The Impact of Biomedical Innovation on Retirement and Disability

Frank R. Lichtenberg
frank.lichtenberg@columbia.edu

In previous research (see attached new working paper), I performed econometric analyses of the hypothesis that biomedical innovation has played a major role in reducing premature mortality and hospital utilization, by investigating whether diseases for which there has been more biomedical innovation tended to have larger declines in mortality and hospital utilization. I developed and analyzed two types of innovation measures: measures of the mean vintage of medical goods and services discussed in thousands of articles about a disease, and a measure of the number of drugs ever approved to treat a disease. My estimates provided strong support for this hypothesis: they indicated that drug innovation reduced premature (before age 65 or 85) mortality by 30-33% between 1999 and 2018, and that all biomedical innovation reduced it by 43-54%.

For the NBER RDRC, I propose to use similar methods to study the impact of biomedical innovation on retirement and disability. From surveys conducted since at least the mid-1990s, such as the Medical Expenditure Panel Survey (MEPS) and the National Health Interview Survey (NHIS), we have the following information about large numbers of individuals: (1) which medical conditions (diseases) they have; (2) whether or not the person is employed, including whether the person has retired due to poor health; and (3) whether the person is disabled, and if so, the extent and nature of his or her disabilities.[1] From these data, we will be able to compute the fraction of people with each medical condition who were unable to work or were disabled in each year, from at least 1996 to the present. To test the hypothesis that biomedical innovation has reduced disability and early retirement due to poor health, I will estimate 2-way fixed-effects model such as:

$$DISAB_{ct} = \beta_1 VINTAGE_ALL_{ct} + \beta_2 \ln(CUM_FDA_{c,t-k}) + \alpha_c + \delta_t + \varepsilon_{ct}$$

where

$DISAB_{ct}$ = the odds that a person with medical condition c in year t is disabled or retired early due to poor health

$VINTAGE_ALL_{ct}$ = the (frequency-weighted) mean vintage of treatment (drug and technique/equipment) descriptors assigned to PubMed articles about medical condition c published in year t

$CUM_FDAc_{,t-k}$ = the number of drugs (or classes of drugs) used to treat medical condition c ever approved by the FDA by the end of year t-k

I believe that the proposed research is related to the following two focal areas: informing long-term projections and models, and trends in disability.

[1] I also hope to obtain additional data, including data on the number of diagnoses cited in initial claims for disability benefits by impairment code, similar to those shown in Table 1 of https://www.ssa.gov/policy/docs/workingpapers/wp113.html

The impact of biomedical innovation on U.S. longevity and hospital utilization, 1999-2018

Frank R. Lichtenberg, PhD

frank.lichtenberg@columbia.edu

Columbia University,
National Bureau of Economic Research, and CESifo

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Abstract

In the first two decades of the 21st century in the U.S., there has been almost no growth in median income, and there have been sharp increases in obesity and "deaths of despair." Despite these trends, premature mortality and hospital utilization have declined substantially. Between 1999 and 2018, the age-adjusted rate of years of potential life lost before age 85 declined by 13% for all Americans, and almost twice as much for African-Americans. And between 2000 and 2015, the crude rate of hospital discharges per 100,000 persons declined by 11%.

In this study, we perform an econometric analysis of the hypothesis that biomedical innovation has played a major role in reducing premature mortality and hospital utilization, by investigating whether diseases for which there has been more biomedical innovation tended to have larger declines in mortality and hospital utilization. We develop and analyze two types of innovation measures: a measure of the number of drugs ever approved to treat a disease, and measures of the mean vintage of medical goods and services discussed in thousands of articles about a disease.

Our estimates provide strong support for this hypothesis: they indicate that drug innovation reduced premature (before age 65 or 85) mortality by 30-33% between 1999 and 2018, and that all biomedical innovation reduced it by 43-54%. Drug innovation appears to have reduced premature mortality among African-Americans as much as it reduced it among other Americans. The estimates also indicate that drug innovation reduced the number of hospital days by 24% between 2000 and 2015, and that all biomedical innovation reduced it by 51%.

Even if we ignore the effect of new drugs on hospital utilization, our estimates indicate that the drugs launched during 1988-2006 were very cost–effective, overall. When the effect of hospital utilization is accounted for, the estimates indicate that drug innovation was cost-saving: the estimated reduction in 2015 hospital expenditure attributable to previous drug approvals was 56% larger than 2015 expenditure on the drugs.

I. Introduction

Longevity increase is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that "improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services." Murphy and Topel (2006) estimated that cumulative gains in life expectancy after 1900 were worth over $1.2 million to the representative American in 2000, whereas post-1970 gains added about $3.2 trillion per year to national wealth, equal to about half of GDP. The United Nations' Human Development Index, which is used to rank countries into four tiers of human development, is a composite statistic of life expectancy, income per capita, and education (United Nations Development Program (2020)).[1]

There is a consensus among macroeconomists that technological progress is the principal source of GDP growth. Romer (1990, p. S71) argued that "growth…is driven by technological change that arises from intentional investment decisions made by profit-maximizing agents." Jones (2002) argued that "long-run growth is driven by the discovery of new ideas throughout the world." Aghion and Howitt (2005) said that "technological progress, the mainspring of long-run economic growth, comes from innovations that generate new products, processes and markets. Innovations in turn are the result of deliberate research and development activities that arise in the course of market competition." Grossman and Helpman (1991) developed "a model of repeated product improvements in a continuum of sectors. Each product follows a stochastic progression up a quality ladder." Bresnahan and Gordon (1996) said that "new goods are at the heart of economic progress." As noted by Jovanovic and Yatsenko (2012), in "the Spence–Dixit–Stiglitz tradition…new goods [are] of higher quality than old goods." And Chien (2015) said that 'it has been shown, both theoretically and empirically, that technological progress is the main driver of long-run growth.'

[1] Between 1999 and 2014, U.S. life expectancy at birth increased from 76.7 to 78.9 years (Arias and Xu (2019)). However, it declined to 78.6 years in 2017. Therefore, the U.S. Human Development Index grew more slowly than per capita income during 2014-2017; it may have even declined.

This study will examine the impact that biomedical innovation had on two important health outcomes—U.S. mortality[2] and hospital utilization rates[3]—during the period 1999-2018. A difference-in-differences, or two-way fixed effects, methodology will be used: we will investigate whether diseases for which there has been more biomedical innovation tended to have larger declines in mortality and hospital utilization. We will examine the impact that biomedical innovation had on mortality of African-Americans as well as of all Americans.

There are two main types of biomedical innovation: pharmaceutical innovation, and innovation in analytical, diagnostic and therapeutic techniques and equipment.[4] Most private biomedical research spending is about pharmaceuticals: according to Dorsey et al (2010), 88% of private U.S. funding for biomedical research came from pharmaceutical and biotechnology firms. We will construct both a composite measure of biomedical innovation and measures of both components.[5]

Two ways of measuring innovation are suggested by the economic growth literature. The first measure is the change in the cumulative number, or stock, of ideas. For example, Jones (2002) argued that "growth in any particular country is driven in the long run by the implementation of ideas that are discovered throughout the world. In the long run, the stock of ideas is proportional to worldwide research effort…" (p. 234). The second measure is the mean *vintage* (year of invention) of goods (e.g. capital) and services. In 1987, the Royal Swedish Academy of Sciences awarded the Alfred Nobel Memorial Prize in Economic Sciences to Robert Solow for his contributions to the theory of economic growth. The Academy cited Solow's 1960 article, *Investment and Technical Progress*, in which he presented a

> new method of studying the role played by capital formation in economic growth. His basic assumption was that technical progress is "built into" machines and other capital goods and that this must be taken into account when making empirical measurements of

[2] Longevity is closely (inversely) related to mortality rates. According to the World Health Organization's Global Health Estimates, 61% of the disability-adjusted life-years lost in the U.S. in 2016 were due to premature mortality.
[3] Hospital care was the single largest component of U.S. health expenditure in 2018, accounting for 33% of expenditure. Physician and clinical services accounted for 20%, and prescription drugs accounted for 9% (Centers for Medicare & Medicaid Services (2020a)).
[4] Two of the main branches of the National Library of Medicine (NLM)'s Medical Subject Headings (MeSH) thesaurus are Chemicals and Drugs (branch D) and Analytical, Diagnostic and Therapeutic Techniques, and Equipment (branch E). MeSH is a controlled and hierarchically-organized vocabulary used for indexing, cataloging, and searching of biomedical and health-related information. MeSH includes the subject headings appearing in MEDLINE/PubMed, the NLM Catalog, and other NLM databases.
[5] However, separate identification of the effects of drug innovation and technique/equipment innovation may be difficult: "drug therapy" is a MeSH Subheading of the MeSH (branch E) Heading "Therapeutics" 19% of the time.

> the role played by capital. This idea then gave birth to the "vintage approach" (a similar idea was discussed by Leif Johansen in Norway at about the same time)…The most important aspect of Solow's article was not so much the empirical outcome, but the method of analyzing "vintage capital." Nowadays, the vintage capital concept has many other applications and is no longer solely employed in analyses of the factors underlying economic growth…The vintage approach has proved invaluable, both from the theoretical point of view and in applications such as the analysis of the development of industrial structures.

Three decades later, Boucekkine, de la Croix, and Licandro (2018) cited the "increasingly common view that some fundamental economic growth issues (like technology diffusion, for example) do require the vintage structure to be better appraised…much work is needed to bring the vintage models closer to the data."

We will develop and analyze both types of innovation measures, i.e. a measure of the number of drugs ever approved to treat a disease,[6] and measures of the mean vintage of medical goods and services discussed in thousands of articles about a disease. Previous studies have examined the impact of only one of these innovation measures on mortality. Several studies (e.g. Lichtenberg (2019a, 2020, 2019b)) have examined the impact of new drug approvals on mortality in Canada, Ireland, and 27 countries. One study (Lichtenberg (2019c)) examined the impact of the mean vintage of medical goods and services on mortality (but not on hospital utilization) in the U.S., but that study was only about cancer, which accounted for less than one-fourth of years of potential life lost before age 85 in the U.S. in 2018 (Centers for Disease Control (2020a)).

In the next section, we describe the measures of biomedical innovation we will analyze. In Section III, we present econometric models of mortality and hospital utilization that incorporate those measures. Data sources are enumerated and descriptive statistics are reported in Section IV. Empirical results are presented in Section V. Key implications of the estimates are discussed in Section VI. The final section provides a summary and conclusions.

[6] At present, it is not possible to construct measures of the number of devices or procedures ever developed to treat a disease.

II. Measuring biomedical innovation

A. Number of drugs ever approved to treat a disease

One of the measures of biomedical innovation we will analyze is the number of drugs (WHO ATC 5th-level chemical substances[7]) ever approved by the FDA to treat a disease.[8, 9] As illustrated in Figure 1, there has been substantial variation across diseases in the growth in the number of drugs ever approved. For example, between 1998 and 2018, the number of anemia drugs ever approved increased by 44%, while the number of tuberculosis drugs ever approved increased by 6%.

The approval of a drug indicates that patients *could* have been treated with that drug, not necessarily that patients *were* treated with that drug. We would prefer to estimate models in which the explanatory variables measured the drugs *actually used* to treat patients, by disease and year. We have annual data for 2007-2017 on the utilization of each drug in the U.S. However, many drugs have multiple indications—50% of drugs have 2 or more indications (causes of disease in the WHO Global Health Estimates disease classification), and 7% of drugs have 5 or more indications—and our data do not enable us to determine how often each drug was used for each of its (labeled) indications.

Since our drug approval variables are imperfect measures of exposure to pharmaceutical innovation, the estimated coefficients on those variables may be biased towards zero, and our

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[7] In the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, active substances are classified in a hierarchy with five different levels. The system has fourteen main anatomical/pharmacological groups or 1st levels. Each ATC main group is divided into 2nd levels which could be either pharmacological or therapeutic groups. The 3rd and 4th levels are chemical, pharmacological or therapeutic subgroups and the 5th level is the chemical substance. The 2nd, 3rd and 4th levels are often used to identify pharmacological subgroups when that is considered more appropriate than therapeutic or chemical subgroups. 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)

Thus, in the ATC system all plain metformin preparations are given the code A10BA02. The complete ATC classification system can be viewed at Wikipedia (2020).

[8] We have also analyzed the number of "drug classes" (WHO ATC 4th-level chemical subgroups) ever approved to treat a disease. The results obtained from that analysis were quite similar to the results obtained from the analysis of the number of drugs.

[9] Investigating the impact of new dosage forms or routes of administration of drugs may also be possible and worthwhile.

estimates of their effect on mortality are likely to be conservative. Here is the first paragraph of the eminent MIT econometrician Jerry Hausman's (2001, p. 57) article on mismeasured variables in econometric analysis:

> The effect of mismeasured variables in statistical and econometric analysis is one of the oldest known problems, dating from the 1870s in Adcock (1878). In the most straightforward regression analysis with a single regressor variable, the least squares estimate is downward biased in magnitude toward zero. While a mismeasured right-hand side variable creates this problem, a mismeasured left-hand side variable under classical assumptions does not lead to bias. The only result is less precision in the estimated coefficient and a lower t-statistic.

The effect of new drug approvals on mortality is likely to be subject to a lag, for two reasons: (1) peak utilization of a drug occurs years after it is approved, and (2) mortality may not decline immediately after utilization increases. Most drugs are consumed to treat chronic conditions, and they may have to be used for several years to achieve peak effectiveness.

We can provide evidence about the first type of lag, from approval to utilization, by estimating the following model:

$$\ln(N_SU_{sn}) = \rho_s + \pi_n + \varepsilon_{sn} \qquad (1)$$

where

N_SU_{sn} = the number of standard units of substance s sold in the U.S. n years after it was approved by the FDA (n = 0, 1,…, 20)

ρ_s = a fixed effect for substance s

π_n = a fixed effect for age n

The expression $\exp(\pi_n - \pi_5)$ is a "relative utilization index": it is the mean ratio of the quantity of a drug sold n years after it was approved to the quantity of the same drug sold 5 years after it was approved. We estimated eq. (1) using annual data for the period 2007-2017 on 818 drugs. Estimates of the "relative utilization index" are shown in Figure 2. These estimates indicate that it takes about 5 years for a drug to attain its peak level of utilization. The number of standard units 5 years after FDA approval is about twice as great as the number of standard units one year after FDA approval. Moreover, Figure 2 provides a conservative estimate of the slope of the

age-utilization profile, because there was zero utilization of some molecules in the first few years after they were first approved.[10,11]

The impact of a new drug approval on mortality is likely to depend on the *quality*, or effectiveness, of the drug as well as on its *quantity*, or utilization; its impact may be proportional to quality×quantity. More recently approved drugs are likely to be of higher quality than drugs approved years before. For a given utilization profile, the greater the rate of quality improvement, the shorter the lag from new drug approval to mortality reduction.

B. Mean vintage of medical goods and services discussed in articles about a disease

The other measure of biomedical innovation we will analyze is the vintage of medical goods and services discussed in articles about a disease. The MEDLINE/PubMED database will be used to construct measures of the vintage of medical goods and services applied to many diseases over time. MEDLINE/PubMED is the U.S. National Library of Medicine's (NLM's) premier bibliographic database; in 2017, it contained about 27 million references to journal articles published since 1946 in 5400 of the world's leading biomedical journals. MEDLINE/PubMED records are indexed with the Medical Subject Headings (MeSH) thesaurus, a controlled vocabulary produced by the NLM. MeSH terms ("descriptors") are organized in a hierarchical structure (the MeSH Tree).[12] Three of the four largest of the 16 main branches of the MeSH tree are Diseases (branch C), Chemicals and Drugs (branch D), and Analytical, Diagnostic and Therapeutic Techniques, and Equipment (branch E). It may be useful to consider C-branch descriptors as descriptors of *problems*, and D- and E-branch descriptors as descriptors of potential *solutions.*

On average, about nine descriptors are assigned to an article.[13] Many articles include both (1) one or more Diseases descriptors, and (2) either Chemicals and Drugs descriptors,

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[10] Since the dependent variable of eq. (2) is logarithmic, observations for which $N_SU_{sn} = 0$ had to be excluded.
[11] Generic entry usually occurs about 12 years after FDA approval, but Figure 2 suggests that utilization continues to decline after generic entry occurs. This may be due to a sharp decline in marketing caused by the loss of market exclusivity; see Duflos and Lichtenberg (2012).
[12] Most Descriptors indicate the subject of an indexed item, such as a journal article, that is, what the article is about. https://www.nlm.nih.gov/mesh/intro_record_types.html..
[13] A total of 247 million descriptors were assigned to the 27 million articles in the 2017 edition of MEDLINE/PubMED.

Analytical, Diagnostic and Therapeutic Techniques, and Equipment descriptors, or both.[14] In other words, many articles discuss both a medical problem and one or more potential solutions to the problem. The NLM publishes MEDLINE Co-Occurrences (MRCOC) Files (U.S. National Library of Medicine (2020)), which summarize the MeSH Descriptors that occur together in MEDLINE citations in each year.[15]

The MeSH Section staff continually revise and update the MeSH vocabulary.[16] Staff subject specialists are responsible for areas of the health sciences in which they have knowledge and expertise. In addition to receiving suggestions from indexers and others, the staff collect new terms as they appear in the scientific literature or in emerging areas of research; define these terms within the context of existing vocabulary; and recommend their addition to MeSH. Professionals in various disciplines are also consulted regarding broad organizational changes and close coordination is maintained with various specialized vocabularies.

We will define the vintage of a descriptor (e.g. a Chemicals and Drugs descriptor) as the year in which the descriptor first appeared in the MEDLINE Co-Occurrences File.[17] As shown in Figure 3, between 1950 and 2015, the number of drug descriptors that had ever appeared in MEDLINE more than tripled, from 2816 to 9471, and the number of techniques and equipment descriptors that had ever appeared in MEDLINE almost doubled, from 1187 to 2306. We will compute the mean vintage of drugs and techniques, by disease and year, by combining data on the frequency of co-occurrences with the vintage data.

The MeSH FTP Archive includes lists of new MeSH descriptors added each year since 1999. For example, one file shows MeSH descriptors added in 2016. Some new MeSH descriptors are not really innovations. For example, one MeSH descriptor added in 2016 was "Alcohol Drinking in College" (UI D000067292); this "idea" undoubtedly occurred to someone well before 2016. Hence, the relative frequency of new MeSH descriptors is a noisy, or imperfect, measure of the penetration of new medical ideas.[18] If this measurement error is random, it will bias the coefficients on our measures of new ideas towards zero.

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[14] For example, 1432 MEDLINE articles included both the Disease descriptor "hyperlipidemia" and the Chemicals and Drugs descriptor "atorvastatin"; the year with the peak number (123) of those articles was 2003.
[15] These files are very large: the summary_CoOccurs_2019 file contains more than 250 million observations.
[16] See Changes to MeSH Terminology.
[17] Due to left-censoring of the data, this definition is imperfect: some drugs (e.g. aspirin) and techniques were invented many years before the year in which they first appeared in MEDLINE.
[18] Lichtenberg (2019c) showed that newer descriptors are assigned to "research articles" (articles that resulted from research funding, when that financial support is mentioned in the articles) than to "non-research" articles.

One measure of vintage we will analyze is the (frequency-weighted) mean vintage of all "treatment descriptors" (i.e. both D-branch and E-branch descriptors) used in articles about disease d published in year t:

$$VINTAGE_ALL_{dt} = \frac{\Sigma_i \, FREQ_{idt} \, FIRST_YEAR_i}{\Sigma_i \, FREQ_{idt}}$$

where

$VINTAGE_ALL_{st}$ = the (frequency-weighted) mean vintage of MeSH D-branch and E-branch descriptors assigned to articles about disease d published in year t

$FREQ_{idt}$ = the number of times MeSH D-branch or E-branch descriptor i was assigned to articles about disease d published in year t

$FIRST_YEAR_i$ = the first year in which MeSH D-branch or E-branch descriptor i appeared in any article in the MEDLINE Co-Occurrences File

Because the time coverage of the MEDLINE Co-Occurrences File is 1965 to the present, the variable $FIRST_YEAR_i$ is left-censored. Therefore, a measure like the following, based on a binary function of FIRST_YEAR, may be more appropriate than a measure based on FIRST_YEAR itself:

$$POST1990_ALL_{dt} = \frac{\Sigma_i \, FREQ_{idt} \, POST1990_i}{\Sigma_i \, FREQ_{idt}}$$

where

$POST1990_ALL_{dt}$ = the (frequency-weighted) fraction of MeSH D-branch and E-branch descriptors that first appeared in the MEDLINE Co-Occurrences File after 1990 assigned to articles about disease d published in year t

$POST1990_i$ = 1 if $FIRST_YEAR_i > 1990$
= 0 if $FIRST_YEAR_i \leq 1990$

We will also analyze a similar measure constructed using a different cutoff year, 2000:

$POST2000_ALL_{dt}$ = the (frequency-weighted) fraction of MeSH D-branch and E-branch descriptors that first appeared in the MEDLINE Co-Occurrences File after 2000 assigned to articles about disease d published in year t

In addition to analyzing measures of the mean vintage of all treatment descriptors (i.e. both D-branch and E-branch descriptors), we will distinguish between the mean vintage of drug (D-branch) descriptors and technique/equipment (E-branch) descriptors. For example, we will analyze the following measures:

$VINTAGE_DRUG_{dt}$ = mean vintage of drug (D-branch) descriptors assigned to articles about disease d published in year t

$VINTAGE_TECH_{dt}$ = mean vintage of technique/equipment (E-branch) descriptors assigned to articles about disease d published in year t

III. Econometric models of mortality and hospital utilization

Our analysis of the impact that biomedical innovation had on U.S. mortality will be based on variants of the following 2-way fixed-effects model:

$$\ln(MORT_{dt}) = \beta_1 \ln(CUM_ATC5_{d,t-12}) + \beta_2 VINTAGE_ALL_{dt} + \alpha_d + \delta_t + \varepsilon_{dt} \qquad (2)$$

where $MORT_{dt}$ is one of the following variables:

$YLL85_TOT_{dt}$ = the number of years of potential life lost by all Americans before age 85 due to disease d in year t (t = 1999, 2018)[19]

$YLL65_TOT_{dt}$ = the number of years of potential life lost by all Americans before age 65 due to disease d in year t[20]

$YLL85_AA_{dt}$ = the number of years of potential life lost by African-Americans before age 85 due to disease d in year t

$YLL65_AA_{dt}$ = the number of years of potential life lost by African-Americans before age 65 due to disease d in year t

and

$CUM_ATC5_{d,t-12}$ = the number of drugs (WHO ATC 5th-level chemical substances) used to treat disease d ever approved by the FDA by the end of year t-12 = $\sum_s TREAT_{sd} * APPROVED_{s,t-12}$

$TREAT_{sd}$ = 1 if substance s is used to treat disease d

[19] 1999 was the first year in which causes of U.S. deaths were classified using the ICD-10 classification.

[20] 85 and 65 are the highest and lowest age cutoffs used in the CDC's *WISQARS Years of Potential Life Lost (YPLL) Report* (Centers for Disease Control (2020a)). The World Health Organization uses a higher age cutoff (approximately 92) in its Global Health Estimates database.

= 0 otherwise

$APPROVED_{s,t-12}$ = 1 if substance s had been approved by the FDA by the end of year t-12
= 0 otherwise

α_d = a fixed effect for disease d

δ_t = a fixed effect for year t

According to eq. (2), mortality depends on the number of drugs that had ever been approved 12 years earlier. We estimated models with different lag lengths. The estimates indicated that mortality is significantly inversely related to the number of drugs that had ever been approved 2-20 years earlier, but that mortality is most strongly related to the number of drugs that had ever been approved 12 years earlier.

It would be ideal to control for the incidence of disease d in year t in eq. (2).[21] Unfortunately, reliable data on the incidence of most diseases are not available. However, we believe that inability to control for incidence will not result in overestimation of the effect of biomedical innovation on mortality; it may even result in *underestimation* of the effect, because an exogenous increase in disease incidence is likely to result in both higher mortality and more biomedical innovation.[22] Orphan drug policy in the U.S. and other countries is predicated on the hypothesis that, in the absence of financial incentives, few new drugs will be developed for rare (low-incidence) diseases. Acemoglu and Linn (2004) found "economically significant and relatively robust [positive] effects of market size on innovation." Sanger et al (2020) reported that "in the three months since the [Coronavirus] began its deadly spread, China, Europe and the United States have all set off at a sprint to become the first to produce a vaccine." A potential indicator of disease incidence is the number of articles published about a disease (although this may be affected by the amount of biomedical innovation). We estimated some versions of eq. (2) that included $\ln(N_PUBS_{dt})$, where N_PUBS_{dt} = the number of publications about disease d in year t. The coefficient on this variable was positive but only marginally significant, and inclusion of this variable had very little effect on estimates of β_1 and β_2.

[21] Controlling for incidence would be better than controlling for prevalence, because (conditional on incidence) prevalence is endogenous: higher mortality reduces prevalence.
[22] The adage "necessity is the mother of invention" appears in translations of Plato's Republic.

Estimates of eq. (2) will provide evidence about the impact of biomedical innovation about a disease on mortality from that disease, but they will not capture possible spillover effects of the innovation on mortality from *other* diseases. These spillovers may be either positive or negative. For example, cardiovascular drug innovation could reduce mortality from cardiovascular disease, but increase mortality from the "competing risk" of cancer. On the other hand, biomedical innovation about mental disorders could reduce mortality from other medical conditions. Prince et al (2007) argued that "mental disorders increase risk for communicable and non-communicable diseases, and contribute to unintentional and intentional injury. Conversely, many health conditions increase the risk for mental disorder, and comorbidity complicates help-seeking, diagnosis, and treatment, and influences prognosis."

Eq. (2) is a model of the (log of the) *level* of mortality. A model of mortality *growth* can be derived from it. Setting t equal to its initial and final values (1999 and 2018, respectively) yields the following equations:

$$\ln(MORT_{d,1999}) = \beta_1 \ln(CUM_ATC5_{d,1987}) + \beta_2 VINTAGE_ALL_{d,1999} + \alpha_d + \delta_{1999} + \varepsilon_{d,1999} \quad (3)$$

$$\ln(MORT_{d,2018}) = \beta_1 \ln(CUM_ATC5_{d,2006}) + \beta_2 VINTAGE_ALL_{d,2018} + \alpha_d + \delta_{2018} + \varepsilon_{d,2018} \quad (4)$$

Subtracting eq. (3) from eq. (4),

$$\Delta\ln(MORT) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon' \quad (5)$$

where

$$\Delta\ln(MORT) = \ln(MORT_{d,2018}/MORT_{d,1999})$$

$$\Delta\ln(CUM_ATC5_{t-12}) = \ln(CUM_ATC5_{d,2006}/ CUM_ATC5_{d,1987})$$

$$\Delta VINTAGE_ALL = VINTAGE_ALL_{d,2018} - VINTAGE_ALL_{d,1999}$$

$$\delta = (\delta_{2018} - \delta_{1999})$$

$$\varepsilon' = (\varepsilon_{d,2018} - \varepsilon_{d,1999})$$

According to eq. (5), the 1999-2018 log change (approximately the percentage change) in mortality from disease d depends on the log change between 1987 and 2006 in the number of drugs ever approved for disease d and on the 1999-2018 change in treatment vintage.

Eq. (5) will be estimated by weighted least-squares, weighting by $(MORT_{d,1999} + MORT_{d,2018})/2$. In addition to estimating eq. (5), we will estimate versions of the equation in which one of the regressors is excluded, and in which the change in VINTAGE_ALL is

disaggregated into its two components: the changes in VINTAGE_DRUG and VINTAGE_TECH.

To assess the impact of biomedical innovation on hospital utilization, we will estimate models similar to eq. (5) for a different sample period (2000-2015), replacing $MORT_{dt}$ by $HOSP_{dt}$, where $HOSP_{dt}$ is one of the following variables:[23]

$HOSP_DAYS_{dt}$ = the number of days of hospital care (= the number of discharges * average length of stay) due to disease d in year t (t = 2000, 2015)

$HOSP_COST_{dt}$ = the cost of hospital care (= the number of discharges * mean cost per discharge) due to disease d in year t

$HOSP_DEATHS_{dt}$ = the number of hospital deaths due to disease d in year t[24]

These models will also be estimated by weighted least-squares, weighting by $(HOSP_{d,2000} + HOSP_{d,2015})/2$.

IV. Data sources and descriptive statistics

A. Data sources

Mortality data. Mortality data were obtained from the 1999 and 2018 Multiple Cause of Death data files (National Center for Health Statistics (2020)).

Hospital utilization data were obtained from HCUPnet - Hospital Inpatient National Statistics (Agency for Healthcare Research and Quality (2020a)).

Drug FDA approval dates. Data on FDA approval dates of drugs (coded by WHO ATC) were obtained from two sources. One source was DrugCentral **(**Ursu et al (2019)**),** an online drug information resource created and maintained by the Division of Translational Informatics at the University of New Mexico in collaboration with the IDG Consortium, a U54 program funded by the NIH Common Fund. The other source was the e-Drug3D-PD data set published by CNRS (the French National Center for Scientific Research (2020)). DrugCentral provided FDA

[23] All 3 variables are measured as rates per 100,000 population.

[24] Hospital deaths include emergency department deaths as well as deaths in the hospital following admission from the emergency department.

approval dates of 2540 ATC5 codes; the CNRS dataset provided FDA approval years of 2211 ATC5 codes. Both datasets provided data on FDA approval years for 2047 ATC5 codes. The correlation between the two sources was very high: 0.97. When the two sources differed, we used the earlier FDA approval year. At least one source provided an FDA approval year for 2704 ATC codes.

Drug indications data. Indications (coded by ICD-10) of chemical substances were obtained from Thériaque, a database produced by the French Centre National Hospitalier d'Information sur le Médicament (2020).[25]

Drug utilization and expenditure data. Data on the quantity (number of standard units) and value (in USD) of prescription drugs sold in the U.S., by WHO ATC5 chemical substance and year (2007-2017) were obtained from the IQVIA MIDAS database.

Treatment vintage data. Data (on $FREQ_{idt}$ and $FIRST_YEAR_i$) required to construct measures of the vintage of drugs and techniques/equipment, by disease and year, were obtained from the 2019 Summary Co-Occurrences File (U.S. National Library of Medicine (2020)). The Unified Medical Language System (U.S. National Library of Medicine (2020b)) mrsat_2019aa file was used to determine whether each descriptor is a drug descriptor or a techniques/equipment descriptor.

Disease classifications. The disease classification used in the mortality analysis is the 113 cause recode of the Underlying Cause of Death (Centers for Disease Control (2020b)).[26] The disease classification used in the hospital utilization analysis is the one used in the Clinical Classifications Software Refined (CCSR) for ICD-10-CM Diagnoses (Agency for Healthcare Research and Quality (2020b)).

B. Descriptive statistics

Aggregate mortality data on all Americans are shown in Panel A of Table 1. Between 1999 and 2018, the number of deaths increased by 18.9%, and YLL85 increased by 14.6%. The YLL85 crude rate (YLL85 per 100,000 population below age 85) declined by 1.7%, and the

[25] Thériaque provides data only on labeled indications; it does not provide data on off-label indications.
[26] I am extremely grateful to Olivier Bodenreider at the U.S. National Library of Medicine for providing a mapping from MeSH disease codes to ICD10 codes.

YLL85 age-adjusted rate declined by 13.1%. The YLL65 crude rate declined by 6.7%, and the YLL65 age-adjusted rate declined by 7.7%.

Aggregate mortality data on African-Americans are shown in Panel B of Table 1. Crude and age-adjusted rates of YLL before ages 65 and 85 declined more for African-Americans than they did for other Americans.

Aggregate hospital data are shown in Panel C of Table 1. Between 2000 and 2015, the rate of discharges per 100,000 persons declined by 11.0%; mean length of stay remained the same. Mean and aggregate costs both increased by about 88%.[27]

Figure 4 shows the number of WHO ATC5 chemical substances and WHO ATC4 chemical subgroups ever approved, 1939-2018.

Data on the vintage of treatment descriptors in 1999 and 2018 are shown in Table 2. Panel A shows data on all treatments. Our vintage calculations are based on 3.4 million and 5.8 million descriptors in 1999 and 2018, respectively. Mean (left-censored) vintage increased by 3.4 years during the period. The fraction of post-1990 treatments increased from 10% to 20%, and the fraction of post-2000 treatments increased from 0% to 5%. Panel B shows data on drugs, which accounted for almost half (46-48%) of treatment descriptors. Panel C shows data on techniques and equipment. The mean vintage of drugs increased by about half as much as the mean vintage of techniques and equipment.

Data on mortality and the number of chemical substances and subgroups ever approved, by disease, are shown in Appendix Table 1.

V. Empirical results

A. Mortality model estimates

Estimates of variants of eq. (5), when $MORT_{dt} = YLL85_TOT_{dt}$ (the number of years of potential life lost by all Americans before age 85 due to disease d in year t), based on data on 85 diseases, are shown in Table 3. Model 1 includes only an intercept. The estimated intercept is

[27] The estimates of "total hospital expenditures" in CMS' National Health Expenditure Accounts (Centers for Medicare & Medicaid Services (2020b)) are much higher and increased much more. According to that source, total hospital expenditures increased by 149%, from $415 billion to $1035 billion.

0.106, indicating that the weighted mean percentage increase in YLL85_TOT was 11.2% (= exp(0.106) - 1). Model 2 also includes $\Delta\ln(\text{CUM_ATC5}_{t-12})$, the log-change in the number of drugs ever approved 12 years earlier, but not the change in treatment vintage. The estimate of β_1 is negative and highly significant (p-value = .001). The estimated percentage reduction in YLL85_TOT attributable to new drug approvals (shown in column 9) is 23% (= 1 – exp (β_1 * mean($\Delta\ln(\text{CUM_ATC5}_{t-12})$))).

Model 3 includes ΔVINTAGE_ALL, the change in the (frequency-weighted) mean vintage of MeSH D-branch and E-branch descriptors, but not $\Delta\ln(\text{CUM_ATC5}_{t-12})$. ΔVINTAGE_ALL is more strongly inversely related to the log change in YLL85_TOT than $\Delta\ln(\text{CUM_ATC5}_{t-12})$ is. The estimated percentage reduction in YLL85_TOT attributable to biomedical innovation (as reflected in the increase in treatment vintage) is 52% (= 1 – exp (β_2 * mean(ΔVINTAGE_ALL))).

In model 4, ΔVINTAGE_ALL is disaggregated into its two components: ΔVINTAGE_DRUG (the change in the (frequency-weighted) mean vintage of drug (MeSH D-branch) descriptors), and ΔVINTAGE_TECH (the change in the (frequency-weighted) mean vintage of technique and equipment (E-branch) descriptors). The coefficients on these two regressors (which we will refer to as $\beta_{2,DRUG}$ and $\beta_{2,TECH}$, respectively) are not very different, and the p-value in column 11 indicates that we cannot reject the null hypothesis that $\beta_{2,DRUG} = \beta_{2,TECH}$. Therefore, it is not surprising that the estimated percentage reduction in YLL85_TOT attributable to biomedical innovation (as reflected in the increase in treatment vintage) is not very different from the estimate in model 3: 58%.[28] The estimated percentage reduction in YLL85_TOT attributable to drug innovation alone, (= 1 – exp ($\beta_{2,DRUG}$ * mean(ΔVINTAGE_DRUG))), is identical to the estimate from model 2: 23%.

Model 5 is the most general (least restrictive) model we have considered so far. It includes $\Delta\ln(\text{CUM_ATC5}_{t-12})$, ΔVINTAGE_DRUG, and ΔVINTAGE_TECH. In this model, the coefficients on both $\Delta\ln(\text{CUM_ATC5}_{t-12})$ and ΔVINTAGE_DRUG are highly significant (p-value $\leq$ .004) , but the coefficient on ΔVINTAGE_TECH is insignificant (p-value = .202). This model implies that pharmaceutical innovation reduced YLL85_TOT by 42% (= 1 – exp(β_1 *

[28] 58% = 1 – exp($\beta_{2,DRUG}$ * mean(ΔVINTAGE_DRUG) + $\beta_{2,TECH}$ * mean(ΔVINTAGE_TECH)).

mean(Δln(CUM_ATC5$_{t-12}$)) + $\beta_{2,DRUG}$ * mean(ΔVINTAGE_DRUG))), and that biomedical innovation overall reduced YLL85_TOT by 59%.

Models 6-8 are similar to models 3-5, but in these models vintage is measured in terms of the fraction of descriptors that first appeared in the MEDLINE Co-Occurrences File after 1990, rather than as the frequency-weighted mean year in which descriptors first appeared. The reductions in mortality attributable to pharmaceutical and all biomedical innovation estimated from models 6-8 are similar to the estimates from models 3-5. Figure 5 is a bubble plot of the relationship across diseases between ΔPOST1990_ALL and Δln(YLL85_TOT); bubble area is proportional to the mean of YLL85_TOT in 1999 and 2018.

In models 9-11, vintage is measured in terms of the fraction of descriptors that first appeared in the MEDLINE Co-Occurrences File after 2000. The estimated coefficient of ΔPOST2000_ALL in model 9 is almost twice as large as the estimated coefficient of ΔPOST1990_ALL in model 6, which is consistent with the hypothesis that the average quality of post-2000 treatments is higher than the average quality of post-1990 treatments.

We estimated the same types of models shown in Table 3 for the other three measures of mortality. Estimates of those models when $MORT_{dt}$ = $YLL65_TOT_{dt}$ (the number of years of potential life lost by all Americans before age 65 due to disease d in year t) are shown in Appendix Table 2. Estimates of those models when $MORT_{dt}$ = $YLL85_AA_{dt}$ and $MORT_{dt}$ = $YLL65_AA_{dt}$ (the number of years of potential life lost by African-Americans before ages 85 and 65 due to disease d in year t) are shown in Appendix Tables 3 and 4.

Overall, the estimates based on the other three measures of mortality are quite consistent with the estimates based on $YLL85_TOT_{dt}$, but there are some differences. For all four mortality measures, the estimates of β_1 (the coefficient of Δln(CUM_ATC5$_{t-12}$)) in model 2 are negative and highly significant. (The estimates of β_1 remain significant in Model 5, when we control for ΔVINTAGE_DRUG and ΔVINTAGE_TECH.) The point estimates of β_1 are larger for YLL65 than for YLL85, and larger for African-Americans than for all Americans. The estimates of β_2 (the coefficient of ΔVINTAGE_ALL) in model 3 are negative and significant for both YLL age cutoffs for all Americans, but they are insignificant for African-Americans. However, the coefficients on ΔPOST1990_ALL and ΔPOST2000_ALL in models 6 and 9, respectively, are negative and significant for both YLL age cutoffs and populations. As noted earlier, due to left-censoring of descriptor vintage, these may be superior measures. The null hypothesis that

$\beta_{2,DRUG} = \beta_{2,TECH}$ is not rejected in model 4 for either YLL age cutoff in either population. As noted earlier, separate identification of the effects of drug innovation and technique/equipment innovation may be difficult: "drug therapy" is a MeSH Subheading of the MeSH (branch E) Heading "Therapeutics" 19% of the time.

Estimates of the mortality reduction attributable to drug innovation and all biomedical innovation (reproduced from columns 9 and 10 of Table 3 and Appendix Tables 2-4) are shown in Table 4. The last row of the table shows the means of the estimates from the different models. For the four mortality measures, the mean estimates of the mortality reduction attributable to drug innovation are almost identical—30-33%—and the mean estimates of the mortality reduction attributable to all biomedical innovation range between 43% and 54%. About two-thirds (61%-71%) of the reduction from all biomedical innovation appears to have been due to drug innovation.

B. Hospital utilization model estimates

We estimated the same types of models shown in Table 3 for the three measures of hospital utilization. Estimates of those models when $HOSP_{dt} = HOSP_DAYS_{dt}$ (the number of days of hospital care due to disease d in year t) based on data on 200 diseases are shown in Table 5. The model 2 estimates indicate that the 1999-2018 growth in hospital days is inversely related to the 1987-2006 growth in the number of drugs ever approved. The model 3 estimates indicate that the 1999-2018 growth in hospital days is more strongly inversely related to the 1999-2018 change in mean treatment vintage. The estimates from models 4 and 5 of the reduction in hospital days due to drug innovation (38-41%) are over three times as large as the estimate from model 2 (12%). Unlike the growth in mortality, the growth in hospital days is more strongly inversely correlated with the change in the mean descriptor year than it is with the change in the frequency-weighted fraction of post-1990 or post-2000 descriptors (compare models 3, 6, and 9).

Estimates of models when $HOSP_{dt} = HOSP_COST_{dt}$ and $HOSP_{dt} = HOSP_DEATHS_{dt}$ (the cost of hospital care and the number of hospital deaths due to disease d in year t) are shown in Appendix Tables 5 and 6. Estimates of the hospital utilization reduction attributable to drug innovation and all biomedical innovation (reproduced from columns 9 and 10 of Table 5 and Appendix Tables 5 and 6) are shown in Table 6. The estimates from models 9-11 are much

smaller than the corresponding estimates from models 3-5 and 6-8. The last row of the table shows the means of the estimates from the different models. These averages indicate that drug innovation reduced the number of hospital days and hospital cost by 22-24%, and the number of hospital deaths by 35%.[29] These averages also indicate that all biomedical innovation reduced the number of hospital days and hospital cost by 46-51%, and the number of hospital deaths by 72%. About half (47-49%) of the reduction in hospital utilization from all biomedical innovation appears to have been due to drug innovation.

VI. Discussion

The mean estimate in Table 4 of the reduction in YLL85_TOT from all biomedical innovation is 54%. This implies that, in the absence of 19 years of all biomedical innovation, YLL85_TOT would have been 117% (= (1 / (1 - 54%)) - 1) higher than it actually was in 2018.[30] As shown in Table 1, actual YLL85_TOT was 38.4 million in 2018, so we estimate that 19 years of all biomedical innovation reduced YLL85_TOT in 2018 by 44.8 million (= 117% * 38.4 million) in 2018. The mean estimate in Table 4 of the reduction in YLL85_TOT from drug innovation is 33%, so we also estimate that 19 years of drug innovation reduced YLL85_TOT in 2018 by 18.9 million in 2018.

The mean estimate in Table 6 of the reduction in hospital costs from 15 years of all biomedical innovation is 46%, and from 15 years of drug innovation is 22%. According to CMS' National Health Expenditure accounts, total U.S. hospital expenditure was $1035 billion in 2015. Hence, we estimate that 15 years of all biomedical innovation reduced 2015 hospital expenditure by $890 billion (= ((1 / (1 - 46%)) – 1) * $1035 billion), and that 15 years of drug innovation reduced 2015 hospital expenditure by $286 billion.

We would like to measure the *cost-effectiveness*, as well as the benefits, in terms of reduced mortality and hospital utilization, of biomedical innovation. This requires estimation of the *cost* (excluding "cost offsets") of biomedical innovation. Estimation of the cost of all biomedical innovation, or even of drug innovation in general, is challenging. However, we can

[29] The latter figure is slightly higher than the 30-33% mortality reduction shown in Table 4, and the hospital estimates are based on a shorter (15 years vs. 19 years) time period.

[30] Of course, since the biomedical sector (and particularly the pharmaceutical industry) is very research-intensive, estimates of mortality growth in the absence of any innovation are extremely out-of-sample estimates.

get a reasonably precise estimate of the cost in 2018 of new drugs that were launched during 1988-2006, and we have estimates (from model 2 in Tables 3 and Appendix Table 5) of the mortality and hospital utilization reductions from those drugs.

According to CMS' National Health Expenditure accounts, total U.S. prescription drug expenditure was $335 billion in 2018. Based on IQVIA MIDAS data, we estimate that about 37% of that expenditure was on drugs approved during 1988-2006.[31] Hence, we estimate that 2018 expenditure on drugs approved during 1988-2006 was about $124 billion (= 37% * $335 billion). The estimate from model 2 in Table 3 of the reduction in YLL85_TOT in 2018 from drugs approved during 1988-2006 is 23%. Hence, we estimate that drugs approved during 1988-2006 reduced YLL85_TOT in 2018 by 11.3 million (= ((1 / (1 - 23%)) – 1) * 38.4 million). This implies that 2018 expenditure on drugs approved during 1988-2006 per life-year before age 85 gained from those drugs was not more than $10,976 (= $124 billion / 11.3 million YLL85_TOT).[32]

As noted by Bertram et al (2016), authors writing on behalf of the WHO's *Choosing Interventions that are Cost–Effective* project (WHO-CHOICE) suggested in 2005 that "interventions that avert one disability-adjusted life-year (DALY) for less than average per capita income for a given country or region are considered very cost–effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost–effective."[33,34] U.S. per capita GDP was $62,869 in 2018, so these estimates indicate that, even if we ignore the effect of new drugs on hospital utilization, the drugs launched during 1988-2006 were very cost–effective, overall.

The estimates of model 2 in Table 5 and Appendix Table 5 indicate that new drugs approved during 1989-2003 reduced the number of hospital days by 12% and hospital cost by 14%. As noted above, total U.S. hospital expenditure was $1035 billion in 2015, so new drugs approved during 1989-2003 may have reduced 2015 hospital expenditure by $173 billion (= ((1 /

[31] The most recent IQVIA MIDAS data we have are for 2017. 37% of 2017 expenditure was on drugs approved during 1987-2005.

[32] Some pharmaceutical expenditure was for patients over the age of 84.

[33] Other authorities use reasonably similar cost-effectiveness thresholds. The U.K. National Institute for Health and Care Excellence (2020) says that, "in general, interventions with an ICER [Incremental Cost-Effectiveness Ratio] of less than £20,000 per QALY [quality-adjusted life-year] gained are considered to be cost effective." The U.S. Department of Veterans Affairs Health Economics Resource Center (2020) says that "a cost-effectiveness analysis may indicate that Drug A is a good value relative to Drug B, because it has an incremental cost-effectiveness ratio (ICER) of $40,000 per Quality-Adjusted Life Year."

[34] The number of DALYs or QALYs gained may be either greater than or less than the number of life-years gained.

(1 - 14%)) – 1) * $1035 billion). According to CMS' National Health Expenditure accounts, total U.S. prescription drug expenditure was $317 billion in 2015. Based on IQVIA MIDAS data, we estimate that about 35% of that expenditure was on drugs approved during 1989-2003, so 2015 expenditure on drugs approved during 1985-1999 was $111 billion (= 35% * $317 billion). The estimated reduction in 2015 hospital expenditure attributable to previous drug approvals was 56% larger than 2015 expenditure on the drugs.

VII. Summary and conclusions

In the first two decades of the 21st century in the U.S., there has been almost no growth in median income, and there have been sharp increases in obesity and "deaths of despair." Between 1999 and 2017, real median household income increased by only 1.8%, from $61,526 to $62,626 (Federal Reserve Bank of St. Louis (2020)). Between 1999-2000 and 2015-2016, the prevalence of obesity increased from 30.5% to 39.6% among adults, and from 13.9% to 18.5% among youths aged 2-19 years (Hales et al (2017)). Obesity-related conditions, including heart disease, stroke, type 2 diabetes and certain types of cancer, are some of the leading causes of preventable, premature death (Centers for Disease Control and Prevention (2020c)). The number of opioid-related deaths in the United States increased by 345% between 2001 and 2016 (Gomes et al (2018)).

Despite these trends, premature mortality and hospital utilization have declined substantially. Between 1999 and 2018, the age-adjusted rate of years of potential life lost before age 85 declined by 13% for all Americans, and almost twice as much for African-Americans. And between 2000 and 2015, the crude rate of hospital discharges per 100,000 persons declined by 11%.

In this study, we performed an econometric analysis of the hypothesis that biomedical innovation has played a major role in reducing premature mortality and hospital utilization, by investigating whether diseases for which there has been more biomedical innovation tended to have larger declines in mortality and hospital utilization.[35] We developed and analyzed two

[35] Declining tobacco use probably also contributed to declining premature mortality: between 1999 and 2017, the cigarette smoking rate declined from 23.5% to 14.0% among adults, and from 34.8% to 8.8% among youths (American Lung Association (2020)).

types of innovation measures: a measure of the number of drugs ever approved to treat a disease, and measures of the mean vintage of medical goods and services discussed in thousands of articles about a disease.

Our estimates provided strong support for this hypothesis: they indicated that drug innovation reduced premature (before age 65 or 85) mortality by 30-33% between 1999 and 2018, and that all biomedical innovation reduced it by 43-54%. Drug innovation appears to have reduced premature mortality among African-Americans as much as it reduced it among other Americans. Our estimates also indicated that drug innovation reduced the number of hospital days by 24% between 2000 and 2015, and that all biomedical innovation reduced it by 51%.

Even if we ignore the effect of new drugs on hospital utilization, our estimates indicate that the drugs launched during 1988-2006 were very cost–effective, overall. When the effect of hospital utilization is accounted for, the estimates indicate that drug innovation was cost-saving: the estimated reduction in 2015 hospital expenditure attributable to previous drug approvals was 56% larger than 2015 expenditure on the drugs.

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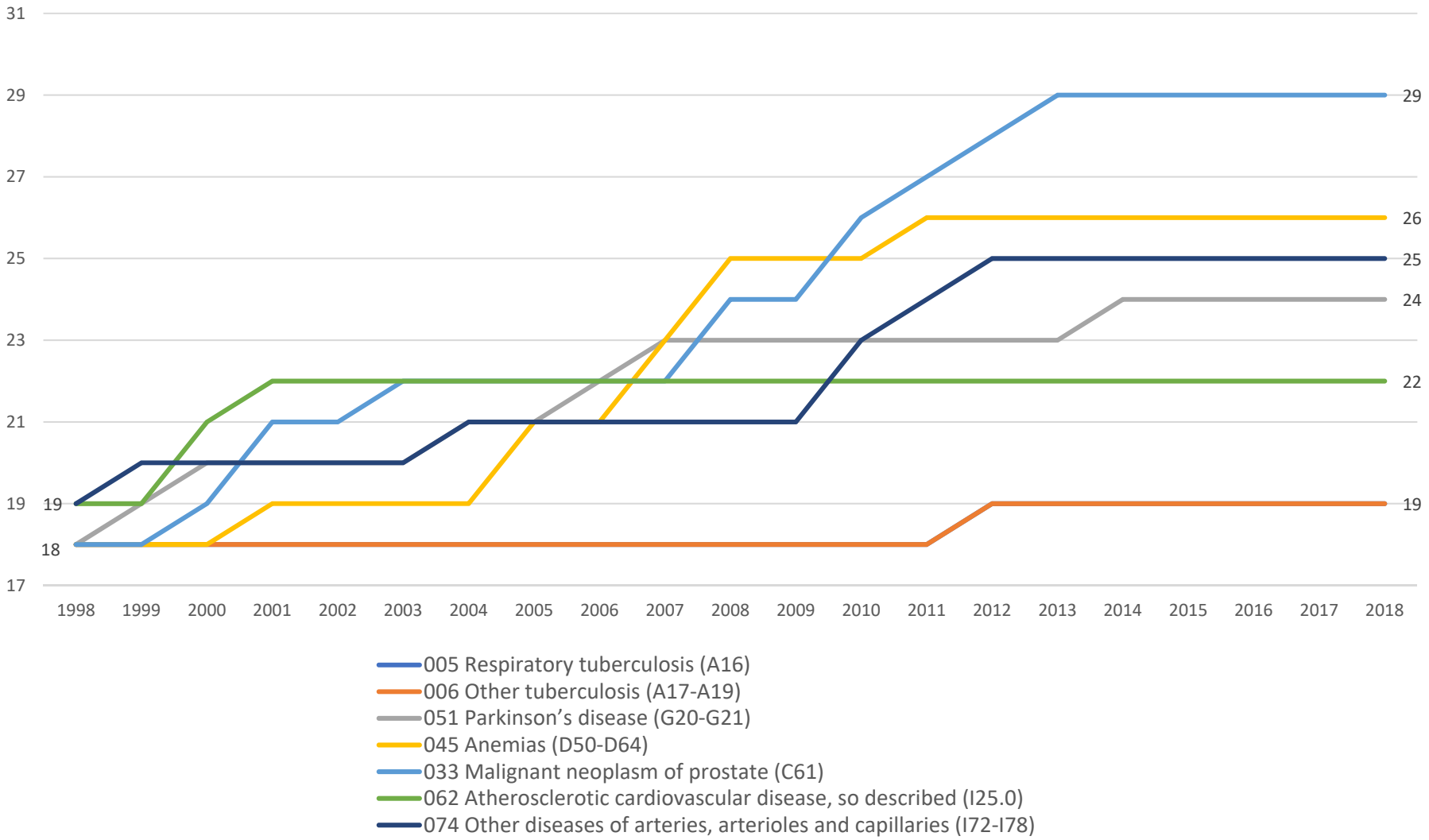
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Figure 1

Number of drugs (WHO ATC5 chemical substances) ever approved by the FDA for 7 diseases, 1998-2018



Source: Author's calculations based on data from Centre National Hospitalier d'Information sur le Médicament (2020), National Center for Scientific Research (CNRS) (2020), and DrugCentral database.

Figure 2
Mean ratio of utilization of a drug n years after FDA approval to its utilization 5 years after FDA approval

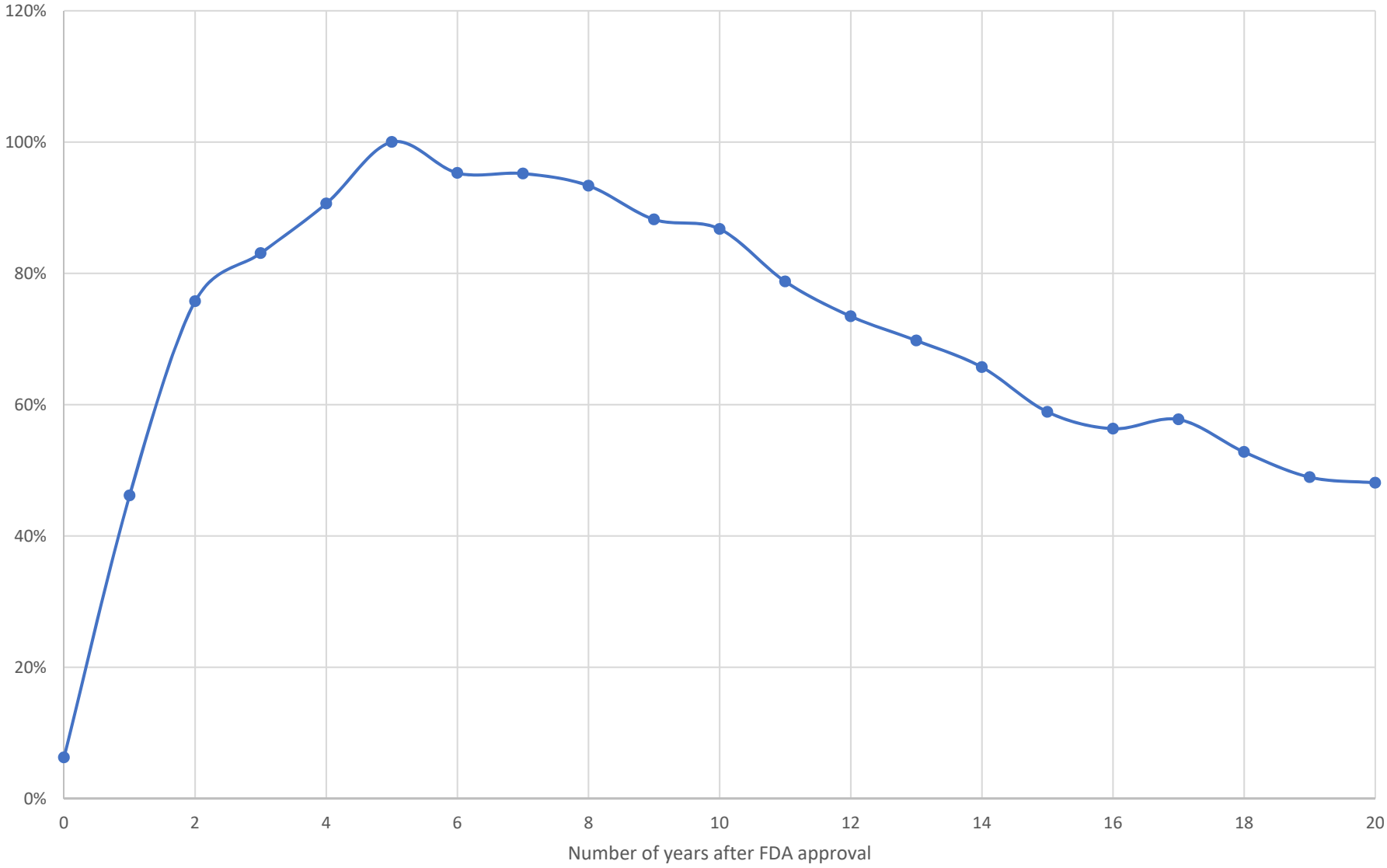


Figure 3

Number of drug and technique descriptors ever established, 1950-2015

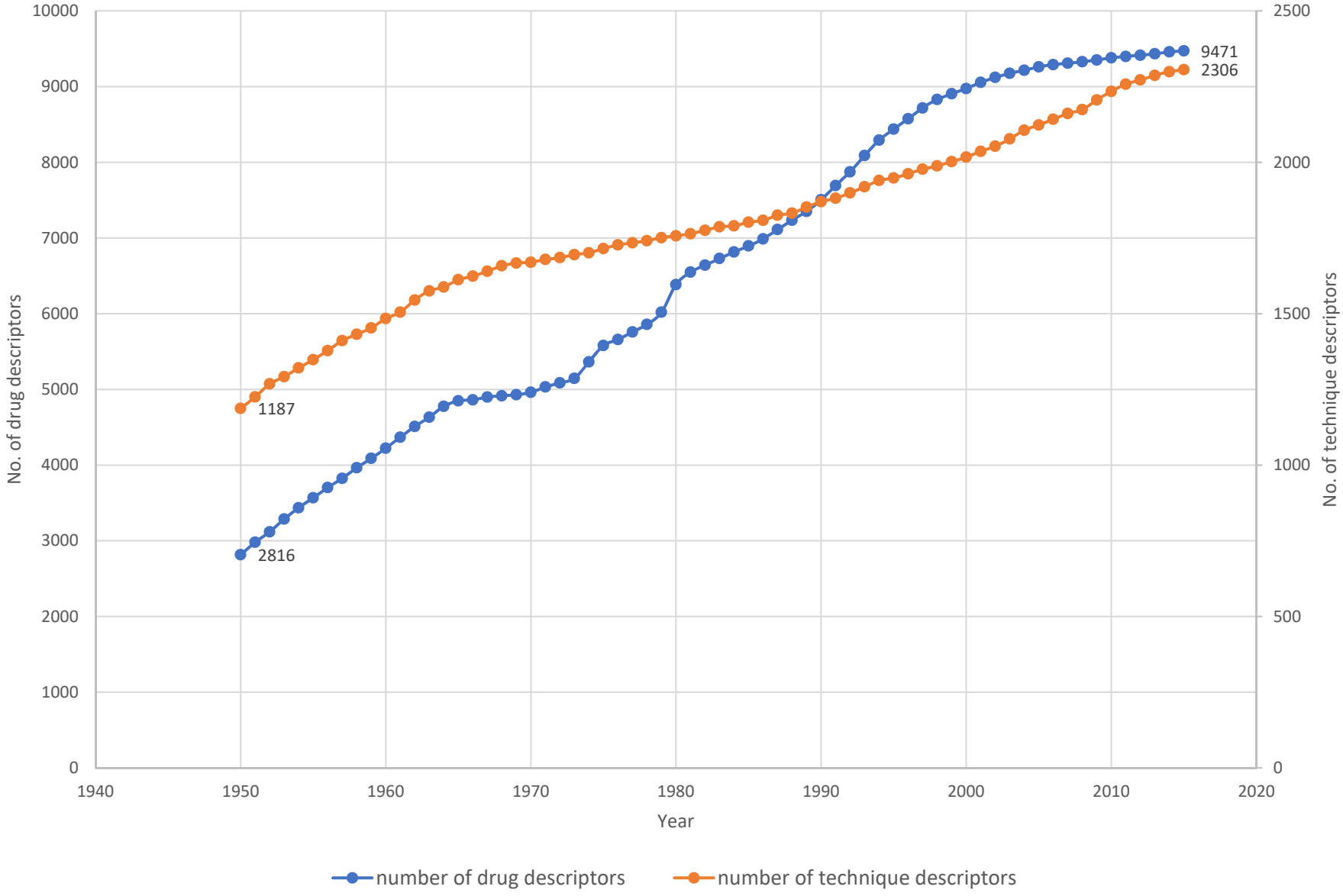
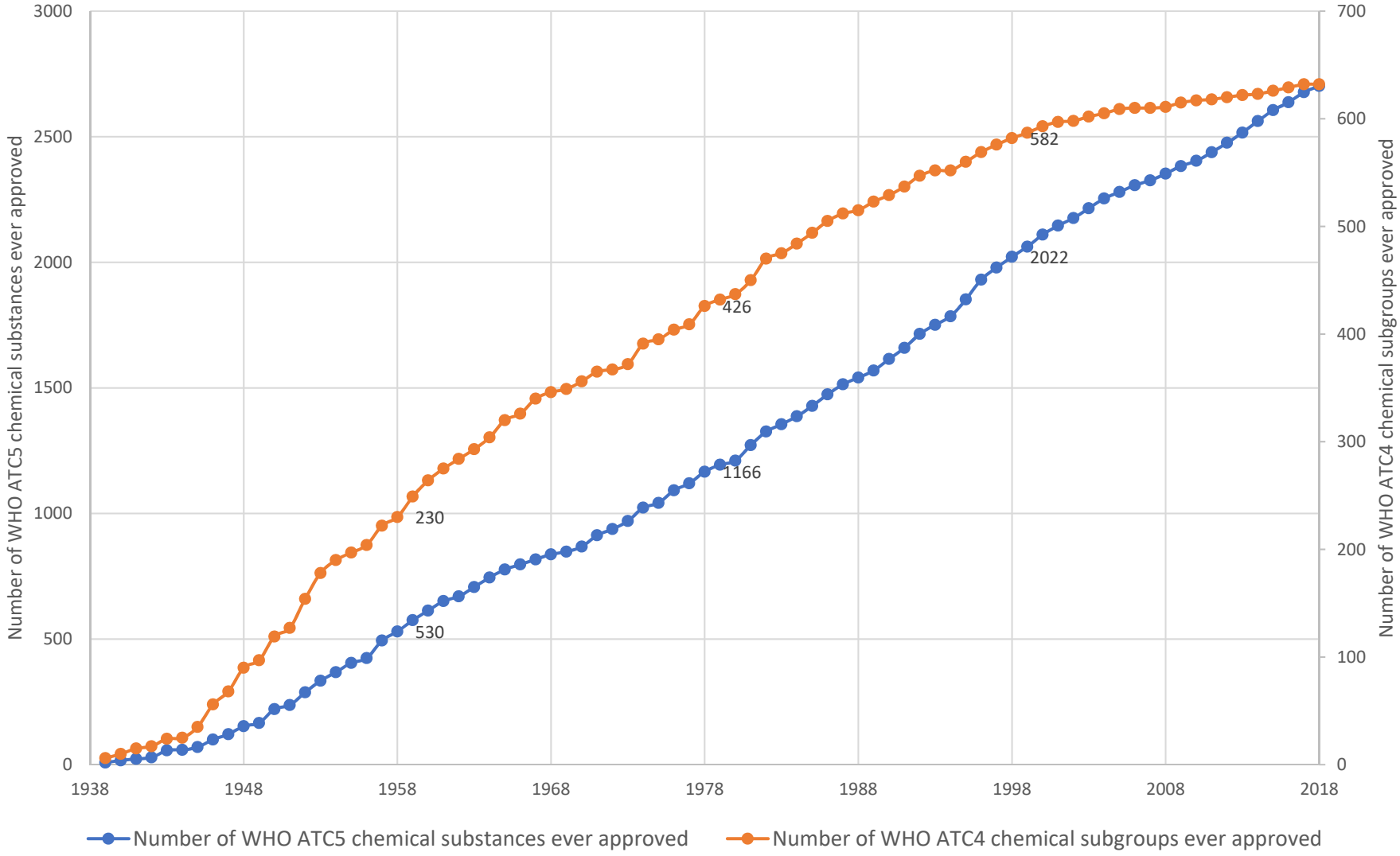


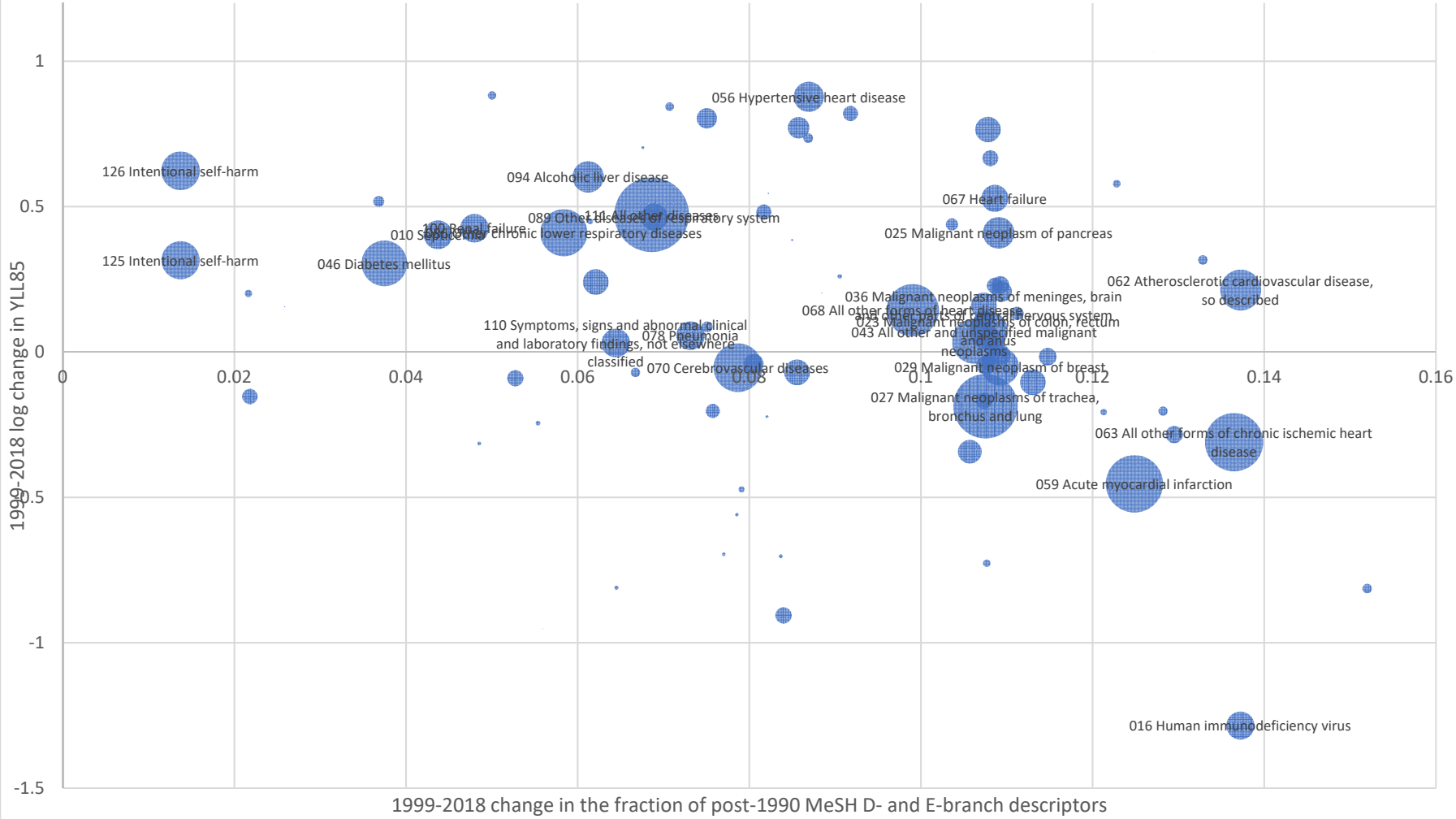
Figure 4

Number of WHO ATC5 chemical substances and WHO ATC4 chemical subgroups ever approved, 1939-2018



Source: Author's calculations based on data from National Center for Scientific Research (CNRS) (2020) and DrugCentral database.

Figure 5
Relationship across diseases between the
change in the fraction of post-1990 MeSH D- and E-branch descriptors and the
log change in the number of years of life lost before age 85 by all Americans, 1999-2018



Bubble area is proportional to mean of YLL85_TOT in 1999 and 2018. MeSH D-branch descriptors are Chemicals and Drugs descriptors, and MeSH E-branch descriptors are Analytical, Diagnostic and Therapeutic Techniques, and Equipment descriptors.

Table 1
Aggregate mortality and hospital data

A. Aggregate mortality data: All Americans			
Year	**1999**	**2018**	**% change**
Number of Years of Potential Life Lost Before Age 65 (YLL65)	11,145,856	11,702,674	5.0%
YLL65 crude rate	4,563	4,260	-6.7%
YLL65 age-adjusted rate 2000	4,593	4,240	-7.7%
Number of Years of Potential Life Lost Before Age 85 (YLL85)	33,530,448	38,432,951	14.6%
YLL85 crude rate	12,198	11,987	-1.7%
YLL85 age-adjusted rate 2000	12,321	10,705	-13.1%
Number of deaths	2,391,399	2,846,305	19.0%

B. Aggregate mortality data: African-Americans			
Year	**1999**	**2018**	**% change**
Number of Years of Potential Life Lost Before Age 65 (YLL65)	2,646,300	2,566,115	-3.0%
YLL65 crude rate	7,945	6,224	-21.7%
YLL65 age-adjusted rate 2000	8,238	6,291	-23.6%
Number of Years of Potential Life Lost Before Age 85 (YLL85)	6,277,026	6,988,961	11.3%
YLL85 crude rate	17,505	15,281	-12.7%
YLL85 age-adjusted rate 2000	20,253	15,200	-24.9%
Number of deaths	285,064	349,831	22.7%

C. Aggregate hospital data: All Americans			
Year	**2000**	**2015**	**% change**
Number of discharges	35,300,425	35,769,942	1.3%
Rate of discharges per 100,000 persons	12,510.70	11,128.80	-11.0%
LOS (length of stay), days (mean)	4.6	4.6	0.0%
Charges, $ (mean)	$13,691	$44,060	221.8%
Costs, $ (mean)	$6,034	$11,255	86.5%
Aggregate charges, $MM (the "national bill")	$482,407	$1,574,778	226.4%
Aggregate costs, $MM	$213,003	$402,591	89.0%
% Died	2.36%	1.91%	-19.1%

Sources:

Number of deaths: 1999 and 2018 Multiple Cause of Death data files (National Center for Health Statistics (2020)).

Years of Potential Life Lost: WISQARS Years of Potential Life Lost (YPLL) Report

Hospital data: https://hcupnet.ahrq.gov/#setup

Table 2

Vintage of treatment descriptors, 1999 and 2018

A. All treatments						
Year	**No. of descriptors**	**vintage_all**	**post2010_all**	**post2000_all**	**post1990_all**	**post1980_all**
1999	3,436,732	1974.9	0%	0%	10%	31%
2018	5,823,021	1978.3	1%	5%	20%	41%

B. Drugs						
Year	**No. of descriptors**	**vintage_drug**	**post2010_drug**	**post2000_drug**	**post1990_drug**	**post1980_drug**
1999	1,638,150	1974.8	0%	0%	9%	30%
2018	2,649,582	1977.1	0%	3%	16%	38%

C. Techniques and equipment						
Year	**No. of descriptors**	**vintage_tech**	**post2010_tech**	**post2000_tech**	**post1990_tech**	**post1980_tech**
1999	1,805,792	1975.1	0%	0%	10%	32%
2018	3,193,954	1979.4	3%	6%	23%	44%

Table 3

Estimates of variants of eq. (5): $\Delta\ln(MORT) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

MORT = the number of years of potential life lost by all Americans before age 85 (YLL85_TOT; N = 85)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	0.106	0.044	2.38	0.019	1.000	0.106				
2	2	Intercept	0.364	0.083	4.37	<.0001	1.000	0.364	23%			0.123
3		**$\Delta\ln(ATC5_{t-12})$**	-0.404	0.113	-3.58	0.001	0.637	-0.258				
4	3	Intercept	0.841	0.167	5.05	<.0001	1.000	0.841		52%		0.190
5		**Δvintage_all**	-0.212	0.047	-4.54	<.0001	3.463	-0.735				
6	4	Intercept	0.970	0.228	4.26	<.0001	1.000	0.970	23%	58%	0.733	0.217
7		**Δvintage_drug**	-0.108	0.046	-2.33	0.023	2.456	-0.264				
8		**Δvintage_tech**	-0.141	0.064	-2.20	0.030	4.244	-0.600				
9	5	Intercept	1.000	0.214	4.67	<.0001	1.000	1.000	42%	59%	0.601	0.307
10		**Δvintage_drug**	-0.131	0.044	-2.98	0.004	2.456	-0.323				
11		Δvintage_tech	-0.081	0.063	-1.29	0.202	4.244	-0.343				
12		**$\Delta\ln(ATC5_{t-12})$**	-0.358	0.105	-3.43	0.001	0.637	-0.228				
13	6	Intercept	0.846	0.128	6.58	<.0001	1.000	0.846		52%		0.295
14		**Δpost1990_all**	-7.878	1.309	-6.02	<.0001	0.094	-0.740				
15	7	Intercept	0.855	0.127	6.71	<.0001	1.000	0.855	34%	53%	0.143	0.329
16		**Δpost1990_drug**	-5.860	1.281	-4.57	<.0001	0.072	-0.419				
17		**Δpost1990_ther**	-2.967	1.087	-2.73	0.008	0.111	-0.329				
18	8	Intercept	1.003	0.129	7.77	<.0001	1.000	1.003	43%	59%	0.243	0.398
19		**Δpost1990_drug**	-5.177	1.231	-4.21	<.0001	0.072	-0.370				
20		**Δpost1990_ther**	-2.981	1.029	-2.90	0.005	0.111	-0.331				
21		**$\Delta\ln(ATC5_{t-12})$**	-0.308	0.095	-3.24	0.002	0.637	-0.196				
22	9	Intercept	0.788	0.110	7.19	<.0001	1.000	0.788		49%		0.336
23		**Δpost2000_all**	-14.860	2.254	-6.59	<.0001	0.046	-0.682				
24	10	Intercept	0.777	0.107	7.29	<.0001	1.000	0.777	30%	49%	0.009	0.383
25		**Δpost2000_drug**	-13.045	2.239	-5.83	<.0001	0.027	-0.354				
26		**Δpost2000_ther**	-5.246	1.504	-3.49	0.001	0.060	-0.317				
27	11	Intercept	0.864	0.116	7.42	<.0001	1.000	0.864	34%	53%	0.152	0.398
28		**Δpost2000_drug**	-10.553	2.630	-4.01	0.000	0.027	-0.286				
29		**Δpost2000_ther**	-5.740	1.512	-3.80	0.000	0.060	-0.347				
30		$\Delta\ln(ATC5_{t-12})$	-0.195	0.112	-1.75	0.084	0.637	-0.124				

Table 4

Summary of estimates of 1999-2018 mortality reduction attributable to drug innovation and all biomedical innovation

Mortality measure		**YLL85**	**YLL65**	**YLL85**	**YLL65**	**YLL85**	**YLL65**	**YLL85**	**YLL65**
Race		**total**	**total**	**black**	**black**	**total**	**total**	**black**	**black**
% effect		**drug innovation**				**all innovation**			
Model	Regressors								
2	$\Delta\ln(ATC5_{t-12})$	23%	29%	31%	36%				
3	Δvintage_all					52%	35%	28%	9%
4	Δvintage_drug, Δvintage_tech	23%	10%	4%	-14%	58%	51%	44%	44%
5	Δvintage_drug, Δvintage_tech, $\Delta\ln(ATC5_{t-12})$	42%	40%	40%	34%	59%	50%	48%	42%
6	Δpost1990_all					52%	52%	48%	55%
7	Δpost1990_drug, Δpost1990_tech	34%	32%	35%	40%	53%	53%	49%	55%
8	Δpost1990_drug, Δpost1990_tech, $\Delta\ln(ATC5_{t-12})$	43%	40%	42%	40%	59%	59%	56%	58%
9	Δpost2000_all					49%	48%	44%	50%
10	Δpost2000_drug, Δpost2000_tech	30%	35%	33%	37%	49%	43%	38%	36%
11	Δpost2000_drug, Δpost2000_tech, $\Delta\ln(ATC5_{t-12})$	34%	37%	36%	38%	53%	46%	43%	38%
	average	**33%**	**32%**	**31%**	**30%**	**54%**	**49%**	**44%**	**43%**

Table 5

Estimates of variants of eq. (5): $\Delta\ln(HOSP) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

HOSP = the number of days of hospital care (HOSP_DAYS; N = 200)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug=tech	adj. R^2
1	1	Intercept	-0.101	0.041	-2.49	0.014	1.000	-0.101				
2	2	Intercept	0.023	0.061	0.38	0.703	1.000	0.023	12%			0.031
3		**$\Delta\ln(ATC5_{t-12})$**	-0.351	0.130	-2.71	0.007	0.354	-0.124				
4	3	Intercept	0.879	0.145	6.08	<.0001	1.000	0.879		62%		0.195
5		**Δvintage_all**	-0.311	0.044	-7.01	<.0001	3.150	-0.980				
6	4	Intercept	0.878	0.144	6.09	<.0001	1.000	0.878	38%	62%	0.651	0.218
7		**Δvintage_drug**	-0.178	0.037	-4.85	<.0001	2.657	-0.473				
8		**Δvintage_tech**	-0.148	0.042	-3.51	0.001	3.414	-0.506				
9	5	Intercept	0.909	0.145	6.28	<.0001	1.000	0.909	41%	64%	0.676	0.225
10		**Δvintage_drug**	-0.170	0.037	-4.62	<.0001	2.657	-0.453				
11		**Δvintage_tech**	-0.143	0.042	-3.39	0.001	3.414	-0.488				
12		$\Delta\ln(ATC5_{t-12})$	-0.197	0.118	-1.67	0.097	0.354	-0.070				
13	6	Intercept	0.596	0.131	4.55	<.0001	1.000	0.596		50%		0.131
14		**Δpost1990_all**	-9.497	1.709	-5.56	<.0001	0.073	-0.697				
15	7	Intercept	0.616	0.129	4.77	<.0001	1.000	0.616	26%	51%	0.808	0.143
16		**Δpost1990_drug**	-4.737	1.460	-3.25	0.001	0.062	-0.296				
17		**Δpost1990_ther**	-5.350	1.573	-3.40	0.001	0.079	-0.422				
18	8	Intercept	0.634	0.130	4.89	<.0001	1.000	0.634	28%	52%	0.704	0.146
19		**Δpost1990_drug**	-4.248	1.504	-2.82	0.005	0.062	-0.265				
20		**Δpost1990_ther**	-5.207	1.574	-3.31	0.001	0.079	-0.410				
21		$\Delta\ln(ATC5_{t-12})$	-0.167	0.127	-1.31	0.192	0.354	-0.059				
22	9	Intercept	0.372	0.110	3.37	0.001	1.000	0.372		38%		0.091
23		**Δpost2000_all**	-17.573	3.839	-4.58	<.0001	0.027	-0.473				
24	10	Intercept	0.367	0.111	3.29	0.001	1.000	0.367	11%	37%	0.519	0.084
25		Δpost2000_drug	-6.757	3.769	-1.79	0.075	0.017	-0.113				
26		**Δpost2000_ther**	-10.196	2.907	-3.51	0.001	0.035	-0.355				
27	11	Intercept	0.376	0.112	3.37	0.001	1.000	0.376	14%	38%	0.445	0.086
28		Δpost2000_drug	-5.340	3.938	-1.36	0.177	0.017	-0.089				
29		**Δpost2000_ther**	-9.426	2.971	-3.17	0.002	0.035	-0.328				
30		$\Delta\ln(ATC5_{t-12})$	-0.168	0.137	-1.22	0.223	0.354	-0.059				

Table 6

Summary of estimates of 2000-2015 hospital utilization reduction attributable to drug innovation and all biomedical innovation

Dependent		**DAYS**	**COST**	**DEATHS**	**DAYS**	**COST**	**DEATHS**
% effect		**drug innovation**			**all innovation**		
Model	**Regressors**						
2	$\Delta\ln(ATC5_{t-12})$	12%	14%	29%			
3	Δvintage_all				62%	51%	82%
4	Δvintage_drug, Δvintage_tech	38%	36%	40%	62%	51%	81%
5	Δvintage_drug, Δvintage_tech, $\Delta\ln(ATC5_{t-12})$	41%	40%	45%	64%	54%	82%
6	Δpost1990_all				50%	41%	74%
7	Δpost1990_drug, Δpost1990_tech	26%	22%	42%	51%	44%	73%
8	Δpost1990_drug, Δpost1990_tech, $\Delta\ln(ATC5_{t-12})$	28%	26%	45%	52%	46%	73%
9	Δpost2000_all				38%	43%	62%
10	Δpost2000_drug, Δpost2000_tech	11%	5%	21%	37%	42%	63%
11	Δpost2000_drug, Δpost2000_tech, $\Delta\ln(ATC5_{t-12})$	14%	9%	25%	38%	43%	63%
	average	**24%**	**22%**	**35%**	**51%**	**46%**	**72%**

Appendix Table 1

Mortality and the number of chemical substances and subgroups ever approved, by disease, 1999 and 2018

113 Cause Recode	No. of deaths		No. of YLL before age 85		No. of YLL before age 65		No. of ATC5 chemical substances ever approved		No. of ATC4 chemical subgroups ever approved	
Year	1999	2018	1999	2018	1999	2018	1999	2018	1999	2018
TOTAL	2,206,418	2,586,311	25,734,458	28,555,621	6,269,601	6,118,766				
002 Shigellosis and amebiasis (A03,A06)	10	6	241	93	141	18	3	5	5	5
003 Certain other intestinal infections (A04,A07-A09)	1,097	7,917	8,485	73,395	1,886	13,662	9	13	9	9
005 Respiratory tuberculosis (A16)	765	356	12,268	5,453	3,855	1,558	18	19	8	8
006 Other tuberculosis (A17-A19)	167	193	3,669	3,713	1,446	1,173	18	19	8	8
007 Whooping cough (A37)	0	9	0	124	0	64	0	0	0	2
008 Scarlet fever and erysipelas (A38,A46)	5	0	35	0	0	0	4	0	2	0
009 Meningococcal infection (A39)	195	30	10,403	772	6,860	354	2	2	3	3
010 Septicemia (A40-A41)	30,434	40,821	337,895	505,646	84,355	110,350	33	33	18	18
011 Syphilis (A50-A53)	31	37	523	611	151	201	6	6	2	2
015 Viral hepatitis (B15-B19)	4,872	4,852	130,565	112,033	50,156	27,553	4	21	5	7
016 Human immunodeficiency virus (HIV) disease (B20-B24)	14,805	5,461	629,901	174,276	336,405	71,155	24	42	8	9
017 Malaria (B50-B54)	6	8	216	234	107	83	6	11	6	8
018 Other and unspecified infectious and parasitic diseases and their sequelae (A00,A05,A20-A36,A42A44,A48-A49,A54-A79,A81-A82,A85.0-A85.1,A85.8, A86-B04,B06-B09,B25-B49,B55-B99)	7,103	8,425	141,482	129,289	53,933	39,485	146	163	78	81
020 Malignant neoplasms of lip, oral cavity and pharynx (C00-C14)	7,497	10,179	135,255	170,440	34,835	33,906	10	14	12	12
021 Malignant neoplasm of esophagus (C15)	11,923	15,435	197,284	242,871	39,979	40,519	12	16	13	13
022 Malignant neoplasm of stomach (C16)	12,724	11,071	185,738	177,463	43,661	42,521	15	20	14	14
023 Malignant neoplasms of colon, rectum and anus (C18-C21)	57,193	53,176	734,080	789,413	144,486	175,821	14	25	14	15
024 Malignant neoplasms of liver and intrahepatic bile ducts (C22)	12,405	27,750	208,590	448,345	51,304	73,697	9	14	9	10
025 Malignant neoplasm of pancreas (C25)	29,113	44,971	406,464	612,189	74,846	90,165	13	21	13	14
026 Malignant neoplasm of larynx (C32)	3,817	3,785	65,045	62,065	12,638	9,747	7	11	7	7
027 Malignant neoplasms of trachea, bronchus and lung (C33-C34)	152,235	142,312	2,316,034	1,922,410	383,124	249,348	25	40	20	21
028 Malignant melanoma of skin (C43)	7,222	8,208	148,126	125,243	48,024	30,348	11	22	11	12
029 Malignant neoplasm of breast (C50)	41,557	43,030	746,193	709,455	216,905	175,910	36	50	24	25
030 Malignant neoplasm of cervix uteri (C53)	4,210	4,151	110,571	107,321	43,931	39,803	12	17	13	13

Appendix Table 1

Mortality and the number of chemical substances and subgroups ever approved, by disease, 1999 and 2018

113 Cause Recode	No. of deaths		No. of YLL before age 85		No. of YLL before age 65		No. of ATC5 chemical substances ever approved		No. of ATC4 chemical subgroups ever approved	
Year	1999	2018	1999	2018	1999	2018	1999	2018	1999	2018
031 Malignant neoplasms of corpus uteri and uterus, part unspecified (C54-C55)	6,474	11,257	88,528	172,399	16,344	27,771	9	13	9	9
032 Malignant neoplasm of ovary (C56)	13,641	13,765	220,900	218,621	51,733	44,229	24	31	18	19
033 Malignant neoplasm of prostate (C61)	31,747	31,535	241,577	254,023	14,554	18,940	18	29	16	18
034 Malignant neoplasms of kidney and renal pelvis (C64-C65)	11,128	14,158	181,194	202,299	42,154	38,654	10	17	11	12
035 Malignant neoplasm of bladder (C67)	11,916	16,663	119,235	149,716	15,756	16,934	17	21	17	17
036 Malignant neoplasms of meninges, brain and other parts of central nervous system (C70C72)	12,766	17,152	311,426	365,414	118,202	116,721	18	24	16	17
038 Hodgkin's disease (C81)	1,406	1,040	38,809	18,766	17,763	6,178	23	30	17	17
039 Non-Hodgkin's lymphoma (C82-C85)	22,831	20,331	335,569	238,133	81,448	44,116	35	50	27	28
040 Leukemia (C91-C95)	21,062	23,412	353,757	318,770	119,417	86,861	32	59	21	22
041 Multiple myeloma and immunoproliferative neoplasms (C88,C90)	11,032	12,824	143,083	145,923	22,817	18,415	17	30	17	18
042 Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue (C96)	82	116	1,363	1,208	396	207	7	14	9	10
043 All other and unspecified malignant neoplasms (C17,C23-C24,C26-C31,C37-C41, C44C49,C51-C52,C57-C60,C62-C63,C66,C68-C69,C73-C80,C97)	66,314	73,894	1,016,321	1,054,673	262,750	240,334	52	88	35	38
044 In situ neoplasms, benign neoplasms and neoplasms of uncertain or unknown behavior (D00-D48)	13,184	15,665	159,539	156,972	44,212	33,627	35	55	30	33
045 Anemias (D50-D64)	4,497	5,273	59,195	64,531	25,792	21,755	18	26	16	18
046 Diabetes mellitus (E10-E14)	68,457	85,112	901,526	1,222,914	193,590	267,725	34	50	20	23
048 Malnutrition (E40-E46)	3,981	9,342	22,686	52,769	4,624	8,666	1	1	1	1
049 Other nutritional deficiencies (E50-E64)	302	284	1,663	2,782	351	620	26	28	19	20
050 Meningitis (G00,G03)	740	634	23,299	14,529	12,061	6,031	20	22	12	12
051 Parkinson's disease (G20-G21)	14,596	33,851	71,689	162,807	1,873	4,678	19	24	14	14
052 Alzheimer's disease (G30)	44,543	122,068	130,502	291,485	2,812	6,423	3	6	2	3
055 Acute rheumatic fever and chronic rheumatic heart diseases (I00-I09)	3,677	3,573	47,710	38,930	11,356	9,985	12	12	7	7
056 Hypertensive heart disease (I11)	22,774	51,745	273,503	657,847	75,577	172,844	67	68	33	33
057 Hypertensive heart and renal disease (I13)	3,328	8,524	31,385	65,505	7,652	12,297	67	68	33	33

Appendix Table 1

Mortality and the number of chemical substances and subgroups ever approved, by disease, 1999 and 2018

113 Cause Recode	No. of deaths		No. of YLL before age 85		No. of YLL before age 65		No. of ATC5 chemical substances ever approved		No. of ATC4 chemical subgroups ever approved	
Year	1999	2018	1999	2018	1999	2018	1999	2018	1999	2018
059 Acute myocardial infarction (I21-I22)	199,772	108,915	2,055,906	1,306,358	365,177	242,744	26	32	16	18
060 Other acute ischemic heart diseases (I24)	3,235	4,363	39,152	53,742	8,544	9,978	2	2	2	2
062 Atherosclerotic cardiovascular disease, so described (I25.0)	72,150	65,413	763,811	945,191	155,673	198,747	19	22	13	15
063 All other forms of chronic ischemic heart disease (I20,I25.1-I25.9)	255,317	188,241	1,998,779	1,465,799	310,789	210,174	37	43	19	21
065 Acute and subacute endocarditis (I33)	1,116	1,665	22,164	39,536	7,565	15,505	23	24	13	13
066 Diseases of pericardium and acute myocarditis (I30-I31,I40)	868	990	23,869	19,416	11,208	7,211	3	3	4	4
067 Heart failure (I50)	54,922	83,687	275,976	468,164	33,247	66,331	38	42	23	25
068 All other forms of heart disease (I26-I28,I34-I38,I42-I49,I51)	108,581	140,074	1,298,775	1,499,722	374,804	375,168	40	53	27	30
069 Essential (primary) hypertension and hypertensive renal disease (I10,I12)	16,971	35,903	149,527	323,348	29,654	59,591	101	107	44	44
070 Cerebrovascular diseases (I60-I69)	167,469	148,146	1,248,806	1,183,317	231,188	214,716	12	15	12	13
071 Atherosclerosis (I70)	14,983	4,939	63,486	28,141	6,415	3,388	4	6	2	2
073 Aortic aneurysm and dissection (I71)	15,863	9,963	173,392	130,537	29,534	31,064	1	1	1	1
074 Other diseases of arteries, arterioles and capillaries (I72-I78)	10,002	9,968	86,160	98,374	15,243	17,495	20	25	17	19
075 Other disorders of circulatory system (I80-I99)	4,010	4,854	60,618	93,995	19,805	32,259	38	49	28	33
077 Influenza (J10-J11)	1,653	11,198	11,005	125,017	3,406	36,589	7	7	6	6
078 Pneumonia (J12-J18)	61,794	48,081	403,390	426,691	95,465	90,563	58	63	24	25
080 Acute bronchitis and bronchiolitis (J20-J21)	326	239	4,972	3,980	2,639	2,141	23	24	15	15
081 Unspecified acute lower respiratory infection (J22)	151	83	630	1,087	208	375	30	30	19	19
083 Bronchitis, chronic and unspecified (J40-J42)	1,152	495	11,695	5,792	3,579	1,939	41	42	19	19
084 Emphysema (J43)	17,794	7,570	194,634	78,683	18,565	8,826	1	1	4	4
085 Asthma (J45-J46)	4,659	3,454	111,982	91,414	50,296	42,430	37	42	18	20
086 Other chronic lower respiratory diseases (J44,J47)	100,592	148,145	906,189	1,365,567	78,882	130,533	33	41	18	19
089 Other diseases of respiratory system (J00-J06,J30-J39,J67,J70-J98)	24,807	43,895	287,829	457,854	67,972	85,826	114	122	59	60
090 Peptic ulcer (K25-K28)	4,607	3,386	46,633	43,471	10,025	10,083	12	14	9	9
094 Alcoholic liver disease (K70)	11,971	23,272	356,923	651,819	138,219	221,784	5	13	5	5

Appendix Table 1

Mortality and the number of chemical substances and subgroups ever approved, by disease, 1999 and 2018

113 Cause Recode	No. of deaths		No. of YLL before age 85		No. of YLL before age 65		No. of ATC5 chemical substances ever approved		No. of ATC4 chemical subgroups ever approved	
Year	1999	2018	1999	2018	1999	2018	1999	2018	1999	2018
095 Other chronic liver disease and cirrhosis (K73-K74)	14,320	19,710	296,241	376,856	87,594	89,261	9	22	8	9
096 Cholelithiasis and other disorders of gallbladder (K80-K82)	2,835	3,785	25,466	31,145	5,455	5,674	1	1	4	5
098 Acute and rapidly progressive nephritic and nephrotic syndrome (N00-N01,N04)	180	686	2,927	5,910	1,099	1,010	12	13	7	7
099 Chronic glomerulonephritis, nephritis and nephropathy not specified as acute or chronic, and renal sclerosis unspecified (N02-N03,N05-N07,N26)	590	267	8,349	4,772	2,638	1,735	9	12	6	6
100 Renal failure (N17-N19)	34,583	50,489	330,119	505,215	64,535	89,317	14	23	13	15
101 Other disorders of kidney (N25,N27)	35	29	520	637	156	214	6	9	5	5
102 Infections of kidney (N10-N12,N13.6,N15.1)	844	865	8,889	11,530	2,490	3,062	26	28	11	12
103 Hyperplasia of prostate (N40)	430	581	1,744	2,563	71	151	6	10	5	5
104 Inflammatory diseases of female pelvic organs (N70-N76)	106	163	2,078	2,495	872	717	15	17	12	12
106 7 Pregnancy with abortive outcome (O00-O07)	31	29	1,708	1,497	1,088	917	5	6	4	5
107 7 Other complications of pregnancy, childbirth and the puerperium (O10-O99)	378	947	20,672	49,968	13,112	31,028	33	33	28	31
108 Certain conditions originating in the perinatal period (P00-P96)	170	10,776	12,731	9,967	9,374	7,100	16	16	16	16
109 Congenital malformations, deformations and chromosomal abnormalities (Q00-Q99)	4,934	9,769	205,650	197,491	122,605	106,264	11	15	13	16
110 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	23,128	32,820	412,719	425,611	185,533	166,045	148	160	124	134
111 All other diseases (Residual) (D65-E07,E15-E34,E65-F99,G04-G12,G23-G25, G31-H93,K00K22,K29-K31,K50-K66,K71-K72,K75-K76,K83-M99,N13.0-N13.5, N13.7-N13.9,N14,N15.0,N15.8N15.9,N20-N23,N28-N39,N41-N64,N80-N98)	170,719	344,510	2,183,126	3,500,876	745,912	934,137	590	768	325	349
129 Assault (homicide) by other and unspecified means and their sequelae (X85-X92,X96Y09,Y87.1)	5,727	4,925	275,473	200,600	166,598	113,405	1	1	1	1
135 Complications of medical and surgical care (Y40-Y84,Y88)	2,779	4,620	46,221	77,603	16,105	21,817	6	10	5	6

Appendix Table 2

Estimates of variants of eq. (5): $\Delta\ln(MORT) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

MORT = the number of years of potential life lost by all Americans before age 65 (YLL65_TOT; N = 85)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	-0.022	0.050	-0.44	0.663	1.000	-0.022				
2	2	Intercept	0.322	0.076	4.25	<.0001	1.000	0.322	29%			0.261
3		**$\Delta\ln(ATC5_{t-12})$**	-0.532	0.096	-5.54	<.0001	0.646	-0.344				
4	3	Intercept	0.410	0.200	2.05	0.043	1.000	0.410		35%		0.045
5		**Δvintage_all**	-0.130	0.058	-2.23	0.028	3.327	-0.432				
6	4	Intercept	0.682	0.278	2.45	0.016	1.000	0.682	10%	51%	0.401	0.069
7		Δvintage_drug	-0.045	0.056	-0.81	0.422	2.317	-0.105				
8		Δvintage_tech	-0.145	0.078	-1.86	0.066	4.137	-0.599				
9	5	Intercept	0.675	0.242	2.79	0.007	1.000	0.675	40%	50%	0.787	0.293
10		Δvintage_drug	-0.076	0.049	-1.54	0.127	2.317	-0.175				
11		Δvintage_tech	-0.047	0.070	-0.67	0.506	4.137	-0.194				
12		**$\Delta\ln(ATC5_{t-12})$**	-0.507	0.098	-5.20	<.0001	0.646	-0.327				
13	6	Intercept	0.720	0.149	4.84	<.0001	1.000	0.720		52%		0.238
14		**Δpost1990_all**	-8.087	1.548	-5.22	<.0001	0.092	-0.742				
15	7	Intercept	0.743	0.151	4.92	<.0001	1.000	0.743	32%	53%	0.346	0.270
16		**Δpost1990_drug**	-5.566	1.405	-3.96	0.000	0.070	-0.390				
17		**Δpost1990_ther**	-3.449	1.325	-2.60	0.011	0.109	-0.375				
18	8	Intercept	0.876	0.139	6.31	<.0001	1.000	0.876	40%	59%	0.988	0.410
19		**Δpost1990_drug**	-3.506	1.343	-2.61	0.011	0.070	-0.246				
20		**Δpost1990_ther**	-3.537	1.191	-2.97	0.004	0.109	-0.385				
21		**$\Delta\ln(ATC5_{t-12})$**	-0.415	0.092	-4.53	<.0001	0.646	-0.268				
22	9	Intercept	0.634	0.127	5.00	<.0001	1.000	0.634		48%		0.259
23		**Δpost2000_all**	-14.825	2.692	-5.51	<.0001	0.044	-0.657				
24	10	Intercept	0.544	0.108	5.06	<.0001	1.000	0.544	35%	43%	<.0001	0.489
25		**Δpost2000_drug**	-15.484	1.720	-9.00	<.0001	0.028	-0.437				
26		Δpost2000_ther	-2.287	1.541	-1.48	0.142	0.057	-0.130				
27	11	Intercept	0.593	0.118	5.03	<.0001	1.000	0.593	37%	46%	0.001	0.489
28		**Δpost2000_drug**	-13.771	2.420	-5.69	<.0001	0.028	-0.388				
29		Δpost2000_ther	-2.685	1.591	-1.69	0.095	0.057	-0.152				
30		$\Delta\ln(ATC5_{t-12})$	-0.115	0.115	-1.01	0.317	0.646	-0.075				

Appendix Table 3

Estimates of variants of eq. (5): $\Delta\ln(MORT) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

MORT = the no. of years of potential life lost by African-Americans before age 85 (YLL85_AA; N = 84)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	0.096	0.049	1.97	0.052	1.000	0.096				
2	2	Intercept	0.462	0.069	6.72	<.0001	1.000	0.462	31%			0.335
3		**$\Delta\ln(ATC5_{t-12})$**	-0.523	0.080	-6.54	<.0001	0.698	-0.365				
4	3	Intercept	0.425	0.199	2.14	0.036	1.000	0.425		28%		0.022
5		Δvintage_all	-0.097	0.057	-1.70	0.093	3.389	-0.329				
6	4	Intercept	0.683	0.256	2.67	0.009	1.000	0.683	4%	44%	0.347	0.045
7		Δvintage_drug	-0.018	0.059	-0.31	0.756	2.427	-0.045				
8		Δvintage_tech	-0.132	0.075	-1.76	0.083	4.122	-0.542				
9	5	Intercept	0.757	0.211	3.59	0.001	1.000	0.757	40%	48%	0.816	0.354
10		Δvintage_drug	-0.061	0.049	-1.25	0.213	2.427	-0.149				
11		Δvintage_tech	-0.038	0.063	-0.60	0.553	4.122	-0.155				
12		**$\Delta\ln(ATC5_{t-12})$**	-0.511	0.081	-6.31	<.0001	0.698	-0.357				
13	6	Intercept	0.741	0.145	5.12	<.0001	1.000	0.741		48%		0.201
14		**Δpost1990_all**	-6.937	1.485	-4.67	<.0001	0.093	-0.645				
15	7	Intercept	0.760	0.140	5.42	<.0001	1.000	0.760	35%	49%	0.095	0.257
16		**Δpost1990_drug**	-5.804	1.364	-4.26	<.0001	0.075	-0.433				
17		Δpost1990_ther	-2.176	1.234	-1.76	0.082	0.106	-0.231				
18	8	Intercept	0.924	0.123	7.48	<.0001	1.000	0.924	42%	56%	0.839	0.456
19		**Δpost1990_drug**	-3.131	1.262	-2.48	0.015	0.075	-0.233				
20		**Δpost1990_ther**	-2.738	1.060	-2.58	0.012	0.106	-0.291				
21		**$\Delta\ln(ATC5_{t-12})$**	-0.434	0.078	-5.54	<.0001	0.698	-0.303				
22	9	Intercept	0.676	0.125	5.40	<.0001	1.000	0.676		44%		0.220
23		**Δpost2000_all**	-12.993	2.633	-4.93	<.0001	0.045	-0.579				
24	10	Intercept	0.580	0.102	5.70	<.0001	1.000	0.580	33%	38%	**<.0001**	0.499
25		**Δpost2000_drug**	-13.674	1.486	-9.20	<.0001	0.029	-0.396				
26		Δpost2000_ther	-1.571	1.421	-1.11	0.272	0.056	-0.088				
27	11	Intercept	0.666	0.112	5.93	<.0001	1.000	0.666	36%	43%	**0.002**	0.511
28		**Δpost2000_drug**	-11.045	2.119	-5.21	<.0001	0.029	-0.320				
29		Δpost2000_ther	-2.248	1.459	-1.54	0.127	0.056	-0.126				
30		$\Delta\ln(ATC5_{t-12})$	-0.178	0.103	-1.72	0.089	0.698	-0.124				

Appendix Table 4

Estimates of variants of eq. (5): $\Delta\ln(MORT) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

MORT = the no. of years of potential life lost by African-Americans before age 65 (YLL65_AA; N = 84)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	-0.116	0.060	-1.95	0.054	1.000	-0.116				
2	2	Intercept	0.327	0.069	4.75	<.0001	1.000	0.327	36%			0.454
3		**$\Delta\ln(ATC5_{t-12})$**	-0.607	0.073	-8.36	<.0001	0.729	-0.443				
4	3	Intercept	-0.018	0.251	-0.07	0.942	1.000	-0.018		9%		-0.010
5		Δvintage_all	-0.030	0.074	-0.40	0.689	3.275	-0.098				
6	4	Intercept	0.465	0.319	1.46	0.149	1.000	0.465	-14%	44%	0.120	0.020
7		Δvintage_drug	0.057	0.074	0.76	0.449	2.326	0.132				
8		Δvintage_tech	-0.178	0.094	-1.89	0.062	4.009	-0.713				
9	5	Intercept	0.430	0.241	1.78	0.078	1.000	0.430	34%	42%	0.750	0.442
10		Δvintage_drug	0.006	0.057	0.11	0.914	2.326	0.014				
11		Δvintage_tech	-0.031	0.073	-0.42	0.676	4.009	-0.124				
12		**$\Delta\ln(ATC5_{t-12})$**	-0.599	0.076	-7.88	<.0001	0.729	-0.437				
13	6	Intercept	0.676	0.173	3.91	0.000	1.000	0.676		55%		0.211
14		**Δpost1990_all**	-8.622	1.793	-4.81	<.0001	0.092	-0.792				
15	7	Intercept	0.684	0.169	4.05	0.000	1.000	0.684	40%	55%	0.126	0.274
16		**Δpost1990_drug**	-6.759	1.517	-4.46	<.0001	0.075	-0.508				
17		Δpost1990_ther	-2.811	1.572	-1.79	0.078	0.104	-0.292				
18	8	Intercept	0.750	0.139	5.40	<.0001	1.000	0.750	40%	58%	0.458	0.513
19		Δpost1990_drug	-1.724	1.472	-1.17	0.245	0.075	-0.130				
20		**Δpost1990_ther**	-3.418	1.291	-2.65	0.010	0.104	-0.354				
21		**$\Delta\ln(ATC5_{t-12})$**	-0.524	0.082	-6.38	<.0001	0.729	-0.382				
22	9	Intercept	0.577	0.150	3.86	0.000	1.000	0.577		50%		0.220
23		**Δpost2000_all**	-15.961	3.227	-4.95	<.0001	0.043	-0.693				
24	10	Intercept	0.328	0.109	3.00	0.004	1.000	0.328	37%	36%	<.0001	0.614
25		**Δpost2000_drug**	-14.388	1.311	-10.98	<.0001	0.032	-0.457				
26		Δpost2000_ther	0.254	1.598	0.16	0.874	0.052	0.013				
27	11	Intercept	0.361	0.119	3.02	0.003	1.000	0.361	38%	38%	<.0001	0.611
28		**Δpost2000_drug**	-13.138	2.214	-5.93	<.0001	0.032	-0.418				
29		Δpost2000_ther	-0.040	1.657	-0.02	0.981	0.052	-0.002				
30		$\Delta\ln(ATC5_{t-12})$	-0.078	0.112	-0.70	0.485	0.729	-0.057				

Appendix Table 5

Estimates of variants of eq. (5): $\Delta\ln(HOSP) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

HOSP = the cost of hospital care (HOSP_COST; N = 200)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	0.583	0.043	13.71	<.0001	1.000	0.583				
2	2	Intercept	0.738	0.066	11.25	<.0001	1.000	0.738	14%			0.040
3		**$\Delta\ln(ATC5_{t-12})$**	-0.427	0.140	-3.06	0.003	0.362	-0.155				
4	3	Intercept	1.295	0.158	8.19	<.0001	1.000	1.295		51%		0.094
5		**Δvintage_all**	-0.220	0.047	-4.66	<.0001	3.236	-0.712				
6	4	Intercept	1.301	0.158	8.24	<.0001	1.000	1.301	36%	51%	0.277	0.118
7		**Δvintage_drug**	-0.160	0.041	-3.88	0.000	2.750	-0.439				
8		Δvintage_tech	-0.080	0.046	-1.75	0.081	3.493	-0.280				
9	5	Intercept	1.359	0.159	8.57	<.0001	1.000	1.359	40%	54%	0.369	0.135
10		**Δvintage_drug**	-0.143	0.041	-3.47	0.001	2.750	-0.394				
11		Δvintage_tech	-0.078	0.045	-1.73	0.085	3.493	-0.273				
12		**$\Delta\ln(ATC5_{t-12})$**	-0.300	0.135	-2.22	0.028	0.362	-0.109				
13	6	Intercept	1.115	0.141	7.88	<.0001	1.000	1.115		41%		0.068
14		**Δpost1990_all**	-6.947	1.766	-3.93	0.000	0.077	-0.533				
15	7	Intercept	1.167	0.141	8.30	<.0001	1.000	1.167	22%	44%	0.915	0.081
16		**Δpost1990_drug**	-3.802	1.581	-2.41	0.017	0.065	-0.247				
17		**Δpost1990_ther**	-4.090	1.648	-2.48	0.014	0.082	-0.337				
18	8	Intercept	1.204	0.141	8.56	<.0001	1.000	1.204	26%	46%	0.724	0.096
19		Δpost1990_drug	-2.966	1.620	-1.83	0.069	0.065	-0.193				
20		**Δpost1990_ther**	-3.918	1.637	-2.39	0.018	0.082	-0.322				
21		**$\Delta\ln(ATC5_{t-12})$**	-0.290	0.142	-2.04	0.042	0.362	-0.105				
22	9	Intercept	1.141	0.117	9.73	<.0001	1.000	1.141		43%		0.110
23		Δpost2000_all	-20.252	3.998	-5.07	<.0001	0.028	-0.558				
24	10	Intercept	1.135	0.116	9.79	<.0001	1.000	1.135	5%	42%	0.058	0.114
25		Δpost2000_drug	-2.946	4.239	-0.69	0.488	0.017	-0.050				
26		**Δpost2000_ther**	-14.029	2.932	-4.78	<.0001	0.036	-0.503				
27	11	Intercept	1.144	0.116	9.88	<.0001	1.000	1.144	9%	43%	0.050	0.118
28		Δpost2000_drug	-1.431	4.361	-0.33	0.743	0.017	-0.024				
29		**Δpost2000_ther**	-12.884	3.033	-4.25	<.0001	0.036	-0.462				
30		$\Delta\ln(ATC5_{t-12})$	-0.208	0.146	-1.42	0.157	0.362	-0.075				

Appendix Table 6

Estimates of variants of eq. (5): $\Delta\ln(HOSP) = \beta_1 \Delta\ln(CUM_ATC5_{t-12}) + \beta_2 \Delta VINTAGE_ALL + \delta + \varepsilon'$

HOSP = the number of hospital deaths (HOSP_DEATHS; N = 149)

col.:	1	2	3	4	5	6	7	8	9	10	11	12
									% reduction			
row	model	Variable	Estimate	Std Err	t Value	Pr > |t|	Mean	Estimate * mean	drug	all	p-value: drug= tech	adj. R^2
1	1	Intercept	-0.322	0.063	-5.12	<.0001	1.000	-0.322				
2	2	Intercept	0.020	0.102	0.20	0.843	1.000	0.020	29%			0.098
3		**$\Delta\ln(ATC5_{t-12})$**	-0.915	0.222	-4.12	<.0001	0.374	-0.342				
4	3	Intercept	1.368	0.162	8.43	<.0001	1.000	1.368		82%		0.443
5		**Δvintage_all**	-0.568	0.052	-10.89	<.0001	2.975	-1.690				
6	4	Intercept	1.363	0.162	8.44	<.0001	1.000	1.363	40%	81%	0.139	0.454
7		**Δvintage_drug**	-0.207	0.054	-3.82	0.000	2.511	-0.519				
8		**Δvintage_tech**	-0.357	0.059	-6.05	<.0001	3.263	-1.166				
9	5	Intercept	1.386	0.161	8.59	<.0001	1.000	1.386	45%	82%	0.149	0.459
10		**Δvintage_drug**	-0.194	0.054	-3.58	0.001	2.511	-0.488				
11		**Δvintage_tech**	-0.341	0.060	-5.71	<.0001	3.263	-1.112				
12		$\Delta\ln(ATC5_{t-12})$	-0.290	0.183	-1.59	0.115	0.374	-0.108				
13	6	Intercept	1.007	0.173	5.81	<.0001	1.000	1.007		74%		0.301
14		**Δpost1990_all**	-18.262	2.270	-8.05	<.0001	0.073	-1.329				
15	7	Intercept	0.970	0.171	5.67	<.0001	1.000	0.970	42%	73%	0.820	0.303
16		**Δpost1990_drug**	-8.657	2.336	-3.71	0.000	0.062	-0.536				
17		**Δpost1990_ther**	-9.608	2.408	-3.99	0.000	0.079	-0.756				
18	8	Intercept	0.972	0.171	5.68	<.0001	1.000	0.972	45%	73%	0.831	0.304
19		**Δpost1990_drug**	-8.044	2.396	-3.36	0.001	0.062	-0.498				
20		**Δpost1990_ther**	-8.937	2.479	-3.61	0.000	0.079	-0.703				
21		$\Delta\ln(ATC5_{t-12})$	-0.246	0.219	-1.13	0.262	0.374	-0.092				
22	9	Intercept	0.658	0.161	4.08	<.0001	1.000	0.658		62%		0.216
23		**Δpost2000_all**	-34.702	5.363	-6.47	<.0001	0.028	-0.980				
24	10	Intercept	0.659	0.170	3.88	0.000	1.000	0.659	21%	63%	0.451	0.202
25		**Δpost2000_drug**	-13.942	5.195	-2.68	0.008	0.017	-0.239				
26		**Δpost2000_ther**	-19.904	4.453	-4.47	<.0001	0.037	-0.742				
27	11	Intercept	0.660	0.170	3.89	0.000	1.000	0.660	25%	63%	0.309	0.204
28		Δpost2000_drug	-10.290	6.139	-1.68	0.096	0.017	-0.177				
29		**Δpost2000_ther**	-18.633	4.594	-4.06	<.0001	0.037	-0.694				
30		$\Delta\ln(ATC5_{t-12})$	-0.298	0.267	-1.11	0.267	0.374	-0.111				