

# The Value of Pharmaceutical Innovation – within the context of policies that impact use of new medicines in Sweden

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May 2013

Report from SNS's research programme  
*The Value of New Pharmaceuticals*



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## **Acknowledgements**

Members of the reference group and the following persons have submitted valuable comments on a draft manuscript:

Mikael Hoffmann, MD, Director of NEPI (network for pharmaceutical epidemiology)

Bengt Jönsson, professor emeritus, Stockholm School of Economics

Katarina Steen Carlsson, PhD, Research Director, Swedish Institute for Health Economics, Lund

## Förord

Innan nya läkemedel introduceras i vården görs en bedömning av deras värde. Denna bedömning baseras i huvudsak på resultat i kliniska prövningar. Men hur blir det när ett läkemedel används i verkligheten, av många olika patienter under lång tid? Vilka värden skapas då för den enskilda patienten, vården och samhällsekonomin? Om detta vet vi förvånansvärt lite. Innebörden är att många beslut som rör användning av läkemedel bygger på bristfällig kunskap. SNS forskningsprogram *Värdet av nya läkemedel* syftar till att påvisa vägar till en mer effektiv läkemedelsanvändning.

Arbetet bedrivs stegvis. I februari 2013 presenterades fem studier som undersökte värdet av läkemedel genom att utgå från olika terapiområden: bröstcancer, leukemi, diabetes, reumatoid artrit och höga blodfetter. För vart och ett av dessa områden gjordes empiriska studier för att dels utveckla och pröva analysmetoder, dels göra illustrativa beräkningar av viktiga läkemedels värden och kostnader. En gemensam ansats var att fånga värden över en längre tidsperiod, när läkemedlen använts i rutinsjukvården. En övergripande slutsats var att bristande uppföljning och kunskapsspridning kan medföra stora välfärdsluster när nya läkemedel inte används på ett optimalt sätt. Det kan gälla både under- och överanvändning. Studierna visade också hur vi i Sverige skulle kunna minska osäkerheten om värdet av nya läkemedel genom att bättre utnyttja våra omfattande registerdatabaser.

Föreliggande rapport är en av sex som går vidare genom att ta upp var sin specifik policyfråga: Vad betyder läkemedelsinnovationer ur ett övergripande perspektiv? Hur bör värdering, beslut och implementering av nya läkemedel gå till? Hur kan regionala skillnader i upptag och användning av läkemedel förklaras? Hur kan analyser av registerdata ge ny kunskap om läkemedelsrelaterad sjuklighet? Kan pragmatiska, registerbaserade prövningar i rutinsjukvården ge bättre uppföljningsinformation? För vilka slag av läkemedel vore det rimligt att patienten själv betalar?

De sex studierna presenteras under maj–september 2013. (Såväl dessa som de tidigare rapporterna finns förtecknade i slutet av denna skrift). En sammanfattande slutrapport publiceras i oktober. Läs gärna mer på SNS hemsida: [www.sns.se](http://www.sns.se)

Arbetet har kunnat genomföras tack vare ekonomiskt bidrag från följande företag, myndigheter och organisationer: AbbVie, Apotekarsocieteten, Apoteket AB, AstraZeneca, HealthCap, Janssen-Cilag AB, LIF, Läkemedelsverket, Merck Sharp & Dohme, Pfizer, Sveriges Kommuner och Landsting, Stockholms läns landsting och VINNOVA.

Värdefulla synpunkter har lämnats av projektets referensgrupp. Ett särskilt tack framförs till för ändamålet utsedda granskare av preliminära rapportversioner. Varken granskarna eller referensgruppen ansvarar dock för studiernas innehåll. För analys, slutsatser och förslag svarar helt och hållet de olika studiernas författare. SNS som organisation tar inte ställning till dessa. SNS har som uppdrag att initiera och presentera forskningsbaserade analyser av viktiga samhällsfrågor.

Stockholm i maj 2013

*Göran Arvidsson*

forskningsledare SNS

# Sammanfattning

Den förväntade livslängden har under de senaste 50 åren ökat dramatiskt, vilket till stor del tillskrivs framgångar i medicinsk teknologi. Samtidigt har utgifterna för sjukvården ökat betydligt. Historiskt sett har det dock varit svårt att kvantifiera förhållandet mellan sjukvårdsutgifter och ökad livslängd. Vi utförde en studie för att undersöka en indikator för förändring i sjukvården – introduktionen av nya läkemedel – och hur den är relaterad till ökad livslängd och till resursanvändning. Introduktionen av nya läkemedel är särskilt intressant eftersom de utgör en betydande andel av de totala medicinska innovationerna.

Vi använde longitudinella data för mortalitet (dödlighet) och för introduktion av nya läkemedel och undersökte sambanden mellan omfattningen av läkemedelsintroduktion och förändringar i livslängd, sjukhusvistelser och vårdutgifter i Sverige under perioden 1997–2010. Vi fann att sjukdomar med fler introducerade läkemedel (mer innovation) kännetecknades av en större ökning i livslängd. Mellan åren 1997 och 2010 ökade medellåldern med 1,88 år, varav introduktion av nya läkemedel kunde förklara lite drygt en tredjedel (31,6 procent). I modellerna justerade vi för såväl generella öknings i livslängd som skillnader i livslängd för olika sjukdomar. Ökad livslängd befanns ha ett samband med *antalet nya substanser* för att behandla en sjukdom, inte med *antalet kemiska undergrupper* som introducerats för att behandla en specifik sjukdom. Detta kan tolkas som att fler alternativa läkemedel att tillgå på ett visst område kan ge bättre effekt på livslängd.

Våra skattningar visade vidare att nya läkemedel som introducerades 1992–2001 åtföljdes av ett minskat nyttjande av sjukhusvård; antalet dagar beräknades ha minskat med 12 procent år 2009. Det fanns indikationer på att nya läkemedel hade varit kostnadsbesparande: minskningen av utgifter för sjukhusvård som förklaras av introduktion av nya läkemedel var större än kostnadsökningar för de nya läkemedlen. Förvisso ökade kostnaden för läkemedel med 91\$ (ca 640 SEK) per capita jämfört med en tänkt situation då nya läkemedel inte introducerats, men då hade man inte heller fått besparingen på 112\$ (ca 780 SEK) per capita som kom från minskat antal sjukhusdagar relaterat till introduktion av nya läkemedel. Innebörden är att denna kostnadsbesparing finansierar ökningen i utgifter för nya läkemedel samtidigt som man får ökad livslängd. Även om vår studie inte påvisar orsak-verkansamband utan statistiska samband på aggregerad nivå tyder den på att introduktionen av nya läkemedel minskade de direkta (medicinska) kostnaderna samtidigt som de ökade livslängden med ca 6 månader åren 2000–2009.

En begränsning med studien är att den ger information om i vilken grad nya mediciner på en *aggregerad* nivå bidrar till ökad överlevnad, men inte om *hur* och om *vilka enskilda* läkemedel som ger detta resultat. En annan begränsning är att utfallet som undersöks är relaterat till överlevnad, som i och för sig är en vida använd indikator för hälsa, men den ger endast information om kvantiteten, inte kvaliteten av ökad hälsa. Många mediciner ger i huvudsak förbättringar i livskvalitet, vilket alltså inte fångas upp i vår studie. Hur mycket introduktion av nya läkemedel bidrar totalt sett till förbättrad hälsa är troligtvis starkt underskattat i denna studie.

Läkemedel är en viktig produktionsfaktor i hälso- och sjukvården och därför är det av stor betydelse att dessa – både nya och gamla läkemedel – används på ett optimalt sätt. Som framgår ovan finns en stor potential att nya läkemedel kan förlänga liv och/eller

bidra till att minska användning av andra resurser. Upptag och användning av (nya) läkemedel bestäms av policys och regleringar på olika nivåer: på en makronivå (sjukvårdssystemnivå), organisationsnivå samt på kliniknivå. Det är därför viktigt att utforma policys som kan stödja en optimal användning av samtliga resurser inklusive läkemedel – nya och gamla. De viktiga frågorna i detta sammanhang är:

- Har vi en optimal användning av nya läkemedel?
- Avsätter vi tillräckligt mycket resurser för nya läkemedel i förhållande till nyttan de tillför?

För att kunna svara på detta behöver man utvärdera tillgänglighet till och upptag av nya produkter och de styrsystem som omgärdar detta. Styrsystemen, t.ex. pris- och subventionssystemet på nationell nivå och de styrsystem som återfinns på regional nivå, är mycket kraftfulla och har därför avgörande betydelse för användningen av nya läkemedel. Om dessa styrsystem motverkar effektiv användning av nya läkemedel, som vissa indikatorer tyder på, hämmar det möjligheter för samhället och för patienterna att tillgodogöra sig värdet av de nya läkemedlen.

Under de två senaste decennierna har en rad olika reformer på läkemedelsområdet introducerats, vilka kan ha haft en betydande effekt på användning av nya läkemedel, men en systematisk och omfattande utvärdering av dessa system har ännu inte skett. Dock talar en rad indikatorer för att användningen av nya läkemedel i Sverige har sjunkit över åren.

En sådan indikator är att utgifterna för läkemedelsförmånen har sjunkit över åren, vilket beror på en mängd faktorer som inte direkt kan hänföras till dessa styrsystem, bl.a. stora patentutgångar, men också på en reell minskning i användning av nya läkemedel. Detta kan vara effekten av ett ökat kostnadsfokus inom landstingen som en effekt av det decentraliserade kostnadsansvaret som överfördes från staten till landstingen 1998. En annan faktor som kan ha påverkat tillgängligheten till nya läkemedel är det nya pris- och subventionssystemet (P&S) som infördes 2002. Av samtliga mediciner, som erhöll marknadsgodkännande åren 2006–2008 i Europa och som finns tillgängliga på de olika marknaderna, var 75 procent tillgängliga inom läkemedelsförmånen i Sverige 2009.

Pris- och subventionssystemet som tillämpas idag, och som tillkom i samband med upprättandet av Läkemedelsförmånsnämnden (sedermera Tandvårds- och läkemedelsförmånsverket, TLV), förändrade systemet i grunden, med tillämpningen av ett värdebaserat prissättningssystem med ekonomiska utvärderingar som grund för subventionsbeslut. Detta system och hur det tillämpas kan verka restriktivt under vissa förutsättningar, t.ex. när det gäller att värdera och premiera stegvis innovation. Förutom att ett restriktivt P&S-system kan verka hämmande för upptag av nya läkemedel och användning av läkemedel generellt kan det på sikt minska incitament för FoU och därmed för framtida försörjning av innovativa läkemedel.

Ovan nämnda reformer och styrsystem som tillkommit över åren skapar tillsammans förutsättningarna för tillgänglighet och upptag av nya läkemedel och är därför avgörande för hur väl samhället kan tillgodogöra sig potentialen i nya läkemedel. För detta krävs en väl utformad och sammanhållen politik. Därför föreslår vi att den sammanlagda effekten av de olika regleringar som införts på området och som kan ha effekt på användning av nya läkemedel under de senaste decennierna utreds och att regelsystemen ses över i syfte att skapa förståelse och underlag för utformning av styrsystem som kan skapa förutsättning för en optimal användning av läkemedel.

# Executive Summary

Life expectancy around the world has increased dramatically over the past fifty years, while at the same time health care spending has risen substantially. Historically it has been difficult to quantify the relationship between health care spending and improvements in longevity. We conducted a study to assess the contribution of one indicator of changes in health care, the introduction of new drugs, to increased longevity. New drug launches are of particular interest because they account for a substantial fraction of medical innovations.

We used longitudinal, disease-level data to analyze the impact of pharmaceutical innovation on longevity and medical expenditure in Sweden during the period 1997–2010. We found that diseases that benefited from more pharmaceutical innovation had greater increases in longevity. Pharmaceutical innovation accounted for almost one third (31.6%) of the 1.88-year increase in mean age at death during the period 1997–2010. We found that longevity depends on the *number of drugs (substances)* to treat a disease, *not the number of chemical subgroups (drug classes)* developed to treat the disease. Diseases that experienced more pharmaceutical innovation saw smaller increases in hospital use. New drugs have been cost saving: the reduction in annual hospital expenditure induced by pharmaceutical innovation has been greater than the induced increase in annual pharmaceutical expenditure. New drugs have reduced lifetime medical expenditure, despite the fact that they increased life expectancy by 6 months during 2000–2009.

One limitation of this study is that while it does provide information about medicines on an aggregate level, it does not indicate medicines in which to invest. Another limitation is that the outcome measure is related to longevity, which is indeed a widely used indicator of the health of a population, but it reflects the quantity rather than quality of life. Many medicines mainly improve quality of life and this will not be covered in our study. Nevertheless, the conclusion is that new pharmaceuticals, on an aggregate level, are an important production factor in health care.

The uptake and use of (new) medicines is determined by policies at several levels: at the macro or healthcare system level, the service organization level and the clinical practice level. During the last two decades a variety of pharmaceutical policies has been introduced in Sweden, which might have had an impact on the use of new medicines, but no thorough and complete review of these policies has yet been carried out. There are potential new pharmaceuticals that increase life expectancy and/or lead to reduced use of other resources. It is important to prioritize so that resources could be allocated to these products. Pharmaceutical policies should be balanced to allow society as well as patients to benefit from the value of improved health from new medicines, now and in the future, while at the same time considering other policy objectives such as cost control.

We suggest that the impact of pharmaceutical policies on the use and rate of uptake of new medicines introduced in recent decades in Sweden be reviewed. It could be useful to consider this study, for instance, when determining how to optimally invest in pharmaceuticals on an aggregate level.

# 1. Introduction

Longevity has constantly been increasing in the Organisation for Economic Co-operation and Development (OECD) countries, with the life expectancy at birth now being almost 80 years, on average. The increase in longevity after the first half of 1900 is largely attributable to progress in medical technology. Over the same period, health care spending has risen substantially. The growth rate in health expenditure has risen more rapidly than the growth in GDP in many countries during the last few decades and constitutes, on average, 10% of GDP in OECD countries<sup>1</sup>, which is also the case for Sweden.

It has historically been difficult to quantify the relationship between health care spending and longevity improvements [1]. We assessed the contribution of one indicator of changes in health care, the introduction of new drugs, to improved longevity. Launches of new medicines are of particular interest because they account for a substantial fraction of medical innovations. For instance, expenditures for pharmaceuticals are around 15% of total health expenditure on average in OECD countries. In Sweden, total expenditures for pharmaceuticals had been rising during earlier decades but have been declining from 14% of total health care expenditures<sup>2</sup> in 2002 to 12.6% in 2010.

Extensive research has shown that pharmaceutical innovation has contributed greatly to improved health. This research is mainly carried out in different therapy areas and not on an aggregate level, which might be limiting if the question is how to optimally invest in pharmaceuticals on an aggregate level, for instance when the level is to be determined within the state budget.

An interesting issue from a policy perspective would be to understand the contribution of pharmaceuticals to the production of health care, in order to ascertain optimal levels of medicine use that would benefit the society, i.e. the return on investment or the value of innovation of pharmaceuticals.

In 2011 the Swedish government launched an inquiry [2] into certain issues that concern pricing, supply and market conditions within the pharmaceutical and pharmacy area. Important starting points for a future pricing model, according to the inquiry's directive, is that it must create preconditions for good cost control at the same time that it must ensure the satisfactory availability of effective pharmaceuticals and offer good preconditions for the research-based pharmaceutical industry.

A report of the inquiry was presented in October 2012 [3]. The report states that new effective treatments that lead to improved health as well as increased productivity of the health care system should be made accessible to patients as early as possible in order to provide the public with as good and modern care as possible. The leading principle for the inquiry is "that the system for uptake as well as follow-up for new and for old drugs should be designed to support optimal use of medicine" (English translation). Based on the materials available, the inquiry concluded however that it was not possible to

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<sup>1</sup> OECD Health Data 2012: <http://stats.oecd.org/Index.aspx?DataSetCode=SHA>

<sup>2</sup>Total expenditure on pharmaceuticals and other medical non-durables

ascertain whether use of medicines in Sweden is optimal, or whether the adoption of new drugs is too extensive or too restrictive. The uptake and use of (new) medicines is determined by policies at several levels: at the macro or healthcare system level, the service organization level and the clinical practice level. A variety of national as well as regional policies which might have had an impact on use of pharmaceuticals were introduced in Sweden during recent decades, but there is no comprehensive evaluation of these policies and what impact these might have had on the uptake and use of new medicines in Sweden.

We carried out a study that provides information on the value of pharmaceutical innovation by estimating the impact of pharmaceutical innovation on longevity and the cost-effectiveness of the new medicines. The contribution of pharmaceutical innovation and the cost-effectiveness of that innovation on an aggregate level could be important indicators of whether pharmaceutical policies are efficient with respect to the rate of uptake and use of new medicines, or when conducting cost-benefit analysis of pharmaceutical policies. This information could be helpful when designing pharmaceutical policies that aim at targeting optimal use of new medicines.

The purpose of this report is to provide estimates on the value of pharmaceutical innovations within the context of policies that might have affected use of new medicines in Sweden. The report starts by providing a background on determinants of use of new medicines, a background on pharmaceutical policies that were introduced during the last decade in Sweden and finally a section where we review indicators and literature on the use of new medicines in Sweden. In Section 3 we present estimates on the value of pharmaceutical innovations that were introduced in Sweden 1997–2010 followed by a discussion of the findings. We present our conclusions and summary in Section 4.



## 2. Background

### 2.1. Determinants influencing the use of new medicines

Pharmaceuticals represent around 15% of overall health expenditure in the OECD countries, and increasing expenditures have led to the introduction of different policies aimed at controlling costs and improving the efficiency of drug use [4]. These policies have important implications for the access, rate of uptake and use of new medicines. Danzon *et al.* observed that only 23–27% of products launched between 1995–2005 were available in countries (such as Sweden) with pricing and reimbursement (P&R) control, compared to 63.8% in the US, where access to the market is generally not restricted by P&R decisions [5].

Use of new medical technology varies widely between countries but also between different disease areas within a country [6]. The causes for variation in diffusion of new drugs could be differentiated into three broad groups, macro- or system-level determinants, service organization determinants and clinical practice determinants [7]. These categories are interrelated. For example, a readiness among clinicians to adopt innovations in clinical practice is determined, to some degree, by the ease with which access to innovation is provided at the system level. The relative importance of these factors will vary depending on the disease area in question and the system context.

In explaining the potential causes of international variation found in the study mentioned above [6], a number of common themes emerges: (1) health technology assessment (HTA) processes and outcomes can have a significant impact on levels of usage; (2) service planning, organization and direction-setting play an important role in enabling or restricting usage; and (3) clinical culture and attitudes towards treatment remain important determinants of levels of acceptance. These themes often work in combination, so, for example, the impact of HTA can either be mitigated or amplified by issues relating to service organization or clinical culture, where the main issues are the availability of or access to specialists.

### 2.2. Pharmaceutical policies in Sweden

During the past two decades, increasing pharmaceutical expenditures led to the introduction of a variety of mainly demand-side policies aimed at restricting the escalation [8–10]. These policies were designed to promote the rational and cost-effective use of drugs at national as well as regional levels. Two of the most important policies were the devolution of the pharmaceutical budget to the county councils in 1998 and implementation in 2002 of a new system for pricing and reimbursement (P&R) according to value-based pricing (VBP). There are indications that the policies introduced might have had a restrictive impact on the use of (new) medicines in Sweden.

The prior P&R scheme was replaced by the current VBP system, where HTA became a foundation for P&R decision-making. HTA has emerged as an important foundation for guiding decision-making and allocating resources in health care by TLV, Sweden's Dental and Pharmaceutical Benefits Agency for making P&R decisions. VBP means that a drug's value, i.e. cost-effectiveness, is evaluated and a price premium over its one or more pre-defined comparators may be determined and used to set the price of that

pharmaceutical. Based on this value assessment, manufacturers are rewarded for the level of innovation they bring.

In principle, the use of VBP can provide benefits, by enabling governments to make decisions driven by value, encouraging innovation, and providing patients and physicians with the information needed to make the best treatment choices. The main difficulty in defining price (or accepting a price level for listing) *via* VBP is determining how to define the value of the medicine in clinical practice and challenges related to measuring that value. Therefore, the utility of VBP in encouraging innovation and value-added health care depends on the assessment process, including when and how a review is performed, the chosen comparators and the resulting decision-making procedures, including implementation. The VBP approach and current methodologies work better in cases with perceived “breakthrough” innovations, while it is much more challenging when it comes to cases with incremental innovation.

The introduction of VBP certainly influenced decision-making concerning new medicines to be listed and made available in the benefits scheme. However, this does not mean that the new medicines are being used. Access problems may arise, if the agency performing value assessments does not have a mandate to implement its decisions/recommendations [11], as is the case in Sweden and other health care systems with decentralized budgets. There isn't always consistency between national and regional authorities regarding guidelines and recommendations. Indeed, at this time, recommendations on some new medicines in the regional guidelines differ from the evaluations and decisions made by the TLV. The P&R system not only affects current access to new medicines, it also serves as a signaling system to the industry: it may have a major impact on investment decisions in R&D and access to new medicines in the future, i.e. dynamic efficiency [12, 13]. As currently implemented, the impact of VBP on dynamic efficiency is not clear at this point [11, 14]. All in all, the VBP approach and current methodologies are limited in their ability to deliver relevant knowledge on incremental innovation and on dynamic efficiency, and this is one of its fundamental flaws.

Another reform that might have had an important impact on access to and use of medicines concerns the drug budget, which was devolved to the counties in 1998 [8]. With the drug budget devolution, an intrinsic conflict arises when the national P&R agency (TLV) makes decisions about pricing and reimbursement based on the cost-effectiveness of drugs, while the budget responsibility for drugs falls to the healthcare providers at the regional level [15]. If health care providers perceive new drugs to be too expensive and therefore restrain from accepting them, the result may be suboptimal decisions and unnecessary societal costs [16]. Other important factors that might have contributed to the limited adoption of innovative medicines are the reforms that were introduced to encourage so-called “rational use” of prescription medicines regionally, which have kept up with the devolved drug budgets and were introduced during recent decades [9, 17, 18]. These reforms include measures managed *via* regional Drug and Therapeutic Committees, such as the production of regional guidelines, academic detailing, benchmarking, prescribing targets, and economic incentives [8].

### **2.3. Access, uptake and use of (new) medicines in Sweden**

In this section we cover the background on indicators for access, uptake and use of medicines in Sweden. Access to medicines refers to whether new medicines are launched/made available on the Swedish market and made available in the reimbursement system. Uptake refers to the rate of use of new medicines while use of medicines refers to an overall use, which could be use of new as well as old medicines.

In a study on international variation in drug usage, volume data were used to measure consumption in various comparable countries and in various different treatment areas [6]. The drugs studied were a combination of new drugs and older drugs. Although some countries emerged as generally high or low users of (new) drugs, there is no uniform pattern across disease areas and categories of drugs. France, Spain, the US and Denmark had high levels of usage generally, but not across all disease areas. Low levels of usage of (new) drugs were also observed for all four countries in some categories. Generally lower than average levels of usage were observed in Norway and Sweden. Sweden had the second lowest ranking out of 14 countries. The ranking for Sweden differed widely between treatment areas, from (3rd to 13th), where the high ranking (3) was in rheumatoid arthritis and the lowest usage was in treatment of osteoporosis (13). The comparison based on cancer treatments could be used as an indicator for use of new drugs. In that respect Sweden was ranked somewhat higher in use of new cancer drugs introduced 0–5 years earlier and older (introduced more than 10 years earlier) but somewhat lower for drugs introduced 5–10 years earlier.

The report stresses that there is not always a consensus about what the optimum level of drug usage in different disease areas would be and that the appropriate level of usage may vary because of different factors at work in different countries. For some disease areas, high usage may be a sign of weaknesses at other points in the care pathway and low usage a sign of effective disease prevention. Equally, for others, low usage may imply that patients' needs are not being met effectively and high usage may imply that patients are receiving the best treatment.

Nevertheless, several indicators have shown that uptake of new medicines has been too restrictive in Sweden during the last decade. The first dispensing of a drug within a year after launch in Sweden was found in 89% of the corresponding in Denmark and in 94% in Norway respectively [19]. Between 2006 and 2008, 65 new drugs were introduced in Europe, of which 65% were available in Sweden, compared to 89% in Denmark and 60% in Norway [20]. In a comparison based on 47 innovative drugs in 25 EU-countries a ranking was made with regard to accessibility. It was found that 22 out of these 47 drugs are used in Sweden, which implies a ranking for Sweden at 8 of 25 countries. The conclusion from the study is that use of medicines varies considerably between countries in Europe [21], but the variation could not be explained and optimal levels were not possible to determine in the study. In a comparison of the uptake of new diabetes and anti-coagulant drugs across Europe, uptake in Sweden was found to be at lower range, far below the average in Europe, while the uptake of new drugs to treat the wet form of age-related macular degeneration (AMD) was far above average [22]. In a comparison of the uptake of new cancer drugs in Europe, Sweden was found to be on an average [23]. And the uptake and use of drugs for multiple sclerosis was above average [24] as was the use of biologic treatments of rheumatoid arthritis also [25]. Furthermore, it is difficult to rank use of medicines on a general level, because of the internal variation due to different treatment traditions, since the ranking will depend heavily on what drugs are included in the comparison. It has been suggested that the main factor

behind the escalation in drug costs in Sweden between 1990 and 2000 has been a change from the use of old to new and expensive drug therapies [26]. During the last decade however, pharmaceutical expenditure has been flat [27], and the percentage of overall drug expenditure in Sweden that was allocated to new medicines introduced during the preceding five years has declined rapidly from 11% in 2005 to 5% in 2011. This mainly reflects the drop in medicines used in outpatient care. For medicines used primarily in hospital care, the development was the opposite, the expenditures on medicines introduced over the preceding 5 years increased from 8% in 2005 to 14% in 2011[3].

Information on the rate of uptake of new medicines is limited. However, the TLV, Sweden's P&R agency, conducted an analysis of medicines for outpatient care, which concluded that Sweden provides relatively early access to new drugs, even if no evidence was found that the system leads to *much earlier* introduction than comparable countries. The government inquiry concluded that Sweden does not provide earlier access to innovative drugs than other countries [3].

All in all, the rate of (early) uptake and use of medicines seems to be more limited in Sweden than it is in several other countries. The impact of this comparatively restrictive use should be evaluated and considered from a policy perspective. The question is whether the present practice is the outcome of an informed and intentional decision or if the policies that were introduced created a system that became too restrictive to be optimal from a societal perspective.

### 3. Value of innovation

Increased longevity is an important part of economic growth and development, broadly defined. In the OECD countries, life expectancy has increased by 10 years since 1960 [28]. The enormous monetary value of increasing life expectancy has been noted in studies by Murphy and Topel [29]. The economic value of increases in longevity over the twentieth century has been estimated by Nordhaus in a first approximation to be about as large as the value of measured growth in non-health goods and services [30] and the increases in medical spending since 1960 in the USA were found to have provided reasonable value [1]. Based on Swedish data, estimates of the monetary value of increasing life expectancy at birth during the period 1900-2000 suggest that the value is about 5 million SEK per person and the value of the total increase in life expectancy was estimated to be about 75% of the increase in GDP during that period, about 1,552 billion SEK [31].

Medical innovation has had a major impact on both healthcare outcomes and the quality of care but it may also have been a major driver of health care spending over the post-war period [32, 33]. Some studies have concluded that medical innovation has been the main reason for the rise in health care costs. However, some of these studies may not have fully accounted for spillover across episodes of care or medical conditions. For example, a recent study of a cohort of US Medicare beneficiaries aged 65 years and older with a diagnosis of cataracts found that patients who had cataract surgery had lower odds of hip fracture within one year after surgery compared with patients who had not undergone cataract surgery [34]. It was found that states that adopted new drugs and diagnostic imaging procedures more rapidly did not have larger increases in per capita medical expenditure, controlling for other factors [35]. Also, Lichtenberg (2011) found that hospital procedure innovation increased survival of Western Australia hospital patients but had a negligible effect on their medical expenditure [36].

#### **3.1. Contribution of pharmaceutical innovation to longevity – evidence from Sweden**

In this section we summarize the evidence based on data from Sweden on the contribution of pharmaceutical innovation to longevity, and to decreasing use of hospital days. We also investigate the pharmaceutical expenditures associated with pharmaceutical innovation and, finally, we use our estimates on effects and costs to estimate the cost effectiveness of pharmaceutical innovation. The entire paper is available as a working paper [37] and is accepted for publication in *Economics of Innovation and New Technology*. We used longitudinal, disease-level data to analyze the impact of pharmaceutical innovation on longevity and medical expenditure in Sweden during the period 1997–2010. The measures of longevity we used are based on the age distribution of deaths caused by a disease in a given year and in the increase in the fraction of deaths that occurred at an age greater than 75.

Pharmaceutical innovation can be measured in several different ways, because active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. In the Anatomical Therapeutic Chemical (ATC) classification system developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology, drugs are classified in groups at five different levels. The highest (1<sup>st</sup>) level is the “anatomical

main group” level; there are 14 anatomical main groups. The 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup> levels are “therapeutic subgroup,” “pharmacological subgroup,” “chemical subgroup,” and “chemical substance,” respectively.<sup>3</sup> The measure of pharmaceutical innovation we used was based on the number of *drug classes* (chemical subgroups) and *number of drugs* (chemical substances) previously introduced to treat a condition.

We will investigate the effects of both new chemical substances and new chemical subgroups on longevity. We pooled data from several rich data sources. Longitudinal disease-level measures of pharmaceutical innovation were constructed from Läkemedelsverket (Sweden’s Medical Products Agency)<sup>4</sup> and from Thériaque.<sup>5</sup> Longitudinal disease-level data on mortality was obtained from the WHO Mortality Database.<sup>6</sup> Longitudinal disease-level data on hospital utilization was obtained from Eurostat.<sup>7</sup> Longitudinal data on pharmaceutical expenditure and innovation, by drug class, was obtained from the IMS Health MIDAS database.<sup>8</sup> Some additional data was obtained from the OECD Health database.

We used longitudinal, disease-level data to estimate difference-in-differences models of the effect of pharmaceutical innovation on longevity. In essence, we investigated whether the diseases that experienced more pharmaceutical innovation had larger increases in longevity. Our models include year and disease fixed effects, so they will control for the overall increase in Swedish longevity and for stable between-disease differences in mortality. From 1997 to 2010, mean age at death increased by 1.88 years, from 78.40 to 80.28 years. We estimate that, if the number of chemical substances marketed up to six years earlier had not increased, mean age at death would have increased by 1.29 years, from 78.40 to 79.69 years (Figure 1). Hence pharmaceutical innovation is estimated to have increased mean age at death in Sweden by 0.60 years (7.15 months) during the period 1997–2010 – almost 1/3 (31.6%) of the overall increase in mean age at death. It accounted for twice as large a fraction (63%) of the increase in the fraction of deaths that occurred at an age greater than 75. We found that longevity depends on the number of drugs to treat a disease, not the number of chemical subgroups (drug classes) developed to treat the disease.

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<sup>3</sup> The complete classification of metformin illustrates the structure of the code:

|         |  |
|---------|--|
| A       | Alimentary tract and metabolism (1st level, anatomical main group)                 |
| A10     | Drugs used in diabetes (2nd level, therapeutic subgroup)                           |
| A10B    | Blood glucose lowering drugs, excl. Insulins (3rd level, pharmacological subgroup) |
| A10BA   | Biguanides (4th level, chemical subgroup)  |
| A10BA02 | Metformin (5th level, chemical substance)  |

<sup>4</sup> [http://www.whocc.no/atc/structure\\_and\\_principles/](http://www.whocc.no/atc/structure_and_principles/)

<sup>5</sup> <http://www.lakemedelsverket.se/Sok-efter-lakemedel-och-mediciner-i-Lakemedelsfakta/>

<sup>6</sup> Thériaque (<http://www.theriaque.org/>) is a database of official, regulatory and bibliographic information on all drugs available in France, intended for health professionals. Funding is provided by the French Centre National Hospitalier d'Information sur le Médicament.

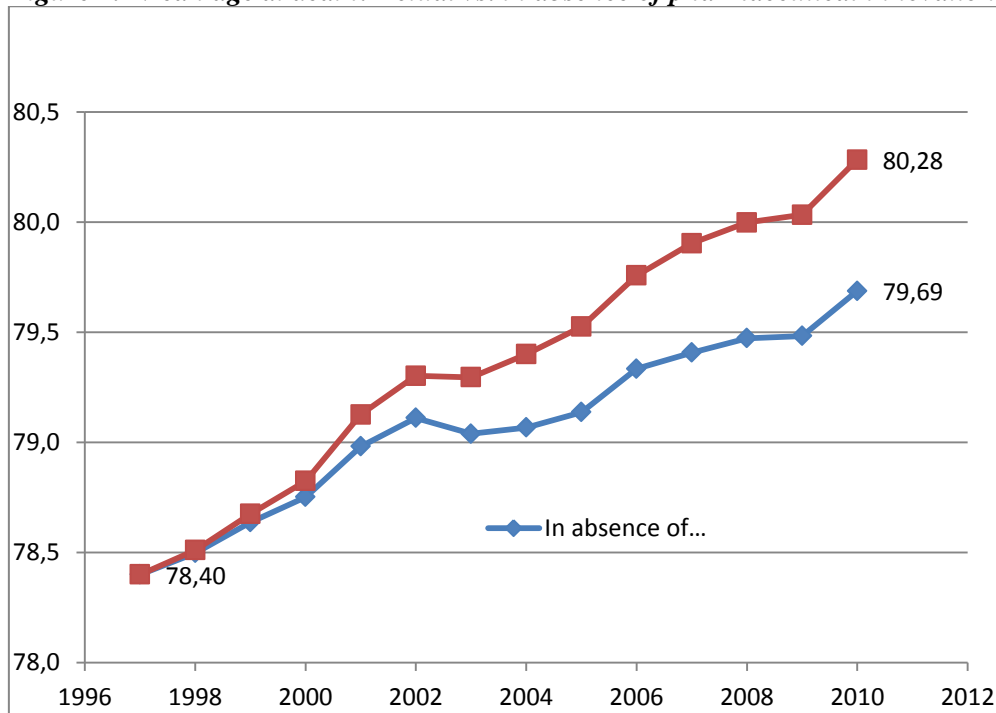
<sup>7</sup> <http://www.who.int/healthinfo/morttables/en/>

<sup>8</sup> [http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search\\_database](http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database)

<sup>8</sup> IMS describes MIDAS as “a unique data platform for assessing worldwide healthcare markets. It integrates IMS national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and providing estimated product volumes, trends and market share through retail and non-retail channels. MIDAS data is updated monthly and retains 12 years of history.” IMS Institute for Healthcare Informatics (2011), *The Global Use of Medicines: Outlook Through 2015*, May.

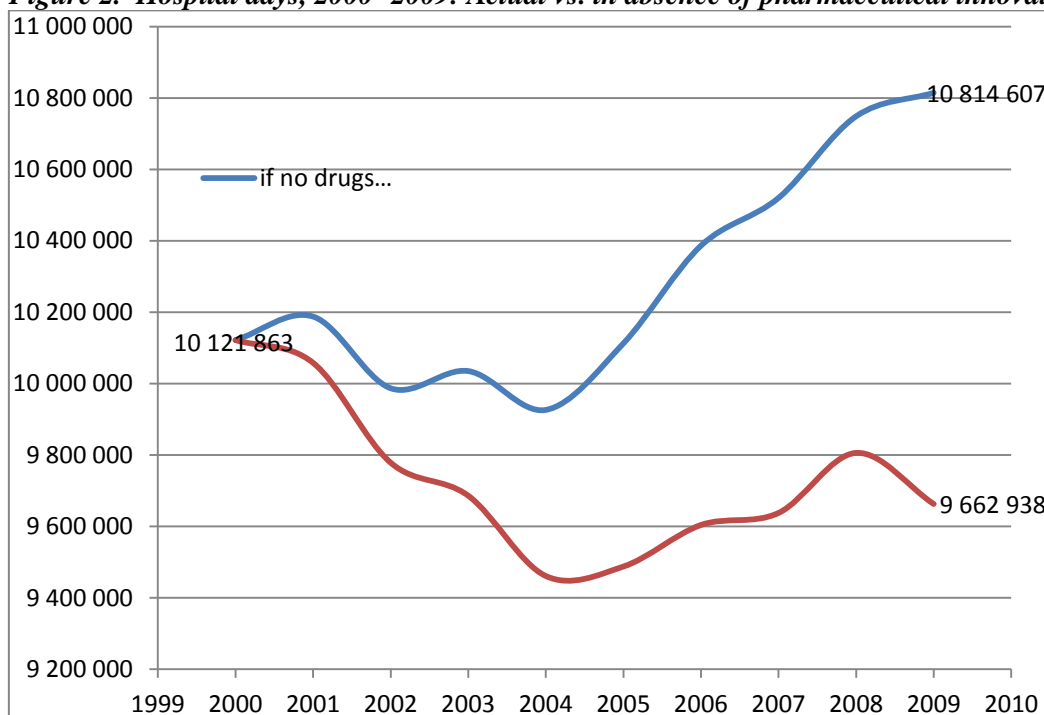
[http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global\\_Use\\_of\\_Medicines\\_Report.pdf](http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20for%20Healthcare%20Informatics/Global_Use_of_Medicines_Report.pdf)

**Figure 1. Mean age at death: Actual vs. in absence of pharmaceutical innovation**



We examined the effect of pharmaceutical innovation on hospital use during the period 2000–2009. The estimates indicate that an increase in the number of drugs marketed for a disease reduces the number of hospital days (number of discharges and length of stay), due to the disease eight years later, primarily due to its effect on the number of hospital discharges. We estimated that if no new drugs had been put on the market during the period 1992–2001, the number of hospital days would have been about 12% higher in 2009 (Figure 2).

**Figure 2. Hospital days, 2000–2009: Actual vs. in absence of pharmaceutical innovation**



We then assessed the impact of pharmaceutical innovation on pharmaceutical expenditure using longitudinal data on about 300 classes of drugs. We estimated that the 1997–2006 increase in the number of chemical substances increased pharmaceutical expenditure in 2009 by 37.2%.

We used our estimates to assess the incremental cost-effectiveness of pharmaceutical innovation, i.e. the cost per life-year gained from the introduction of new drugs (Table 1). First we calculated a “baseline” estimate of the incremental cost-effectiveness ratio (ICER), based on our estimates that, if no new chemical substances had been marketed during a previous 9-year period, (1) mean age at death in 2009 would have been 0.47 years (5.64 months) lower; (2) per capita pharmaceutical expenditure in 2009 would have been \$91 lower; and (3) per capita hospital expenditure in 2009 would have been \$112 higher. Assuming that pharmaceutical innovation had no effect on other medical expenditures, lifetime medical expenditure would have been slightly lower in the absence of prior pharmaceutical innovation, due to the reduction in life expectancy. The baseline estimate of the cost per life-year gained from the introduction of new drugs is \$233 (= -\$109/ -0.47 years), which is a very small fraction of leading economists’ estimates of the value of (or consumers’ willingness to pay) for a one-year increase in life expectancy.



**Table 1. Estimation of incremental cost effectiveness of pharmaceutical innovation**

| <b>Line</b> | <b>Variable</b>   | <b>Actual values, 2009 (<math>Y_{actual}</math>)</b> | <b>Estimated values in 2009 in the absence of 9 prior years of pharmaceutical innovation (<math>Y_{no\_innovation}</math>)</b> | <b>Difference (<math>Y_{no\_innovation} - Y_{actual}</math>)</b> |
|-------------|---|--|--|--|
| 1           | <b>Life expectancy (Mean age at death)</b>  | 80.03  | 79.56  | -0.47  |
|             |   |  |  |  |
|             | <b><u>Per capita medical expenditure in 2009, USD PPP</u></b>                               |  |  |  |
| 2           | Prescription drug expenditure   | \$336  | \$245  | -\$91  |
| 3           | Hospital expenditure  | \$935  | \$1 047  | \$112  |
| 4           | Other medical expenditure   | \$2 450  | \$2 450  | \$0  |
| 5           | Total medical expenditure   | \$3 721  | \$3 742  | \$21   |
|             |   |  |  |  |
| 6           | <b>Lifetime medical expenditure (= life expectancy * total medical expenditure in 2009)</b> | \$297 792  | \$297 682  | -\$109   |

We then performed sensitivity analyses. If we assume that there is no hospital cost reduction from pharmaceutical innovation, the results indicate that costs are well below the consensus value of a statistical life-year. If we assume that the hospital cost reduction is half as large as our estimates indicate, and that pharmaceutical innovation also reduced other medical expenditure (e.g. nursing home expenditure) proportionally, pharmaceutical innovation would be cost-saving.

## 3.2. Discussion

Findings based on Swedish data confirmed findings from earlier studies on the contribution of pharmaceutical innovation to longevity using aggregate data [38-40]. For instance, the contribution of pharmaceutical innovation to recent longevity growth in Germany was investigated using longitudinal, annual, and state-level data during the period 2001–2007 [40]. The estimates of the effect of the vintage of prescription drugs (and other variables) on life expectancy and age-adjusted mortality rates of residents of Germany implied that about one-third of the 1.4-year increase in German life expectancy during the period 2001–2007 was due to the replacement of older drugs by newer drugs. Using patient-level data similar results were observed to the studies based on aggregate data. Patient-level data on health care use from a large number of patients in Quebec, Canada, were linked to survival [41]. The hypothesis was that patients using newer medicines were likely to live longer than patients using older medicines, controlling for their medical conditions, age, gender, location and so forth. The findings suggested that new treatments introduced during the last three decades reduced mortality by 51% in the entire study population. Similar results were obtained for mortality of cancer and of cardiovascular diseases. For review of other studies based on patient level data, see [42, 43].

Innovation is often classified as revolutionary, radical or incremental [44]. The term ‘revolutionary’ innovations can be used to describe major conceptual advances, such as the identification of microbes and classes of anti-infection agents. A new understanding of a disease mechanism and a new mode of action that interferes with the disease process at a molecular level can be described by the term ‘radical’ innovation. A “first-in-class” medicine (the first medicine of its type) is normally considered to be a radical product. Closely related compounds with different attributes that may offer significant value in treating particular disease variants or patient segments can be referred to as ‘incremental’ innovations.

Following Freeman’s classification for products with respect to degree of innovation, the term “substances” in our study refers to incremental innovation, while “classes” refers to radical innovation. A notable finding of our study is that longevity seems to depend on the number of *substances*, not the number of drug *classes* launched. This finding means that incremental (same class, but different substances) innovation on an aggregate level can be seen to contribute to improved health and also could be cost saving.

The increased number of drug substances that we used as a proxy for innovation could also mean that *more patients* are treated, and therefore that benefits arise from extended patient populations, i.e. a *volume* component.

In addition to the volume component, more innovative substances mean more treatment options that could be used for a better fit with different patients, and therefore result in better outcomes. This finding is important to consider from a policy perspective since it indicates that horizontal or incremental innovation contributes to health improvement and should not be discouraged by policy measures.

Overall, the estimates provide support for the hypothesis that an increase in the number of substances that have been marketed and that may be used to treat a disease causes a rightward shift of the age distribution of deaths from the disease *several years later*.

This could be explained by the fact that a new substance generally will not be widely used until a few years after it is on the market. The lag in effects might be due to disease-specific progression, but it could also indicate that the uptake of new medicines is slow and that the use is limited at initial launch. Therefore, policies slowing down the uptake of new medicines could delay and reduce the health benefits of the innovation.

We found that diseases that were the target of more pharmaceutical innovation had smaller increases in hospital use, a finding that has also been shown in earlier studies. For instance, there is a study investigating how the use of newer cardiovascular drugs could affect cardiovascular hospitalization, where data from twenty OECD countries were used [45]. In countries that adopted new cardiovascular medicines more rapidly, there occurred a more rapid decline in cardiovascular hospitalization. The reduction in expenditure on cardiovascular hospitalization from the use of new drugs was almost four times as great as the increase in expenditure on cardiovascular medicines.

Another study showed that the increase in the use of HIV-Aids medicines led to a significant reduction in hospitalization among these patients and this saved about \$5,000 per patient per year [46]. The consequences of differential adoption of new medicines on mortality and hospitalization were also assessed using US state-level data. States in the US that had greater increases in the proportions of new medicines had smaller increases in the number of hospitalizations and nursing home admissions per person, and the reduction in costs of admission to hospitals and nursing homes was about four times as great as the increase in medication costs associated with the use of newer medicines [47]. Other studies have shown similar results [47–52].

When using the estimates of the effects of pharmaceutical innovation on longevity, hospitalization and expenditure to assess the cost-effectiveness of innovation on an aggregate level, innovation seems to be cost-saving compared to no innovation. This result may seem to be counter-intuitive and in opposition to what is often demonstrated in studies evaluating the cost-effectiveness of a specific treatment. In a cost-effectiveness analysis of a new treatment the comparison of the effects and costs is typically made with another available treatment. Only about 20% of all studies in the Tufts-New England Medical Center Cost-effectiveness registry indicated that treatments were found to be cost-saving [53], i.e. new drugs could be cost-effective but they are seldom presented as saving costs as compared to older treatments.

The diverging results could be due to a difference in methods and materials to capture health effects and the perspective of the analysis, i.e. which costs are included in the analysis. One possible explanation for why our results indicate cost savings, while others do not could be that in most cost-effectiveness studies, some health benefits are not accounted for. Also extrapolation from clinical trials might not capture all health benefits for a specific patient or patient population over time. The cost savings found in our study resulted from decreased hospital days: the reduction in annual hospital expenditure induced by pharmaceutical innovation was greater than the induced increase in annual pharmaceutical expenditure on an *aggregate level*, which differs from the approach in cost-effectiveness studies where the comparisons are mostly carried out on specific treatments and for specific patient populations.

Studies can be carried out based on aggregate data and on patient-level data. Each approach has its strengths and limitations. For a detailed methodological discussion

about the strengths and limitations in respective approaches see the review report by Steen Carlsson *et al.* [54]. In our study the analysis was performed using aggregate data. The most serious criticism of the aggregate approach is the issue of ecological fallacy. This fallacy means that *individual* members of a group are assumed to have the *average characteristics* of the group at large. However, statistics that accurately describe *group* characteristics do not necessarily apply to *individuals* within that group. Therefore, it may be argued that patient level data might produce more precise estimates of an intervention in contrast to aggregate data. However, Grunfeld and Griliches (1960, p. 1)[55] showed that “aggregation of economic variables can, and in fact frequently does, reduce...specification errors. Hence, aggregation does not only produce an aggregation error, but may also produce an aggregation gain.” In particular, patient-level data are surely more subject to selection effects (the sickest patients might get the newest – or oldest – treatments) than aggregate data.

However, it is still important to acknowledge that the aggregate approach does not produce estimates of the effects of specific treatments. From the present study we are only able to draw conclusions about the impact of pharmaceutical innovation on longevity on an aggregate level, and not the impact of specific classes or substances. It is possible that some treatments contributed significantly to the results, while other groups have not contributed at all, or even had a negative impact. Nevertheless, this study and other similar studies are useful as complements to studies on disaggregated data.

To conclude: although studies on an aggregate level have their limitations, they can provide useful evidence about the overall value of innovation. This information could be useful for evaluating and designing pharmaceutical policies on a system level, since these policies are important determinants of the use and uptake of new drugs. Studies of the impact of medical innovation on longevity and other health outcomes can be conducted using experimental, or quasi-experimental or observational design. The main limitation to the interpretation of observational studies, such as ours, is often the possible presence of unobserved confounders. Selection bias is one of the major problems of causal inference based on observational data. We used difference-in-differences (DID) models, which is a quasi-experimental technique used in econometrics that measures the effect of a treatment at a given period in time, while avoiding confounding factors, even if DID models do not overcome all bias problems [56]. In our equations we include variables to represent disease fixed effects and year fixed effects, respectively, and inclusion of these effects is therefore a difference-in-differences model. Since our models include year and disease fixed effects, they will control for the overall increase in Swedish longevity and for stable between-disease differences in mortality.

A correlation between two variables does not necessarily imply that one variable causes the other. The model must be well specified such that there is a theoretical reason to believe that any such spurious correlation is avoided. We believe the theoretical reasons as well as empirical findings from experimental clinical research (on the impact from different treatments and effects on morbidity and mortality, and resource consumption) can be used as complementary evidence of the policy relevance of studies such as ours.

## 4. Summary and conclusions

In summary, our study as well as other studies clearly indicates that pharmaceutical innovation, on an aggregate level, contributes to improved health and might decrease the need for other health care resources. It is therefore important to design pharmaceutical policies that allow society and patients to fully benefit from the value of new medicines. However, new medicines also add to pharmaceutical expenditures, which on average constitute about 15% of overall health expenditures in the OECD countries and about 10% in Sweden. Limited resources and budget constraints are challenges for policy makers. Clearly, policies of investment in health and access to medicines need to be balanced and coordinated with other policy goals, i.e. economic, industrial and intergenerational policies.

One important limitation of our study, since we use aggregate data, is that it lacks ability to inform as to which products contributed to the increased life expectancy. It could be that some products contributed to a large extent, while others did not. It is therefore important to prioritize so that resources could be allocated to these products, where the most potential benefits exist.

Several indicators show that the early uptake and use of new medicines have declined during the last decades in Sweden, which could be due to the pharmaceutical policies introduced during the period. An interesting question is therefore whether investment in faster uptake and increased use of medicines within the total health care budget could produce even more benefits. Neither the recent Swedish government inquiry nor our study answered that question. However, we found that the introduction of new drugs accounted for about a third of the longevity increase during the period, while expenditure for pharmaceuticals has been stable at around 10% of the total health care budget. At the same time, our findings suggested that hospital days were reduced, indicating a decreasing pressure on other health care resources.

Another important consideration is that in our study we only analyzed how new pharmaceuticals contributed to longevity, which is not the only contribution from pharmaceutical innovation. Many treatments affect mainly patients' quality of life, but this is not captured in this study. Hence, the contribution of pharmaceutical innovation could be strongly underestimated with this approach.

Early *availability* of new drugs is just one step towards patients' access to new and more effective pharmaceutical therapies. Of crucial importance is the timing at which the health care providers adopt the new therapies. Our study showed that the benefits in terms of longevity and decreasing number of hospital days depended on the introduction of new medicines several years earlier. This could mean that the benefits could occur earlier, if the rate of uptake was accelerated.

Accessibility of new substances within a class and not the number of classes was found to have significant effects on longevity. One conclusion could be that there is a benefit to encouraging incremental innovation as well as breakthrough innovation. The utility of VBP in encouraging innovation and value-added health care depends largely on the assessment process, including when and how the review was performed, and resulting decision-making procedures. Overall, it could be argued that the VBP approach and current methodologies are limited in their ability to deliver relevant knowledge on

incremental innovation and on dynamic efficiency, and that this is one of its fundamental flaws. It is however important to prioritize so that resources could be allocated to these products, where the potential of new pharmaceuticals that increase life expectancy and/or lead to lower use of other resources exist.

There is obviously a need for further discussions of how to shape a system in a way that would allow the correct balance between rewarding and encouraging manufacturers to produce innovative new treatments, while at the same time ensuring sustainable health care budgets. The question is, did the policies that were introduced create a system that became too restrictive to be optimal from a societal perspective? We believe that current policies, such as the VBP together with the regional reforms and decentralized budgets that impact the rate of uptake and use of new medicines should be carefully reviewed before shaping a new system. This is critical to ensure a system with the right and desired balance.

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## Rapporter från SNS forskningsprogram *Värdet av nya läkemedel*

*Värdet av nya läkemedel – en förstudie* av Ulf-G Gerdtham, Ulf Persson och Katarina Steen Carlsson, Institutet för Hälso-och Sjukvårdsekonomi (IHE), Lund. Maj 2011

*Målinriktad behandling av bröstcancer* av Adam Lundqvist, Nils Wilking, Ulf-G Gerdtham, Ulf Persson och Katarina Steen Carlsson, samtliga knutna till IHE. Januari 2013

*Medicinska framsteg i behandling av kronisk myeloisk leukemi* av Adam Lundqvist, Anne-Charlotte Norlenius Ohm, Paul Dickman, Martin Höglund, Leif Stenke, Ulf-G Gerdtham, Ulf Persson, Magnus Björkholm och Katarina Steen Carlsson, samtliga knutna till IHE. Februari 2013

*Reumatoid artrit, biologisk behandling och förlorade arbetsdagar – exempel på användning av svenska hälsodataregister* av Martin Neovius, Institutionen för medicin, Karolinska Institutet. Februari 2013

*Värdet av statiner – användningsmönster och följsamhet vid behandling* av Ingegärd Anveden Berglind, Helle Kieler, Marie Linder, Anders Sundström, Björn Wettermark, Anna Citarella och Morten Andersen, Institutionen för medicin, Karolinska Institutet. Februari 2013

*Behandling av diabetes i ett hundraårigt perspektiv* av Katarina Steen Carlsson, Christian Berne, Pierre Johansen, Gustav Lanne och Ulf-G Gerdtham, samtliga knutna till IHE. Februari 2013

*The Value of Pharmaceutical Innovation – within the context of policies that impact use of new medicines in Sweden* av Billie Pettersson, MSD (gästforskare vid SNS i detta projekt) och Frank R. Lichtenberg, Columbia University, New York. Maj 2013

*Värdering och implementering av nya läkemedel – med exempel från cancerområdet* av Bengt Jönsson, Handelshögskolan i Stockholm, och Nils Wilking, Karolinska Institutet. Maj 2013

*Professionen, pennan och pengarna – regionala skillnader i användning av läkemedel* av Mats Brommels, Johan Hansson, Emma Granström och Emma Wåhlin, Medical Management Centrum (MMC), Karolinska Institutet. Maj 2013

*Nya läkemedel i tidig implementeringsfas – om förekomst av och kostnader för läkemedelsrelaterad sjuklighet* av Hanna Gyllensten, Nordic school of public health NHV, Göteborg, och Katarina Steen Carlsson, IHE. September 2013 (prel.)

*Räkna med register och randomisera mera!* av Martin Neovius och Joakim Ramsberg, Karolinska Institutet. September 2013 (prel.)

*Egenansvar och finansiering av läkemedel – när är det rimligt att betala själv?* av Per Carlsson och Gustav Tinghög, Institutionen för medicin och hälsa, Linköpings universitet. September 2013 (prel.)

*Slutrapport.* Oktober 2013 (prel.)