delivered nationally and provincially

This graph shows the percentage of low-cost DDD vs the total number of DDD delivered. Besides one bar per region, an additional bar is displayed for the Belgian population. The dotted line also depicts this total ratio.



Example: Percentage of 'low-cost' medication delivered nationally and provincially

xxi. Graph: Distribution of DDD by “low-cost” drug class

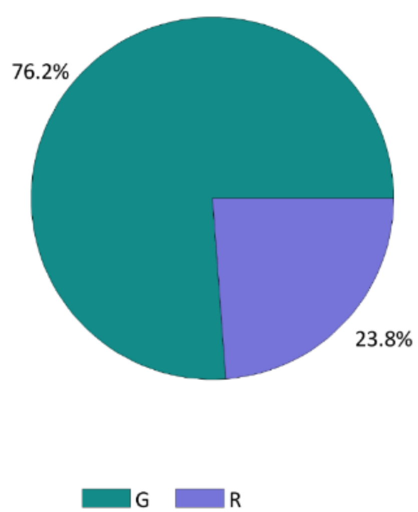
The percentage of low-cost drugs is calculated per CNK code (The CNK code is a unique identification number per package, assigned to all drugs and parapharmaceuticals (medical devices, food supplements, cosmetics ...) delivered in pharmacies.

The "low-cost" status is given based on the situation in August of the year of this report.

The drug classes are:

- G : generic medecines,
- Gr : reference generic medicines
- R : branded reference drugs
- BIOSIM : biosimilar medicines
- BIO : biological medecines

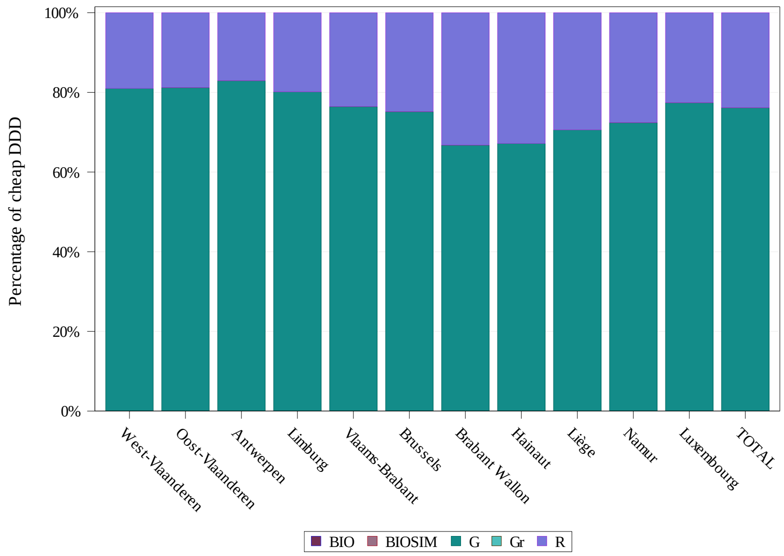
This pie chart shows the distribution based on DDD of the low-cost drugs over the categories of « low-cost ».



Example: Distribution of DDD by “low-cost” drug class

xxii. Graph: Type of low-cost drug (DDD) by province

There can be differences in the choice of type of low-cost drug. This potential variation is illustrated in a 100% stacked histogram by province.

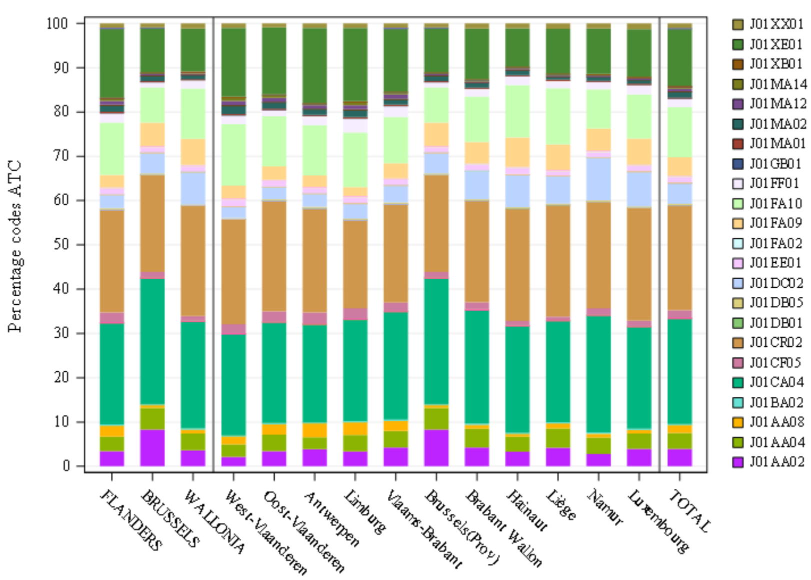


Example: Type of low-cost drug (DDD) by province

3. Variations in the type of medication delivered (based on DDD)

xxiii. Graph : Variations in prescription based on ATC codes

In this visualisation we present the distribution by region and province, of the volumes of the ATC codes selected for the analysis, in order to determine whether this distribution is homogeneous over the territory. The data are from the last available year and the list is limited to the 23 most delivered ATC codes.

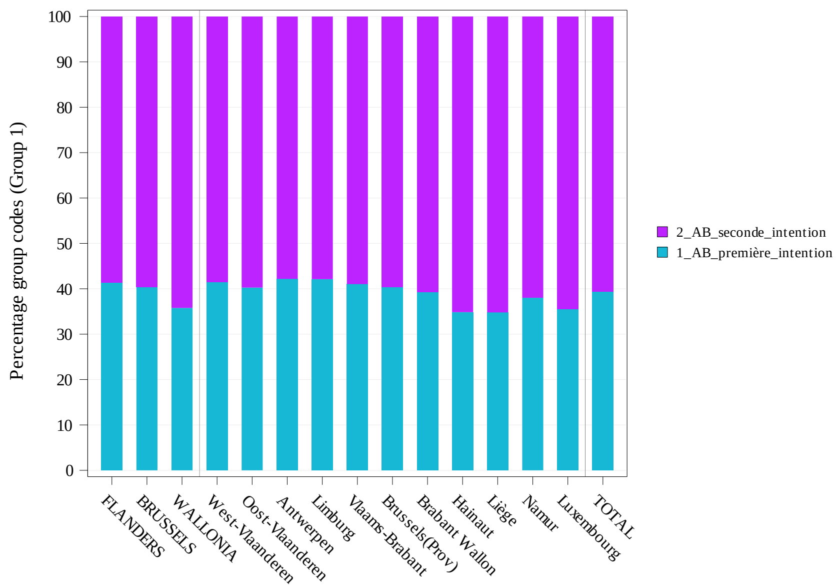


Example : Variations in prescription based on ATC codes

xxiv. Graph: Variations in prescription by group of medication

When different alternative treatments can be identified for the theme analysed, these are illustrated in this histogram that allows to visualize the distribution of the choice of treatment on the national level and on the level of the regions and provinces. The graph is a 100% stacked histogram. For the same analysis, up to two different splitting logics can be presented, identified in the report as “Group 1” and “Group 2“.

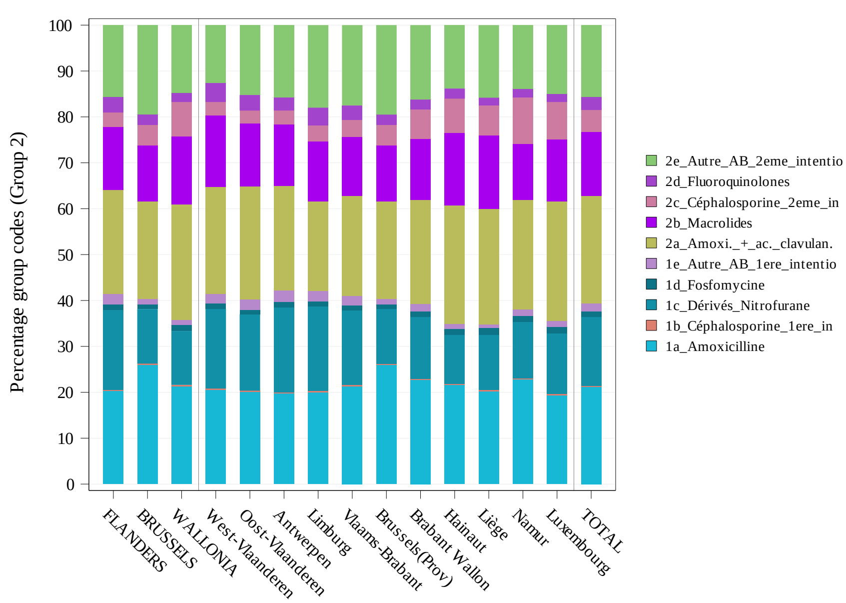
The grouping of the ATC codes corresponding to each alternative are listed in a separate table.



xxv. Graph: Variations in prescription by group of medication

In certain cases, the grouping of drugs can be refined. This is illustrated in the histogram using a gradient of the same colour to have a clear visualisation of the different groups of alternatives.

The grouping of the ATC codes corresponding to each alternative is presented in a separate table.



xxvi. Table: Share sold outside health insurance per ATC group

The comparison of Pharmanet with the database of IQVIA (that consist of the sales by wholesalers to the public pharmacies) converted in DDD allows to estimate the approximative part of drugs that are delivered outside the health insurance at the level of ATC5 code (level of chemical subgroup).

The data are from the last available year, which is indicated below the table.

Code ATC5	Description	Volume total	Volume remboursé	% non remboursé*
J01AA	TETRACYCLINES	8.131.639,90	7.554.226,25	7,10%
J01BA	AMPHENICOLES	634.322,00	41.470,00	93,46%
J01CA	PENICILLINES A LARGE SPECTRE	14.813.609,67	14.481.211,33	2,24%
J01CE	PENICILLINES SENSIBLES AUX BETA-LACTAMASES	6.951,28	6.296,92	9,41%
J01CF	PENICILLINES RESISTANTES AUX BETA-LACTAMASES	1.223.048,00	1.161.670,75	5,02%
J01CR	ASSOCIATIONS DE PENICILLINES, INHIB. DE LA BETALACTAMASE INCLUS	16.114.964,88	15.667.349,99	2,78%
J01DB	CEPHALOSPORINES DE LA PREMIERE GENERATION	159.170,00	124.935,91	21,51%
J01DC	CEPHALOSPORINES DE LA DEUXIEME GENERATION	3.237.808,75	3.195.254,50	1,31%
J01DD	CEPHALOSPORINES DE LA TROISIEME GENERATION	15.926,95	4.506,52	71,71%
J01DH	CARBAPENEMES	415	411,33	0,88%
J01EE	ASSOCIATIONS DE SULFAMIDES ET DE TRIMETHOPRIME, DERIVES INCLUS	1.059.507,50	1.005.344,00	5,11%
J01FA	MACROLIDES	10.273.798,42	9.566.091,92	6,89%
J01FF	LINCOSANIDES	1.648.987,50	1.530.755,48	7,17%
J01GB	AUTRES AMINOGLYCOSIDES	42.299,09	40.277,81	4,78%
J01MA	FLUOROQUINOLONES	5.243.291,50	1.860.004,25	64,53%
J01XA	GLYCOPEPTIDES	2.108,00	1.045,50	50,40%
J01XB	POLYMYXINES	51.082,75	47.150,88	7,70%
J01XE	DERIVES DU NITROFURANE	9.780.988,00	9.780.988,00	0,00%
J01XX	AUTRES ANTIBACTERIENS	883.258,00	769.206,00	12,91%
TOTAL		73.323.177,17	66.838.197,35	8,84%

Example: Share sold outside health insurance per ATC group 2021

5. BIBLIOGRAPHIE

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