

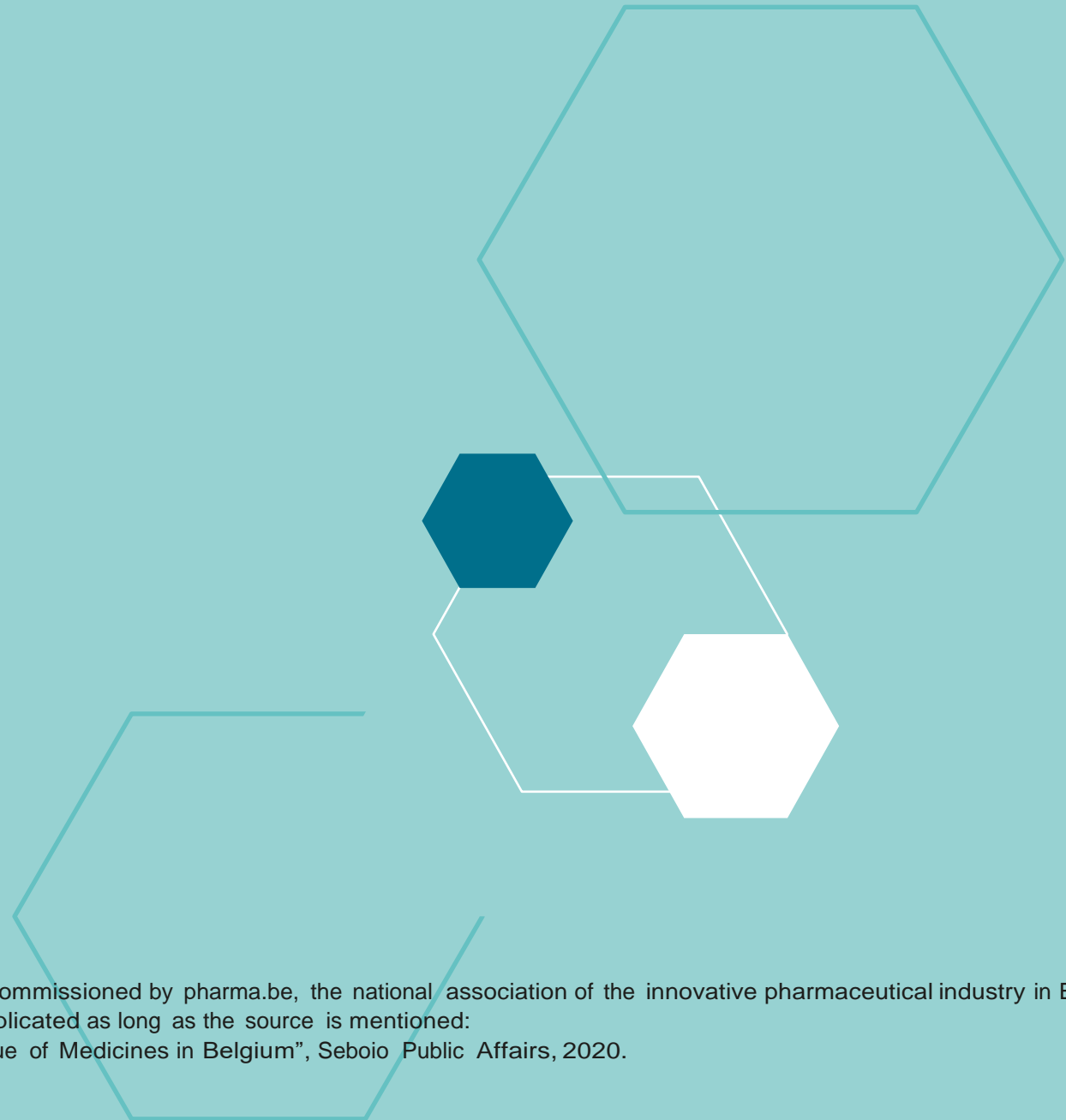


Twenty years
of high societal impact



The Value of Medicines
in **Belgium**

SEBOIO
Public Affairs



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EXECUTIVE SUMMARY

In this report, we analyse the value of innovative medicines over the last two decades, both for individual patients and their families and for society as a whole. This means that we look at the personal value for patients, such as survival, maintained or restored quality of life, avoidance of comorbidities, social inclusion and others. Value can also be looked at in economic terms. Patients can continue to work or go back to work after their disease. Productive life years are gained because less people die from a disease, and as a consequence they generate income for themselves, for employers and they contribute to society by paying taxes. Even if the goal of healthcare is not to generate these economic benefits, they should be taken into consideration when calculating value.

In the first part of the report, we look at what has been achieved in the last two decades. Today, life expectancy in Belgium has increased to 81.3 years, and premature mortality has decreased with 22% since the year 2000. The reason for this is multiple: better lifestyle choices, better prevention, better healthcare systems, earlier detection, better diagnostics, better surgery, better pharmaceuticals ... For several diseases, the role of pharmaceuticals has been significant, including cardiovascular diseases, infectious diseases such as HIV and hepatitis C, diabetes and several types of cancer such as leukemia,

myeloma, breast cancer, colorectal cancer, prostate cancer and melanoma. Next to this, for many chronic diseases, innovative medicines have played a significant role in improving the quality of life of patients, for instance with the arrival of biologicals to treat rheumatoid arthritis, psoriasis, colitis and crohn's disease. In the treatment of mental health, improvements have been made such as in bipolar and schizophrenia. In the last twenty years, people at working age have 3.4 additional life years per 100,000 inhabitants. This results in an additional economic contribution of 5.4 billion € in 2017 alone, of which 73% could be attributable to new innovative medicines.

In the second part of the report we go into more detail to identify what the value has been in six diseases, which were chosen because of their complementarity in type of disease, patient population and treatment options: [breast cancer](#), [rheumatoid arthritis](#), [hepatitis C](#), [epilepsy](#), [major depression](#) and [cervical cancer](#).

In [breast cancer](#) we see that the value for patients has improved, by adding productive life years, while at the same time offering better quality of life. Furthermore, the number of pharmaceutical treatments has increased, allowing for much better targeting of the disease, and avoiding useless treatments.

This resulted in an increase of the budget for treatment, yet the health economic gains appear to be positive, because of avoidance of premature mortality and re-integration in the workforce after treatment. Health economic calculations demonstrate that on average 3,869 € per patient was gained in Belgium between 2000 and 2017.

For moderate to severe [rheumatoid arthritis](#), the introduction of a new generation of innovative medicines – the “biologicals” – around the year 2000 significantly improved the lives of patients. They are now able to lead close to normal lives – socially and professionally – whereas previously they lived with pain, swellings, stiffness, reduced mobility or worse. The new generation medicines results in less absenteeism and account for 4,000 € in productivity gains on average per year per patient treated with biologicals. For Belgium that represents a total productivity gain of 16.5 million € per year.

A major pharmaceutical breakthrough was also achieved in the treatment of **hepatitis C**, a disease which can now be cured, and this for the first time in history. Today, treatments of eight to twelve weeks can completely eliminate the virus from the body. Health economic calculations show that the new medicines result in a societal gain of 11,000 € per patient. The higher cost of the more effective treatment is offset by a reduction of other pharmaceuticals, the avoidance of complications such as cirrhosis, liver cancer and liver transplants and it results in labour productivity gains. The economic benefit of the new treatments at society level was 146 million € in 2017.

In **epilepsy**, a neurological disease with a huge impact on the lives of patients, advancements have been made yet the burden of the disease remains high for patients. Uncontrolled seizures lead to a number of physical, mental and social consequences. New anti-epileptics have managed to achieve seizure-free patients when treated at early stages of the disease, but for many patients the unmet medical need remains high. A new add-on treatment increases the effectiveness of anti-epileptic treatments, reducing the medical costs with 2,600 € per patient per year. The health economic value on labour productivity remains unclear in the Belgian situation.

Major **depressive disorder** is an imposing challenge for the individual patient and for society at large. It may lead to a severe deterioration of the ability to function properly in private, social and professional contexts. The burden of disease on society is huge, and the total estimated annual costs of the disease in Belgium is around 10 billion €. Anti-depressant pharmaceuticals have demonstrated their effect on the quality of life of individual patients. The total cost of anti-depressants in Belgium was 90 million € in 2017 which is a decrease with 35% since 2010. From a medical, societal and economic point of view, systemic inefficiencies prevent patients from getting the best possible treatment. Therefore, pharmaceuticals remain just one of more important facets in the broader mental healthcare ecosystem. Their current value cannot be calculated in isolation for lack of data.

In **cervical cancer**, the introduction of vaccines in Belgium in 2006 will eventually cause the prevalence of the disease to drop by an estimated 90 %. With current 5-year overall survival rates at 65 % and a prevalence of 3,000 to 4,000 patients in Belgium, the vaccines save thousands of lives. The current total cost for society of cervical cancer in Belgium is calculated at 94.4 million € per year, including inpatient and outpatient treatment cost, morbidity, premature mortality and long-term sick leave costs. The annual cost for vaccination is 24 million €. With a projected reduction of cervical cancer patients by 90 %, economic benefits may reach 69.5 million € per annum.

INTRODUCTION

How has pharmaceutical development contributed to better healthcare in Belgium?

Belgium has one of the best healthcare systems in Europe. Medical advances made in the last two decades have contributed to a significant improvement in the health of the Belgian population as this report will demonstrate: people live longer and in better health.

The focus of this report is on how pharmaceutical development – new medicines and vaccines – has contributed to this positive evolution. This report will illustrate, both qualitatively and quantitatively, the value of medicines for the patient, our society and the economy.

Better health outcomes for patients are always the result of advances in all medical disciplines such as diagnostics, imaging, surgery and systems innovation. Pharmaceuticals are part of this treatment pathway, and for many diseases even the most important one. Because medicines are an integral part of this treatment continuum, for many diseases early administration of the right pharmaceuticals may lead to cost-savings in the rest of the system. It can lead to reduced hospitalisation, less surgical interventions and/or reduced severity of the disease.

Belgium also has a strong biopharmaceutical ecosystem, in which academic collaborations, industrial research and manufacturing, global exports and clinical development all contribute to economic gains. This also means that academic researchers and hospitals are at the forefront of pharmaceutical innovation, resulting in better knowledge of new medicines, which in turn results in earlier patient access to new treatments. We will not go into this topic, but focus on the value of medicines apart from their industrial context.

What is the value of medicines?

This report describes merits in different areas: first and foremost the medical outcomes for the patients and the effect on their survival and physical well-being, secondly the impact on the family and caregivers and the social surroundings of the patients in general and lastly the impact on the professional life, work productivity and the economy as a whole.

Recent new pharmaceutical treatments bring strong benefits: most obviously, life expectancy has increased significantly for some diseases such as HIV and some types of cancer. At the same time, the quality of life for chronic patients has also improved, as a result of pharmaceutical innovation. Patients have less pain, their disease progresses more slowly, some are still professionally active instead of being incapacitated, the new treatments are better tolerated and have less side effects.

When people become ill, this has also an impact on family and social life. Patients cannot function as before, can no longer participate in all social activities and, depending on their condition, need help from medical and social professionals as well as from families and friends.

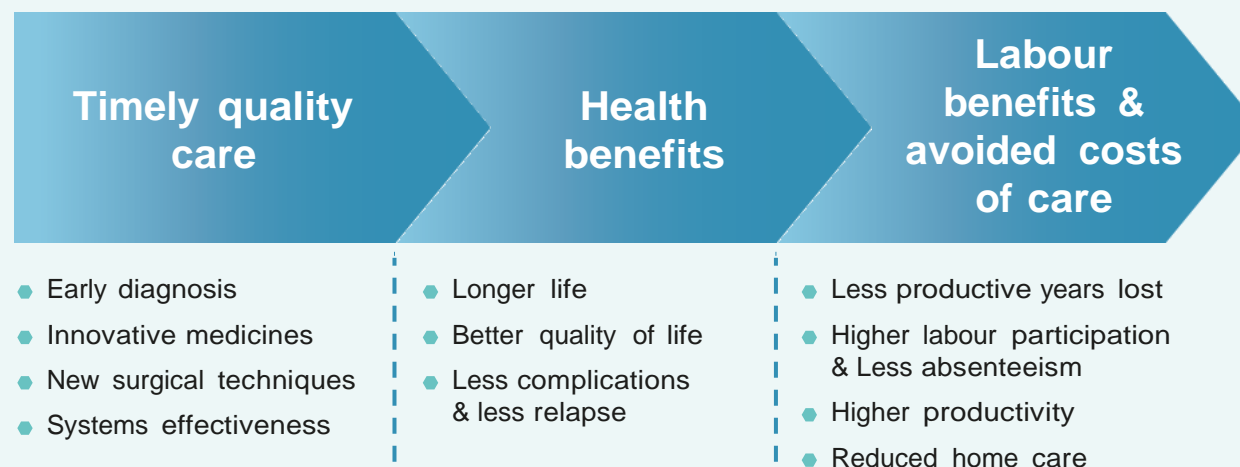


FIGURE 1 – THE TOTAL VALUE OF HEALTHCARE

The value of medicines for patients, for their environment, for the economy and society at large is the topic of this report.

When patients get ill, this also impacts their job performance: some take sick leave, some stop working, sometimes for a short time, sometimes for a longer time. Most patients want to get back to their normal life as soon as possible, including getting back to work. The economic cost of illness in our society is obvious: loss of income and medical costs for the patient, productivity loss, replacement and labour disruption costs for employers, healthcare reimbursement and replacement income for public social insurance. Any new treatment that avoids people from getting ill, that avoids mortality and that speeds up recovery and a possible return to work will lead to higher labour productivity and economic gains for society. The graph above gives a non-exhaustive overview of these benefits.

The value of medicines for patients, for their environment, for the economy and society at large is the topic of this report. This report will first assess the current state of health in Belgium and the progress that has been achieved in the last two decades thanks to medicines. Second, it will describe the pharmaceutical treatment progress in six diseases in more detail: Breast Cancer, Depression, Hepatitis C, Rheumatoid Arthritis, Cervical Cancer and Epilepsy. The selection of these six diseases aims at representing a wide array of therapeutic areas as well as different types of pharmaceutical treatments (small molecules, biologicals, vaccines). They serve as an example of how value is created by improved pharmaceutical treatment. Third, an outline of the challenges of the future is depicted, underlining the importance of continued efforts to bring new treatments to the patient.

Methodology

The analysis of this report is based on existing data from various sources and was conducted throughout 2019. First, a review of medical and health economic literature was made for each of the major diseases that are the topic of this report. Belgian and international databases were consulted, with the database of the Institute of Health Metrics & Evaluation¹ as the leading one, as it provides the data from the Global Burden of Disease study. It offers data on incidence, prevalence and mortality. We also used the World Health Organisation's Global Mortality Database and OECD reports.

For pharmaceutical expenditure in Belgium, we relied on information from the RIZIV/INAMI report "Monitoring Of Reimbursed Significant Expenses" (MORSE), published in 2018. Furthermore, specific information on long term sick leave for the selected diseases for Belgium was received from RIZIV/INAMI and from the pharmaceutical companies active in the selected disease areas.

To calculate labour productivity and premature mortality cost, we used the employment activity rate of 68 % for the entire population, with an annual average productivity per employee of 35,000 € for 2018², which is the standard approach to calculate health economic value. If the employment rate data are available by disease, then those disease-specific figures are used, as well as the average employee cost.

- 1 The Institute for Health Metrics and Evaluation (IHME) is an independent global health research center at the University of Washington, that has developed a measurement tool based on the Global Burden of Disease study of the World Health Organisation
- 2 Source: Belgian Federal Public Service Employment, Labour and Social Dialogue

A Comment on data availability

Unfortunately, health and economic impact parameters of disease and treatment are not collected, calculated and maintained in a systematic way in Belgium. That is why the data about the different disease areas could not be presented in an identical format. There are, however, many smaller studies that focus on different value aspects of specific disease treatment. Some of these were used to illustrate value parameters in specific disease areas. Priority was given to studies using Belgian data. In some cases, data from other Western European Countries was used and recalculated to Belgian epidemiology if possible.

All data sources are mentioned in the Appendix.

The demographic context

This report will assess medical progress in the last two decades, from the year 2000 till now. In order to fully appreciate the burden of disease and its evolution over the years, two major demographic changes have to be understood.

First, the Belgian population grew with 1.2 million citizens, from 10.2 million inhabitants in 2000 to 11.49 million people today³. This growth with 10% has its obvious consequences on healthcare organisation and expenses.

Second, the age pyramid has continued to change shape. Today, around 18.5% of the population, or

- 3 Statbel, 2019. This is the standard calculation to assess labour productivity value within the working population: the percentage of active people multiplied by the average productivity of that population. In the case of Belgium this is 68 % and 35,000 €.

2.095.097 people, are older than 65 years⁴, and the largest population group is between 45 and 60. From a healthcare perspective, this is important since most medical treatment is for the benefit of people older than 60, as can be seen in the graph⁵. More than 60 % of all healthcare expenditure goes to citizens older than 60.

Because of these changing demographics, both in absolute numbers as well as changes across age ranges, statistics are used either on a per patient basis or as the age-standardised rate per 100,000 inhabitants to be able to track progress over time. Such a calculation filters out the demographic effect and is as such a good indicator of the impact of healthcare policies and practices in the investigated time period.

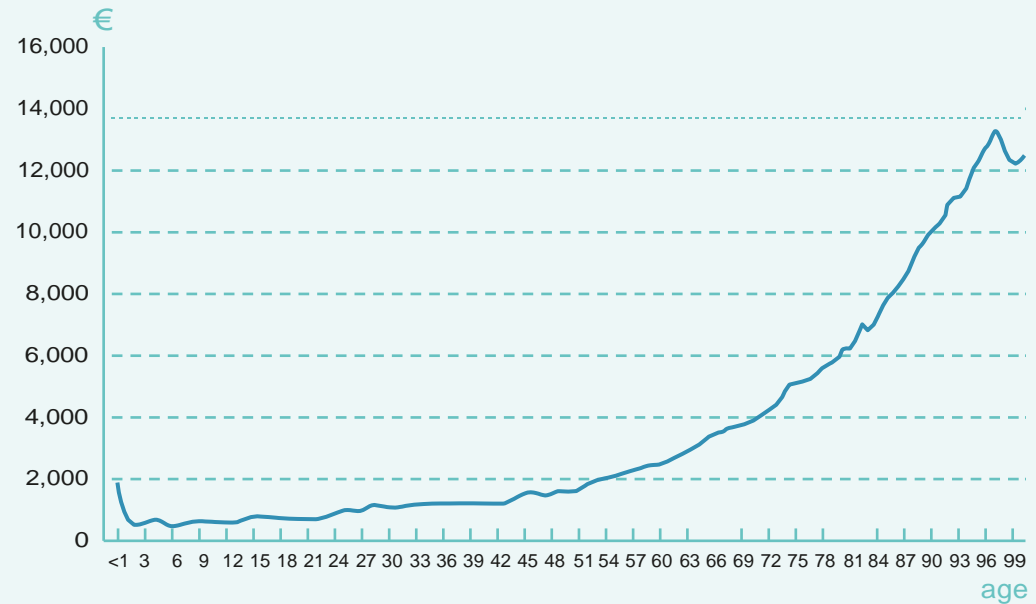
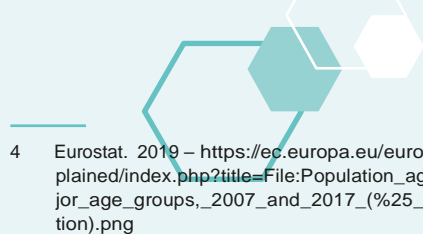


FIGURE 2 – ANNUAL HEALTH EXPENDITURE PER PERSON AND PER AGE IN THE MANDATORY HEALTH INSURANCE⁶

To evaluate the value of medicines, we will look at how new medicines avoid other direct and indirect costs in the healthcare system.



4 Eurostat. 2019 – [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Population_age_structure_by_major_age_groups,_2007_and_2017_\(%25_of_the_total_population\).png](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=File:Population_age_structure_by_major_age_groups,_2007_and_2017_(%25_of_the_total_population).png)
 5 Commissie Vergrijzing in “De lastige toekomst van de Belgische gezondheidszorg”, Econopolis, 2018

A classification of healthcare costs

Very often, health expenditure is looked at in isolation, as a separate budget with no impact outside the immediate benefits for patients. But from a true patient perspective, or even societal perspective, the actual costs of a disease are much higher and comprise the elements given in the following table. The direct healthcare costs are the costs that are covered in the healthcare budget (in green in the table below), and that are used to measure the cost-effectiveness of new medical technologies. But the actual cost to individuals and society is much larger. The “indirect

costs” include the costs related to sick leave (absenteeism), but also the costs related to people being at work with reduced productivity because of illness (migraine, depression, lower back pain, ...). This is defined as ‘presenteeism’ (being at work without being productive). Premature mortality is the lost economic contribution because of an earlier death than the normal life expectancy. Finally, the costs of caregivers should be added. For many diseases, family members take some time off from work to look after the patient. In some cases, this may even become full-time care. For the calculation of labour productivity and absence, two options are possible:

6 “Welke factoren beïnvloeden de gezondheidszorg van 65-plussers?”, Onafhankelijke Ziekenfondsen, 2018

the 'human capital method' implies that productivity losses are accounted for during the whole period of work absenteeism. The 'friction cost' approach assumes that absent workers will be replaced by others after a friction period of searching and learning. We will use the human capital method in this report because of the difficulty in the current economic environment to find adequate replacement for employees.

To evaluate the value of medicines, we will look at how new medicines avoid other direct and indirect costs in the healthcare system. If better treatments lead to less surgery and hospitalisation, or less long term sick leave, these values can be calculated. Because all diseases are different, the way to calculate the value of medicines may also differ: when a new medicine is life-saving (as in cancer or HIV), we will calculate reduced mortality and healthy and productive life years gained. If the disease is chronic (as in rheumatoid arthritis), the value of medicine can be measured in increase in quality of life and in maintained or increased labour productivity.

	Nature	Examples
Direct Costs	HEALTHCARE COSTS	Doctors, hospitals, nurses, imaging, pharmaceuticals, revalidation ...
	NON-HEALTHCARE COSTS	Transport, childcare and house-keeping, legal costs, social services, adjustments to home or vehicles ...
Indirect Costs	LABOUR PRODUCTIVITY	Presenteeism (being at work with low productivity because of disease). Absenteeism, disability pensions, reduced or absent private income generation, reduced tax payments
	PREMATURE MORTALITY	Lost economic contribution because of death earlier than normal life expectancy
	CARER COSTS	Part-time to full-time support

FIGURE 3 – THE VARIOUS COMPONENTS OF HEALTH ECONOMIC COSTS

GLOSSARY

Cost-Effective – means that the new treatment has benefits compared to the standard of care that outweigh its higher price

Cost-Saving – means that the new treatment reduces the cost of the treatment of the disease.

DALY (Disability Adjusted Life Year): One DALY can be thought of as one lost year of “healthy” life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability.

Hazards Ratio: A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo.

Incidence: the number of new diagnoses made for a disease in the course of a year. Can be measured as the total number of patients or as the number of patients per 100,000 inhabitants.

LY: Life years gained is a measure in health economics. It expresses the additional number of **years of life** that a person lives as a result of receiving a treatment.

Overall Survival (OS) – Overall survival is the percentage of patients who survive non-chronic diseases such as cancers or infectious disease. For cancer, the Overall survival is usually calculated after a period of 5 years after treatment.

Premature Mortality Cost – Premature mortality cost calculates the total cost to society of the premature death of active citizens.

Prevalence: the number of patients with a diagnosis of a disease. Can be measured as the total number of patients or as the number of patients per 100,000 inhabitants.

QALY – The **quality-adjusted life year** or **quality-adjusted life-year (QALY)** is a generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluations to assess the value for money of medical interventions. One QALY equates to one year in perfect health. If an individual’s health is below this maximum, QALYs are accrued at a rate of less than 1 per year. To be dead is associated with 0 QALYs.

YLL (Years of Life Lost): the YLL basically correspond to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. For instance: if male life expectancy is 80 years old in a country, and a person dies at the age of 60 because of a disease, then 20 years of life were lost. To calculate the total “years of life lost”, the figure is multiplied by the number of deaths.

CHAPTER I

The Value of Pharmaceutical Innovation in the last 20 years

Major improvements in health outcomes since the year 2000

Over the past twenty years, significant health outcomes (survival, recovery, improvement of quality of life) have been generated for a large number of deadly diseases. The number of Disability Adjusted Life Years (DALY – the number of years lost by patients to ill-health, disability or early death) has significantly decreased in many disease areas.

Between 1990 and 2016 life expectancy in Belgium at birth has increased with 4.1 years for women and even 5.8 years for men⁷ to reach an average of 81.3 years today⁸ for the entire population. The premature mortality rate decreased by 22% between 2001 and 2015.⁹

The decrease of Disability Adjusted Life Years for the most common diseases is illustrated in the graph. It lists the most important causes of death in Belgium by gender, together with the change in DALYs between 1990 and today. Especially in cardiovascular diseases (ischemic heart disease, stroke), but also in breast and colorectal cancer, the improvement is significant. The DALYs are not calculated in absolute numbers but as a percentage per 100,000 inhabitants to standardise the evolution of the population¹⁰. This is the best way to exclude the effect of the growth of the population that took place in Belgium in this period.

7 Maertens de Noordhout et al. "Changes in Health in Belgium, 1990-2016, BMC Public Health (2018)

8 Kerncijfers 2017, Statbel

9 Health Belgium – <https://www.healthybelgium.be/en/health-status/mortality-and-causes-of-death/overall-mortality>

10 Institute for Health Metrics & Evaluation, consulted in July 2019

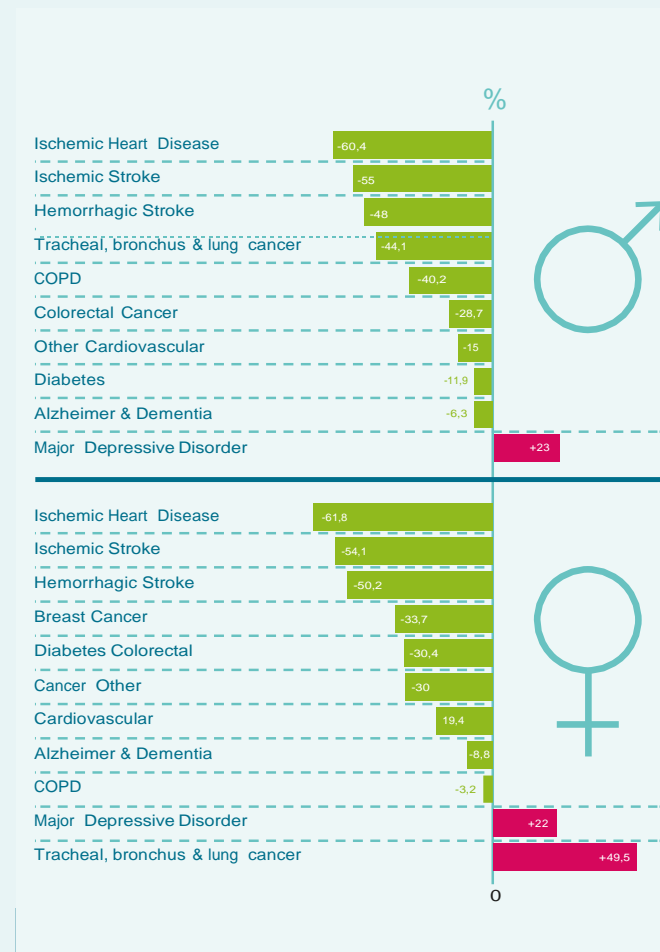


FIGURE 4 – AGE-STANDARDISED EVOLUTION IN DALYS IN BELGIUM (FROM 1990 TO DATE) PER 100,000 INHABITANTS FOR THE MAJOR CAUSES OF DEATH (IN %)¹¹.

11 Maertens de Noordhout et al. "Changes in Health in Belgium, 1990-2016, BMC Public Health (2018)

These results seem to be the consequence of an overall improvement of health management and healthcare in these decades. New innovations in diagnostics, surgery, imaging and pharmaceuticals have been made, leading to an increase of life expectancy and an overall improvement of the quality of life. Furthermore, health literacy, better lifestyle choices (smoking e.g.), active prevention, and screening have also contributed to avoid citizens from becoming ill.

The next table presents a qualitative appreciation by the authors of this report of how the role of pharmaceuticals per major disease for the period 1999-2019 could be visualised based upon the overall reduction of DALYs or the survival rate increase. The relative role of pharmaceuticals in achieving these favourable outcomes is indicated with a colour coding: dark green when pharmaceuticals are the primary treatment and light green when it is the secondary treatment in combination with surgery.

For diseases such as COPD, stroke, heart failure and Type I diabetes, the DALYs have decreased between 8% and 40%.

	Stroke	Heart Failure	Diabetes Type I	COPD	HIV	Hep C	Breast Cancer	Pros5ate Cancer	Colon Cancer	Leukemia (ALL)	Multiple Myeloma	Melanoma
Decrease in % of DALY	-17%	-40%	-30%	-8%	-65%	-60%						
Overall Survival (5 year)					99%	99%	91% +6%	94% +5%	67% +6%	95% +24,5%	58% +9%	94% +8%
Pharmaceuticals	Primary	Primary	Primary	Primary & external	Primary	Primary	Secondary	Secondary	Secondary	Primary	Primary	Secondary

● Primary treatment
 ● Secondary treatment
 ○ Primary treatment and improving external conditions
 green % are percentage points evolution since 1999.

TABLE 1 – HEALTH OUTCOMES FOR MAJOR DISEASES IN BELGIUM (1999-2019)¹²

For diseases such as COPD, stroke, heart failure and Type I diabetes, the DALYs have decreased between 8% and 40% and pharmaceuticals are the primary treatments in these disease areas. For Chronic Obstructive Pulmonary Disease (COPD) improvement in air quality, lifestyle changes and work conditions also contributed. The most significant advances have been achieved in HIV and hepatitis C. In HIV, no treatment can be considered a cure today, but out of a population of 17,000 infected citizens in Belgium, 66 died in 2018, which is comparable to the death rates among the general population. With hepatitis C, the new pharmaceuticals lead for the first time in history to a

real cure, with no virus remaining in the body after an 8-week treatment. In cancer, significant advances in 5-year Overall Survival are observed for various types of cancer. In oncology, pharmaceuticals – chemotherapy and hormonal therapy – are often used in combination with surgery as primary treatment in breast, prostate and lung cancer, whereas in hematological cancers such as leukemia and myeloma, pharmaceuticals act as the primary treatment and bone marrow transplant as a secondary treatment¹³.

¹² The table gives an overview for several diseases. Data are collected from different sources: the Belgian Cancer Registry, the CONCORD Study, the Global Burden of Disease Survey and the Belgian Health Statistics website. Because the improvement in diseases is calculated differently by disease, not all disease statistics (for instance “Overall Survival” are relevant for each disease and are typically not calculated as a result. The point of comparison for HIV and hepatitis C are the years 1995-2018

¹³ Belgian Cancer Registry and CONCORD Study, The Lancet 2018

New pharmaceuticals: progress in treating chronic diseases, improving quality of life for patients and overall survival

Also in other disease areas major pharmaceutical achievements were made in this time period by improving the quality of life of patients with chronic diseases. Examples include rheumatoid arthritis, psoriasis, Crohn's disease, diabetes, multiple sclerosis, schizophrenia and bi-polar disorder, migraine, epilepsy, and rare diseases such as hemophilia, cystic fibrosis, spinal muscular atrophy and mucopolysaccharidosis. Pharmaceuticals are the primary treatment option for all these diseases and many more.

For the purpose of this study about the effect of innovative pharmaceutical treatments on public health, a number of diseases where the advent of new treatments had a significant impact were selected and are treated in more detail in Chapter 2. But there are many more examples where new pharmaceuticals play a decisive role: cardio-vascular disease, HIV/AIDS, respiratory disease, cancer, diabetes, schizophrenia and psoriasis of which snapshots are presented below.

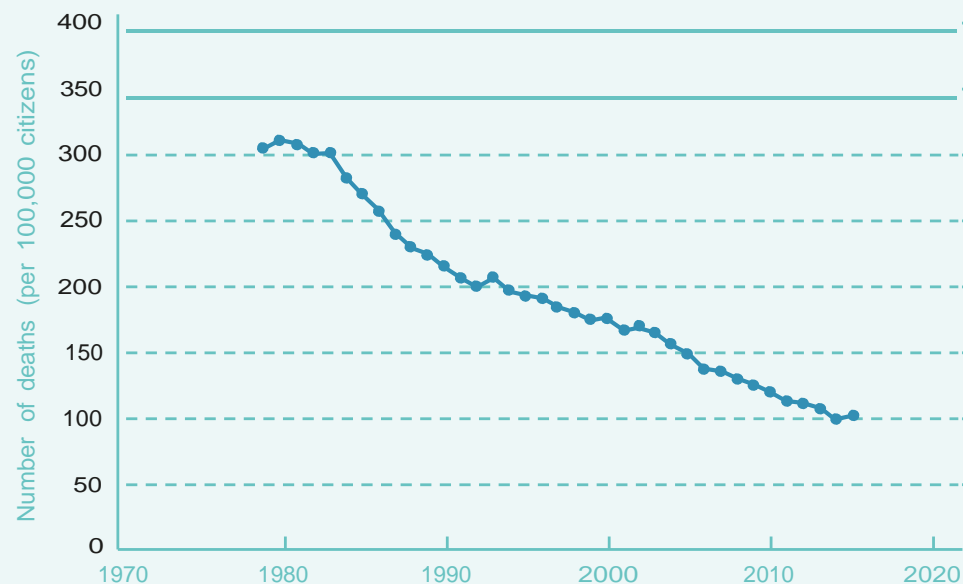


FIGURE 5 – EVOLUTION OF THE NUMBER OF DEATHS FOR DISEASES OF THE CARDIOVASCULAR SYSTEM, IN BELGIUM, BOTH SEXES PER 100,000 CITIZENS (WHO Mortality Database, 2019)

Cardio-vascular disease: many lives saved

In cardiovascular disease, the mortality in Belgium has been reduced by 45 % since the year 2000¹⁴.

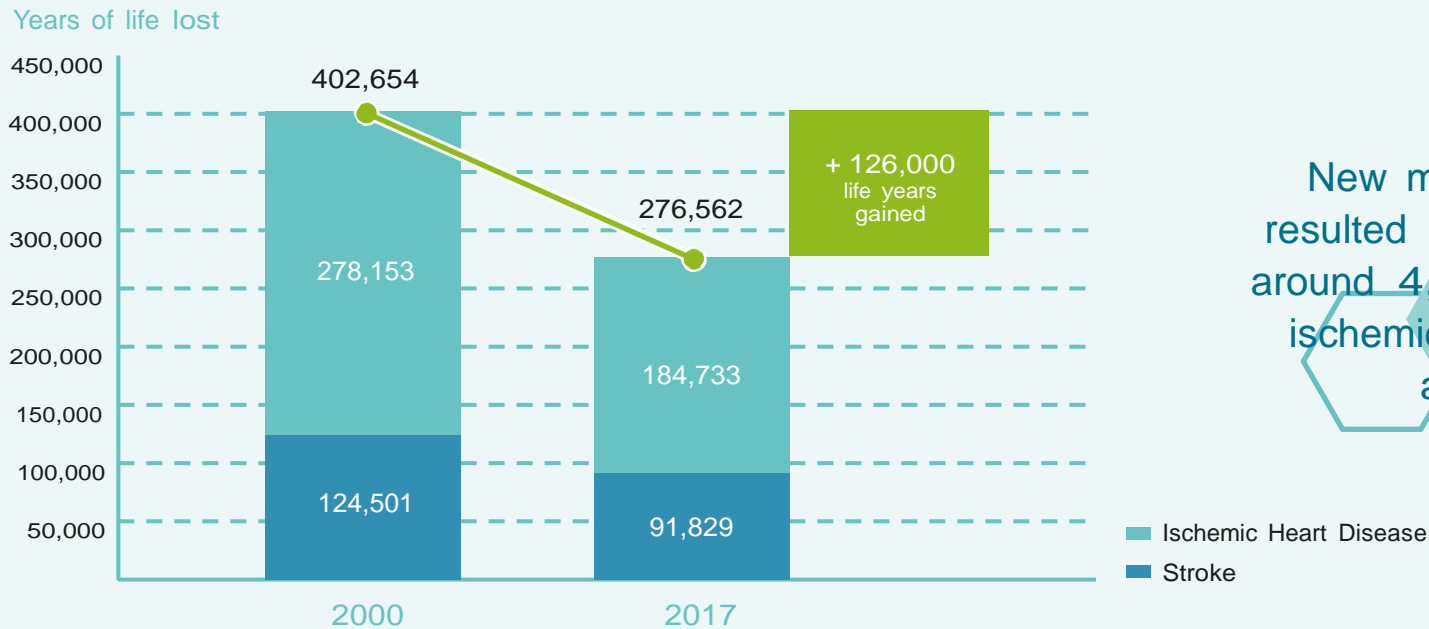
Medicines play a central role in transforming the trajectory of this disease area, resulting in decreased death rates, improved health outcomes and better quality of life for patients.

A whole array of new drugs has been introduced in the last decades: statins, beta-blockers, ACE-inhibitors, anti-coagulants, resulting in better outcomes for hypertension, cholesterol levels and in the prevention of blood clotting.

14 World Health Organisation: Global Mortality Database, consulted July 2019

At the level of the total population, the number of Life Years Gained between 2000 and 2017 in stroke and ischemic heart disease is substantial: 126,000 years of life gained in Belgium (which can be explained as variations of 12,600 people living an extra 10 years or 126,000 people living one year extra, and this in full health)¹⁵.

In Belgium, around 15,000 people die every year (2017) from ischemic heart disease¹⁶, down from 19,000 in the year 2000. In broad terms, new medicines have resulted in a reduction of around 4,000 deaths from ischemic heart disease in Belgium, annually.



New medicines have resulted in a reduction of around 4,000 deaths from ischemic heart disease annually.

FIGURE 6 – YEARS OF LIFE LOST (YLL) IN TWO CARDIOVASCULAR DISEASES IN BELGIUM (Belgium, 2000-2017, Institute of Health Metrics & Evaluation, 2019)

15 Institute for Health Metrics & Evaluation, own calculations, 2019

16 European Cardiovascular Disease Statistics, 2017

HIV/AIDS: from deadly disease to normal life expectations

In HIV the drop in 'life years lost' since 1995 has been significant. What was once a death sentence, has been reduced to a chronic condition allowing patients to live normal lives. The development of HIV treatments has been a good example of a steady pipeline of ever more effective and patient-friendly medicines.

Between 2000 and 2017, 18,867 citizens were diagnosed with an HIV infection, or a little above 1,000 new cases per year, and over the whole period, 1,065 of them died (5.6%). This means that roughly 17,000 Belgian citizens are alive today who would

not have survived without pharmaceuticals, of which around 90 % are within working age¹⁷. This means these patients can lead normal professional lives, create value and contribute to the economy of the country. With an average labour productivity of 35,000 € per year and a 68 % labour participation, this would lead to an incremental economic value of 364 million € in 2017. In comparison, the estimated cost of HIV drugs in Belgium is around 135 million €¹⁸ in the same year, resulting in positive economic gains of 229 million € in 2017.

Respiratory diseases

In respiratory diseases, mortality has decreased with 30 % between 2000 and 2018. Around 1.3 million Belgians suffer from a variety of respiratory diseases, and the number of patients is increasing. Lifestyle choices, air pollution and cleaner work environments play a significant role in the prevalence of the disease. In the past decades, many new medicines have come to the market¹⁹, and at the same time, efforts to reduce exposure to harmful substances have been made as well, and overall health education has increased among the population.

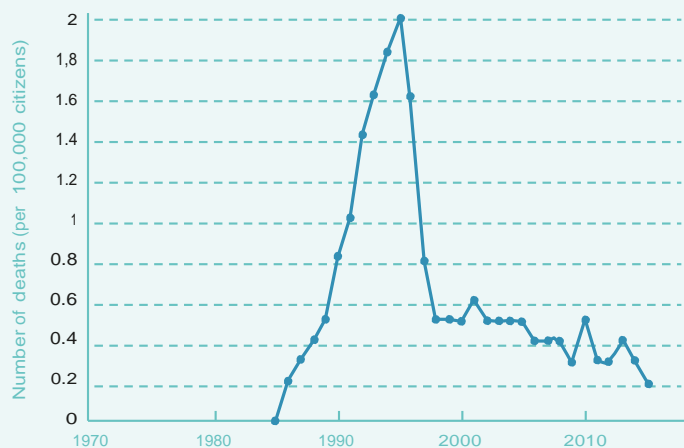


FIGURE 7 – EVOLUTION OF THE NUMBER OF DEATHS AMONG HIV PATIENTS, IN BELGIUM, BOTH SEXES PER 100,000 CITIZENS (WHO Mortality Database, 2019)

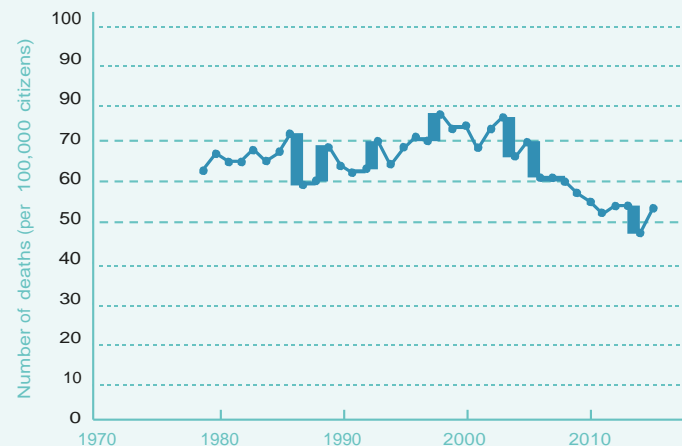


FIGURE 8 – EVOLUTION OF THE NUMBER OF DEATHS FOR DISEASES OF THE RESPIRATORY SYSTEM, IN BELGIUM, BOTH SEXES PER 100,000 CITIZENS (WHO Mortality Database, 2019)

17 Sciensano – Epidemiologie van AIDS en HIV-Infectie in België, 2018

18 MORSE Report, 2018

19 long-acting β 2-agonists, long-acting muscarinic antagonists, safer inhaled corticosteroids (ICS), long-acting bronchodilators and longer acting antibiotics

Cancer: more and more survivors

From 1980 to 2017, cancer mortality has decreased with 18% overall. Despite the increasing incidence of cancer, the number of people surviving their disease is also increasing, thanks to new treatments. Today, there are 339,000 cancer survivors in Belgium²⁰. This figure includes all patients who are undergoing treatment or who are in complete remission²¹. The result of what has been achieved in the last decade is significant. The role and impact of pharmaceuticals differs according to the type of cancer. In lymphoma, myeloma and leukemia, drugs are the first

and most important treatment. In breast cancer and prostate cancer, they represent half the investment in healthcare, and less so for other types of cancer such as lung cancer, where their impact is yet more limited²². Overall, achieving this reduced mortality is for 73% due to new treatments²³. In the coming five years, 11,000 life years – of which 9 500 healthy life years – can be gained in Belgium by the introduction of innovative immunotherapy treatments as compared to current standard treatments²⁴.

The graph below²⁵ shows how early detection and new treatments have kept the cancer mortality for both men and women under control. Without new treatments, the red trend line would have significantly increased.

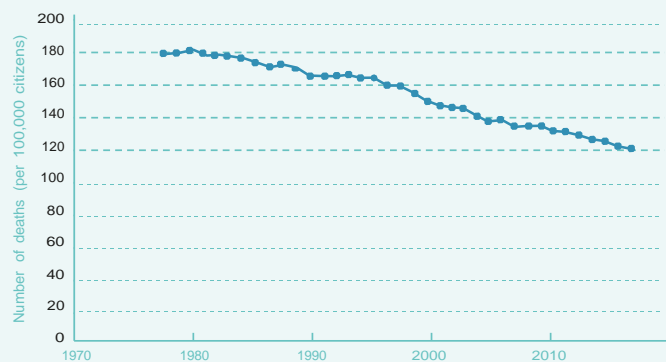


FIGURE 9 – EVOLUTION OF THE NUMBER OF CANCER DEATHS, IN BELGIUM, BOTH SEXES PER 100,000 CITIZENS (WHO Mortality Database, 2019)

20 "Kankerbeleid in België, Vroeger en Nu", Sciensano, 2019
21 Stichting Tegen Kanker – Memorandum 2018-2019



FIGURE 10 – EVOLUTION OF CANCER IN BELGIUM WITH (blue line) AND WITHOUT NEW TREATMENT (red line)

22 Ramon Luengo-Fernandez, Jose Leal, Alastair Gray, Richard Sullivan, Economic burden of cancer across the European Union: a population-based cost analysis, The Lancet, 2013
23 S. Seabury, "Quantifying Gains in the War on Cancer Due to Improved Treatment and Earlier Detection," Forum for Health Economics and Policy 2016
24 Prof. Lieven Annemans, UGent, Interview De Morgen, June 2018
25 Belgian extrapolation of study by Rebecca L. Siegel, MPH; Kimberly D. Miller, MPH; Ahmedin Jemal, DVM, PhD – Cancer Statistics 2017

Diabetes: lower mortality, less amputations

In type II diabetes, the number of patients is increasing over the years. The estimate is that around 600,000 Belgian citizens have type II diabetes²⁶, of which one out of three are not even aware they have the disease.

On the positive side, many new treatments have reached patients in the previous decade, improving the management of the disease and its effects, and improving the overall quality of life. The oldest treatment is insulin, but 70 new treatments have been approved in the last 20 years, including drugs to low-

er blood sugar levels with less risk of causing hypoglycaemia, drugs that help the pancreas make more insulin, and drugs that imitate the natural hormone activity of the body, preventing the kidneys from holding up the glucose.

Even if the incidence increases year after year, with around 50,000 new patients in 2018, the Years of Life Lost has equally decreased over the same period because patients have a better quality of life and live longer. This includes a sharp decrease in one of the more devastating consequences of diabetes: the amputations of affected limbs. A recent study in Belgium

concludes: “significant decrease (is observed) in the rate of any major amputation in the population with diabetes, from 42.3 per 100,000 person-years in 2009 to 29.9 in 2013, with an annual reduction of 8%. In contrast, no decline was observed in the population without diabetes”²⁷.

The treatment cost of diabetes is estimated to be 6,000²⁸ € per patient per year. The cost of medicines is approximately 520 € per year²⁹, and despite recent innovations, this cost has barely increased over the years on a per patient basis³⁰.

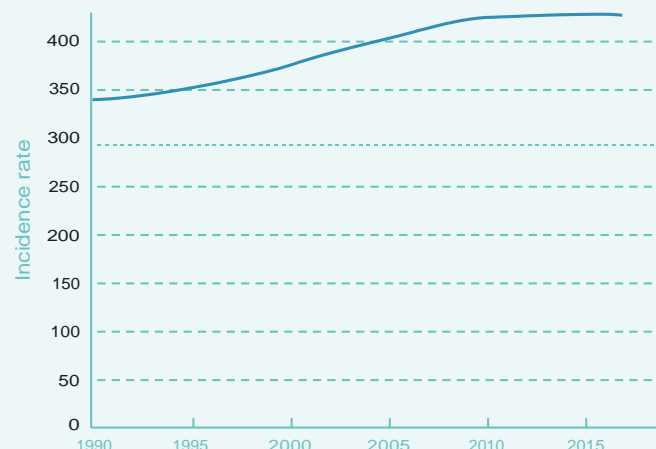


FIGURE 11 – YEARS OF LIFE LOST AND INCIDENCE RATES OF DIABETES II PER 100,000 PEOPLE, IN BELGIUM, BOTH SEXES, ALL AGES (Belgium, 2000-2017, Institute of Health Metrics & Evaluation, 2019)

26 Diabetes Atlas, 2017

27 Decreasing rates of major lower-extremity amputation in people with diabetes but not in those without: a nationwide study in Belgium (Diabetologica, 2018)

28 Diabetes Atlas, 2017

29 MORSE Report 2018: 182,000 mio € spent on anti-diabetics divided by 350,000 patients.

30 The costs to treat diabetes include: Inpatient hospital treatment, outpatient costs include GP, specialist, physiotherapy, nursing, pharmacy, dentistry and laboratory. Other costs include injection devices, self-blood glucose monitoring equipment, insulin pumps, oxygen-therapy and other medical devices.

Schizophrenia: keeping patients out of the hospital

The incidence of schizophrenia is relatively stable. In the year 2000, 1,300 new patients were diagnosed in Belgium, and around 1,400 in the year 2017. Today, around 32,000 patients live with the disease. Major advances have been made in the treatment of schizophrenia. In the past, most patients were treated in residential care in psychiatric hospitals. Today, with early treatment and good adherence, most patients can have a relatively normal life outside of psychiatric institutions. Newer, long-acting treatments (one injection per month, replacing daily oral regimen) were launched in the past decade, which increase adherence and as a consequence reduce relapse and hospitalisation.

Today, the total cost of schizophrenia treatment in Belgium is around 1.13 billion €³¹, of which 83 million is spent on medication, and with additional indirect costs such as decreased labour productivity and absenteeism possibly reaching 205 million €³². The more expensive long-acting injectable treatments, requiring an additional investment of 2.1 million € have led to a reduction in hospitalisation costs and resulted in total savings of 4.4 million €³³. The real value of the new medicines is on the patient's and the caregiv-

- 31 L Annemans, I Eijgelshoven, A Smet, A Jacobs & G Bergman (2012) The Impact of Treatment with Risperidone Long-Acting Injection on the Belgian Healthcare System: Results From a Budget Impact Model, *Acta Clinica Belgica*, 67:2, 108-119
- 32 Andrea Marcellusi et al. "Economic burden of schizophrenia in Italy: a probabilistic cost of illness analysis", *BMJ*, 2017
- 33 L Annemans, I Eijgelshoven, A Smet, A Jacobs & G Bergman (2012) The Impact of Treatment with Risperidone Long-Acting Injection on the Belgian Healthcare System: Results From a Budget Impact Model, *Acta Clinica Belgica*, 67:2, 108-119

er's quality of life, leading to better clinical recovery defined by symptom severity and level of functioning, and subjective personal recovery related to the patient's Quality of Life, self-confidence, future hopes, willingness to ask for help, reliance on others and no domination by symptoms. The two dimensions are mutually linked, such as better cognitive functioning which leads to better social integration and lower rates of anxiety and depression³⁴.

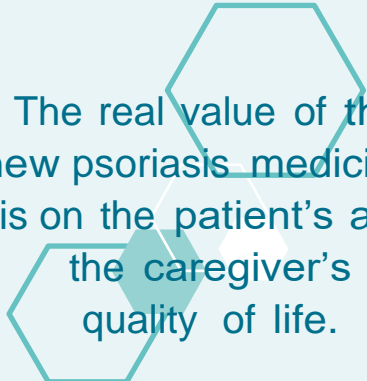
Psoriasis: back to work and social life

Biological treatments have improved the treatment of moderate to severe psoriasis in the past decade. For some patients, who suffered from plaque psoriasis for decades, three injections a year resulted in a completely clear skin. The new biological treatments, introduced in the last twenty years, work in the same way as the new rheumatoid arthritis drugs and reduce the impact of the patient's immune system on its own biochemical processes. Studies demonstrated that new biologicals reach the score of PASI 90 (Psoriasis Area and Severity Index), which translates into a 90 % improvement³⁵.

- 34 Francesco Pietrini et al. The modern perspective for long-acting injectables antipsychotics in the patient-centered care of schizophrenia in "Neuropsychiatric Disease and Treatment", 2019
- 35 Cochrane Review: "Systemic (oral or injected) medicines for psoriasis, 2017

To patients, the improvement of the quality of their daily lives is the most important advantage of the new treatments: better social interaction and less isolation, less time lost with applying ointments and creams, and better mental health.

Pharmacoeconomic studies have identified positive economic benefits of the treatments for psoriasis: patients continue to work and do not need sick leave and invalidity pensions and they are more productive through the reduction of physical symptoms. They also indicate that these economic benefits offset the healthcare costs for the treatments. One study demonstrated a greater than 47 % reduction in sick days after 12 weeks of treatment.³⁶ In the meantime, the first biologic treatments have become off-patent, reducing treatment costs further.



The real value of the new psoriasis medicines is on the patient's and the caregiver's quality of life.

- 36 Boggs, R.L. et al Employment is maintained and sick days decreased in psoriasis/psoriatic arthritis patients with etanercept treatment. *BMC Dermatology* 2014

Some initial conclusions about the value of medicines

Patient value

The general remarks and examples elaborated in this chapter give some indications about the value of medicines for the patients and society at large in Belgium. In conclusion, we can say that significant advances have been made in the treatment of many diseases – and not just the ones mentioned – resulting in an increase in life expectancy among the total population. For each of these diseases, it is possible to give a broad assessment of the role of pharmaceuticals in achieving these outcomes, which – with a few exceptions – often get their full effect in combination with other medical interventions.

This seems to confirm an international study with an analysis conducted on the first decade of the century: innovative pharmaceuticals would be responsible for 73% of the increase in life expectancy in OECD member states³⁷ including Belgium.

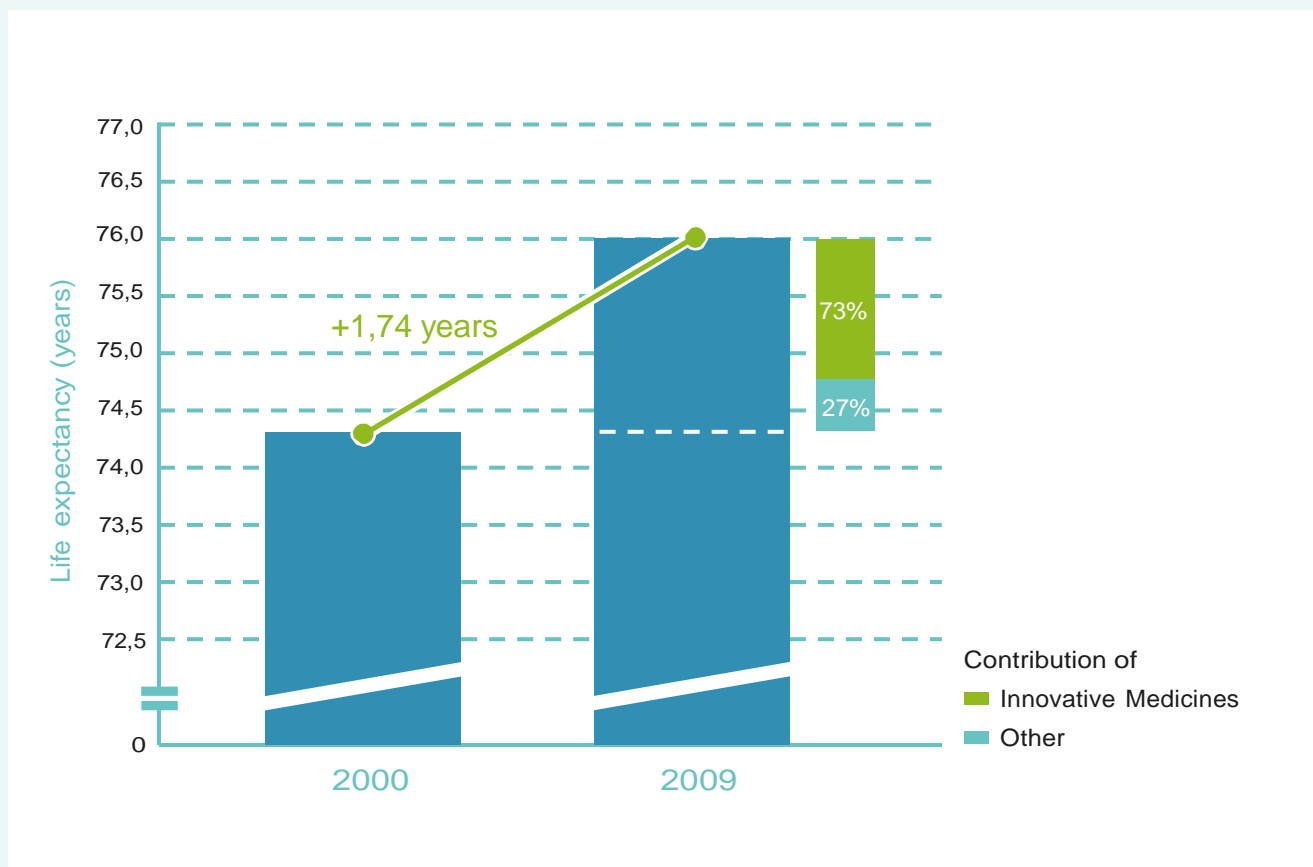


FIGURE 12 – EVOLUTION OF LIFE EXPECTANCY IN BELGIUM (2000-2009) WITH INDICATION OF THE RELATIVE IMPORTANCE OF NEW TREATMENTS (Source: Statbel, Lichtenberg)

37 Frank R. Lichtenberg, "Pharmaceutical Innovation and Longevity Growth in 30 Developing and High-Income Countries, 2000-2009," Health Policy and Technology, Vol. 3, No. 1, March 2014

Socio-economic value

A relevant indication of the socio-economic value of successfully treating patients is calculating the productivity gains. The avoidance of premature mortality in the working population between 2000 and 2017 stands at 3,455 life years per 100,000 inhabitants annually. With an employment activity rate of 68% for the entire population, and with an annual average productivity cost per employee of 35,000 € this represents an economic contribution of 5.4bln € in 2017 alone³⁸. Other economic gains that could be considered are lower treatment costs such as hospitalisation, a reduction in replacement income, less burden for informal carers and so on. In the assumption that indeed 73% of the increase in life expectancy is the result of new pharmaceutical treatments, the potential economic gains almost completely cover the current pharmaceuticals budget expenditure.

The following graph illustrates the overall decrease in number of life-years lost.

These are the cumulative data for the entire population. In Chapter II we will now focus on six diseases and evaluate the role of pharmaceutical innovation on improving patients' lives and how they benefit society as a whole.

Years of life lost

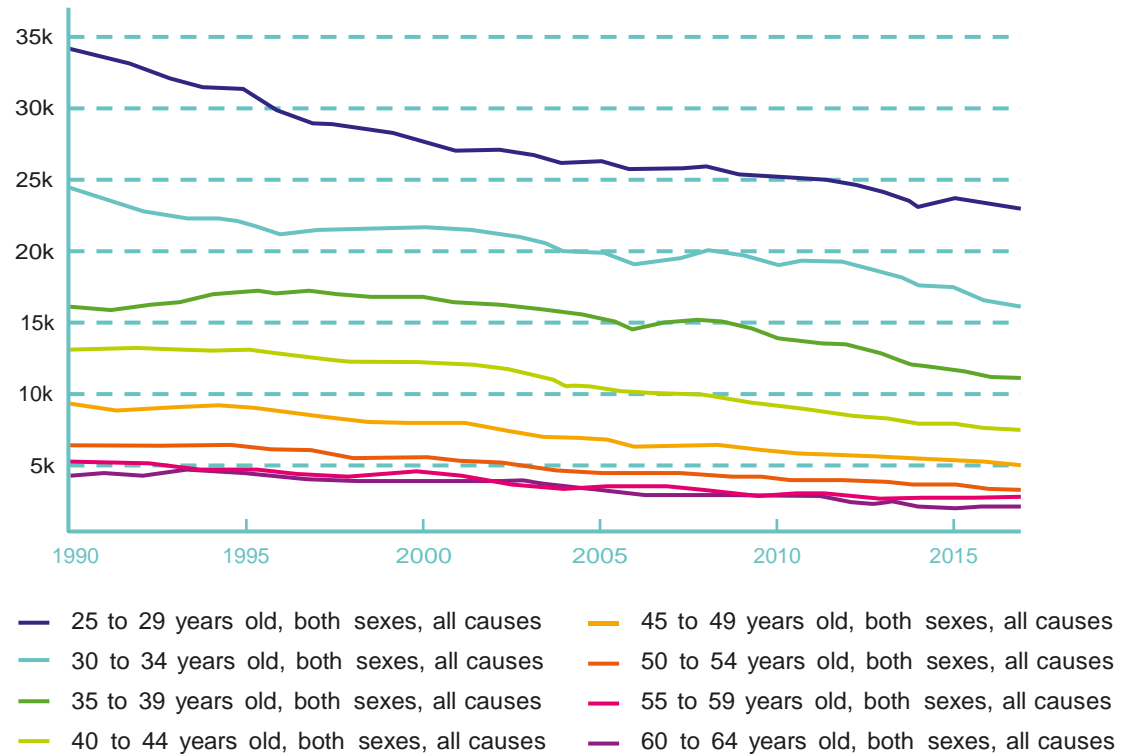


FIGURE 18 – YEARS OF LIFE LOST PER 100,000 INHABITANTS IN BELGIUM, PER AGE GROUP IN THE WORKING POPULATION, 1990-2017 (Source: Institute of Health Metrics & Evaluation, 2019)

38 Institute of Health Metrics and Evaluation, and own calculations, 2019

CHAPTER II

Six Case Studies

In this second chapter, we will look at six diseases in more depth: breast cancer, rheumatoid arthritis, hepatitis C, epilepsy, depression and cervical cancer.

We started by determining a set of criteria to have a balanced selection as presented in the table below: acute, chronic, infectious, physical or mental, with high and low prevalence, and where pharmaceutical treatment is part of a broader treatment or of a different type (small “chemical” molecule, big “biologic” molecule or vaccine). Based on these criteria, we selected a number of relevant diseases.

We also took into consideration the innovation in pharmaceuticals. For some diseases, such as depression, very few innovations have reached the patient in the last years, whereas in others such as rheumatoid arthritis, breast cancer, hepatitis C and epilepsy, new classes of medicines have been approved.

In some of these, the effects are already visible, in others, such as cervical cancer, the true value will be found in the future, based on today’s use of the vaccination. On the other hand, we also wanted to avoid cherry-picking diseases where pharmaceutical innovation played a decisive role.

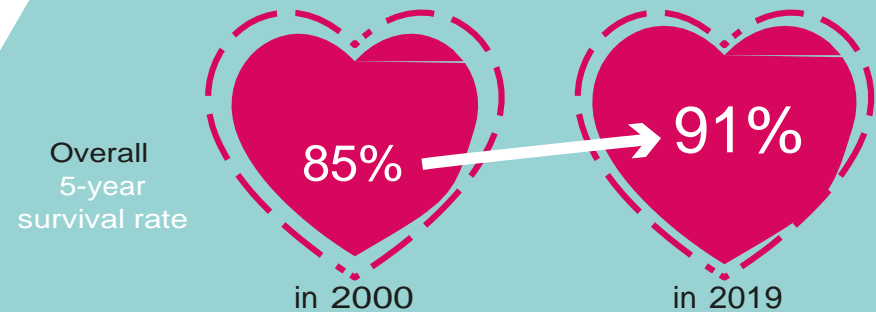
In the past few years we have seen a significant increase in new orphan drugs. We did not include them in our evaluation, even if innovation has resulted in significant value for individual patients. Because of the limited number of patients, very few studies are conducted that evaluate the aspects of productivity in patients suffering from a rare disease. Survival and quality of life are obviously the key determinants to invest in this innovation. It is also not always possible to attribute the precise role of each new technology in obtaining health outcomes.

	Type of disease	Prevalence	Treatment	page
Breast cancer	Acute/physical	High	Variety	23
Rheumatoid Arthritis	Chronic/physical	High	Biologics	28
Hepatitis C	Infectious disease	Low	Anti-infectives	32
Epilepsy	Chronic/neurological	Medium	Small molecule	36
Depression	Chronic/mental	High	Small molecule	40
Cervical cancer	Acute/infection	Low	Vaccine	44

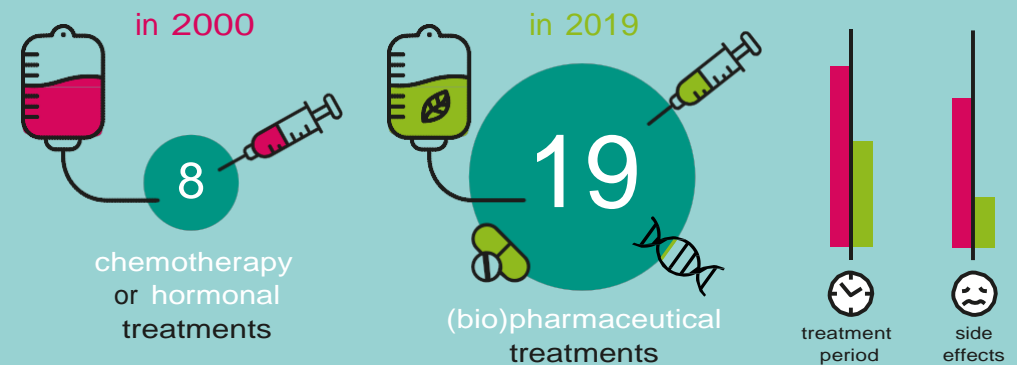
TABLE 2 – SELECTION CRITERIA TO IDENTIFY SIX CASE STUDIES

The value of better treatments for Breast Cancer

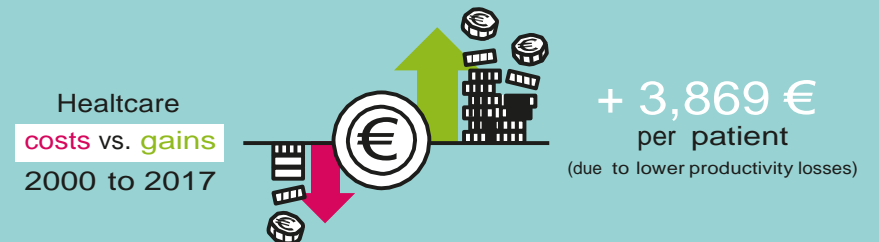
- In the last two decades, overall **survival for breast cancer** five years after treatment has **increased from 85% to 91%** in Belgium. The average number of **life years gained** per patient has **increased by 1.9 years** between 2000 and 2017.



- Significant treatment innovations were introduced in the areas of surgery, radiotherapy and better medicines. In the year 2000, patients were treated with a portfolio of **8 chemotherapy or hormonal treatments**. Today, an oncologist has a portfolio of **19 (bio)pharmaceutical treatments**. Today, the treatment periods are **shorter** and there are **less side effects**.



- Health economic calculations demonstrate that on average **3,869 € per patient per year is gained in Belgium between 2000 and 2017**.



Breast Cancer

Breast cancer in Belgium: more survival, better quality of life, decreasing societal cost per patient.

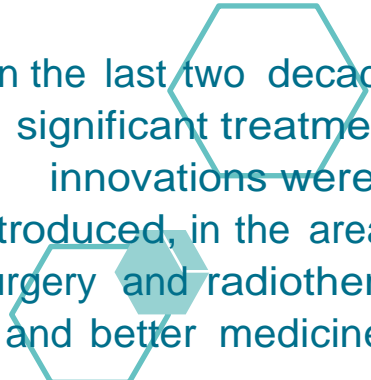
The challenges for patients

Breast cancer is the most frequent cancer among women, and Belgium is one of the countries in the world with the highest breast cancer incidence³⁹.

Despite the current success of treating breast cancer, any diagnosis still has a serious impact on the patient's personal and family life. The outcome is uncertain, and the treatment may have serious impact on the quality of life, such as self-image, physical intimacy and the need for reconstructive therapy. Often, the professional situation of the patient changes due to the disease, with some patients suffering from financial hardship as a result.

Breast cancer in Belgium

In the year 2000, around 9,300 new patients were treated for breast cancer, and more than 10,500 in 2017. The overall breast cancer incidence among women has been relatively stable the last decades, showing even a slight (non-significant) downward trend between 2000 and 2014: from 106.8 to 106.0 per 100,000 women⁴⁰. The breast cancer incidence displays a positive association with age, reaching a peak above the age of 60, with around 410 cases per 100,000 women⁴¹. In contrast, the incidence is around 280 per 100,000 for women aged 45-60 and is as low as 13/100,000 for women aged 20⁴². Therefore, the increase is due to an increase in population size, as well as an ageing population in combination with higher incidence rates in elderly women.



In the last two decades, significant treatment innovations were introduced, in the areas of surgery and radiotherapy, and better medicines.

³⁹ International Agency for Research on Cancer, 2018

⁴⁰ Kankerregister, 2019

⁴¹ With a range from 374 to 444 per 100,000).

⁴² Kankerregister, 2019

The value of medical innovation

In the last two decades, significant treatment innovations were introduced, in the areas of surgery and radiotherapy, and better medicines. In addition, breast cancer screening and awareness campaigns have certainly had an effect on the earlier detection of this cancer. In the year 2000, patients were treated with a portfolio of 8 chemotherapy or hormonal treatments. Today, an oncologist has a portfolio of 19 (bio) pharmaceutical treatments. Most of the new innovations are active on segmented parts of the patient population, as for example monoclonal antibodies that target the HER2 receptor of breast cancer patients with HER2 positive breast cancer (15-20% of all cases) and very recently the first immunotherapy has been approved by the European Commission for the treatment of triple negative breast cancer (10-20% of all cases). These new innovations are used in the metastatic settings but some also in the early setting as well. They are resulting in increased quality of life, overall survival, and less recurrence.

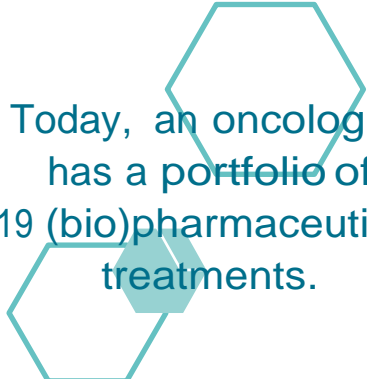
The value of these new medicines and of other advances in breast cancer treatment will not only be determined by their clinical efficacy, but will also be determined by the two trends discussed above:

- Breast cancer incidence has a strong association with age, and the age distribution changes over time, with higher age groups being more represented in 2017 compared to two decades earlier.
- Earlier detection and a better treatment portfolio results in more women being treated in earlier stages of the disease, in combination with treatments in the earliest stage being less expensive and with higher treatment success rates compared to treatments of metastatic breast cancer.

The effect of these two trends on the value of new medicines are intertwined with the improved clinical efficacy of breast cancer treatments and with changes in economic productivity. The following sections will outline the effect that innovations in medicines between 2000 and 2017 have had on changes in (1) survival and life years; (2) treatment-related costs and other health care costs; and (3) productivity losses.

Breast cancer survival has improved significantly over the past two decades. Different sources are available showing trends in 5-year Overall Survival over time.

The 5-year relative survival rate after treatment has increased from 85.5% to 91.4%. Despite the increasing number of patients affected by the disease, the number of 'years of life lost' for the total patient population has decreased from 59,000 years to 47,000 years in this period (1999-2017).



Today, an oncologist has a portfolio of 19 (bio)pharmaceutical treatments.

Year	5-year overall survival in Belgium
1999-2003	85.5 %
2004-2008	88.4 %
2009-2013	90.3 %
2014-2017	91.4 %

TABLE 3 – EVOLUTION OF THE 5-YEAR OVERALL SURVIVAL IN BREAST CANCER PATIENTS IN BELGIUM
(Source: Belgian Cancer Registry, 2019)

When we calculate the number of life years gained, we come to the following results⁴³:

	2000				2017			
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 1	Stage 2	Stage 3	Stage 4
Total life years per stage	87,838	77,547	20,467	483	121,246	88,321	25,631	2,105
Total life years for all patients, undiscounted	186,335				237,303			
Calculation of expected life years over a full-time horizon	50,968							

TABLE 4 – CALCULATION OF EXPECTED LIFE YEARS OVER A FULL-TIME HORIZON (Source: own calculations)

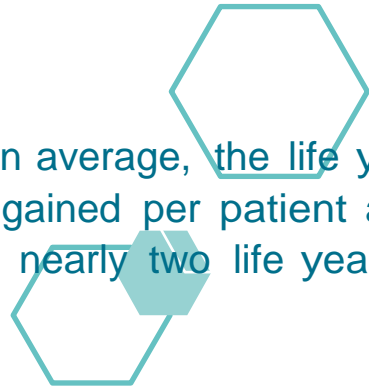
	2000	2017
Total life years per patient	20.06	21.92
Average number of life years gained per patient	1.86	

TABLE 5 – TAKING OUT THE EFFECT OF HIGHER PATIENT NUMBERS IN 2017 (Source: own calculations)

Interpretation

There are 50,968 life years gained among breast cancer patients over a 17-year period, which represents an increase of 27.4 %. This difference is partly due to higher patient numbers in 2017 but is mostly due to the increases in overall survival achieved for each breast cancer stage, and thanks to an earlier detection of the cancer with proportionally more patients treated in earlier stages. Treating patients earlier is important because the expected life years diminish dramatically in stages 3 and 4. On average, the life years gained per patient are nearly two life years; this effect is entirely due to advances in breast cancer detection, care and medicines.

On average, the life years gained per patient are nearly two life years.



⁴³ The “stages” in cancer refer to the severity of the cancer, from early detection of the presence of invasive cancer (Stage I) to metastatic cancer that has spread to other organs (Stage IV).

Health economic value attributable

The total costs attributable to breast cancer were 1.07 billion € in 2017 compared to 623 million € in 2000, including direct medical health care costs, productivity losses due to morbidity and mortality. The total increase in costs from a societal perspective in 2017 compared to 2000 is therefore 453 million €⁴⁴. All cost categories are higher in 2017 compared to 2000; but this higher number is partly due to population growth and to inflation.

When removing the effect of inflation, by valuing the 2000 cost data at 2017 prices, the difference of 453 million € decreases to 116 million €. The direct medical care costs and the productivity losses due to morbidity are still higher in 2017, but this is partially offset by lower productivity costs due to mortality.

Finally, when removing the effect of population growth by looking at the cost per patient instead of for the total population, and keeping on calculating all costs at 2017 prices, it is found that costs in 2017 are lower per patient than in 2000. The direct medical health care costs are still substantially higher, but this additional 13,496 € cost for breast cancer treatments is fully offset by lower productivity losses, both for mortality and for morbidity. A saving of 3,869 € is generated per patient, and this is also accompanied by a gain in life years of 1.86 years per breast cancer patient in 2017 compared to 2000. Improvements in overall survival have a substantial impact on the outcomes— and gains in survival are the result of earlier detection, improved surgical methods, and innovations in drug treatments.

⁴⁴ Own calculations based on currently available data for Belgium

	2000	2017
Total health care costs	126,456,342 €	350,249,409 €
Total productivity costs due to morbidity	253,966,865 €	464,433,661 €
Total productivity costs due to mortality	243,192,905 €	262,633,338 €
TOTAL COSTS	623,616,112 €	1,077,316,409 €
Difference	453,700,297 €	

TABLE 6 – CALCULATING TOTAL COSTS

	2000	2017
Total health care costs	175,190,586 €	350,249,409 €
Total productivity costs due to morbidity	402,301,046 €	464,433,661 €
Total productivity costs due to mortality	383,195,163 €	262,633,338 €
TOTAL COSTS	960,686,795 €	1,077,316,409 €
Difference	116,629,614 €	

TABLE 7 – REMOVING THE EFFECT OF INFLATION

	2000	2017
Average health care cost per patient	18,859 €	32,355 €
Average productivity costs due to morbidity per patient	43,306 €	42,903 €
Average productivity costs due to mortality per patient	41,250 €	24,261 €
TOTAL COSTS PER PATIENT	103,414 €	99,518 €
Difference in cost per patient	-3,896 €	

TABLE 8 – REMOVING THE EFFECT OF INFLATION AND OF POPULATION GROWTH

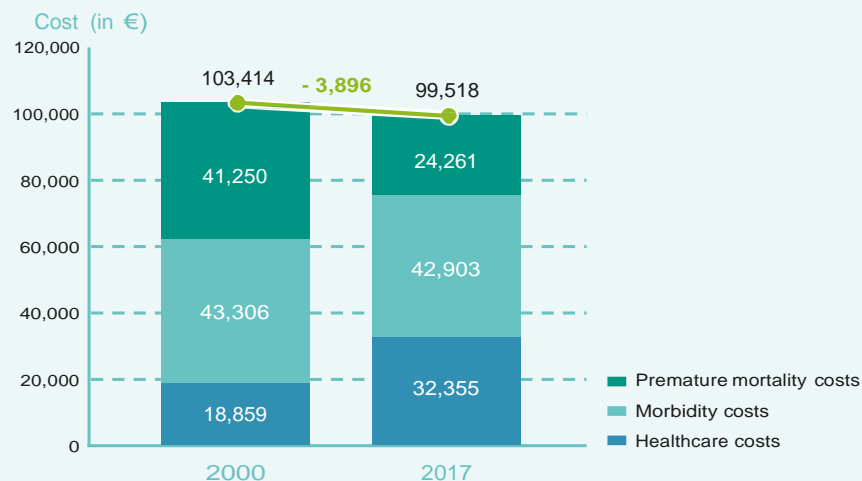


FIGURE 14 – EVOLUTION OF TOTAL COSTS OF BREAST CANCER IN BELGIUM, 2000-2017 (Source: own calculations)

Methodology

We evaluated the demographic and epidemiological data based on Belgian information sources such as the Belgian statistics office⁴⁵ and the Cancer Registry. We calculated changes in patient numbers by disease stage and by age.

Survival rates were calculated over a period of 10 years based on the study by Vondeling⁴⁶ and extrapolated with Belgian Life Table data and standardized mortality ratios for breast cancer patients in comparison to the general population. We calculated a Hazard Ratio representing changes in overall survival between 2000 and 2017, to assess the impact of earlier detection, improved surgery and new medicines. These data allowed calculating the additional life years gained per patient of 1.86 years in 2017 in comparison with 2000.

45 Statbel, 2019

46 G.T. Vondeling, et al. Burden of early, advanced and metastatic breast cancer in The Netherlands, BMC Cancer, 2018

Total healthcare costs were based on data by Broeckx⁴⁷ and pharmaceutical expenditure was calculated by a study by Blumen⁴⁸. The total direct health-care cost has increased with 223 million €. Adjusting for the higher number of patients and inflation leads to an increased direct health care cost of 13,496 € per patient.

Productivity losses, including premature mortality cost were calculated by age-group, taking into account a recent study by the Christian Sick Fund on return-to-work for breast cancer patients by stage. Based on these data, we made the calculated assumption that 10% more patients were back at work in 2017 versus 2000.

The total cost of productivity losses due to morbidity in 2000 was around 254 million € versus 464 million €

47 Broeckx et al. The European Journal of Health Economics, 2011

48 Helen Blumen, Kathryn Fitch, Vincent Polkus. Comparison of Treatment Costs for Breast Cancer, by Tumor Stage and Type of Service. Am Health Drug Benefits. 2016;9(1):23-32

in 2017, and the total cost of mortality was 243 million € in 2000 versus 262 million € in 2017. When adjusting the data for inflation, the difference per patient is 17,392 € less productivity loss per patient in 2017.

In conclusion

In breast cancer, significant improvements have been made in the past decades.

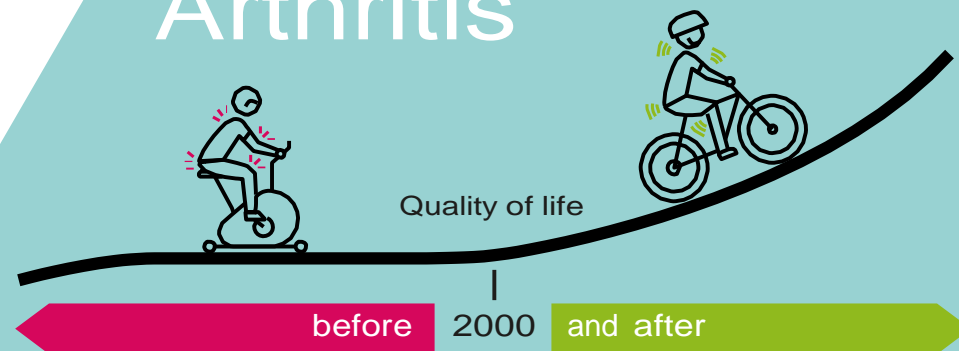
Many new technological innovations at the surgical and pharmaceutical level, together with a heightened awareness for early symptoms, have led to increased overall survival.

The cost of pharmaceutical expenditure has increased over the years, in parallel with their precision and effectiveness, also resulting in better quality of life and re-integration in the work environment.

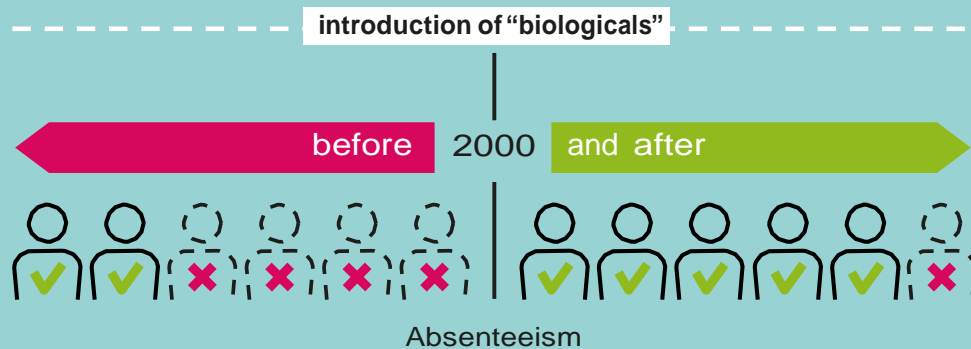
The value of pharmaceutical treatment for

Rheumatoid Arthritis

- The introduction of a new generation of innovative medicines - the “biologicals” - around the year 2000 significantly **improved the lives of patients** suffering from moderate to severe Rheumatoid Arthritis. They are now able to **lead close to normal lives** - socially and professionally - whereas previously they lived with pain, swellings, stiffness, reduced mobility or worse.



- The new generation medicines result in **less absenteeism** and account for **4,000 € in productivity gains on average per year per patient** treated with biologicals. For Belgium that represents a **total productivity gain of 16.5 million € per year**.



Despite the increase of the health investments, at the level of society, the innovations have led to cost-savings.

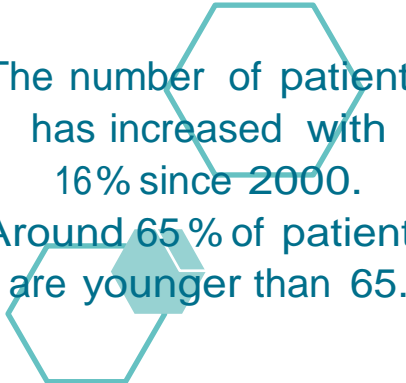
Rheumatoid Arthritis

The introduction of biologicals: a medical game changer with labour productivity benefits.

The challenges for patients

Rheumatoid Arthritis (RA) is a progressive debilitating disease affecting and ultimately destroying the joints if left untreated. Symptoms range from stiffness and swollen joints in the early stage to complete loss of joint functioning, leading over time to irreversible joint destruction, reduced mobility, disability and increased mortality. Patients are in constant pain, and become increasingly limited in their mobility, often first of the fingers and hands, then other joints in the extremities are affected. Compared with the general population, health-related quality of life in rheumatoid arthritis patients is still enormously impaired.⁴⁹

Rheumatoid arthritis can impact patients' productivity even during the very early phase of the disease. The time for the disease to develop may range from 4.5 to 22 year, from early onset until 50 % probability of being permanently work disabled⁵⁰.



The number of patients has increased with 16% since 2000. Around 65% of patients are younger than 65.

The disease in Belgium

In Belgium around 57,000 patients are diagnosed with rheumatoid arthritis and treated with different pharmaceutical regimens. The number of patients has increased with 16% since 2000⁵¹. Around 65 % of patients are younger than 65⁵². Around 20 % or 11,350⁵³ patients are treated with biologicals. Non-biological pharmaceutical treatments in Belgium cost 335-625 € per patient per year, biological treatments cost on average 9,000 € per patient per year in 2016⁵⁴. It should be noted that prices of TNF- α inhibitors have substantially decreased in recent years.

49 Gerhold K, Richter A, Schneider M et al. Health-related quality of life in patients with long-standing rheumatoid arthritis in the era of biologicals: data from the German biologics register RABBIT. *Rheumatology* 2015;54:1858-1866

50 Burton W, Morrison A, Mclean R, Ruderman E. Systematic review of studies of productivity loss due to rheumatoid arthritis. *Occupational Medicine* 2006; 56:18-27

51 Institute for Health Metrics & Evaluation, 2019

52 Marc Pomp : "Arbeidsbaten en Uitgespaarde Zorgkosten door Innovatieve Geneesmiddelen", 2016

53 TARDIS Database, 2019

54 RIZIV – MORSE Report, 2018– data 2016.

The medical value of new medicines

Today, treatment is mostly pharmaceutical with surgical joint replacement in fewer cases in the end stage.

The introduction of biologicals around 2000 was an innovative game changer for the treatment of rheumatoid arthritis, especially for moderate to severe cases. Previously, rheumatoid arthritis was treated with symptom alleviation (mainly painkillers), anti-inflammatory medicines and joint replacement surgery in the last stage. A new type of treatment was launched in the last decades, the biologicals^{55,56}. In contrast to earlier treatments, biologicals are active on the cause of the disease: they have a significant effect on the immune system and change the body's inflammatory response. The new biologic treatments have been shown to be extremely effective not only in reducing signs and symptoms of the disease, but

also in halting or slowing down the underlying joint destruction, and even improve cardiovascular events and mortality. Great gains have been achieved in improving quality of life, resulting in halving productivity losses due to the disease, and shifting inpatient care to pharmaceutical treatment.

Patients who receive biological treatments for rheumatoid arthritis no longer suffer or suffer considerably less from inflammation at the joints.

55 Disease Modifying Anti-Rheumatic Drugs (DMARD): TNF- α inhibitors (infliximab, etanercept, adalimumab, golimumab, certolizumab, pegol); T cell co-stimulatory blocker (abatacept); anti-IL-6 receptor (tocilizumab); anti-CD20 (rituximab), JAK-inhibitors such as baricitinib, tofacitinib and upadacitinib and the targeted synthetic drug tofacitinib

56 David S. Pisetsky: Advances in the Treatment of Rheumatoid Arthritis, NCMJ vol. 78, 2018

The treatment generally stops the destruction of cartilage and bones. Days that are otherwise spent trying to control or live with pain, swellings, stiffness, reduced mobility or worse, can now be spent leading close to normal lives – socially and professionally – for many patients. Patient testimonials and studies show that this patient population gains about 50 % in quality of life on average. Although sometimes difficult to measure exactly, indicators such as reduction of hospital days, days missed at work, unemployment, self-reporting score systems such as the Health Assessment Questionnaire or clinical reporting based on the Disease Activity Score demonstrate huge improvements after administration of biologicals.

The health economic value of new medicines

The total cost of rheumatoid arthritis for patients and society includes direct medical costs, direct non-medical costs, informal care and production losses. Costs vary considerably according to the disease stage, age, comorbidities and treatment options. The introduction of biologicals has significantly increased the total cost of the treatment, but since several of these treatments have now lost their exclusivity, the expenditures no longer increase. International studies among patients who use biological treatments have demonstrated a slight reduction in hospital stays and hospital duration, and less need for physiotherapy. The number of doctor's visits remained relatively unchanged⁵⁷. This increase in treatment costs for

57 Huscher D, et al. Ann Rheum Dis 2015 "Evolution of cost structures in rheumatoid arthritis over the past decade

rheumatoid arthritis over the last decade was associated with lower hospitalisation rates, better functional status and a lower incidence of work disability, offsetting a large proportion of risen drug costs.

Work disability occurs in 40 % of people in early rheumatoid arthritis and in 60 % of people in longstanding rheumatoid arthritis of more than three years⁵⁸.

The total cost of rheumatoid arthritis in Belgium can be estimated to be around 800 million € today⁵⁹. This amount includes both direct healthcare related costs and the indirect costs of lost labour productivity, informal carer cost, transportation and other costs.

The cost of presenteeism and reduced productivity at work is estimated at around 10,000 € per patient per year. Recent calculations in the Netherlands came to 8,452 € per patient per year .

60

In 2016, the total cost of the TNF- α inhibitors reached 251 million €, but these drugs are also indicated for the treatment of psoriasis and Crohn's disease. The current estimate is that biologicals used to treat patients with moderate to severe rheumatoid arthritis is 102 million €, or 9,000 € per patient.

58 Cindy Noben et al. "Economic evaluation of an intervention program with the aim to improve at-work productivity for workers with rheumatoid arthritis", Journal of Occupational Health, 2017

59 Gisela Kobelt, Frida Kasteng, Access To Innovative Treatments in Rheumatoid Arthritis, 2009. The figure of 618 million € for 2008 in Belgium was adapted for increased prevalence and inflation to the 2018 situation. When we extrapolate based on more recent health economic data in the Netherlands, the amount is around 790 million €.

60 M. Pomp : "Arbeidsbaten en uitgespaarde zorgkosten door innovatieve geneesmiddelen", 2015



Most health economic studies conducted at international level demonstrate that the productivity loss (work-disability, absenteeism and presenteeism) of patients suffering from rheumatoid arthritis is on average halved when treated with biologicals in comparison with non-biological treatments⁶¹. The productivity gain for patients treated with biologicals varies between 1,800 € and 6,000 € per person per year. Working with an average productive gain estimate of 4,000 € per year per patient, the total benefits can be calculated as follows. For the rheumatoid arthritis patients who receive biologicals, with 65 % of patients of working age⁶² and labour participation at 56 %⁶³, the productivity gain for Belgium is 16,525,600 € annually. The mandatory price reductions following the loss of exclusivity for biologicals decreases the treatment cost at the individual level, yet at the same time the number of patients using these biologicals is expected to increase.

In several European countries such as Germany and Sweden, statistics of the entire patient population with rheumatoid arthritis demonstrate an increase in work participation and a decrease in long term work disability in patients with moderate to severe rheumatoid arthritis, sometimes even up to 30 %⁶⁴, yet the Belgian statistics show a steady increase of the long term disability expenditure for this patient

61 I. Blankers et al. : "Zorgkosten en maatschappelijke baten van reumatherapieën", APE, 2012 & M. Pomp: "Arbeidsbaten en uitgespaarde zorgkosten door innovatieve geneesmiddelen", 2015

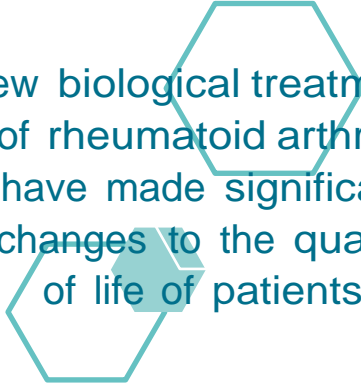
62 Marc Pomp : "Arbeidsbaten en Uitgespaarde Zorgkosten door Innovatieve Geneesmiddelen", 2016

63 Blankers (2012)

64 Almina Kalkan et al. Costs of rheumatoid arthritis during the period 1990-2010, Rheumatology Advance Access, 2013

group, with an increase from 26 million € in 2009 to 36 million in 2017 or an increase with 39 %⁶⁵, which may be partly due to the increase in the prevalence of the disease, but which could also be attributed to suboptimal treatment – not all patients receive biologicals – or ineffective professional re-integration opportunities.

In sum, new biological treatments of rheumatoid arthritis have made significant changes to the quality of life of patients, resulting in more active lives and less mortality. The increase of the cost of the new treatments have been partially offset by productivity gains at the level of the individual. Because of the increase in the prevalence of the disease and the wider use of biologics, this effect may not be seen at the level of the population.



New biological treatments
of rheumatoid arthritis
have made significant
changes to the quality
of life of patients.

65 RIZIV/INAMI, 2019

Methodology

We investigated the medical and health economic literature for Belgium and abroad on rheumatoid arthritis. We consulted official Belgian healthcare data sources such as RIZIV-INAMI and TARDIS. With regard to prevalence and use of biologicals we made use of Belgian data or data on Belgium. When no Belgian data were available in particular for labour related data, we extrapolated the data from comparable countries to the Belgian situation (Netherlands, Germany), based on Belgian incidence and prevalence numbers.

The data for the total cost of the disease include medical costs, drugs, non-medical costs, informal care and production losses (indirect costs). Non-medical costs include services (formal help in home, transportation) and products (aids/devices/adaptations/other).

The number of Belgian patients suffering from rheumatoid arthritis was taken from the Global Burden of Disease report 2017 (56,600) or an estimated 57,000 today. The number of patients treated with biologicals is known from the TARDIS database: 11,350 in May 2019.

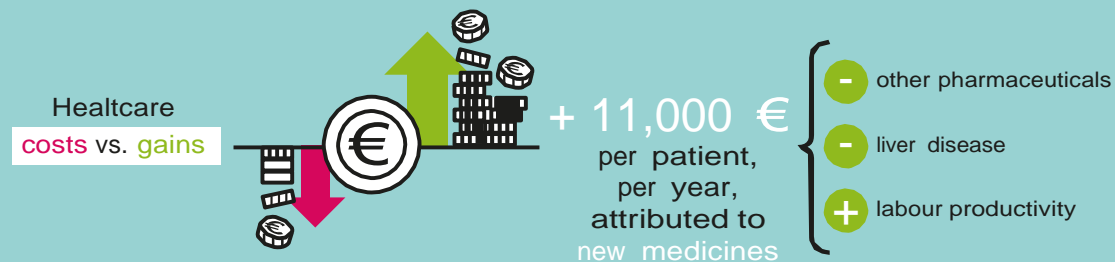
The value of pharmaceutical treatment for

Hepatitis C

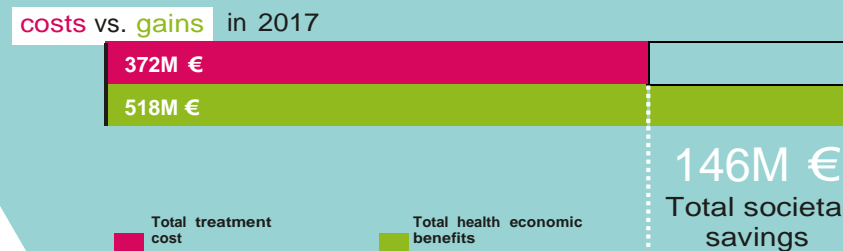
- Recently introduced **pharmaceutical treatments cure patients suffering from Hepatitis C**, and this for the first time in history. Today, treatments of eight weeks completely eliminate the virus from the body. With improved screening and today's cures, **hepatitis C will be a rare disease by 2036**.



- Health economic calculations show that the **total benefit per patient** treated with the new medicines amounts to **11,000 € for society**. The cost of the more effective treatment is off-set by a reduction of other pharmaceuticals, the **avoidance of complications** such as cirrhosis, liver cancer, liver transplants and results in **labour productivity gains**.



- For Belgium, the estimated expenditure on Hepatitis C pharmaceuticals was around **90 million € in 2017**. On a population basis, the **total cost to treat all chronic patients** in Belgium would be **372 million €**, entirely compensated by reduced medical care and **productivity gains and an economic benefit of 146 million € in addition**.

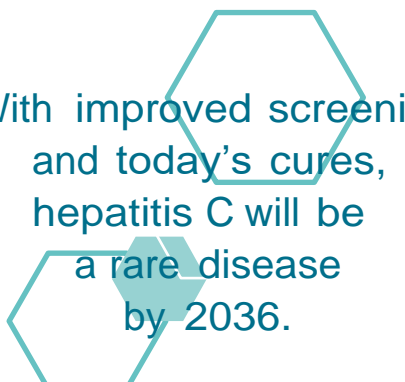


Hepatitis C

Treating a hidden disease with new pharmaceuticals, avoiding costs of previous treatments, making labour productivity gains.

The challenge for patients

Hepatitis C is a slow, and often hard to diagnose disease. Patients suffer initially from fatigue, and as the disease progresses, it can lead to liver complications, including liver cirrhosis and liver cancer. For many late stage patients, liver transplants are the only solution left. The initial symptoms are vague, but the fatigue may lead to depression, reduced work productivity and unemployment.



With improved screening and today's cures, hepatitis C will be a rare disease by 2036.

The disease in Belgium

The actual number of citizens infected with hepatitis C is unclear. A recent analysis estimates the number of patients with chronic hepatitis C infection to be around 13,300 people⁶⁶, and the total seroprevalent population at 24,400. The number of patients has decreased over the years because the cause of the disease has also decreased (blood transfusions, needle exchange programmes for drug users).

Medical treatments

In the past decade, a revolution has taken place in the treatment of hepatitis C. New drugs completely eliminate the virus from the body, and this in a much shorter treatment period of eight to twelve weeks.

Just seven years ago, the only available treatment was effective in just half of the patients and caused debilitating side effects. Today, a broad range of treatments with minimal side effects and cure rates approaching 100 percent are available for patients with all forms of the disease. Looking forward, researchers project that with improved screening and today's cures, hepatitis C will be a rare disease by 2036.

⁶⁶ Litzroth et al. BMC Public Health (2019) Low hepatitis C prevalence in Belgium: implications for treatment reimbursement and scale up"

Health economic benefits

With regard to the total cost calculation of the disease, we have to rely on data from abroad⁶⁷. The impact of the new treatment per patient is significant.

(list price between 24,000 and 30,000 €) is off-set by a reduction of other pharmaceuticals (22,000 €), the avoidance of complications such as cirrhosis (2,000 €), labour productivity gains (14,000 €), and the avoidance cost of further contamination⁶⁸ (1,000 €). The total benefit per patient would amount to a saving for society of 11,000 €. The estimated expenditure on hepatitis C pharmaceuticals is around 90 million € in 2017⁶⁹.

Furthermore, the average cost of liver transplant

transplants in Belgium are the result of a hepatitis C infection. If these could be avoided, it would result in another 6 million € of savings on an annual basis.

On a population basis, the total cost to treat all chronic patients would be 372 million €⁷¹, but the total eventual savings to society would be 146 million €.

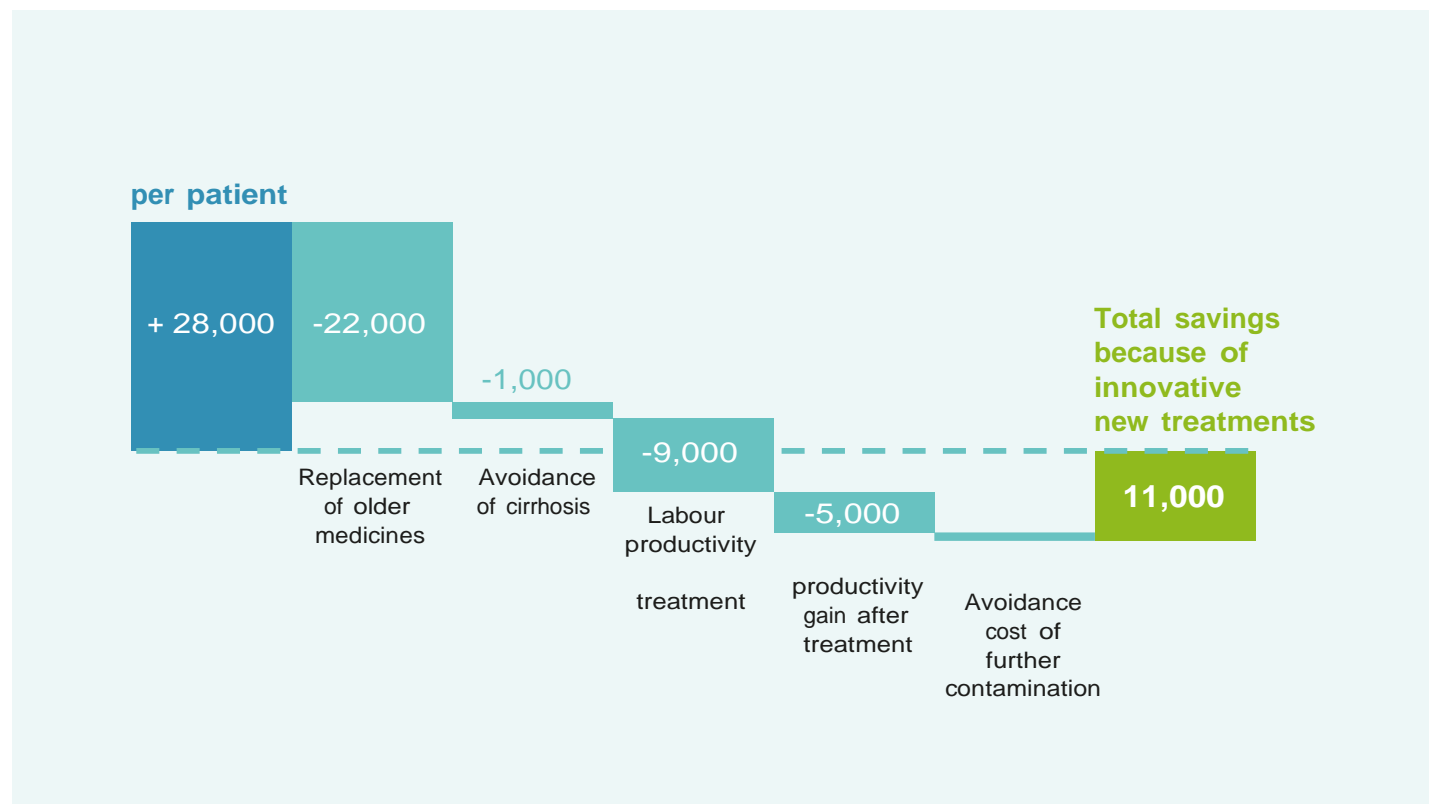


FIGURE 15 – COSTS AND SAVINGS BY AREA OF ACTIVITY AS A RESULT OF THE INTRODUCTION OF NEW HCV TREATMENTS, IN BELGIUM (Source: own calculations)

67 Marc Pomp: Kosten en Baten van de Nieuwe Hepatitis C Middelen, April 2019

68 The 'avoidance cost' calculates the value of decreased health-care costs of treating infected patients: by reducing the number of infected people, the chance of further contamination of other people diminishes.

69 RIZIV – MORSE Report, 2018


70 Ministry of Public Health, website <https://tct.fgov.be/webetct/etct-web/anonymous?lang=fr>

71 372 million € = 28,000 € for the new treatment times 13,000 patients.

Methodology

We did a literature review in Belgium^{72,73} and abroad^{74,75,76}, with additional data for Belgium received from pharmaceutical companies. The cost of HCV treatments has significantly increased with the arrival of treatments that offered a cure, then they dropped to the average of 24,000 to 30,000 € in 2017 for the newest treatments. In the methodology, we looked at the direct treatment cost of the newest medicines versus the treatment in 2014 (interferon + ribavirin +boceprevir or telaprevir), the cost of the treatment of liver cirrhosis, the labour productivity gain during and after treatment. Eventually, the avoidance of further contamination was also examined. We used the model developed in the Netherlands by Marc Pomp, because they offer the most recent data from a comparable neighbouring country. The value of long-term overall survival of the newest treatments were not incorporated due to a lack of available data.

The impact on liver cirrhosis includes liver cancer and liver transplants due to hepatitis C and were calculated based on a recent article in the United States⁷⁷. We used the lower variant of 2,000 € on average per patient. Liver cirrhosis occurs in around 15% of patients. Data from the Netherlands⁷⁸ show that all patients on the newest treatment keep working as before without any productivity loss, as compared to a low 40 % labour participation with the less recent treatments (interferon+ribavirin). We used the lower variant of the calculations to be on the conservative side.



Innovative hepatitis C medicines could amount to 11,000 euro of savings for society per patient treated.

72 Sciansano "JAARRAPPORT 2016: HEPATITIS C VIRUS"

73 P. Stärkel Et al. "The Disease Burden of Hepatitis C in Belgium: An update of a realistic disease control strategy", Acta Gastro-Enterologica Belgica, Vol. LXXVIII, April-June 2015

74 Papatheodoridis et al. Hepatitis C: The beginning of the end—key elements for successful European and national strategies to eliminate HCV in Europe, Journal of Viral Hepatitis, 2018

75 Younoussi et al. "Impact of eradicating hepatitis C virus on the work productivity of chronic hepatitis C (CH-C) patients: an economic model from five European countries", Journal of Viral Hepatitis, 2016

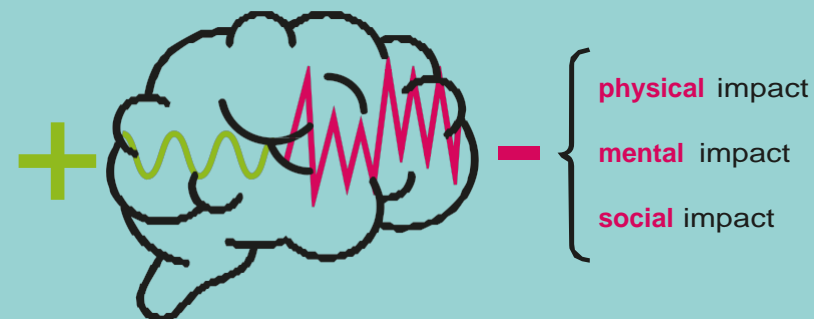
76 Jun Su et al. "The Impact of Hepatitis C Virus Infection on Work Absence, Productivity, and Healthcare Benefit Costs" Hepatology, 2010

77 Chhatwal, Jagpreet, et al. "Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States." Annals of internal medicine, 2015

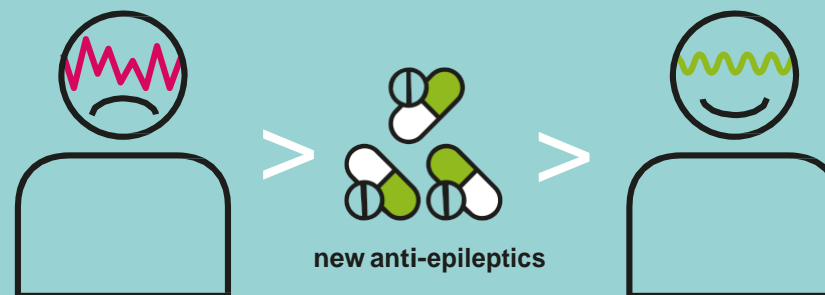
78 Marc Pomp, ibidem

The value of pharmaceutical treatment for Epilepsy

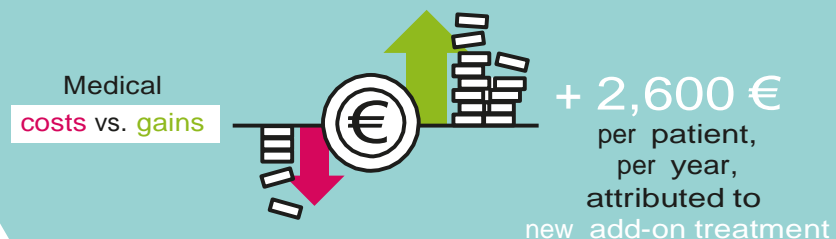
- Epilepsy is a **neurological disease** with a huge impact on the lives of patients. Uncontrolled seizures lead to a number of **physical, mental and social consequences** that negatively impact the lives of patients.



- New anti-epileptics have managed to achieve **seizure-free patients** when treated at early stages of the disease, but for many patients the unmet medical need remains high.



- A **new add-on treatment** increases the effectiveness of anti-epileptic treatments, **reducing the medical costs with 2,600 euro** per patient per year.



Epilepsy

Improved Quality of Life.

The challenges for patients

Epileptic seizures greatly impact a patient's quality of life by increasing the risk of injury and death, and it results in socioeconomic and educational disadvantages. This disorder is associated with substantial comorbidities including injury, drowning, depression, anxiety and high suicide rates. Uncontrolled seizures and the progression of epilepsy can compromise memory, cognition and endocrine function. Mortality rates, including "sudden unexplained death in epilepsy" are three times higher than in the general population. Worldwide, epilepsy inflicts the additional hidden burden of stigmatisation, prejudice, and discrimination against patients at home, in school, in the workplace and in the community. The emotional distress, social isolation, dependence on family, poor employment opportunities, and personal injury add to the suffering of these patients.

Epilepsy is the most common serious brain condition, affecting more than 50 million people worldwide and around 1 out of 150 to 200 people in Belgium



Epilepsy is often sub-optimally diagnosed and managed, even in developed countries and particularly among certain socioeconomic groups⁷⁹.

The disease in Belgium

Epilepsy is the most common serious brain condition, affecting more than 50 million people worldwide⁸⁰ and around 1 out of 150 to 200 people in Belgium. Even though the diagnosis of epilepsy can occur at any age, the incidence has a bimodal distribution with the highest risk in infants and older age groups. In most cases epilepsy will remain for the duration of the patients' lives, requiring them to manage their condition carefully⁸¹. Prognosis of epilepsy is mostly dependent on its aetiology⁸².

Focal epilepsy is most frequently caused by chronic subtle brain abnormalities, with epileptic seizures being the most prominent clinical symptomatology. Treatment commonly requires the long-term intake of anticonvulsive medicines, which might suppress seizure recurrence. The majority of patients with epilepsy do benefit from these drugs but a considerable number fail and thereby continue to experience seizures despite adequate treatment attempts.

The International League Against Epilepsy defines drug-resistant epilepsy as the failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom⁸³. Drug-resistant epilepsy is a progressive disease where the likelihood of achieving complete seizure control diminishes as the number of failed antiepileptic drug regimens increases. When patients with drug-resistant epilepsy have not been able to control their seizures despite treatment with 4 or more antiepileptic drug regimens, the likelihood

79 Ventola, 2014

80 WHO, 2018

81 Thijs et al. 2019

82 Semah, 1998

83 Kwan et al, 2010

of achieving complete seizure control with another antiepileptic drug regimen is further reduced to between 1 and 4 %⁸⁴. A population-based study conducted in Western Europe estimated that 22.5 % of all patients have drug-resistant epilepsy⁸⁵. Another population-based study of active and drug-resistant epilepsy in northern Italy, concluded that the frequency of drug-resistant epilepsy was 15.6% of all active epilepsies and 10.5% of incident cases⁸⁶.

In patients with drug-resistant epilepsy, seizures have a negative impact on mortality, psychosocial functioning, and Quality of Life across multiple domains. These patients are prone to falls and injuries, cannot drive, can rarely live independently, feel isolated and stigmatized, have difficulty finding and keeping a job, and often depend on disability benefits⁸⁷. In addition, patients with drug-resistant epilepsy with focal-onset seizures (FOS) and complex partial (recently renamed “focal unaware”) or tonic-clonic seizures have a 5 to 10 times higher mortality rate⁸⁸, including a risk of sudden unexpected death in epilepsy⁸⁹ when compared to the general population. An estimated 1% of patients diagnosed with drug-resistant epilepsy die every year of sudden unexpected death in epilepsy, and 12% die within 2 years of the diagnosis from all causes⁹⁰.

84 Chen et al, 2018; Schiller and Najjar, 2008; Mohanraj and Brodie, 2006

85 Picot et al, 2008

86 Giussani et al, 2016

87 Azuma and Akechi, 2014; Taylor et al, 2001; Baker et al, 1997

88 Fazel et al, 2013; Hesdorffer and Tomson, 2013; Holst et al, 2013; Sperling, 2004

89 Devinsky, 2011

90 Jehi, 2016

The burden of comorbidities in patients with drug-resistant epilepsy is high and includes depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis⁹¹. Moreover, patients with epilepsy and comorbid conditions generally report poorer health related Quality of Life outcomes than the general population, the extent of which is positively correlated with increasing seizure frequency and adverse drug reactions. Comorbid conditions may be exacerbated by antiepileptic drug therapy, and in turn may increase the economic burden of disease.

The medical value of new medicines

Antiseizure drugs, also referred to as anticonvulsants or antiepileptic drugs are meant to prevent the occurrence of seizures in patients with epilepsy. The majority of patients (70 %) with new-onset epilepsy achieve seizure freedom when treated with one or more antiepileptic drugs or combination therapy. Although first-generation AEDs are familiar and often effective, many patients treated with them experience refractory seizures and intolerable adverse events. Since 1993, many second-generation antiepileptic drugs have been introduced, each differing in efficacy spectrum, mechanism of action, pharmacokinetics, and safety and tolerability profiles. Many of these newer agents have proven to be safer, better tolerated, and easier to use, with broader spectrums and reduced drug interactions than the first-generation drugs⁹². However, despite these advances, overall efficacy and advantages in treating drug-resistant epilepsy is

91 Strzelczyk et al, 2017

92 Toledo et al. 2016, Ventola 2014

modest. Patients with drug resistant epilepsy do still have a number of options available, including epilepsy surgery, Vagus Nervus Stimulation, deep brain stimulation, and ketogenic diet.

The health economic value

Overall, epilepsy accounts for 0.75 % of the global burden of disease and economic implications in terms of healthcare needs, premature death and lost work productivity are significant⁹³. In Belgium, the estimated cost of epilepsy for an estimated number of 53,116 patients was 296 million €⁹⁴. However, there is a need for better data collection to assess the full impact of the cost of epilepsy on the healthcare budget, including costs not related to treatment.

One study on the value of an innovative add-on treatment demonstrates that the number of seizures is reduced from 52.9 to 47.8 per patient per year, resulting in a net savings of 2,618€ per patient per year⁹⁵. This new treatment is only used for around 10% of the patient population for whom three other drugs have failed to generate a satisfactory response.

The actual impact on work-related benefits and value has not been measured so far.

93 WHO, 2015

94 Gustavsson et al., 2011

95 Steven Simoens, Liesbet De Naeyer and Peter Dedeken: Cost Effectiveness of Lacosamide in the Adjunctive Treatment of Patients with Refractory Focal Epilepsy in Belgium in CNS Drugs, 2012.

A systematic review of cost-of-illness studies suggested that antiepileptic drugs are becoming the main driver of direct healthcare costs of epilepsy⁹⁶. However, several studies show that these treatments are in fact cost-effective. Lacosamide⁹⁷ as an adjunctive treatment of patients with difficult-to-treat epilepsy results in a decrease of total direct costs, fewer number of seizures and an increase in Quality Adjusted Life Years when compared to standard treatment.

Time horizon 12 months	Standard AED plus lacosamide	Standard AED plus lacosamide	Difference
Total direct healthcare costs	35,940 €	33,322 €	-2,618 €
Number of seizures	52.9	47.8	-5.1
Number of QALYs	0.604	0.638	0.034

TABLE 9

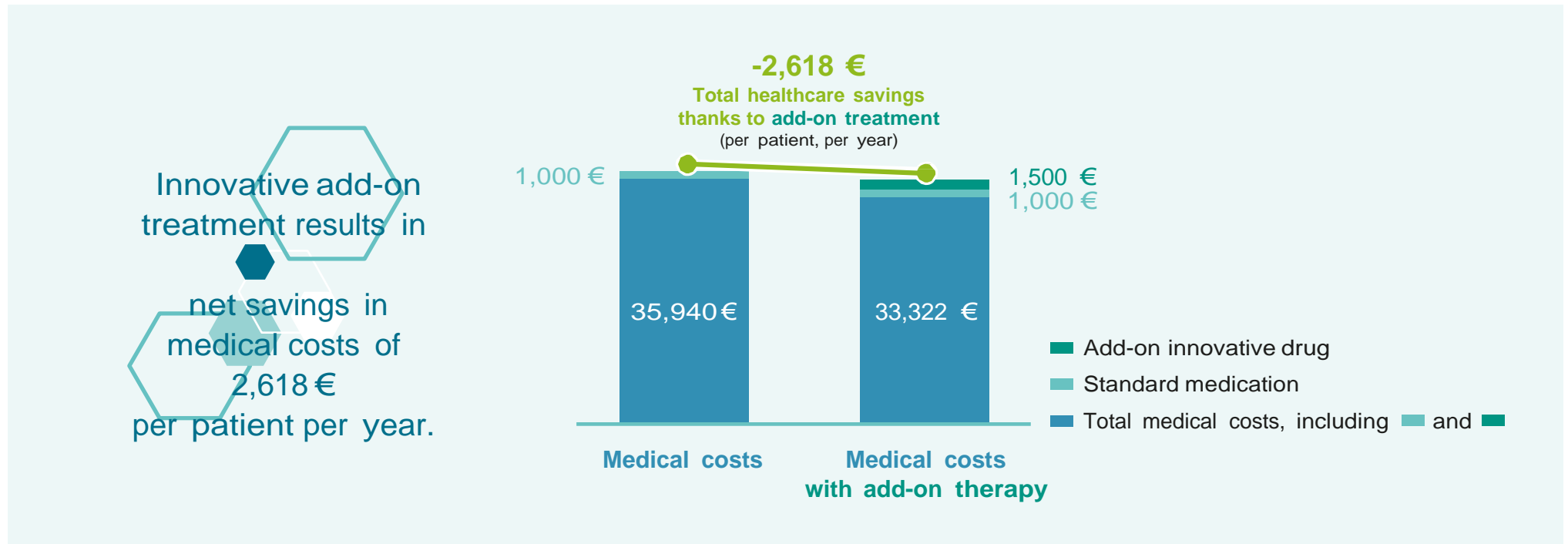


FIGURE 16 – TOTAL HEALTHCARE SAVINGS PER PATIENT AND PER YEAR BY USING ADD-ON EPILEPTIC TREATMENT, IN BELGIUM (Source: own calculations, 2019)

96 Strzelczyk et al., 2008

97 Steven Simoens, Liesbet De Naeyer and Peter Dedeken: Cost Effectiveness of Lacosamide in the Adjunctive Treatment of Patients with Refractory Focal Epilepsy in Belgium in CNS Drugs, 2012

The value of pharmaceutical treatment for Depression

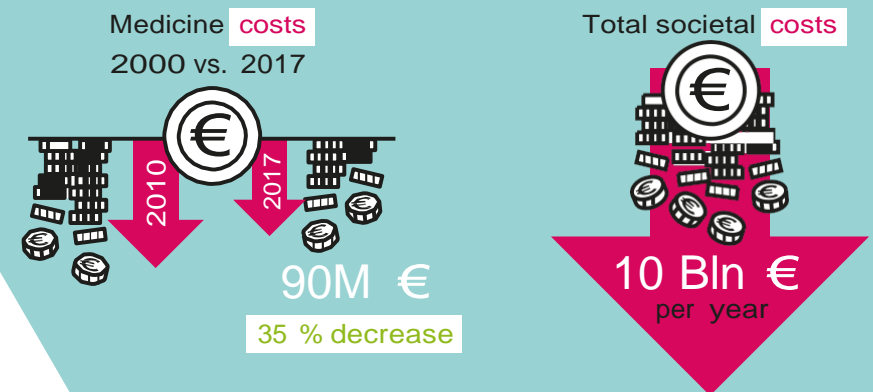
- Major depressive disorder (MDD) is an **imposing challenge** for the individual patient and for society at large. At least **5 to 7 %** of the Belgian population will eventually encounter a major depressive disorder. According to studies, **half of these people won't ever find the way to professional care** due to various reasons. A (major) depressive disorder might lead to a severe deterioration of the ability to function properly in a private, social and professional context.



- International studies demonstrate the impact of effective anti-depressant approaches in the work environment, with presenteeism potentially decreasing with 50 % and **absenteeism even with 75 %**.



- The total cost of anti-depressants in Belgium was **90 million euro** (in 2017) which is **a decrease with 35 %** since 2010. The total societal costs for Belgium have risen up to an incredible amount of no less than **10 billion euro**. From a medical, societal and economic point of view, there currently are systemic inefficiencies that prevent patients from getting better. Therefore, pharmaceuticals are an important facet in the broader health ecosystem.



Depression

Anti-depressant pharmaceuticals have significantly increased the quality of life for most patients, but depression continues to have an enormous impact on society.

The challenges for patients

Major depressive disorder is a very debilitating disease, affecting the self-image of the patient and his or her outlook on life. The disease is characterized by a depressed mood, a loss of interest or pleasure, feelings of worthlessness or guilt, diminished ability to think or concentrate and so on. Some patients are even confronted with intrusive and recurrent thoughts of death or suicide. Sadly, around 70 % of people who commit suicide were reported to suffer from depression⁹⁸, or the equivalent of 4 suicides per day in Belgium. The Belgian suicide rate remains the highest in Europe. Depression also has an impact on the patient's physical well-being: sleeplessness, low energy and fatigue, cardiovascular problems, inflammation, sexual and gastro-intestinal problems, losing or gaining unintended weight and so on. The disease has an important and often devastating impact on relationships, family life, broader social environment and professional activities.

98 Marquet, Bartelds, Kerkhof, Schellevis, & van der Zee, 2005

The disease in Belgium

At this very moment, around 320,000 citizens in Belgium are diagnosed with major depressive disorder⁹⁹. The annual prevalence of the disease fluctuates between 5 and 7% of the Belgian population¹⁰⁰, which is twice the current diagnostic percentage. Around 10% of men and 20% of women will sooner or later suffer a period of depression in their lives¹⁰¹. On average, depressive symptoms start between the age of 30 and 40 years, the most productive phase of a human life. People who suffer from major depressive disorder see their life expectancy diminished with ten years¹⁰².

Within the major depressive disorder population, up to one third¹⁰³ of depressive patients do not respond adequately to the current treatment options.

99 Institute for Health Metrics & Evaluation, 2019 and KCE, 2014

100 Bruffaerts et al., 2008

101 Vlaamse Vereniging voor Geestelijke Gezondheid, 2019

102 Walker, 2015 and WHO, 2018.

103 IQVIA, 2019

Scientific literature refers to these patients as being 'treatment resistant'. Treatment resistant depression is most commonly defined as a failure to respond to two separate trials of different antidepressants of adequate dose and duration in the current major depressive disorder episode. This significant subset of major depressive disorder patients has an increased mortality risk of 35%, due to a seven times higher suicide risk and higher recurrence of comorbidities such as cardiovascular diseases. Successive lines of anti-depressant pharmaceuticals do not achieve meaningful effects and lower the likelihood for a patient of going into remission and getting better. Patients with treatment resistant depression tend to relapse more frequently and severely and thus face a higher hospital readmission risk with longer stays and increased costs.

Depression is one of the greatest public health challenges in the European Region as measured by prevalence, burden of disease and disability (disability-adjusted life years – DALYs)¹⁰⁴. The World Health Organization calls out major depressive disorder as the most important contributor to worldwide disability¹⁰⁵. Considering Belgium, depression is the fourth largest cause of lost life years¹⁰⁶ and is the leading cause of long-term absence from work. In 2019, more than 65.000 people diagnosed with depression received an invalidity allowance¹⁰⁷. According to an analysis by the Independent Sick Fund, 27 % of the patients remain on long term sick leave for three years, and 20 % even more than five years¹⁰⁸. The societal and economic burden of major depressive disorder is mainly located within the area of indirect costs.

Moreover, when looking at treatment resistant patients, their depressive episodes tend to last longer with enhanced chances for relapse. This results in more emergency admissions and hospitalisation and longer absence from the workplace. A treatment resistant depression doubles both direct and indirect costs for society¹⁰⁹. Besides the obvious impact on the quality of life for the individual patient, the immense toll for our country is crystal clear.

104 Smith. A world of depression. Nature 2014; 515:181.

105 Walker, 2015 and WHO, 2018.

106 Evaluation, 2017

107 RIZIV, 2019.

108 Onafhankelijke Ziekenfondsen. Welke invloed heeft depressie van actieve personen op de kostprijs van geneeskundige verzorging en uitkeringen. 28 sept 2015

109 Amos et al., 2018; Ivanova et al., 2010; Mrazek et al., 2014.

The medical value of new medicines

There is not one single cause of depression. Rather, depressive episodes originate from various reasons, including faulty mood regulation by the brain, genetic vulnerability, stressful life events or medical problems. A multifactorial approach is necessary, especially since the medical pathophysiology of depression is (still) poorly understood.

When facing a mild depression, psychotherapy should be the first line of treatment without instantly referring patients to a medicated treatment¹¹⁰. But, for most of the patients suffering from a moderate to severe depressive disorder, the introduction of pharmaceuticals in the treatment pathway is necessary to regain control over one's life and prevent future setbacks and accompanied costs. Diminishing anxiety, improving sleeping patterns and reconnecting with positive thoughts are some of the encouraging effects. The medication increases quality of life and allows better social functioning when administered correctly. Current treatment guidelines recommend that anti-depressant medication should be administered for at least four to nine months, but in practice almost four out of ten patients adhere to their treatment for less than three months¹¹¹, resulting in suboptimal care.

Remarkably, almost all anti-depressants are available in generic form and the current pipeline for innovative treatments is rather limited. From a scientific and medical point of view, new treatments based on innovative mechanisms haven't been introduced the past fifty years.

110 Domus Medica, 2014

111 KCE – Performance of the Belgian Health System, 2019

However, there are two noteworthy trends that demand attention. First, the enormous amount of people taking anti-depressant medicines: 1,2 million patients or almost 15% of the entire adult population. This exceeds by far the average major depressive disorder prevalence of the country and is not in line with the guidelines of Belgian Society of General Practitioners, Domus Medica, stating that for mild depression pharmaceuticals should be avoided if possible. Second, there is no annual decline in indirect costs for society. The significant share of treatment resistant patients is undoubtedly co-responsible for this tendency. When both are taken into account it is clear that, at least for a substantial segment of patients, there exists a suboptimal and inaccurate form of mental healthcare. These systemic inefficiencies result in many additional costs for society as a whole.

These trends suggest that there is a certain need to revise patient pathways and align them towards more integrated healthcare. While for many diseases early administration of the right pharmaceuticals may lead to cost-savings in the rest of the system, it appears that in the field of depression the answer is more ambiguous. Pharmaceuticals will be part of the answer, hopefully fueled by new innovations in the domain of depression. Targeting patients in the right way at the right time will become utmost essential if we want to truly tackle this severe disease and its burden.

The health economic value of new medicines

In 2016, the total cost of anti-depressants was 90 million €¹¹², a decrease with 35 % since 2010¹¹³. The main reason of course being the introduction of many generics and the complete absence of innovation the past fifty years.

The total hospitalisation cost for major depressive disorder is estimated at 280 million €¹¹⁴ with an average of 11,984 € per hospitalised patient. Despite reforms trying to deinstitutionalise patient pathways, the number of psychiatric hospitalisation days remains high. The estimated total treatment cost of depression in Belgium is estimated to be around 1 billion €. With only 6,1% public spending on mental healthcare, it is somewhat surprising that mental health receives such a low funding priority. The benchmark lays at 10%, based on an advice on the Global Ministerial Mental Health Summit of OESO in 2018.

Patients suffering from major depressive disorder have a five times higher absenteeism rate than people who don't suffer from major depressive disorders. International studies clearly demonstrated the impact of anti-depressants in the work environment, with presenteeism potentially decreasing with 50 % and absenteeism even with 75 %¹¹⁵.

112 RIZIV – MORSE Report, 2018

113 Christelijke Mutualiteiten, De Top 10 van de therapeutische klassen, 2018

114 TCT Database, 2019

115 Manish K. Jha: "Early Improvement in Work Productivity Predicts Future Clinical Course in Depressed Outpatients: Findings From the CO-MED Trial", American Journal of Psychiatry, 2016

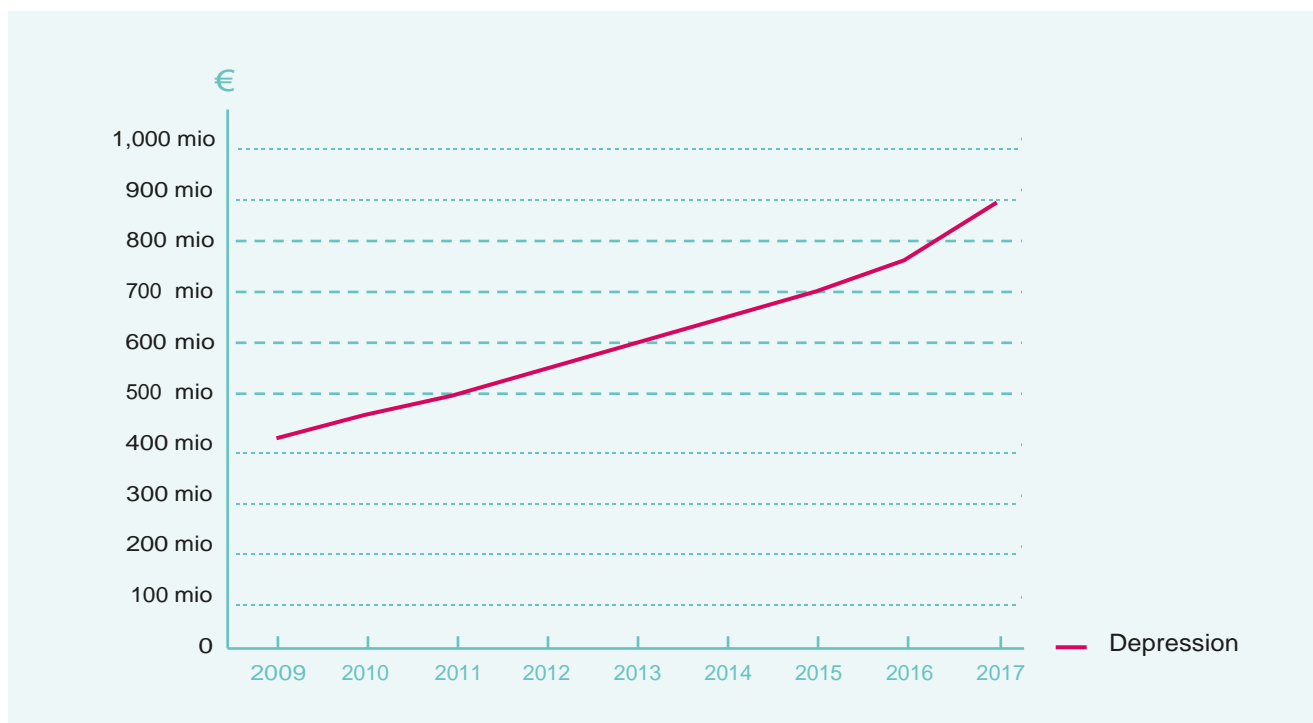


FIGURE 17 – TOTAL COST OF LONG TERM DISABILITY IN BELGIUM (RIZIV/INAMI, 2019)

A Canadian study demonstrated that patients who received medical treatment increased their work productivity with 2.5 times for moderately depressed patients and 7 times for severely depressed patients¹¹⁶. However, these data were obtained in an environment with less social protection than in Belgium, making it hard to extrapolate the data to our context.

116 Centre for Addiction and Mental Health, Treatment of depression can increase work productivity, 2012

Comparable data in a similar context of the Belgian reimbursement system were not found. However, keeping the existing treatment gaps in our Belgian healthcare landscape in mind, there is hope of still making giant leaps forward.

According to the figures of RIZIV/INAMI, the cost of long-term sick leave for citizens suffering from depression has significantly increased over the years, reaching an annual cost of 900 million € in 2017 compared to 400 million € in 2009¹¹⁷. Around 19% of all people on long term sick leave suffer from depression¹¹⁸.

The total cost of the decline in labor productivity through absenteeism due to major depressive disorder is estimated at 6.8 billion €¹¹⁹. In the Netherlands, the cost of depression on presenteeism, lower productivity whilst being at work, is estimated to be 4 billion €. Through extrapolation based on MDD prevalence, the Belgian presenteeism costs would amount to 3.1 billion €.

The OECD estimates the total burden of mental health in Belgium to be 20.7 billion € of which 5.4 billion € on direct healthcare costs, 5.8 billion on social benefits, and 9.4 billion on indirect labor related costs¹²⁰. This high cost impact corresponds with 5,1% of the Belgian gross domestic product.

The cost of suicide as a result of major depression is hard to assess. Estimates vary significantly. Around 1,900 Belgians commit suicide every year. The estimated cost of this is 1 billion €, of which 70 %¹²¹ can be ascribed to depression, or 700 million €.

117 RIZIV/INAMI, 2019

118 Sciensano, Gezondheidsenquête 2013

119 OECD, Health At A Glance 2018 – extrapolating total mental health costs vs depression (242 bln vs 176 bln) to Belgium (9.4 to 6.8 bln)

120 OECD, Health At A Glance 2018

121 Marquet, Bartelds, Kerkhof, Schellevis, & van der Zee, 2005

The following table contains all depression-related costs:

Cost type	Cost item	in million €
Healthcare costs	Hospitalisation	300
	Ambulant care	610
	Pharmaceuticals	90
	TOTAL	1,000
Indirect costs	Long term sick leave	900
	Decline in labor productivity of which presenteeism: 3,100	6,800
	Suicide	700
	TOTAL	8,400
TOTAL COST		9,400

TABLE 10 – TOTAL MEDICAL AND NON-MEDICAL COSTS OF DEPRESSION IN BELGIUM (RIZIV/INAMI, 2019)

According to a recent study by the World Health Organization, “every US\$ 1 invested in scaling up treatment for depression and anxiety leads to a return of US\$ 4 in better health and ability to work”¹²² or even a five-fold return according to other analyses.

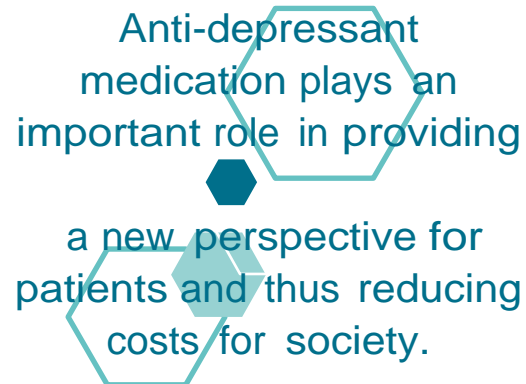
122 The Lancet Psychiatry, 2016

The noteworthy increase in quality of life and productivity¹²³ should drive the debate on how limited funds should be allocated as efficiently as possible.

123 Chisholm et al., 2016; WHO, 2019

Methodology

We reviewed all the existing data in Belgium^{124,125} and we complemented those by data from international studies¹²⁶ and from comparable countries. For instance, the total treatment costs for major depression in the Netherlands are estimated at 1.6 billion €¹²⁷. When we extrapolate this figure to the Belgian population, the amount is around 1 billion €.



Anti-depressant medication plays an important role in providing a new perspective for patients and thus reducing costs for society.



In conclusion

Pharmaceuticals have demonstrated great value in treating major depressive disorder. Anti-depressant medication plays an important role in providing a new perspective for patients and thus reducing costs for society.

The societal burden of major depressive disorder is still immense and will be one of the great medical (and political) challenges for the next decades. Despite a high unmet need and increasing public awareness, mental health care remains a low funding priority. Additionally, suboptimal pathways seem to lead to suboptimal care. Some patients take pharmaceuticals when they shouldn't, while other patients receive yet another anti-depressant treatment with limited effects. Proper adherence is still a delicate challenge.

124 Kenniscentrum : "Majeure Depressie (bij Volwassenen) : Doeltrouffendheid op de Lange Termijn van Psychotherapie, op zichzelf of in Combinatie met Antidepressiva", 2014

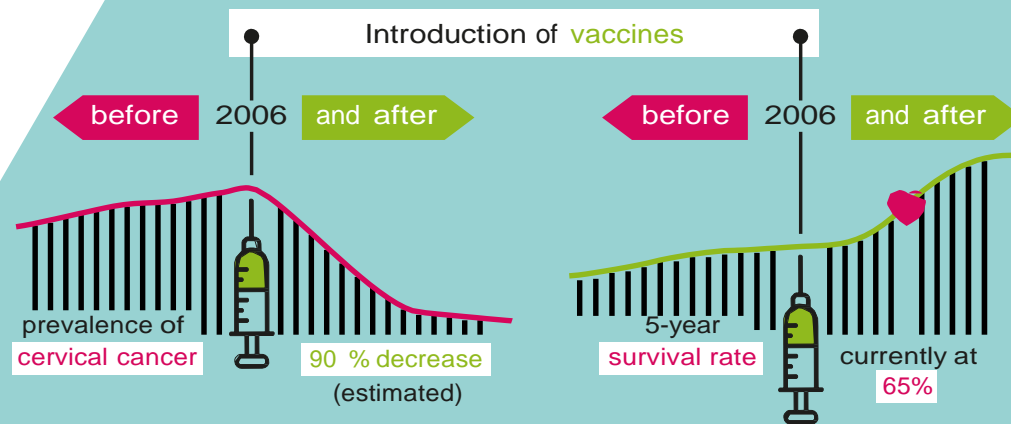
125 Lieven Annemans, Cost-Effectiveness Analysis of Pharmaceutical Treatment Options in the First-Line Management of Major Depressive Disorder in Belgium, PharmacoEconomics, 2014

126 Anders Gustavsson et al. Costs of Disorders of the Brain in Europe, European Neuropsychopharmacology (2011)

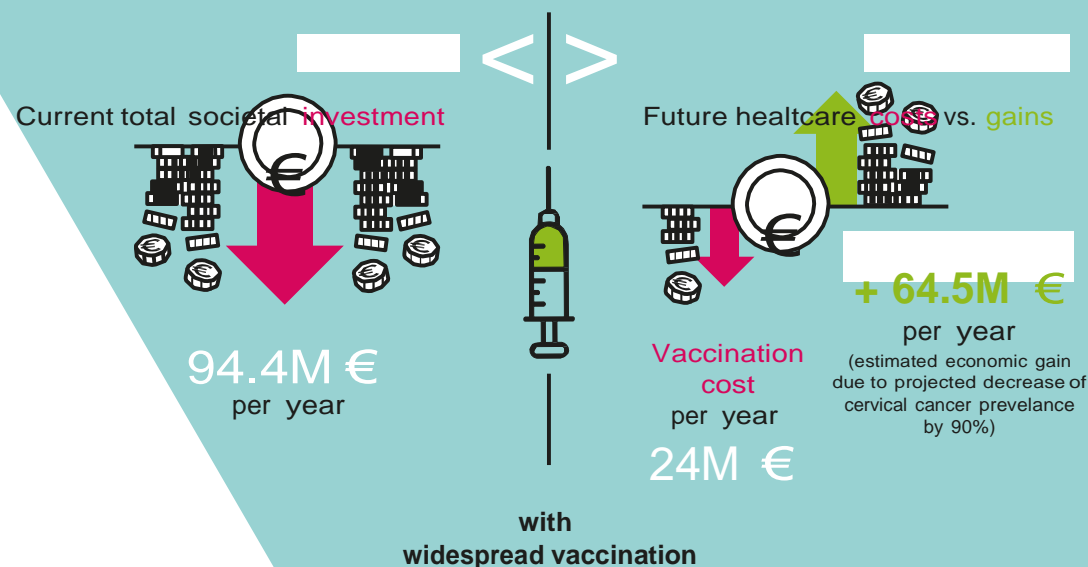
127 RIVM – Kosten en Ziekten Database 2013.

The value of pharmaceutical treatment for Cervical Cancer

- The introduction of vaccines for the prevention of cervical cancer in Belgium in 2006 will cause **the prevalence of the disease to drop by an estimated 90%**.
With current 5-year overall **survival rates at 65%** and a prevalence of 3000 to 4000 patients in Belgium, the vaccines save thousands of lives.



- The current total cost for society of cervical cancer in Belgium is calculated at **94.4 million € per year**, including inpatient and outpatient treatment cost, morbidity, premature mortality and long-term sick leave costs.
The annual cost for vaccination is 24 million €. With a projected reduction of cervical cancer patients by 90%, **economic benefits** may reach **69.5 million €** per annum.



Cervical Cancer

Eradicating a disease and the associated costs.

The challenges for patients

Cervical cancer typically develops from precancerous changes over a 10 to 20-year period. Diagnosis is typically done by cervical screening followed by a biopsy. Medical imaging then determines whether or not the cancer has spread. In Belgium, the 5-year overall survival of cervical cancer treatment is around 65 %¹²⁸.

The treatment consists of radiotherapy, surgical intervention (including trachelectomy and hysterectomy) and chemotherapy. Cervical cancer usually occurs around the age of 50, even if the original infection may have occurred much earlier.

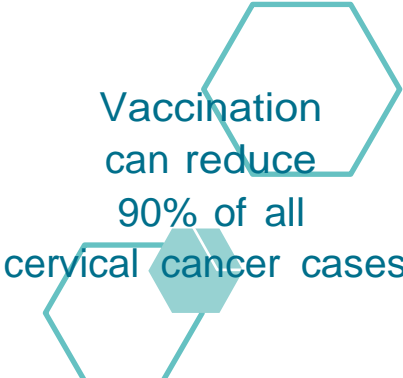
Screening for cervical cancer is organised in most European countries, including in Belgium. Early stage cancers are difficult to detect, and vaginal bleeding is usually one of the first symptoms for late stage cancers, together with pelvic pain or pain during intercourse.

Cervical cancer in Belgium

Compared to other cancers, cervical cancer has a relatively low prevalence, and it has decreased in Belgium from 4530 patients in 2000 to 3700 patients in 2017. Infection by the human papillomavirus is the main cause of this cancer, and the virus is transmitted through sexual intercourse. Three vaccines were introduced in Belgium relatively recently, in 2006 and 2007, with additional indications for use among men in 2011 (to prevent anal cancer, oropharyngeal cancer and genital warts).

The value of medical innovation

Vaccines are – from the patient perspective – a special category of pharmaceutical products: they do not cure a condition but prevent patients from developing the disease. With the cervical cancer vaccine current estimates are that 90 % of cervical cancer cases can be avoided by vaccination. The discomfort of two or three injections for all women clearly outweighs the tragic suffering of women who would have developed cervical cancer.



Vaccination
can reduce
90% of all
cervical cancer cases.

128 CONCORD Study, The Lancet, 2018

The health economic value of vaccination

The total inpatient and outpatient costs of the treatment of cervical cancer is around 24 million € on an annual basis (detection, treatment, and follow-up of HPV-related precancers and cancers), and the total indirect cost (reduced labour productivity and premature mortality) is around 70 million €¹²⁹. The total cost of the vaccination in Belgium is around 24 million € per year¹³⁰.

The recent results from a Scottish study demonstrate that after twenty years of systematic vaccination, the number of cervical cancer cases has dropped with 90 %¹³¹. In order to achieve this success, vaccination programmes need to have high levels of coverage. In Flanders, coverage was 91 % in 2016, but less so in Brussels and Wallonia with 36 and 50 % of girls being vaccinated¹³². In the assumption of a full coverage of the female population in the future, the potential savings for the economy can be significant. The current total direct and indirect cost is estimated at 94,4 million €/year.

129 Ellinor Östenson, The economic burden of human papilloma-virus-related precancers and cancers in Sweden, PLOS Online, 2017 – Swedish data were extrapolated to the Belgian situation

130 KCE – HPV Vaccinatie ter Preventie van Baarmoederhalskanker in België: Health Technology Assessment, 2007

131 Tim Palmer et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study, BMJ 2019

132 KCE -Cost-Effectiveness Analysis of HPV Vaccination of Boys in Belgium, 2019

	(x 1,000 €)	Current costs without vaccination	Estimated total costs per year after full vaccination (reduction of 90 %)
Direct cost		24,784	2,478
Inpatient		15,242	
Outpatient		9,542	
Indirect cost		69,689	6,968
Premature mortality		43,764	
Short term labour productivity cost		3,886	
Long term labour productivity cost		12,404	
Early retirement		9,635	
TOTAL		94,473	9,446
Cost of vaccination			24,000
TOTAL COST		94,473	33,446

TABLE 11 – TOTAL DIRECT AND INDIRECT VALUE OF VACCINATION IN BELGIUM

Vaccination will reduce this cost with 90 % to 9,5 million €/year but will come at a cost of 24 million €/year itself. The net difference between the current investment and vaccination will ultimately result in a saving of 61 million €/year.

It is expected that by 2028 Australia will be the first country to eradicate cervical cancer because of their vaccination programme. The investments will have a lasting economic benefit for society.

In the current model, the costs of cancer screening are not included, as the expectation is that it needs to continue alongside the vaccination programme to be completely effective.

Methodology

We first reviewed the Belgian data on the disease and its treatments^{133,134,135,136}, which was either relatively fragmented or outdated. The most detailed study on the labour-costs and premature mortality cost was made in Sweden for all HPV-related cancers. We extrapolated the Swedish data to the Belgian population taking the incidence of the disease into account and adjusting for the economic context. We took the assumption that the disease-related absences from work were the same. All indirects costs were based on the human capital method. The annual cost calculated in Sweden of 41,000 € labour productivity per year, was reduced to a more conservative Belgian cost of 35,000 € per year. The total was adjusted for inflation.

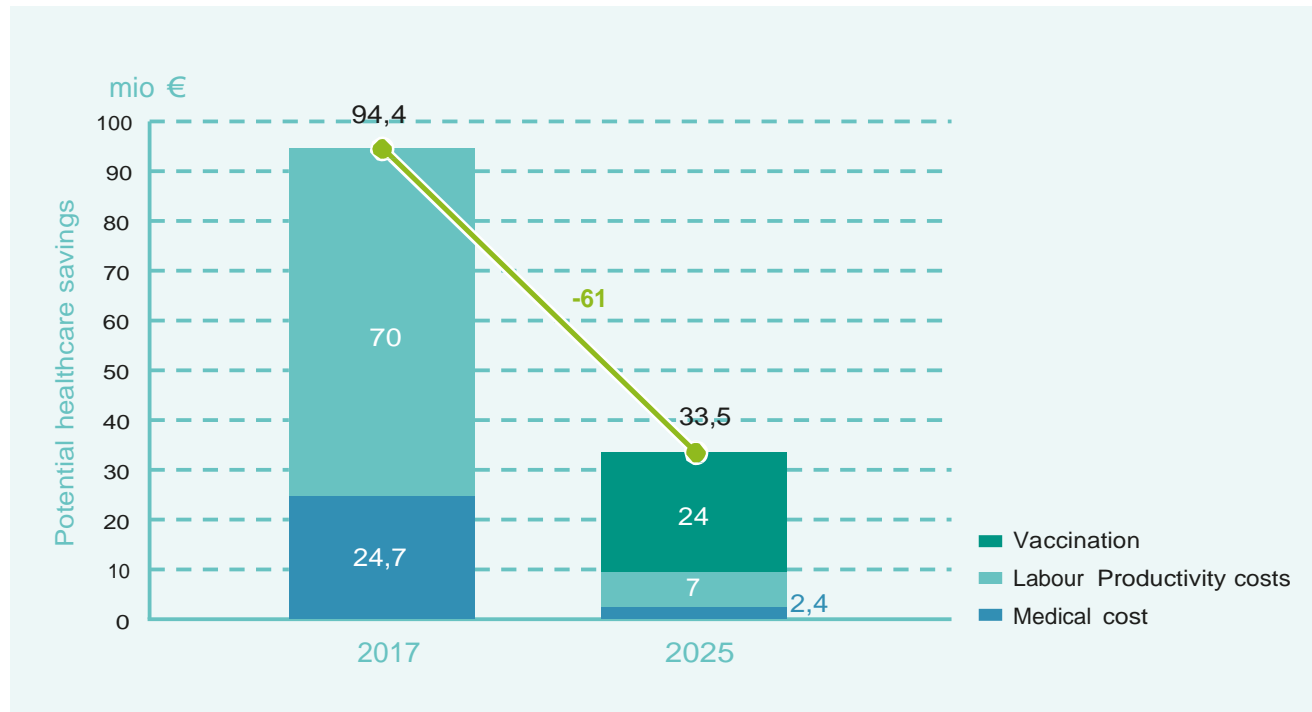


FIGURE 18 – THE POTENTIAL HEALTHCARE SAVINGS THANKS TO POPULATION-WIDE HPV VACCINATION AGAINST CERVICAL CANCER IN BELGIUM (in mio €)

- 133 KCE – HPV Vaccinatie ter Preventie van Baarmoederhalskanker in België: Health Technology Assessment, 2007
- 134 Corinne Vandermeulen, MD, PhD, HPV VACCINATION PROGRAM IN BELGIUM – LESSONS LEARNT AND THE WAY FORWARD, HPV Vaccination Board, Unpublished slide deck, 2018
- 135 Nadia Demarteau, Georges Van Kriekinghe, Philippe Simon Incremental cost-effectiveness evaluation of vaccinating girls against cervical cancer pre- and post-sexual debut in Belgium, Vaccine 31, 2013
- 136 Maaike Fobelets & Lore Pil, De kosteneffectiviteit van het bevolkingsonderzoek naar baarmoederhalskanker in Vlaanderen: gezondheidseconomische evaluatie, VUB & UZ Gent, 2012.

Conclusion

We have seen that our healthcare investments of the last decades have been increasing, yet they have resulted in major progress in many diseases.

- In **breast cancer**, better overall survival rates and return-to-work strategies, partially due to pharmaceutical innovation, have led to significant value, off-setting the increasing treatment costs.
- We have seen a similar but less outspoken result in the use of biologicals for the treatment of **rheumatoid arthritis**.
- In **hepatitis C**, the results are even stronger, with better treatment resulting in actual cost savings to the entire system.
- In **epilepsy**, new anti-epileptics have resulted in significantly less seizures, and a new add-on therapy reduces the overall cost of treatment. Broader effects on labour productivity have not yet been assessed.

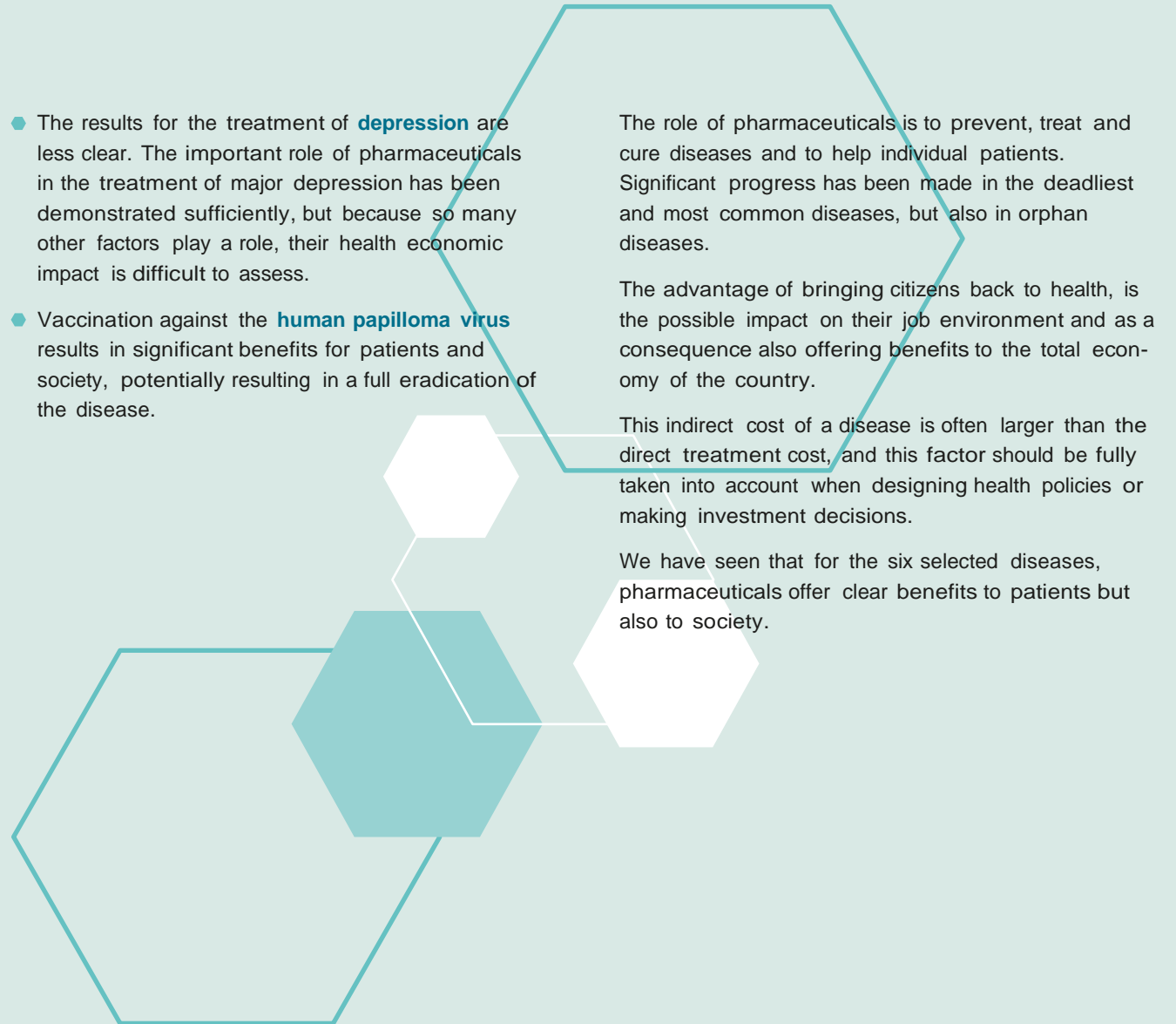
- The results for the treatment of **depression** are less clear. The important role of pharmaceuticals in the treatment of major depression has been demonstrated sufficiently, but because so many other factors play a role, their health economic impact is difficult to assess.
- Vaccination against the **human papilloma virus** results in significant benefits for patients and society, potentially resulting in a full eradication of the disease.

The role of pharmaceuticals is to prevent, treat and cure diseases and to help individual patients. Significant progress has been made in the deadliest and most common diseases, but also in orphan diseases.

The advantage of bringing citizens back to health, is the possible impact on their job environment and as a consequence also offering benefits to the total economy of the country.

This indirect cost of a disease is often larger than the direct treatment cost, and this factor should be fully taken into account when designing health policies or making investment decisions.

We have seen that for the six selected diseases, pharmaceuticals offer clear benefits to patients but also to society.



The authors of the report

Stefan Gijssels acted as the project coordinator. He founded Sebio Public Affairs in 2016 as an independent health policy consultancy, working for public health authorities, patient organisations and industry. Stefan is currently the pro bono Chief Executive Officer of Digestive Cancers Europe, the umbrella organisation of national associations representing patients with digestive cancers. He is a member of the European Commission's Innovative Partnership for Action Against Cancer (iPAAC), the Co-chairman of the Patient Advisory Committee of the European Cancer Organisation (ECCO), the Co-chairman of the Scientific Committee of Sharing Progress in Cancer Care (SPCC). Stefan worked many years in major public policy consultancies and was Vice-President Communications & Public Affairs at Janssen Europe, Middle East & Africa for fifteen years. He has a master's degree in Literature & Philosophy from Leuven University, Belgium.

Sara Dewilde, PhD is a statistician and health economist, with 17 years of experience as a senior consultant. She obtained her PhD at the faculty of Medicine, Department of Public Health, at the University of Ghent on "New insights in costs and quality of life after stroke. Implications for health care policy." She is an occasional member of expert panels for government agencies in Belgium. Sarah started her career in 1990 at the HIVA (Higher Institute for Labour Studies) in Leuven, after which she worked as a Senior Research Associate at MedTap in London, and later at United Biosource in Brussels. She created her own consultancy in 2008. She holds Master degree in Economics from KULeuven, a Master in Statistics from KUL, and Master in Health Economics from the University of York (UK).

Lay-out and graphic design

The lay-out and graphic design were developed by **Magelaan** (www.magelaan.be): Ben Arickx is responsible for the design and Joke Ongena for the project management.

Dr. Christian De La Porte, PhD offers consultancy and advice in healthcare: organisation, knowledge transfer, representation, management. He is member of the transparency committee of the Federal Medicines Agency, representing the Health, Science & Technology Group. From 1996 till 2015 he was Director Medical Affairs and Public Affairs at Janssen Belgium, responsible for the relationships with the Belgian regulatory and political authorities. In this capacity, he was responsible for Medical Affairs, Clinical Research, Regulatory Affairs, Pricing & Reimbursement and Health Economics, and Pharmacovigilance. From 1982 to 1996 he was neurosurgeon at the University Hospital of Antwerp, and In 1994, he was nominated Extraordinary Professor Neurosurgery at the University of Antwerp. He is Doctor of Medicine, Surgery and Obstetrics, magna cum laude, from Antwerp University, with specialisation in neurosurgery.

Luc De Coster has over 30 years of experience in corporate communication in complex multi-stakeholder environments. For the last 10 years he has been active as an independant communications consultant serving customers in the healthcare sector, supporting and managing corporate communication and public affairs projects. He specialises in translating complex health topics into clear language and narratives. Luc De Coster has a master's degree in Linguistics and Literature from Leuven University, Belgium.



Twenty years
of high societal impact



The Value of Medicines
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