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ORIGINAL ARTICLE

How many life-years have new drugs saved? A three-way fixed-effects analysis of 66 diseases in 27 countries, 2000–2013

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Background: We analyzed the role that the launch of new drugs has played in reducing the number of years of life lost (YLL) before three different ages (85, 70 and 55 y) due to 66 diseases in 27 countries.

Methods: We estimated two-way fixed-effects models of the rate of decline of the disease- and country-specific age-standardized YLL rate. The models control for the average decline in the YLL rate in each country and from each disease.

Results: One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-85 y YLL rate (YLL85) in year t by 3.0%, and one additional drug launch ≥12 y before year t is estimated to have reduced YLL85 by 5.5%. (A drug's utilization peaks 8–10 y after it is launched.) Controlling for the number of drugs previously launched, YLL rates are unrelated to the number of drug classes previously launched.

Conclusions: The estimates imply that, if no new drugs had been launched after 1981, YLL85 in 2013 would have been 2.16 times as high as it actually was. We estimated that pharmaceutical expenditure per life-year saved before age 85 y in 2013 by post-1981 drugs was $2837. This amount is about 8% of per capita GDP, indicating that post-1981 drugs launched were very cost-effective overall. But the fact that an intervention is cost-effective does not necessarily mean that it is 'affordable.'

Keywords: cost-effectiveness, innovation, longevity, mortality, pharmaceuticals

Introduction

Global health has improved during the twenty-first century. Life expectancy at birth increased from 66.5 y in 2000 to 72.0 y in 2016.[1] Also, according to the WHO's Global Health Estimates, the number of years of life lost (YLL) per 100 000 population declined by 29% between 2000 and 2016.[2] (Note that YLL is an estimate of the average years a person would have lived if he or she had not died prematurely. It is, therefore, a measure of premature mortality. One can calculate the number of YLL before different ages. If a person died at age 60 y, he or she lost 10 y before age 70 y and 25 y before age 85 y.) Longevity has increased, despite the fact that the global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population,[3] and the global prevalence of obesity (body mass index ≥30 kg/m^2) among adults increased 39% (from 8.7% to 12.1% of the population) between 2000 and 2013.[4]

Some researchers have argued that biomedical innovation has been the principal cause of recent improvements in health. Fuchs[5] said that 'since World War II…biomedical innovations (new drugs, devices, and procedures) have been the primary source of increases in longevity,' although he did not provide evidence to support this claim. Cutler et al.[6] performed a survey of a large and diverse literature on the determinants of mortality, and 'tentatively identif[ied] the application of scientific advance and technical progress (some of which is induced by income and facilitated by education) as the ultimate determinant of health.' They concluded that 'knowledge, science, and technology are the keys to any coherent explanation' of mortality. Other research has shown that most technological progress is 'embodied:' to benefit from technological progress, people must use new products and services. Solow[7] argued that 'many if not most innovations need to be embodied in new kinds of durable equipment before they can be made effective. Improvements in technology affect output only to the extent that they are carried into practice either by net capital formation or by the replacement of old-fashioned equipment by the latest models…' Hercowitz[8] concluded that '"embodiment" is the main

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transmission mechanism of technological progress to economic growth' (p. 223).

Most scholars agree with Jones'[9] statement that 'technological progress is driven by research and development (R&D) in the advanced world' (pp. 89–90). R&D intensity is the ratio of R&D to sales. In 1997, the medical substances and devices sector was the most R&D-intensive major industrial sector in the USA, almost twice as R&D-intensive as the next highest sector (information and electronics), and three times as R&D-intensive as the average for all major sectors.[10] According to Dorsey,[11] in 2008, 88% of privately funded US biomedical research expenditure was funded by pharmaceutical and biotechnology firms; the remaining 11% was funded by medical device firms.

The purpose of this study is to assess econometrically the role that pharmaceutical innovation – the introduction and use of new drugs – has played in reducing the number of YLL before three different ages (85, 70 and 55 y) in 27 countries. The US Food and Drug Administration (FDA) defines a new chemical entity (NCE) as a drug that contains no active moiety that has been approved by the FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During the period January 1982–November 2015, 1300 NCEs were launched – the launch of a drug is defined as the first commercial sale of the drug – in one or more of those 27 countries. For reasons discussed below, there is likely to be a substantial lag between the launch of a new drug and its maximum impact on the burden of disease, so we allowed for considerable lags in the relationship between new drug launches and the burden of disease.

Figure 1 shows the number of NCE launches during 1982–2015 by country. The number of NCE launches in the two countries with the smallest number of launches (Israel and Venezuela) was about half as large as the number of NCE launches in the two countries with the highest number of launches (the USA and Germany). The number of new drug launches also varied considerably across diseases. Figure 2 shows the number of new chemical substances used to treat 30 diseases that were launched in at least one country during 1982–2015.

We have ('three-dimensional') data on both the number of drug launches and the age-standardized premature mortality rate by country, disease and year, so our analysis is based on a three-way fixed-effects model of the premature mortality rate. From that model, a two-way fixed-effects model (which is easier to estimate) of the rate of decline of the premature mortality rate was derived. That model includes both country fixed effects, which control for the average (across diseases) decline in the premature mortality rate in each country, and disease fixed effects, which control for the average (across countries) decline in the premature mortality rate from each disease. This approach is feasible because the relative number of drugs launched for different diseases has varied considerably across countries. This is illustrated by Figure 3, which shows the number of drugs launched during 2006–2015 in Japan and Portugal for 19 types of cancer. The mean (across cancer sites) number of drugs launched during 2006–2015 was almost identical in Japan and Portugal (3.3 and 3.2, respectively), but Japan launched four more drugs for leukemia and four fewer drugs for ovary cancer.

Different organizations use different age thresholds to compute YLL. The age threshold used in the Organisation for Economic Co-operation and Development (OECD) Health Statistics database[12] is 70 y. A US Centers for Disease Control and Prevention website[13] allows one to calculate YLL before ages 65, 70, 75, 80 and 85 y. The Global Burden of Disease (GBD) 2010 reference life table

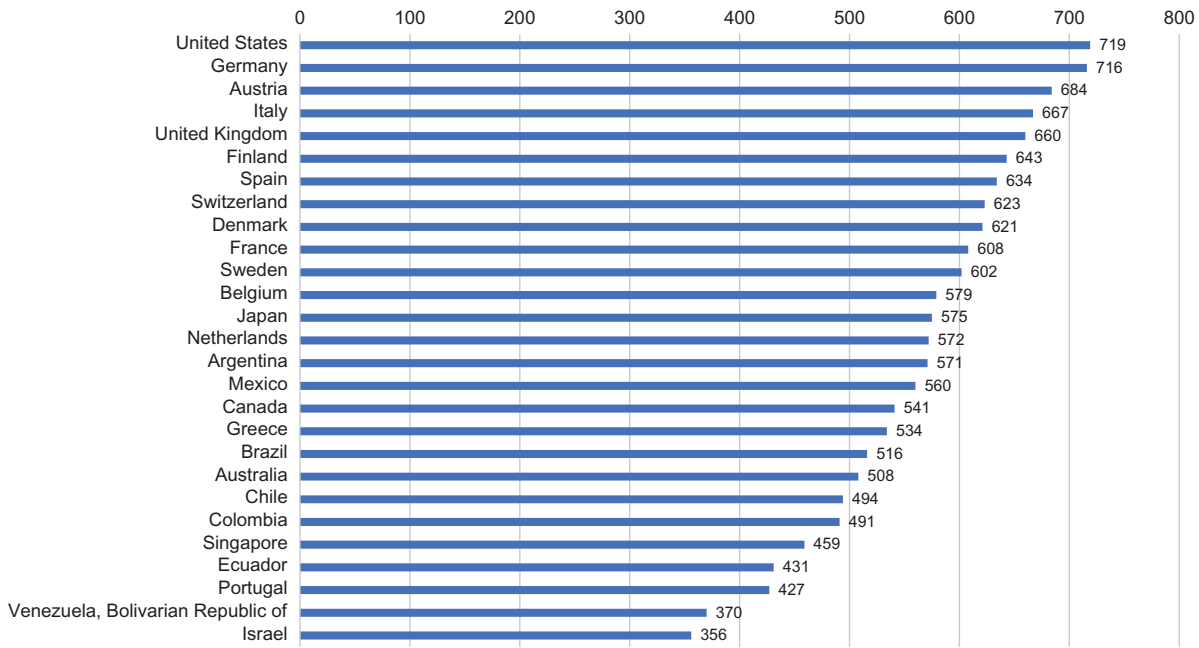

Figure 1. Number of post-1981 New Chemical Entity (NCE) launches, 1982–2015, by country.

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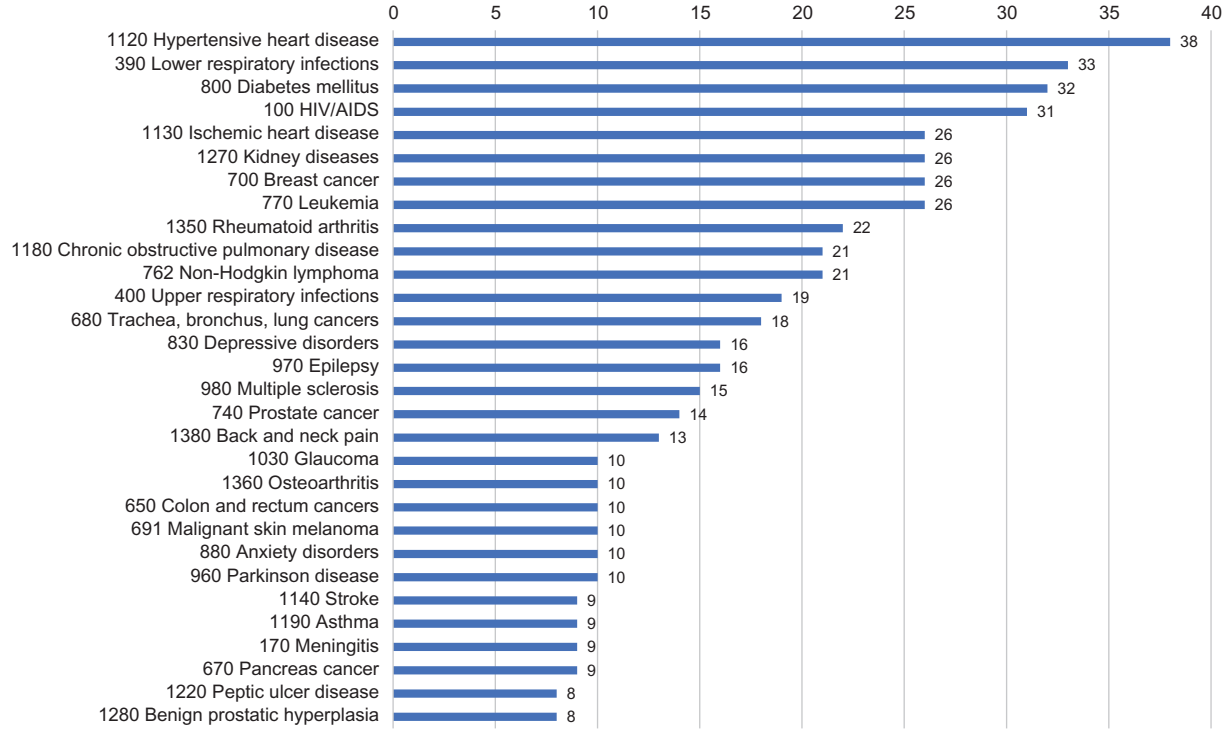

Figure 2. Number of new fifth level ATC codes, by selected medical condition.

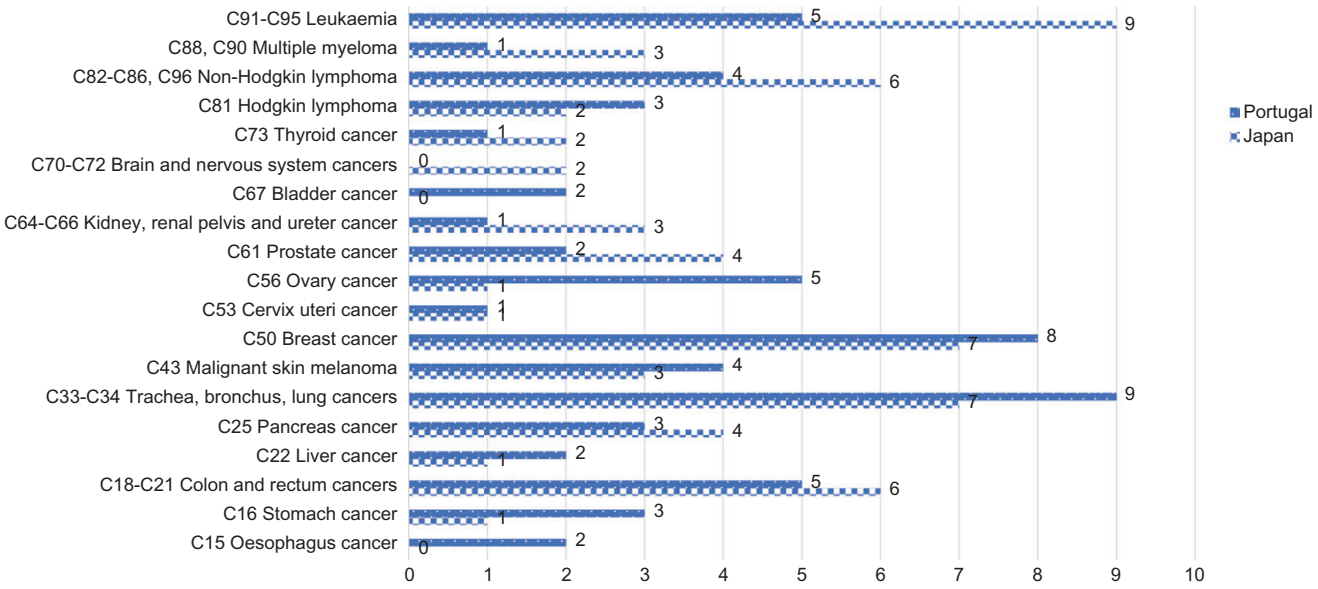

Figure 3. Number of drugs launched during 2006–2015 in Japan and Portugal for 19 types of cancer.

used an age threshold of 86 y. The WHO's Global Health Estimates uses an age threshold of 91.93 y. We analyzed the age-standardized rate of YLL before three ages (85, 70 and 55 y).

Some of the experts consulted by WHO argued that it was not appropriate to set the normative YLL in terms of currently observed death rates, since even for the lowest observed death rates there are a proportion of deaths that are preventable or avertable. In fact, Japanese females have already exceeded the GBD 2010 reference life expectancy at birth, with a life expectancy at birth in 2013 of 87.1 y. Since the loss function is intended to represent the maximum life span of an individual in

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good health, who is not exposed to avoidable health risks or severe injuries and receives appropriate health services, the WHO chose to base its Global Health Estimates YLL age threshold on the frontier national life expectancy projected for the year 2050 by the World Population Prospects 2012. The highest projected life expectancies for the year 2050 are projected to be achieved by women in Japan and the Republic of Korea, with a life expectancy at birth of 91.9 y. While this may still not represent the ultimate achievable human life span, it does represent a set of life spans which are thought likely to be achieved by a substantial number of people who are alive today.[14,15]

In the next section, the econometric model used to assess the role that pharmaceutical innovation has played in reducing premature mortality from 66 diseases in 28 countries during the period 2000–2013 is described.

Methods

The first models used to assess the impact that pharmaceutical innovation had on premature mortality was based on the following three-way fixed-effects equation:

$$\ln(Y_{dct}) = \beta_{0-11}\text{LAUNCHES\_0\_11}_{dct} + \beta_{12+}\text{LAUNCHES\_GE\_12}_{dct} + \alpha_{dc} + \delta_{dt} + \gamma_{ct} + \varepsilon_{dct} \quad (1)$$

where Y_{dct} is one of the following variables:

$YLL85_{dct}$=the age-standardized rate of YLL before age 85 y per 100 000 population below age 85 y due to disease d in country c in year t (t=2000, 2013)

$YLL70_{dct}$=the age-standardized rate of YLL before age 70 y per 100 000 population below age 70 y due to disease d in country c in year t

$YLL55_{dct}$=the age-standardized rate of YLL before age 55 y per 100 000 population below age 55 y due to disease d in country c in year t

and

$\text{LAUNCHES\_0\_11}_{dct}$=the number of new drugs to treat disease d that were launched in country c ≤11 y before year t

$\text{LAUNCHES\_GE\_12}_{dct}$=the number of new drugs to treat disease d that were launched in country c >11 y before year t

α_{dc}=a fixed effect for disease d in country c

δ_{dt}=a fixed effect for disease d in year t

γ_{ct}=a fixed effect for country c in year t

Eq. (1) may be considered a health production function,[16] and the number of new drugs launched may be considered a measure of the stock of pharmaceutical 'ideas'. Jones[17] argued that 'long-run growth is driven by the discovery of new ideas throughout the world'. The discovery of new ideas could increase economic output for two different reasons. First, output could simply be positively related to the quantity (and variety) of ideas ever discovered. Second, output could be positively related to the (mean or maximum) quality of ideas ever discovered, and new ideas may be better (of higher quality), on average, than old ideas. Nordhaus[18] 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 100 y is about as large as the value of measured growth in non-health goods and services.' The specification of eq. (1) incorporates the assumption of diminishing marginal productivity of drug launches: each additional drug launch for a disease results in a diminishing absolute reduction in mortality.

Estimates based on eq. (1) will provide evidence about the impact of the launch of drugs for a disease on the burden of that disease, but they will not capture possible spillover effects of the drugs on the burden of other diseases. These spillovers may be either positive or negative. For example, the launch of cardiovascular drugs could reduce mortality from cardiovascular disease, but increase mortality from the 'competing risk' of cancer. On the other hand, the launch of drugs for mental disorders could reduce mortality from other medical conditions. Prince et al.[19] 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.'

The launch of a drug in a country indicates that patients could have been treated with that drug, not necessarily that patients were treated with that drug. We prefer to estimate models in which the explanatory variables measured the drugs actually used to treat patients, by disease, country and year. We had annual data for 2007–2017 on the utilization of each drug in each country. However, many drugs have multiple indications – 50% of drugs have ≥2 indications (causes of disease in the WHO's Global Health Estimates disease classification), and 7% of drugs have ≥5 indications – and our data did not enable us to determine how often each drug was used for each of its indications.

Since our drug launch variables are imperfect measures of exposure to pharmaceutical innovation, the estimated coefficients on those variables are likely to be biased towards zero, and our estimates of the number of life-years saved by new drugs were likely to be conservative. Here is the first paragraph of the eminent Massachusetts Institute of Technology (MIT) econometrician Jerry Hausman's article on mismeasured variables in econometric analysis[20] (p. 57):

> *'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.'*

Models based on eq. (1) were estimated using data on 66 diseases in 27 countries in 2000 and 2013. Data on drug launches or (in a few cases) on YLL rates were not available for other countries. We also estimated models based on more general versions of eq. (1) that allowed either (1) the effect of drugs launched 0–5 y before year t to differ from the effect of drugs launched 6–11 y before year t, and (2) mortality to depend on

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the number of new classes of drugs launched in addition to the number of new drugs launched.

In eq. (1), drugs launched in two periods (≤11 y before year t vs >11 y before year t) were allowed to have different effects on mortality in year t. We performed tests of the null hypothesis $\beta_{0\text{-}11}=\beta_{12+}$, but expected $|\beta_{0\text{-}11}|<|\beta_{12+}|$, i.e. we expected drugs launched >11 y before year t to have a more negative impact on mortality in year t than drugs launched ≤11 y before year t. There is likely to be a substantial lag between the launch of a new drug and its maximum impact on the burden of disease. Utilization of recently launched drugs tends to be much lower than utilization of drugs launched many years earlier. Evidence about the shape of the drug-age (number of years since launch) drug-utilization profile was obtained by estimating the following equation:

$$\ln(N\_SU_{mcn})=\rho_{mc}+\pi_n+\varepsilon_{mcn} \quad (2)$$

where

N_SU_{mcn}=the number of standard units of molecule m sold in country c n years after it was first launched (n=0, 1,…, 18)

ρ_{mc}=a fixed effect for molecule m in country c

π_n=a fixed effect for age n

The expression $\exp(\pi_n - \pi_8)$ is a 'relative utilization index': it is the mean ratio of the quantity of a drug sold in country c n y after it was launched to the quantity of the same drug sold 8 y after it was launched. We estimated eq. (2) using annual data for the period 2007–2017 on 721 molecules. Estimates of the 'relative utilization index' are shown in Figure 4. These estimates indicate that utilization of a drug reaches a peak about 8–10 y after it was launched. It is used about twice as much then as it was 2 y after it was launched.

Due to gradual diffusion of new drugs, the maximum impact of a drug on disease burden is likely to occur a number of years after it was launched, but the peak effect could occur either more or less than 8–10 y after launch. The lag might be longer because some drugs for chronic diseases (e.g. statins) may have to be consumed for several years to achieve full effectiveness. But the lag might be shorter because the impact of a drug on disease burden is likely to depend on its quality (or effectiveness) as well as on its quantity (utilization), and drugs launched more recently are likely to be of higher quality than earlier vintage drugs. Grossman and Helpman[21] argued that 'innovative goods are better than older products simply because they provide more product services in relation to their cost of production.' Bresnahan and Gordon[22] stated simply that 'new goods are at the heart of economic progress,' and Bils[23] said that 'much of economic growth occurs through growth in quality as new models of consumer goods replace older, sometimes inferior, models.' As noted by Jovanovic and Yatsenko,[24] in 'the Spence–Dixit–Stiglitz tradition…new goods [are] of higher quality than old goods.' The impact on mortality may depend on the (quantity*quality) of the two variables. The mortality impact will increase with respect to drug age (time since launch) if the rate of increase of quantity with respect to age is greater

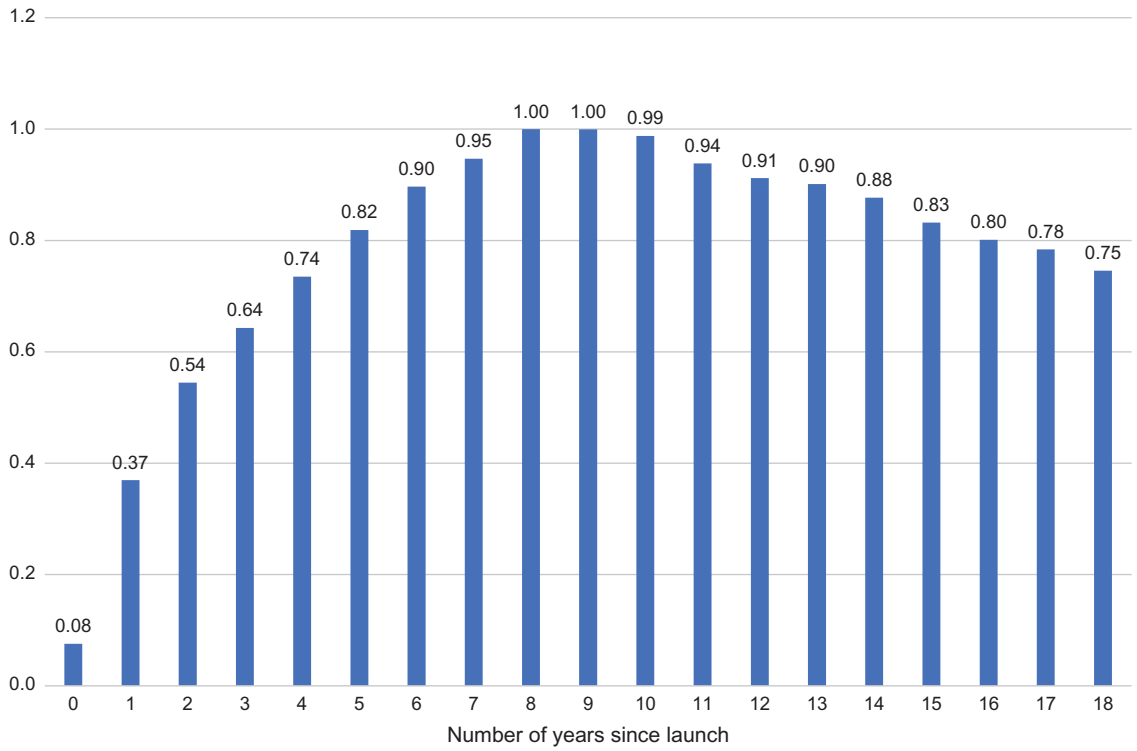

Figure 4. Estimates of relative drug utilization, by number of years since launch.

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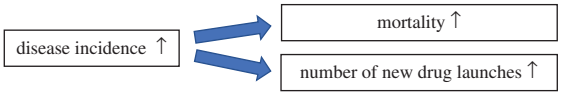
than the rate of decline of quality with respect to age; otherwise the mortality impact will decline.

In our analysis, a drug is a (fifth level) chemical substance as defined in the WHO Anatomical Therapeutic Chemical (ATC) Classification System (e.g. atorvastatin, ATC code C10AA05). The ATC Classification System divides drugs into different groups according to the organ or system upon which they act, their therapeutic intent or nature, and the drug's chemical properties.[25] Different brands share the same code if they have the same active substance and indications. Each bottom-level ATC code stands for a pharmaceutically used substance, or a combination of substances, in a single indication (or use). This means that one drug can have more than one code, for example, acetylsalicylic acid (aspirin) has A01AD05 as a drug for local oral treatment, B01AC06 as a platelet inhibitor and N02BA01 as an analgesic and antipyretic; also, one code can represent more than one active ingredient, for example, C09BB04 is the combination of perindopril with amlodipine, two active ingredients that have their own codes (C09AA04 and C08CA01, respectively) when prescribed alone.

A new drug launch is the first observed launch of a (fifth level) chemical substance corresponding to an NCE, as defined by IQVIA. Our data on NCE launches were left-censored: we only had data on NCEs that were launched anywhere in the world after 1981; data on pre-1982 launches are not available. Consequently, our drug launch variables (especially LAUNCHES_GE_12) are subject to measurement error: if a drug that was first launched anywhere in the world before 1982 was first launched in one of our 27 countries after 1982, it will not, but should have been, counted as a new drug launch. If this measurement error is random, it is likely to bias estimates of the drug launch coefficients (especially β_{12+}) towards zero.

Due to data limitations, LAUNCHES_0_11 and LAUNCHES_GE_12 are the only disease- and country-specific, time-varying regressors in eq. (1). The very large number of fixed effects in this equation – there are 1782 (=66×27) fixed effects for disease d in country c (α_{dc}'s) – control for many unobserved potential determinants of premature mortality, e.g. they control for the possibility that the severity of ischemic heart disease tends to be greater in Brazil than it is in the USA. The country-year fixed-effects (γ_{ct}s) control for changes in a country's attributes (e.g. its average income, educational attainment and healthcare expenditure) to the extent that they have similar effects on mortality from different diseases. For example, suppose that $\ln(Y_{dct})$ depends on EDU_{ct} (where EDU_{ct}=average educational attainment in country c in year t) and that γ_d – the marginal effect of EDU_{ct} on $\ln(Y_{dct})$ – does not vary across diseases ($\gamma_d=\gamma$, all d). Then $\gamma_d\ EDU_{ct}=\gamma\ EDU_{ct}$, which can be written as γ_{ct}.

If the data were available, we would have liked to include other regressors in eq. (1), including (1) disease incidence and (2) the number of non-pharmaceutical medical innovations (e.g. medical device innovations) for disease d that had been launched in country c. However, there is good reason to believe that failure to control for those variables was unlikely to result in overestimation of the magnitudes of $\beta_{0\text{-}11}$ and β_{12+}; exclusion of those variables may even have resulted in an underestimation of the magnitudes of those parameters. Higher disease incidence is likely to result in both higher disease burden and a larger number of drug launches:



Previous studies have shown that both innovation (the number of drugs developed) and diffusion (the number of drugs launched in a country) depend on market size. Acemoglu and Linn[26] found 'economically significant and relatively robust effects of market size on innovation.' Danzon et al.[27] found that 'countries with lower expected prices or *smaller expected market size experience longer delays in new drug access*, controlling for per capita income and other country and firm characteristics' (emphasis added).

Although incidence data were not available for most diseases, annual incidence data for Canada during the period 1992–2010 were available for 31 cancer sites (breast, lung, etc). As expected, there is a significant positive correlation across cancer sites between $\ln(CASES_{st})$ (where $CASES_{st}$=the number of Canadian patients diagnosed with cancer at cancer site s in year t) and $\ln(CUM\_DRUG_{st})$ (where CUM_DRUG_{st}=the number of chemical substances to treat cancer at site s that had ever been launched in Canada by the end of year t). But estimates of the equation $\ln(CUM\_DRUG_{st})=\pi\ \ln(CASES_{st})+\alpha_s+\ \delta_{st}+\varepsilon_{st}$ indicated that the growth rate of CUM_DRUG was uncorrelated across cancer sites with the growth rate of incidence. This suggested that estimates of $\beta_{0\text{-}11}$ and β_{12+} in eq. (1) were unlikely to be biased by the omission of incidence in that equation.

Failure to control for non-pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures and medical devices) was also unlikely to bias estimates of the effect of pharmaceutical innovation on the burden of disease, for two reasons. First, as noted earlier, 88% of privately funded US funding for biomedical research came from pharmaceutical and biotechnology firms.[11] Much of the rest came from the federal government (i.e. the National Institutes of Health [NIH]), and new drugs often build on upstream government research.[28] The National Cancer Institute[29] says that it 'has played a vital role in cancer drug discovery and development, and, today, that role continues.' Second, previous research based on US data[30,31] indicated that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

The dependent variable of eq. (1) is the log of the level of premature mortality in year t. We used data for 2000 and 2013. From the three-way fixed-effects model of the log of the level of premature mortality in year t, which includes 1970 parameters, we derived a two-way fixed-effects model of the 2000–2013 growth of premature mortality, which includes only 95 parameters. Substituting the two values of t into eq. (1) yields:

$$\ln(Y_{dc,2000})=\beta_{0-11}LAUNCHES\_0\_11_{dc,2000}+\beta_{12+}LAUNCHES\_GE\_12_{dc,2000}+\alpha_{dc}+\delta_{d,2000}+\gamma_{c,2000}+\varepsilon_{dc,2000} \quad (3)$$

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$$\ln(Y_{dc,2013}) = \beta_{0-11}\text{LAUNCHES\_0\_11}_{dc,2013} + \beta_{12+}\text{LAUNCHES\_GE\_12}_{dc,2013} + \alpha_{dc} + \delta_{d,2013} + \gamma_{c,2013} + \varepsilon_{dc,2013} \quad (4)$$

Subtracting eq. (3) from eq. (4) yields:

$$\Delta \ln(Y_{dc}) = \beta_{0-11}\Delta\text{LAUNCHES\_0\_11}_{dc} + \beta_{12+}\Delta\text{LAUNCHES\_GE\_12}_{dc} + \delta_d + \gamma_c + \varepsilon_{cd} \quad (5)$$

where

$$\Delta \ln(Y_{dc}) = \ln(Y_{dc,2013}/Y_{dc,2000})$$

$$\Delta\text{LAUNCHES\_0\_11}_{dc} = \text{LAUNCHES\_0\_11}_{dc,2013} - \text{LAUNCHES\_0\_11}_{dc,2000}$$

$$\Delta\text{LAUNCHES\_GE\_12}_{dc} = \text{LAUNCHES\_GE\_12}_{dc,2013} - \text{LAUNCHES\_GE\_12}_{dc,2000}$$

$$\delta_d = \delta_{d,2013} - \delta_{d,2000}$$

$$\gamma_c = \gamma_{c,2013} - \gamma_{c,2000}$$

$$\varepsilon_{dc} = \varepsilon_{dc,2013} - \varepsilon_{dc,2000}$$

Eq. (5) is a two-way fixed-effects regression of the 2000–2013 growth in premature mortality from disease d in country c on the 2000–2013 changes in the number of drugs launched 0–11 y and >11 y earlier. To address the issue of heteroscedasticity – growth rates of observations with low average mortality exhibit much greater variance and volatility than growth rates of observations with high average mortality – eq. (5) was estimated by weighted least squares, weighting by ($POP_{c,2000}$*($Y_{dc,2000}$+$Y_{dc,2013}$)/2), where $POP_{c,2000}$=the population of country c in 2000. Disturbances were clustered within diseases.

In eqs (1) and (5), all new drugs launched within a given period (e.g. 0–11 y before year t) are assumed to have the same effect on mortality in year t. It is possible that the launch of some drugs reduces mortality more than the launch of other drugs. In particular, it is possible that the launch of the first drug in a drug class, or fourth level ATC chemical subgroup, reduces mortality more than the launch of subsequent drugs in the same fourth level ATC chemical subgroup. For example, the launch of lovastatin (C10AA02), the first HMG CoA reductase inhibitor (C10AA), might have reduced mortality more than the launches of the seven subsequently launched HMG CoA reductase inhibitors. We can assess the relative mortality impact of the launch of new drugs and the launch of new classes of drugs by generalizing eq. (5) to include two additional variables:

$$\Delta \ln(Y_{dc}) = \beta_{0-11}\Delta\text{LAUNCHES\_0\_11}_{dc} + \beta_{12+}\Delta\text{LAUNCHES\_GE\_12}_{dc} + \mu_{0-11}\Delta\text{CLASSES\_0\_11}_{dc} + \mu_{12+}\Delta\text{CLASSES\_GE\_12}_{dc} + \delta_d + \gamma_c + \varepsilon_{cd} \quad (6)$$

where

$\Delta\text{CLASSES\_0\_11}_{dc}$=the 2000–2013 change in the number of new classes (fourth level ATC chemical subgroups) of drugs to treat disease d that were launched in country c ≤11 y earlier

$\Delta\text{CLASSES\_GE\_12}_{dc}$=the 2000–2013 change in the number of new classes of drugs to treat disease d that were launched in country c ≥12 y earlier

If mortality depends only, or primarily, on the number of new chemical subgroup launches rather than on the number of new chemical substance launches, estimates of $\mu_{0\text{-}11}$ and μ_{12+} will be statistically significant and estimates of $\beta_{0\text{-}11}$ and β_{12+} will be insignificant. Due to left-censoring of the drug launch data, our data on the number of new drug classes, as well as our data on the number of new drugs, were subject to measurement error. Errors in the measurement of the number of new drug classes were likely to be greater than errors in the measurement of the number of new drugs.

Data sources

Age-standardized rates of YLL. Age-standardized rates of YLL before ages 85, 70 and 55 y, by disease, country and year, were constructed from death registration data published by the WHO,[32] and from population data published by the UN (UN Population Division).[33] The disease classification used is described in Annex Table A of the WHO.[15] Age-standardized rates of YLL due to all causes before ages 85, 70 and 55 y per 100 000 population, by country, are shown in Table 1.

Drug launch data. Data on the years in which post-1981 NCEs were first launched in each of 28 countries were obtained from IQVIA's New Product Focus database.

Drug indications data. Indications (coded by ICD-10) of chemical substances were obtained from Theriaque, a database produced by the French Centre National Hospitalier d'Information sur le Médicament.[34] Theriaque provides data only on labeled indications; it does not provide data on off-label indications.

Drug utilization and expenditure data. Data on the quantity (number of standard units) and value (in US$) of prescription drugs sold, by chemical substance, country and year (2007–2017), were obtained from the IQVIA MIDAS database.

Results

Estimates of drug launch coefficients from nine different models of the 2000–2013 log change in the disease- and country-specific age-standardized rate of YLL are presented in Table 2. Models 1–3 in the table are estimates of eq. (5) for each of the three YLL age thresholds (ages 85, 70 and 55 y). The YLL age threshold in the first model, shown in rows 1 and 2, is age 85 y. Complete estimates of this model are shown in Appendix Table 1. Estimates of the coefficients of both drug-launch regressors (ΔLAUNCHES_0_11 and ΔLAUNCHES_GE_12) are

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Table 1. Age-standardized rates of years of life lost (YLL) due to all causes before ages 85, 70 and 55 y per 100 000 population, by country

	YLL85		YLL70		YLL55		population (000s)
Country	2000	2013	2000	2013	2000	2013	2000
Argentina	14 155	11 867	7679	6185	4572	3553	37 047
Australia	8667	6297	3961	2858	2045	1393	19 057
Austria	10 722	7851	4421	3080	1958	1247	8060
Belgium	11 710	8957	4805	3509	2216	1462	10 273
Brazil	15 163	12 496	9360	7711	5784	4730	175 279
Canada	9048	7159	3921	3222	1825	1539	30 728
Chile	9833	7931	5202	4171	2900	2298	15 256
Colombia	14 796	9111	9789	5818	6482	3790	40 394
Denmark	12 213	8417	4799	3219	1948	1197	5332
Ecuador	14 145	9080	9593	5924	6552	3907	12 620
Spain	9939	6643	4119	2539	1971	1028	40 894
Finland	11 673	8517	4974	3498	2127	1398	5180
France	10 474	7819	4668	3388	2166	1449	59 600
Germany	11 742	9015	4586	3390	1904	1271	81 480
Greece	10 463	8049	4037	3091	1895	1306	11 131
Israel	8571	5623	4057	2563	2239	1319	6004
Italy	10 114	7253	3831	2709	1721	1164	57 285
Japan	8939	6911	3559	2718	1471	1093	127 525
Mexico	12 138	10 647	7719	6596	4931	4145	101 711
The Netherlands	10 165	7149	4094	2823	1808	1169	15 916
Portugal	12 996	8421	5699	3401	2917	1403	10 346
Singapore	6368	3585	2858	1586	1264	679	3907
Sweden	9277	7270	3422	2691	1402	1132	8872
Switzerland	9110	6357	3858	2571	1794	1133	7159
UK	11 137	8076	4316	3240	1929	1434	58 943
USA	11 838	10 151	5624	4943	2783	2408	281 973
Venezuela	14 063	13 509	9250	8982	6097	5893	24 482

negative and highly significant ($p<0.0001$). This signifies that premature (<85 y) mortality from a disease in a country is inversely related to the number of drugs for that disease that were previously launched in that country, ceteris paribus. The magnitude of the ΔLAUNCHES_GE_12 coefficient is 85% larger than the magnitude of the ΔLAUNCHES_0_11 coefficient. The chi-square statistic and its associated p-value (in the two columns on the right of the table) indicate that the null hypothesis of equality of the two coefficients is strongly rejected ($p=0.012$). One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-85 y YLL rate in year t by 3.0% (=1 – exp(–0.031)), and one additional drug launch ≥12 y before year t is estimated to have reduced the pre-age-85 y YLL rate by 5.5%. The larger estimated effect of drugs launched ≥12 y before year t is not surprising, considering the gradual diffusion of new drugs and the likelihood of a lag from utilization to mortality reduction.

The YLL age threshold in the second model in Table 2, shown in rows 3 and 4, is age 70 y. Once again, estimates of the coefficients of both drug-launch regressors are negative and highly significant ($p<0.0001$). The null hypothesis of equality of the two coefficients is strongly rejected. One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-70 y YLL rate in year t by 3.6% and one additional drug launch ≥12 y before year t is estimated to have reduced the pre-age-70 y YLL rate by 6.6%.

The YLL age threshold in the third model in Table 2, shown in rows 5 and 6, is age 55 y. The estimates are qualitatively similar to, but larger in magnitude than, the pre-age-85 y and pre-age-70 y YLL estimates. One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-55 y YLL rate in year t by 4.3% and one additional drug launch ≥12 y before year t is estimated to have reduced the pre-age-55 y YLL rate by 7.3%.

In models 4–6 of Table 2, ΔLAUNCHES_0_11 is separated into two parts: changes in the number of drug launches 0–5 y and 6–11 y before year t (ΔLAUNCHES_0_5 and ΔLAUNCHES_6_11, respectively). In each model, the coefficients of all three regressors are negative and significant, but the chi-square statistics indicate that the hypothesis of equality of the ΔLAUNCHES_0_5 and ΔLAUNCHES_6_11 coefficients cannot be rejected.

Models 7–9 in Table 2 are estimates, for each of the three YLL age thresholds, of the model (eq. (6)) that includes two additional variables (ΔCLASSES_0_11 and ΔCLASSES_GE_12), enabling

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Table 2. Estimates of models of the 2000–2013 log change in the disease- and country-specific age-standardized rate of years of life lost (YLL) before ages 85, 70 and 55 y

Row	Model	YLL age	Regressor	Estimate	Std. error	Z	Pr>|Z|	χ^2	Pr>χ^2
1	1	85 y	ΔLAUNCHES_0_11	−0.031	0.008	−3.79	0.000	6.27	0.012
2			ΔLAUNCHES_GE_12	−0.057	0.013	−4.46	<0.0001		
3	2	70 y	ΔLAUNCHES_0_11	−0.036	0.011	−3.18	0.002	9.00	0.003
4			ΔLAUNCHES_GE_12	−0.068	0.018	−3.76	0.000		
5	3	55 y	ΔLAUNCHES_0_11	−0.044	0.016	−2.79	0.005	6.52	0.011
6			ΔLAUNCHES_GE_12	−0.076	0.026	−2.93	0.003		
7	4	85 y	ΔLAUNCHES_0_5	−0.035	0.009	−3.93	<0.0001	1.27	0.260
8			ΔLAUNCHES_6_11	−0.023	0.011	−2.15	0.031		
9			ΔLAUNCHES_GE_12	−0.055	0.013	−4.06	<0.0001		
10	5	70 y	ΔLAUNCHES_0_5	−0.040	0.014	−2.95	0.003	0.58	0.447
11			ΔLAUNCHES_6_11	−0.030	0.012	−2.45	0.014		
12			ΔLAUNCHES_GE_12	−0.066	0.018	−3.71	0.000		
13	6	55 y	ΔLAUNCHES_0_5	−0.046	0.020	−2.34	0.019	0.15	0.701
14			ΔLAUNCHES_6_11	−0.040	0.013	−3.22	0.001		
15			ΔLAUNCHES_GE_12	−0.075	0.025	−3.05	0.002		
16	7	85 y	ΔLAUNCHES_0_11	−0.032	0.015	−2.23	0.025		
17			ΔLAUNCHES_GE_12	−0.060	0.021	−2.91	0.004		
18			ΔCLASSES_0_11	0.005	0.021	0.23	0.816		
19			ΔCLASSES_GE_12	0.009	0.030	0.31	0.760		
20	8	70 y	ΔLAUNCHES_0_11	−0.043	0.018	−2.37	0.018		
21			ΔLAUNCHES_GE_12	−0.082	0.027	−3.10	0.002		
22			ΔCLASSES_0_11	0.020	0.024	0.84	0.399		
23			ΔCLASSES_GE_12	0.040	0.038	1.04	0.297		
24	9	55 y	ΔLAUNCHES_0_11	−0.056	0.023	−2.46	0.014		
25			ΔLAUNCHES_GE_12	−0.099	0.035	−2.80	0.005		
26			ΔCLASSES_0_11	0.035	0.027	1.33	0.184		
27			ΔCLASSES_GE_12	0.070	0.050	1.42	0.156		

assessment of the relative mortality impact of the launch of new drugs and the launch of new classes of drugs. The coefficients of both variables are insignificant in all three models: controlling for the number of drugs previously launched, YLL rates are unrelated to the number of drug classes previously launched. This finding may be interpreted in several different ways. It may signify that patients benefit from having multiple drugs within a chemical subgroup. A later entrant in a chemical subgroup ('drug 2') may be therapeutically superior to the first-in-class drug ('drug 1'). Even if drug 2 is not superior to drug 1, on average, it may be superior for a subset of patients. Alternatively, perhaps health outcomes depend on the number of drug classes, but some drug classes are more important or valuable than others, and more valuable classes may have larger numbers of drugs. If the YLL rate depends on the number of drug classes previously launched, weighted by their therapeutic value, and the number of drugs in a class is indicative of the therapeutic value of the class, the YLL rate would depend on the number of drugs. The insignificance of the ΔCLASSES_0_11 and ΔCLASSES_GE_12 coefficients may also be partly attributable to the fact that these variables are subject to greater measurement error than ΔLAUNCHES_0_11 and ΔLAUNCHES_GE_12.

Discussion

Now we will use the estimates of $\beta_{0\text{-}11}$ and β_{12+} in models 1–3 in Table 2 to calculate several important measures: (1) the number of life-years saved (i.e. the reduction in YLL) before ages 85, 70 and 55 y in 2013 by new drugs launched after 1981; (2) pharmaceutical expenditure per life-year saved before age 85 y in 2013 by new drugs launched after 1981; and (3) the 2000–2013 decline in YLL rates attributable to new drug launches.

The first set of calculations is shown in Table 3. Calculation of the number of life-years saved before age 85 y is shown in rows 1–3. The mean reduction (which we denote by Φ) in ln(YLL85) in 2013 attributable to drugs launched after 1981 is $\Phi=\beta_{0\text{-}11}$*mean ($LAUNCHES\_0\_11_{dc,2013}$)+β_{12+}*mean ($LAUNCHES\_GE\_12_{dc,2013}$). The estimated ratio of YLL85 in the absence of new drugs to actual YLL=1/exp(Φ). The estimates imply that, if no new drugs had been launched after 1981, YLL85 in 2013 would have been 2.16 times as high as it actually was. Actual total YLL85 in a subset of 22 countries (listed in Table 4) for which complete 2013 pharmaceutical expenditure data were available was 128.1 million. For the year 2000, the WHO's Global Health Estimates figure for YLL (based on an age threshold of 91.93 y) is 63% higher

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Table 3. Calculation of the number of life-years saved (i.e. the reduction in years of life lost [YLL]) before ages 85, 70 and 55 y in 2013 by new drugs launched after 1981

Row	YLL age	Parameter	Variable	Parameter estimate	Weighted mean (variable)	Estimate* weighted mean	Estimated ratio of YLL in absence of new drugs to actual YLL = 1/exp(Φ)	YLL		
								Actual YLL	Estimated YLL, in absence of post-1981 new drug launches	Number of life-years gained in 2013 from post-1981 new drug launches
1	85 y	$\beta_{0\text{-}11}$	LAUNCHES_0_11	−0.031	5.2	−0.159	2.16	128 128 140	276 784 982	148 656 842
2		β_{12+}	LAUNCHES_GE_12	−0.057	10.8	−0.611				
3						sum (Φ):	−0.770			
4	70 y	$\beta_{0\text{-}11}$	LAUNCHES_0_11	−0.036	5.1	−0.184	2.45	56 931 332	139 553 867	82 622 535
5		β_{12+}	LAUNCHES_GE_12	−0.068	10.5	−0.712				
6						sum (Φ):	−0.897			
7	55 y	$\beta_{0\text{-}11}$	LAUNCHES_0_11	−0.044	5.0	−0.219	2.83	24 494 810	69 429 796	44 934 986
8		β_{12+}	LAUNCHES_GE_12	−0.076	10.8	−0.822				
9						sum (Φ):	−1.042			

than YLL85. Therefore, the estimates imply that if no new drugs had been launched after 1981, YLL85 in 2013 would have been 276.8 million, and that the number of life-years before age 85 y gained in 2013 from drugs launched after 1981 was 148.7 million.

Calculations of the number of life-years saved before ages 70 and 55 y are shown in rows 4–6 and 7–9, respectively, of Table 3. The estimated ratios of YLL in the absence of new drugs to actual YLL are higher (2.45 and 2.83, respectively) for the lower YLL age thresholds. We estimate that drugs launched after 1981 saved 82.6 million life-years before age 70 y and 44.9 million life-years before age 55 y in 22 countries in 2013.

The figures in Table 3 indicate that 79% of the life-years saved before ages 85, 70 and 55 y in 2013 by new drugs launched after 1981 were saved by drugs that were launched ≥12 y before (i.e. during 1982–2001). Most of those drugs probably faced generic competition: Danzon and Furukawa[35] (Figure 2) showed that, in 10 countries, (unweighted) mean molecule age at generic entry was 10.2 y. Duflos and Lichtenberg[36] showed that in the USA, the average price of a drug 17 y after it was launched is 61% lower than the average price of the drug 12 y after it was launched.

For all three YLL age thresholds, the share of the 2013 YLL reduction attributable to drugs launched <12 y before (i.e. during 2002–2013) is 21%. This share is slightly (17%) higher than the ratio (18%) of the number of standard units ('number of pills') sold in 2013 of drugs launched during 2002–2013 to the number of standard units sold in 2013 of drugs launched during 1982–2013. The fact that the fraction of life-years saved by more recent drugs is larger than their fraction of drug volume is consistent with the hypothesis discussed above that the average quality of new drugs is superior to the average quality of older drugs, especially when we consider the likelihood of a lag from drug utilization to YLL reduction.

Now we will calculate an estimate of pharmaceutical expenditure per life-year saved before age 85 y in 2013 by new drugs launched after 1981. Data on pharmaceutical expenditure, by country, are shown in Table 4. The first column of figures shows 2013 expenditure on drugs launched after 1981, derived from the IQVIA MIDAS database. The second column shows 2013 expenditure on all drugs, derived from the same source. Post-1981 drugs accounted for 54% (=$346 billion/$638 billion) of total drug expenditure. An estimate of total expenditure in 2014 from an alternative source[37] is 22% (=($778 billion/$638 billion)–1) higher than the IQVIA estimate of total expenditure in 2013. We will use the higher International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) estimate of total expenditure, and assume that 54% of that expenditure was on post-1981 drugs, so our estimate of 2013 expenditure on post-1981 drugs was $421.8 billion (54% of $778 billion). As shown in Table 3, the number of life-years before age 85 y gained in 2013 from post-1981 drugs was 148.7 million, so we estimate that pharmaceutical expenditure per life-year saved before age 85 y in 2013 by post-1981 drugs was $2837 (=$421.8 billion/148.7 million).

As noted by Bertram et al.,[38] 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

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Table 4. Prescription drug expenditure (US$ millions), by country

Country	2013 expenditure on drugs launched after 1981 (source: IQVIA MIDAS database) (US$ millions)	2013 expenditure, total (source: IQVIA MIDAS database) (US$ millions)	2014 expenditure, total (source: International Federation of Pharmaceutical Manufacturers & Associations [2017]) (US$ millions)
Australia	5280	10 516	12 150
Austria	2160	3942	8100
Belgium	3006	5451	7730
Brazil	7391	20 624	26 350
Canada	9865	17 665	21 830
Chile	320	1323	3470
Colombia	226	1278	4320
Ecuador	259	1040	1500
Finland	1304	2453	3780
France	17 317	34 706	44 700
Germany	22 104	42 051	68 860
Ireland	1392	2223	3160
Italy	13 693	25 750	35 330
Japan	40 806	75 929	106 140
Mexico	2345	6489	12 960
Portugal	1084	3512	4550
Singapore	365	736	820
Spain	10 766	19 013	32 780
Sweden	1779	3691	5490
Switzerland	2820	5274	7710
UK	10 037	19 427	50 140
USA	191 558	335 030	316 340
Total	**345 879**	**638 120**	**778 210**

capita income per DALY averted are still considered cost-effective.' (Other authorities use reasonably similar cost-effectiveness thresholds. The UK National Institute for Health and Care Excellence[39] says that, 'in general, interventions with an Incremental Cost-Effectiveness Ratio [ICER] of less than £20 000 per Quality-Adjusted Life Year [QALY] gained are considered to be cost-effective.' The US Department of Veterans Affairs Health Economics Resource Center[40] says that 'a cost-effectiveness analysis may indicate that Drug A is a good value relative to Drug B, because it has an ICER of $40 000 per QALY.') In our study, weighted (by population) mean per capita GDP was $35 543 in 2013, so these estimates indicate that the new drugs launched after 1981 were very cost-effective overall.

Several considerations suggest that $2837 may be an overestimate of the true net cost in 2013 per life-year saved of post-1981 drugs. First, that estimate is based on drug cost measured at invoice price levels; rebates and discounts are not reflected. In the USA in 2014, rebates reduced total brand name drug cost by 17.5%.[41] Second, a previous study based on US data[42] showed that about 25% of the cost of new drugs is offset by reduced expenditure on old drugs. That study also demonstrated that pharmaceutical innovation has reduced work-loss and school-loss days.

The last calculation we performed was the 2000–2013 decline in YLL rates attributable to new drug launches. This calculation is similar to the ones in Table 3, but instead of the 2013 levels of LAUNCHES_0_11 and LAUNCHES_GE_12, we used the 2000–2013 changes in those variables. The estimated drug launch-induced 2000–2013 log change in YLL is ($\beta_{0\text{-}11}$*mean (ΔLAUNCHES_0_11) +β_{12+}*mean (ΔLAUNCHES_GE_12)). The weighted mean values of ΔLAUNCHES_0_11 and ΔLAUNCHES_GE_12 were about −3.6 and 9.4, respectively. Note that there were fewer launches during 2002–2013 than there were during 1989–2000. Consequently, the estimated log change in YLL85 was −0.417, i.e. post-1981 drug launches are estimated to have reduced YLL85 by 34% (=1 − exp (−0.417)) between 2000 and 2013. This is larger than the actual 2000–2013 reduction in YLL85 of 23%. Similarly, the estimated 2000–2013 reductions in YLL70 and YLL55 (39% and 42%, respectively) are larger than the actual (24% and 28%) reductions.

One possible explanation for the finding that the estimated drug launch-induced YLL declines were larger than the actual declines is that trends in other factors were increasing mortality. As noted above, the global prevalence of diabetes and obesity have increased sharply. However, another behavioral risk factor – smoking – has been declining. For example, smoking prevalence among men declined from 44.2% in 2000 to 36.1% in 2013 (https://data.worldbank.org/indicator/SH.PRV.SMOK.MA). Another possible explanation is that mortality-increasing between-disease spillover effects (e.g. cardiovascular drug launches might increase cancer mortality) outweigh mortality-reducing spillover effects (e.g. mental health drug launches might reduce cardiovascular

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mortality). But even if the number of life-years saved in 2013 was 33% or 50% lower than the calculations in Table 3 (which do not account for between-disease spillover effects) indicate, our estimates imply that drugs launched since 1982 have been highly cost-effective overall.

Conclusions

We have performed an econometric analysis of the role that pharmaceutical innovation – the introduction and use of new drugs – has played in reducing the number of YLL before three different ages (85, 70 and 55 y) due to 66 diseases in 27 countries. We used 'three-dimensional' data on both the number of drug launches and the premature mortality rate by country, disease and year to estimate two-way fixed-effects models of the rate of decline of the disease- and country-specific age-standardized premature mortality rate. The models controlled for the average (across diseases) decline in the premature mortality rate in each country and the average (across countries) decline in the premature mortality rate from each disease. This approach was feasible because the relative number of drugs launched for different diseases has varied considerably across countries.

This study is subject to a number of limitations. Our measures of pharmaceutical innovation (the number of drugs and drug classes launched in a country) are imperfect. Our drug launch data are left-censored: only drugs launched anywhere in the world after 1981 are captured. Off-label use of drugs is not accounted for. Our drug indications data were obtained from a French database, and some drugs launched in other countries have not been launched in France. Our estimates provide evidence about the impact of the launch of drugs for a disease on the burden of that disease, but they do not capture possible spillover effects of the drugs on the burden of other diseases. Also, our estimates control for the effects on YLL of changes in a country's health system and macroeconomic conditions to the extent that those effects don't vary across diseases, but those effects might vary across diseases.

Premature (before age 85 y) mortality from a disease in a country is inversely related to the number of drugs for that disease that were previously launched in that country, ceteris paribus. One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-85 y YLL rate (YLL85) in year t by 3.0% and one additional drug launch ≥12 y before year t is estimated to have reduced YLL85 by 5.5%. The larger estimated effect of drugs launched ≥12 y before year t is not surprising, considering the gradual diffusion of new drugs and the likelihood of a lag from utilization to mortality reduction.

When lower YLL age thresholds are used, the estimates are qualitatively similar to, but larger in magnitude than, the YLL85 estimates. One additional drug launch 0–11 y before year t is estimated to have reduced the pre-age-55 y YLL rate (YLL55) in year t by 4.3% and one additional drug launch ≥12 y before year t is estimated to have reduced YLL55 by 7.3%.

Controlling for the number of drugs previously launched, YLL rates are unrelated to the number of drug classes previously launched.

We used the estimates to calculate several important measures: (1) the number of life-years saved (i.e. the reduction in YLL) before ages 85, 70 and 55 y in 2013 by new drugs launched after 1981; (2) pharmaceutical expenditure per life-year saved before age 85 y in 2013 by new drugs launched after 1981; and (3) the 2000–2013 decline in YLL rates attributable to new drug launches.

The estimates implied that, if no new drugs had been launched after 1981, YLL85 in 2013 would have been 2.16 times as high as it actually was. For a subset of 22 countries for which complete 2013 pharmaceutical expenditure data were available, we estimated that the number of life-years before age 85 y gained in 2013 from drugs launched after 1981 was 148.7 million. We also estimated that drugs launched after 1981 saved 82.6 million life-years before age 70 y and 44.9 million life-years before age 55 y in 22 countries in 2013.

The fraction of life-years saved by more recent drugs is slightly larger than their fraction of drug volume, which is consistent with the hypothesis that the average quality of new drugs is superior to the average quality of older drugs.

We estimated that pharmaceutical expenditure per life-year saved before age 85 y in 2013 by post-1981 drugs was $2837. This amount is about 8% of per capita GDP, so these estimates indicate that the new drugs launched after 1981 were very cost-effective overall.

Post-1981 drug launches were estimated to have reduced YLL85 by 34% between 2000 and 2013, which is larger than the actual 2000–2013 reduction in YLL85 of 23%. Similarly, the estimated 2000–2013 reductions in YLL70 and YLL55 (39% and 42%, respectively) were larger than the actual (24% and 28%) reductions. One possible explanation for the finding that the estimated drug launch-induced YLL declines were larger than the actual declines is that trends in other factors (e.g. diabetes and obesity prevalence) were increasing mortality. Another possible explanation is that mortality-increasing between-disease spillover effects (e.g. cardiovascular drug launches might increase cancer mortality) outweigh mortality-reducing spillover effects (e.g. mental health drug launches might reduce cardiovascular mortality). But even if the number of life-years saved in 2013 was 33% or 50% lower than the amount implied by our estimates (which do not account for between-disease spillover effects), the evidence indicates that drugs launched since 1982 have been highly cost-effective overall.

As several scholars have pointed out, the fact that an intervention is cost-effective does not necessarily mean that it is 'affordable'. Sendi and Briggs[43] argued that 'decision-makers are constrained by a fixed-budget and may not be able to fund new, more expensive interventions, even if they have been shown to represent good value for money.' In response to this limitation, those authors introduced the 'affordability curve,' which reflects the probability that a program is affordable for a wide range of threshold budgets. They argued that the joint probability that an intervention is affordable and cost-effective is more useful for decision-making since it captures both dimensions of the decision problem faced by those responsible for health service budgets. In a similar vein, the US Department of Veterans Affairs Health Economics Resource Center argues that in addition to a cost-effectiveness analysis – which evaluates whether an intervention provides value relative to an existing intervention (with value defined as cost relative to health outcome) – it

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may be necessary to conduct a budget impact analysis. That analysis estimates the financial consequences of adopting a new intervention, and evaluates whether the high-value intervention is affordable.

We estimated the impact on the 2013 pharmaceutical budget – $421.8 billion – as well as the average cost-effectiveness of the drugs that were launched since 1982. Presumably, decision-makers considered those drugs to be 'affordable'. However, as shown in Figure 1, many potential drug launches did not occur, perhaps because decision-makers did not consider those drugs to be both cost-effective and affordable.

Supplementary data

Supplementary data are available at *International Health* online (http://inthealth.oxfordjournals.org).

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