Review

The offset effect of pharmaceutical innovation: A review study

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Abstract

It is well known that pharmaceutical innovation has improved the health and quality of life of patients. It is however sometimes forgotten that new drugs also have the potential of improving the efficiency and the sustainability of the healthcare system. The objective of this review is to shed light on the magnitude of the offset effect that drugs may have in the realm of the healthcare system and for society as a whole. A narrative literature review was carried out. This review demonstrated that a growing body of literature has tried to measure the magnitude of the offset effect associated with pharmaceutical innovation, both at the aggregate level and for different diseases. There is evidence that the aggregate use of new drugs can generate net savings to the healthcare system and to society, as they may release both healthcare and non-healthcare resources for alternative uses. A high degree of heterogeneity in the magnitude of the effect has been found across different pathologies and different types of drugs.

Keywords

Pharmaceutical innovation, drugs, offset effect, savings, costs, economic impact

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Introduction

Pharmaceutical innovation (PI) has contributed to substantial improvements in the health and quality of life of people in modern societies. Indeed, drug innovation has not only allowed for the cure and the prevention of diseases but has also helped to reduce symptoms, increase life expectancy, accelerate recovery time, reduce adverse effects and negative interaction with other drugs, and find new routes of administration that are more comfortable for the patient.[1]

PI implies a complex scientific and technological process associated with long research periods and high financial investment. It is estimated that developing a new molecule may cost up to USD 2700 million and take up to 15 years of research.[2] Nevertheless, despite the cost that PI may represent to healthcare systems, an offset effect is often produced on other costs, which may lead to significant global savings in the total costs associated with the new drug's introduction to the market.

Hence, beyond their clinical impact, drugs often have additional benefits on the healthcare system and society in general. Indeed, by preventing or treating more effectively different illnesses, PI, as many healthcare interventions, may reduce several direct and indirect costs associated with the disease and therefore become a very useful tool for optimal resource utilization.[3]

In the health economics literature, direct costs refer to both direct healthcare costs (DHC) and direct non-healthcare costs (DNHC). The former refers to the use of resources that is strictly related to illness management,

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such as medication costs, medical visits, hospitalizations and laboratory tests. The latter refers, among other costs, to the value of the care that the patient receives at home, in the form of formal caregiving (i.e. when care is provided by paid professionals) or of informal caregiving (i.e. when care is provided by relatives and friends). Indirect costs are defined as those that include permanent and temporary labour productivity losses caused by the illness, which represent a loss of wealth for society.

The objective of this study is to shed light on the potential that drugs have to generate savings for the healthcare system and for society in general. Throughout the article, we provide different illustrative examples, both in concrete therapeutic areas and in general, that were found through a narrative literature review.

Methods

A narrative literature review was carried out using Medline (PubMed) and Google Scholar. The search included full-text articles and documents published until September 2017 that analysed or measured the offset effect of drugs. Only documents written in English or Spanish were included. The search terms used included 'offset effect', 'savings', 'costs', 'productivity' and 'drugs'. References of the included studies were also examined. The search was complemented with grey literature and documents of relevant organizations, such as government departments.

Results

Savings in DHC

By improving the patients' health status, the use of new drugs is often translated into a decrease in the utilization of healthcare resources, such as hospitalizations, medical visits, and concomitant medication, leading to financial savings, or releasing resources for other uses within the healthcare system. A growing body of literature has tried to measure the magnitude of this *offset effect* that is associated with PI, both at the aggregate level and for different concrete pathologies.

Lichtenberg was one of the first authors who quantified the offset effect of drugs at the general level, leading to the notion that PI's economic and social contribution could significantly exceed its costs. In a study published in 2001, the author estimated that if a 15-year-old drug was to be replaced by a 5.5-year-old one, per capita pharmaceutical expenditure in the United States would increase by USD 18 on average, while non-pharmaceutical expenditure would decrease by USD 72, leading to a savings ratio of almost 4 times the cost of the introduction of the newest drug.[4] He later updated his analysis for the years 1997 and 1998 and obtained a savings ratio of 7.2 in the entire population and 8.3 for the population covered by Medicare, basically due to savings in hospitalizations.[5] In another study, Lichtenberg[6] estimated that, even under a most conservative cost methodology, the net cost of new drugs was negative, as they would generate savings in hospitalization and nursing home costs equivalent to 2.4 times the cost of the drugs.

Other authors later found that the magnitude of the aggregate offset effect of new drugs in the United States actually amounted to intermediate values. For example, Civan and Koksal focused on Medicare- and Medicaid-covered population and obtained a net per capita savings ratio of 5.5 when using newer drugs (actually, when the average age of the drug being assessed was reduced in 1 year). However, the authors also found significant heterogeneity among different drug classes.[7] In another study, Santerre (2011) obtained estimations for the United States and six other Organisation for Economic Co-operation and Development (OECD) countries and found larger offset effects in the long run than in the short run. Indeed, according to the author, the marginal effect of commercializing a new medication was equivalent to net per capita savings in healthcare costs of USD 5.9 in the short run and USD 11.4 in the long run. These findings implied aggregated savings at the national level of USD 1800 million and USD 3400 million in the short and long run, respectively.[8]

Public organizations like the Congressional Budget Office have also validated the offset effect of PI in the United States. Their study highlighted that, in the case of the Medicare-covered population, a 1% increase in the number of annual prescriptions translated into a 0.2% decrease in annual healthcare costs.[9] Based on this finding and on the volume of prescriptions filled in 2014, Lakdawalla et al.[10] estimated that each additional prescription led to savings of USD 94 in DHC in that same year.

The existence of an offset effect associated with PI has also been confirmed in other countries. For example, in Canada, Crémieux et al.[11] estimated that each additional dollar invested in new drugs yields an average reduction of CAD 4.7 in hospital expenditure and of CAD 1.5 in global healthcare expenditures. In Spain, an increase of 10% in hospital drugs expenditure between 1995 and 2005 led to net per capita savings of EUR 1.1 in total hospital expenditures.[12]

Savings by therapeutic area

Many studies have analysed the economic impact that drugs have in specific therapeutic areas, finding that in those cases, PI also often translates into net savings in costs. In what follows, we summarize some examples found in the literature.

In the oncology area, drugs that were commercialized between 1980 and 1997 in Canada avoided 1.7 million

hospitalization days per year, which translated into savings that approximated CAD 4700 million (base year 2012), a significantly higher amount than the annual expenditure in cancer drugs in that country.[13] Likewise, in the United States, a study estimated that cancer treatments launched between 1989 and 2005 avoided 1.55 million hospitalization days in 2013, thereby reducing hospitalization costs by USD 4800 million in that same year.[14] There is also evidence that oncological PI increased healthcare cost savings in Australia.[15]

Multiple examples of offset effects have also been found in the cardiovascular area. In OECD countries, pharmaceutical expenditure in cardiovascular illnesses increased by USD 24 per capita between 1995 and 2004, which in turn led to estimated hospitalization savings of USD 89 per capita.[16] A study by the British National Health Service estimated that treating atrial fibrillation patients with anticoagulant therapy was associated with net per capita savings of GBP 412 in the short run and GBP 2408 throughout the patient's lifetime. This same study found additional savings for society of GBP 94 and GBP 1379 in the short and long run, respectively.[17] Likewise, according to a clinical trial conducted in the United States, the use of statins has led to a 27% reduction in other healthcare costs related to illness management, thereby allowing for an 11% reduction in total cardiovascular healthcare costs.[18] Another study found that the use of antihypertensive medication was associated with a benefit–cost ratio of 6:1 in women and of 10:1 in men.[19]

Other examples can be found for other illnesses, such as depression, asthma and HIV/AIDS. In the United States, the total net healthcare cost per patient diagnosed with depression was reduced during the 1990s by 18%, mainly due to the decrease in hospitalization costs that was produced by innovations in drug treatment.[20] In Ireland, the use of new monoclonal antibodies in asthmatic patients led to a reduction in exacerbations and allowed for a decrease of 14.5% in net DHC.[21] Finally, studies have demonstrated that while the use of antiretroviral therapy has increased drug expenditure in patients with HIV/AIDS, it has also decreased other healthcare costs, leading to net savings of 10%.[22]

The power of vaccines. Vaccines are one of the most cost-effective public health interventions.[23] Their economic value has been studied from different angles,[24–26] with benefits that can be measured in terms of decreases in morbidity and mortality rates, savings for the healthcare system, gains in labour productivity and positive externalities in both the short and the long run.[27]

Traditional vaccines have generated important net savings for the healthcare system and for society. The eradication of smallpox is associated with savings in global costs of over USD 2000 million per year.[23] The net benefit of the polio vaccine in the United States has reached over 6 times its cost.[28] According to another study, each dollar invested in the United States in nine types of children vaccines led to savings of USD 13 in the short run, of which USD 10 corresponded to indirect costs.[25] In the long run, savings in social costs associated with vaccines for children could reach USD 27 for each dollar invested, of which USD 9 would correspond to savings for the healthcare system.[26] It has been estimated that, in low- and middle-income countries, children vaccination programmes generate a return of 44 times their cost (uncertainty range: 27–67) if all social and economic benefits in the long run are taken into account.[24]

Influenza vaccines have proved to be an efficient health intervention, especially in high-risk populations, such as the elderly, whose vaccination could avoid up to 39% of influenza- and pneumonia-related hospitalizations,[29] leading in turn to a benefit–cost ratio of over 1 in countries such as England and Wales.[30] A recent systematic review concluded that these vaccines were generally a cost-effective option in the European Union.[31]

The newest vaccines, such as those to prevent hepatitis and the human papilloma virus, came out of more complex research processes and are therefore more costly than older vaccines. However, they still have proved to be cost-effective under a EUR 30,000 per quality-adjusted life-year cost-effectiveness threshold.[32]

Adherence to treatment as a cost savings driver. A determinant driver for cost savings is the degree of adherence to treatment, as it does not only favour the treatment's success but it also reduces the risk of the patient suffering a relapse. The highest the degree of adherence to treatment, the higher the drug costs associated with it but the lower the total healthcare costs associated with medical visits, hospitalizations and emergency admissions.[33]

According to a recent systematic review that was carried out on 14 groups of illnesses, the economic cost of the lack of adherence to treatment ranged between USD 949 and USD 44,190 per year in the United States.[34] Another study found that each dollar invested in improving adherence to treatment led to net average savings in healthcare costs equivalent to USD 7.1 in diabetes, USD 5.1 in hypercholesterolemia and USD 4 in hypertension. According to this same study, a patient with high adherence level (80%–100%) would save the healthcare system an average of 29% of the costs in hypercholesterolemia, 27% in diabetes, 9% in heart failure and 7% in hypertension, compared to a patient with a medium adherence level (60%–79%)[35] (Figure 1). Yet, another study carried out in the United States has estimated that a higher adherence to treatment in the case

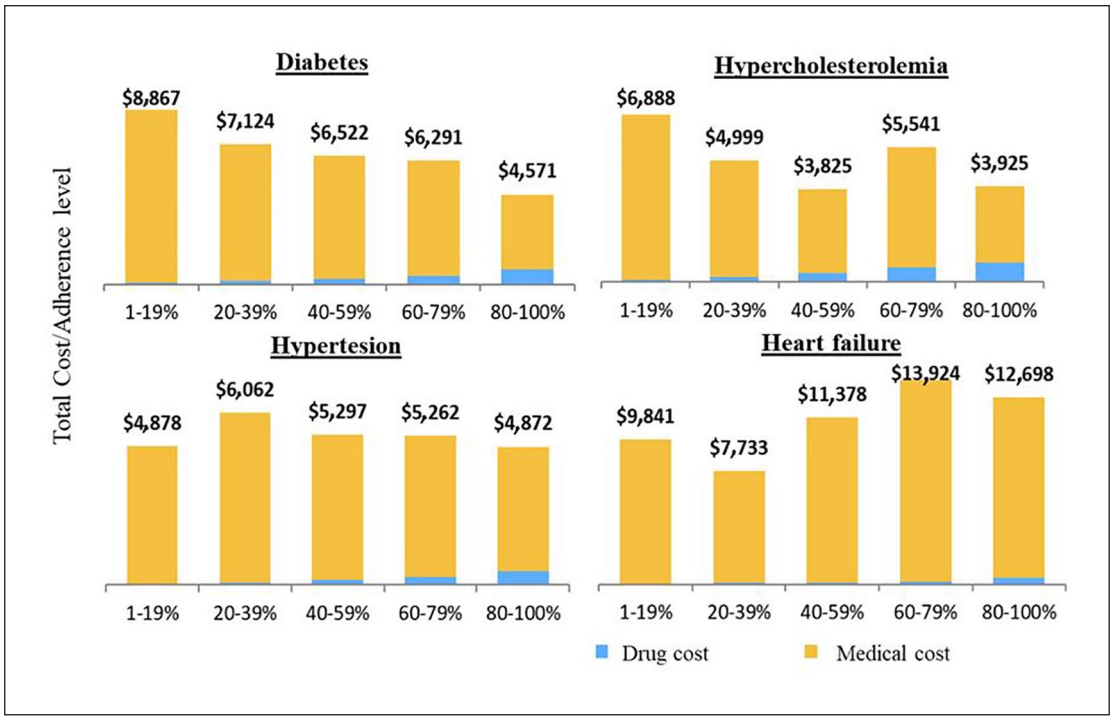

Figure 1. Costs related to four chronic illnesses, by degree of patients' adherence (%), the United States 1997–1999.
Source: Generated by the authors based on Sokol et al.[35]
This figure was created by Microsoft Office Excel.

of chronic illnesses like chronic obstructive pulmonary disease (COPD), diabetes and heart failure would reduce Medicare costs between 29% and 49%.[36]

In diabetes, in the context of an integrated disease management programme, a reduction from 8.2% to 7.7% in glycosylated haemoglobin has been associated with a 22% decrease in hospital admissions and a 34% decrease in the patient's average length of stay.[37] Other studies also confirmed that changes in the insulin administration route led to a higher adherence level, reduced hypoglycaemias and generated savings in the average DHC per patient.[38,39]

Savings in DNHC

As a consequence of illness, many patients have limited autonomy and therefore need personal caregivers, who may either be formal caregivers (professional health workers) or informal caregivers (family or friends). Medication may reduce many limitations patients have when performing daily activities and thereby reduce the amount of personal care they need. Even though literature on the economic impact that drugs may have on caregiving costs is scarce, some studies have been published on this topic.

Regarding informal care, a meta-analysis concluded that medical treatment for dementia reduced both the care burden (with a 0.27 difference in the care burden questionnaire) and the time dedicated to caregiving (a reduction between 25 and 58 minutes per day).[40] In psoriasis, new biologic medications reduced the average burden of care at home from 28 to 10 days in Italy, which in turn reduced missed days at work of caregivers from 8 to 2 days per year.[41]

In addition to easing the burden on caregivers, medications may promote efficiency and sustainability within the healthcare system by freeing up resources for other activities. For example, according to a Dutch study that analysed the effect on comprehensive care to patients in a group of 10 PIs that were commercialized between 1995 and 2007, these new drugs represented annual savings that were equivalent to employing 7200 healthcare professionals.[42]

Improvements in labour productivity

Clinical advancements produced by PI may in turn improve the patient's work capacity, which could be directly translated into a lower degree of absenteeism and presenteeism in the labour market. Thus, at the aggregate level, new medicines may contribute to the economic prosperity of a country by increasing its labour supply, the number of hours worked per person and the average productivity per hour, which will result in an improvement in total labour productivity for the whole society.

In Germany, it has been estimated that each new drug has avoided on average around 200 annual years of lost labour productivity due to early retirement and premature mortality. The cumulative gain in this country, in terms of

years of work produced between 1988 and 2004 thanks to new medicines, is estimated at around 10% of the labour loss for the year 2004.[43]

In some of his studies, Lichtenberg analysed the impact of PI on productivity. He estimated that each additional year of novelty of a drug would lead to a 1% savings in labour productivity losses. Also, according to the author's findings, reducing labour losses in 1 day would require an average cost in medicines of between USD 18 and USD 34. This is at least 4 times lower than the average daily wage in the United States (USD 140), which suggests that this investment in drugs would be convenient for society.[44] In a later study, Lichtenberg estimated the stock value of new drugs in terms of the increase they brought in labour productivity in between 2.3 and 8.1 times the investment they represented.[45]

A large amount of the studies in this field focus on specific pathologies. For example, it has been estimated that each dollar invested in medical treatment for depression in the Unites States during the 1990s decade spared USD 0.56 in labour productivity losses.[20] In Italy, among patients with moderate or severe psoriasis, biologic therapies have allowed a reduction of 71.4% in indirect costs associated with the disease.[41] In Germany, new drugs against rheumatoid arthritis have allowed indirect costs to decrease in 8% (from EUR 10,609 per patient in the year 2000 to EUR 9754 per patient in 2012).[46]

Adherence to treatment also improves productivity. For instance, adherent workers with diabetes, hypertension, dyslipidaemia, asthma or COPD reduced their absenteeism between 1.7 and 7.1 days per year and had work leaves between 1.1 and 5 days shorter than non-adherent workers.[47] Annual savings in indirect costs associated with adherence to treatments for asthma and COPD approximate USD 1700 per worker in the United States. In Spain, labour productivity losses significantly decrease when asthma/COPD is adequately controlled (from 22% of total costs when not controlled to 2.6% when adequately controlled).[48]

Discussions and conclusions

This narrative review of the literature has shed light on the value of PI. New drugs may not only improve population's health but also improve efficiency and sustainability within the healthcare system and society as a whole.

A string of literature indicates the existence of an offset effect of PI and suggests that investment in drugs often releases both healthcare and non-healthcare resources for alternative uses. When this is the case, allocation of resources in drugs procurement can be considered as an investment rather than expenditure. As stated before, numerous examples prove that new drugs can not only be cost-effective but can also generate net savings (Table 1).

Lichtenberg was one of the first and most proliferous authors in this field. However, myriad other authors have subsequently refined and clarified initial findings. In general, published studies have used two different approaches to analyse offset effects: the aggregate level and the disease level. Both approaches have found significant offset effects of PI, even if a high degree of heterogeneity in the magnitude of the effect has been found across different pathologies and different types of drugs.[7] Most studies focused on the United States, where the offset effect of drugs has helped to design changes in Medicare's coverage policies.

The appropriateness of the methodology used to reach any study's results and conclusions is of the highest importance. There is a string of literature that questions the methods and the evidence used when eliciting published results. These authors sustain that the use of new drugs does not necessarily decrease the demand for other types of healthcare. Thus, at least in the short run, PI would lead to an increase in total healthcare costs.[49–55] The way in which novelty, savings and costs are measured may have a profound impact on final results. One should also be aware of possible publication bias in one or the other direction.

The review has several limitations. The first one is that it is a narrative review that is aimed at providing a broad overview of the studied domain. It does not differentiate between different types of medicines and populations. It does not always distinguish existing medicines from latest generation products, neither their mode of use. The second limitation is that, it does not judge the methodological quality of the scientific evidence of studies. Finally, a common limitation of many included studies is the inability to establish a causal link between medication adherence and total healthcare costs.

In any case, it seems clear that there is a growing tendency to try to associate investment in PIs with the value they bring to society. Value-based approaches are increasingly being used in decision-making processes in many developed countries that are implementing reforms to promote efficiency and sustainability within their healthcare systems.[56] Value-based prices will depend not only on those health and quality-of-life outcomes attributable to the new drug but also on the savings it may generate, and on society's willingness to pay for the new drug's marginal increase in health compared to that of its comparator.[57]

Indeed, countries such as Australia, England and Sweden take into account evidence related to drugs' offset effect in order to decide whether to allow a price premium or not when it comes to a new drug for a particular illness, including evidence on potential savings that may arise in non-healthcare services.[49,58] Nevertheless, in many countries, the possibility that the consumption of new drugs may generate non-pharmaceutical healthcare costs or savings either in the very short run or in the medium long run seems to be a missing consideration in deliberations regarding drug price control policy deliberation.

Table 1. Savings due to the introduction of new drugs in the market – summary of findings.

Area of impact	Author (year)	Country	Therapeutic area	Time horizon	Main results
DHC	Lichtenberg (2001)[4]	The United States	Aggregate level	1996	Replacing a 15-year-old drug with a 5.5-year-old drug leads to a savings ratio of almost 4 times the cost of the drug.
DHC	Lichtenberg (2007)[5]	The United States	Aggregate level	1996–1998	Savings ratio: 7.2 for the general population and 8.2 for Medicare-covered population.
DHC	Lichtenberg (2007)[6]	The United States	Aggregate level	1993–2003	New drugs generate savings in hospitalizations and nursing home admissions equal to 2.4 times their cost.
DHC	Santerre (2011)[8]	7 OECD countries	Aggregate level	2007	Savings ratio: 5.9 in the short run and 11.4 in the long run.
DHC	Civan and Koksal (2010)[7]	The United States	Aggregate level	1993–2004	Per capita savings ratio: 5.5 in Medicare population for a reduction of 1 year in the average age of the drug under assessment.
DHC	Congressional Budget Office (2012)[9]	The United States	Aggregate level	Variable	A 1% decrease in prescription drug use would cause medical spending to increase by roughly one-fifth of 1%.
DHC	Crémieux et al. (2007)[11]	Canada	Aggregate level	1980–2002	Each CAD invested in drugs would lead to an average decrease of CAD 1.5 in total healthcare expenditure.
DHC	Sánchez (2009)[12]	Spain	Aggregate level	1999–2005	A 10% increase in hospital drug expenditure would generate net per capita savings of EUR 1.1 in total hospital expenditure.
DHC	Lichtenberg (2016)[13]	Canada	Oncology	1980–1997	The use of oncologic drugs led to savings of CAD 4700 million, a significantly higher amount than the expenditure on drugs in the same period of time.
DHC	Lichtenberg (2016)[14]	The United States	Oncology	1989–2005	Cancer treatments reduced hospitalization costs by USD 4800 million in 2013.
DHC	Lichtenberg (2017)[15]	Australia	Oncology	1989–2002	PI was cost-saving regarding hospital expenditure.
DHC	Lichtenberg (2009)[16]	20 OECD countries	Cardiovascular	1995–2003	Per capita pharmaceutical expenditure increased by USD 24 but allowed per capita savings of USD 89 in hospitalizations.
DC/IC	Kerr (2014)[17]	The United Kingdom	Cardiovascular	2012–2013	Per capita savings for the healthcare system: GBP 412 in the short run and GBP 2498 in the long run (for society: GBP 94 and GBP 1379, respectively).
DHC	Gotto et al. (2000)[18]	The United States	Cardiovascular	NA	The use of statins has led to a 27% decrease in healthcare costs associated with the illness, compared to placebo.
DHC	Cutler et al. (2007)[19]	The United States	Cardiovascular	1999–2000	The use of antihypertensive medication was associated with benefit–cost ratio of 6:1 in women and 10:1 in men.
DHC/IC	Greenberg et al. (2003)[20]	The United States	Depression	1990–2000	DHC and IC per patient decreased by 18.7% and 10.1%, respectively.
DHC	Costello et al. (2011)[21]	Ireland	Asthma	6 months before and after treatment	The use of monoclonal antibodies reduced exacerbations and led to a 14.5% savings rate in DHC.

(Continued)

Table 1. (Continued)

Area of impact	Author (year)	Country	Therapeutic area	Time horizon	Main results
DHC	Bozzette et al. (2001)[22]	The United States	HIV/AIDS	1996–1999	The use of antiretroviral therapies decreased annual per capita DHC by 10%.
DHC/IC	Polistena et al. (2015)[41]	Italy	Psoriasis	2009	Biologic therapy reduced DNHC and IC by 60% and 71%, respectively.
DHC	Ehreth (2003)[23]	Global	Vaccines	1980–2003	Eradication of smallpox was associated with global cost savings of over USD 2000 million per year.
DC/IC	Ozawa et al. (2016)[24]	Países de ingresos medios y bajos	Vaccines	2011–2020	Children vaccination programmes will generate a rate of return equivalent to 44 times their cost if all social and economic benefits are taken into account.
DC/IC	Zhou et al. (2014)[25]	The United States	Vaccines	2009–lifetime	The direct and societal benefit–cost ratios for routine childhood vaccination were 3.0 and 10.1, respectively.
DC/IC	Ekwueme et al. (2000)[26]	The United States	Vaccines	1997–2012	Benefit–cost ratios for infant vaccination programmes from a societal and healthcare system perspective were 27:1 and 9:1, respectively.
DC/IC	Thompson and Tebbens (2006)[28]	The United States	Vaccines	1955–2015	The benefit of the polio vaccine has reached 6 times its cost.
DHC	Scuffham and West (2002)[30]	England and Wales	Vaccines	1999–2000	Influenza vaccine in the elderly is associated with a cost–benefit ratio >1.
DNHC	Schoenmakers et al. (2009)[40]	NA	Dementia	No time restriction	Drugs reduce caregiving time by 42 minutes per day.
DNHC	Tsiachristas et al. (2009)[42]	The Netherlands	Aggregate level	1995–2007	The use of 10 PI drugs allowed savings in resources equivalent to hiring 7200 healthcare professionals per year.
IC	Bui and Stolpe (2010)[43]	Germany	Aggregate level	1988–2004	Each PI has avoided 200 years of lost work.
IC	Lichtenberg (2002)[44]	The United States	Aggregate level	1985–1996	The cost of achieving one less restricted activity day is USD 18 to USD 34, which is about 4 times lower than the average daily employee compensation.
IC	Lichtenberg (2005)[45]	The United States	Aggregate level	1982–1996	The stock value of new drugs is between 2.3 and 8.1 superior to the expenditure they represented.
IC	Huscher et al. (2015)[46]	Germany	Rheumatoid arthritis	2002–2011	New drugs have led to an 8% reduction in IC.

Source: Compiled by authors.
OECD: Organisation for Economic Co-operation and Development; AIDS: acquired immunodeficiency syndrome; CAD: Canadian dollar; DC: direct costs (including DHC and DNHC); DHC: direct healthcare costs; DNHC: direct non-healthcare costs; EUR: Euro; GBP: Great Britain Pound; HIV: human immunodeficiency virus; IC: indirect costs; NA: not available; PI: pharmaceutical innovation; QALY: quality-adjusted life-year; USD: US dollar.

Given that the offset effect has important healthcare policy implications, gathering robust evidence is critical. Decision-makers need more rigorous longitudinal studies to assess whether different drug groups or specific drugs improve health results and decrease global costs. Evidence must consider all possible cost spectrum, including not only DHC but also possible impacts on caregiving burden and labour productivity. Time is also an important factor, that is, addressing whether the use of a given medication precedes, is contemporaneous with, or follows non-drug healthcare costs in a given year.

In conclusion, in order to assess the real social value of new drugs, researchers should consider not only their cost but also their potential offset effect in terms of savings to the healthcare system and to society as a whole. Further subgroup analyses are needed to endorse current published results. However, there is enough evidence that sustains the notion that PI often contributes to society not only in terms of clinical benefits but also in terms of efficiency and sustainability.

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of conflicting interests

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