The impact of pharmaceutical innovation on the burden of disease in Ireland, 2000–2015

Frank R. Lichtenberg¹,²

¹Columbia University, New York, NY 10027, USA
²National Bureau of Economic Research, Cambridge, MA 02138, USA

Address correspondence to Frank R. Lichtenberg, E-mail: frank.lichtenberg@columbia.edu.

ABSTRACT

Background We perform an econometric assessment of the impact that pharmaceutical innovation had on the burden of disease in Ireland.

Methods We use a difference-in-differences (or two-way fixed effects) research design: we investigate whether diseases for which more new drugs were launched had larger subsequent reductions in mortality. This design controls for the effects of general economic and societal factors (e.g. income, education, and behavioral risk factors), to the extent that those effects are similar across diseases.

Results New Chemical Entities launched during 1983–1997 are estimated to have reduced the total number of disability-adjusted life-years (DALYs) lost in 2015 by about 234,600.

Conclusions Pharmaceutical expenditure per DALY gained in 2015 from drugs launched during 1983–1997 was €1,137, which indicates that the new drugs launched during 1983–1997 were very cost–effective, overall.

Keywords pharmaceutical, innovation, mortality, longevity, Ireland

Introduction

The health status of the Irish people improved during the period 2000–2015. Life expectancy at birth increased from 76.6 years in 2000 to 81.5 years in 2015.¹ Also, the number of disability-adjusted life years (DALYs) lost per 100,000 population declined by 17.5% between 2000 and 2015.²

Some researchers have argued that biomedical innovation has been the principal cause of recent improvements in health. Cutler et al.² concluded that ‘knowledge, science, and technology are the keys to any coherent explanation’ of mortality. Other research³,⁴ has shown that most technological progress is ‘embodied’: to benefit from technological progress, people must use new products and services. Most scholars agree with Jones⁵ statement that ‘technological progress is driven by research and development (R&D) in the advanced world’. Dorsey⁶ showed that, in 2008, 88% of private 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 improving the health of Irish people. During the period 1989–2014, 532 new drugs (i.e., new chemical entities. A new chemical entity (NCE) is a drug or chemical that is without precedent among regulated and approved drug products. The NCE designation indicates that a drug in development is not a version or derivative of an existing and previously investigated, trialed and approved substance. http://www.glossary.pharma-mkt.com/NME. htm) were launched in Ireland: about 20 new drugs per year, on average. (These figures refer to the number of post-1981 NCEs launched in Ireland. A post-1981 NCE is an NCE that was first launched anywhere in the world after 1981). The analysis will be performed using a difference-in-differences (or two-way fixed effects) research design: we will investigate whether diseases for which more new drugs were launched had larger subsequent reductions in mortality. This design controls for the effects of general economic and societal factors (e.g. income, education, and behavioral risk factors
The trend in one behavioral risk factor—obesity—may have increased mortality. Between 2002 and 2015, the fraction of Irish people who were overweight increased from 33 to 35%; the fraction of Irish people who were obese increased from 15 to 18%. Both figures are based on self-reported data. Source: OECD Health Statistics database, to the extent that those effects are similar across diseases, e.g. smoking increases mortality from respiratory and cardiovascular disease as well as lung cancer, and education reduces mortality from all diseases.

The number of new drug launches varied considerably across diseases. For example, as shown in Appendix Figure A1, during the period 2000–2015, 12 new drugs for treating non-Hodgkin's lymphoma, and 5 new drugs for treating prostate cancer, were launched. Only 2 new drugs for treating Parkinson disease, and no new drugs for treating otitis media, were launched. (An identical number of—6—post-1981 NCEs had been launched for each disease by the year 2000.)

There is likely to be a substantial lag between the launch of a new drug and its maximum impact on the burden of disease, for 2 reasons:

- drug launch → drug utilization → burden of disease

First, utilization of recently launched drugs tends to be much lower than utilization of drugs launched many years earlier. As shown in Appendix Fig. A2, mean utilization of drugs launched 10 years earlier is about 5 times as high as mean utilization of drugs launched 2 years earlier; mean utilization of drugs launched 20 years earlier is about 11 times as high as mean utilization of drugs launched 2 years earlier. Second, the effect of using a drug on the burden of disease may be subject to a lag, e.g. because some drugs for chronic diseases (e.g. statins) may have to be consumed for a sustained period to achieve full effectiveness. We will therefore allow for considerable lags in the relationship between new drug launches and the burden of disease. We will analyze data on premature mortality and DALYs, by age group, for 66 diseases (causes of death) of all types, e.g. cardiovascular diseases, respiratory diseases, cancer, etc.

In the next section, we will describe the econometric models that we will use to assess the role that pharmaceutical innovation has played in improving the health of Irish people. Empirical results are presented in Section III. Some implications of the estimates are discussed in Section IV. Section V provides a summary.

**Methods**

To assess the impact that pharmaceutical innovation had on the burden of disease, we will estimate models based on the following equation:

\[
\ln (\text{BURDEN}_{dt}) = \beta_k \text{CUM}_d \text{NCE}_{d,t-k} + \alpha_d + \delta_t + \epsilon_{dt} \tag{1}
\]

where BURDEN_{dt} (the burden of disease d in year t) is one of the following variables:

- \(\text{YPLL}_{a dt} = \text{the number of years of potential life lost before age } a (=70, 75, 80) \text{ due to disease } d \text{ in year } t (t = 2000, 2015)\)
- \(\text{DALYS}_{a dt} = \text{the number of disability-adjusted life years lost in age group } a \text{ due to disease } d \text{ in year } t\)

and

- \(\text{CUM}_d \text{NCE}_{d,t-k} = \sum_m \text{IND}_{md} \text{LAUNCHED}_{m,t-k} = \text{the number of post-1981 NCEs to treat disease } d \text{ that had been launched in Ireland by the end of year } t-k (k = 0, 2, 4, \ldots, 18)\)
- \(\text{IND}_{md} = 1 \text{ if NCE } m \text{ is used to treat (indicated for) disease } d \text{ (Many drugs have multiple indications: 46% of drugs have 2 or more indications (as defined in the World Health Organization disease classification), and 8% of drugs have 5 or more indications) = 0 if NCE } m \text{ is not used to treat (indicated for) disease } d\)
- \(\text{LAUNCHED}_{m,t-k} = 1 \text{ if NCE } m \text{ had been launched in Ireland by the end of year } t-k = 0 \text{ if NCE } m \text{ had not been launched in Ireland by the end of year } t-k\)
- \(\alpha_d = \text{a fixed effect for disease } d\)
- \(\delta_t = \text{a fixed effect for year } t\)

Equation (1) may be considered a health production function, and the number of NCEs ever launched may be considered a measure of the stock of pharmaceutical ‘ideas’. Jones argued that ‘long-run growth is driven by the discovery of new ideas throughout the world’.

Due to data limitations, CUM_NCE is the only disease-specific, time-varying regressor in equation (1). If the data were available, we would like to include other regressors in equation (1), including (1) disease incidence, and (2) the number of non-pharmaceutical medical innovations (e.g. medical device innovations) that had been launched in Ireland. However, there is good reason to believe that failure to control for those variables is unlikely to result in overestimation of the magnitude of \(\beta_k\); exclusion of those variables may even result in underestimation of the magnitude of \(\beta_k\). Higher disease incidence is likely to result in both higher disease burden and a larger number of NCE launches.
Previous studies\textsuperscript{10–12} have shown that both innovation (the number of drugs developed) and diffusion (the number of drugs launched in a country) depend on market size.

Failure to control for non-pharmaceutical medical innovation (e.g. innovation in diagnostic imaging, surgical procedures, and medical devices) is also unlikely to bias estimates of the effect of pharmaceutical innovation on premature mortality, for 2 reasons. First, as noted earlier, 88\% of privately funded US funding for biomedical research came from pharmaceutical and biotechnology firms.\textsuperscript{6} (Pharmaceutical and biotechnology firms accounted for just over half (51.3\%) of total US funding for biomedical research in 2007; the government accounted for 38.2\% of that total. New drugs often build on upstream government research.\textsuperscript{13} The National Cancer Institute\textsuperscript{14} 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\textsuperscript{15,16} indicated that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation. (Drug therapy alone for heart disease patients with blocked coronary arteries may save lives as effectively as bypass or stenting procedures, a large federal study showed.\textsuperscript{17})

Estimates based on equation (1) will provide evidence about the impact of the launch of drugs for a disease on mortality from that disease, but they will not capture possible spillover effects of the drugs on mortality from other diseases. These spillovers may be either positive or negative. The semilogarithmic specification of equation (1) incorporates the assumption of diminishing marginal productivity of NCE launches: each additional NCE launch for a disease results in an diminishing absolute reduction in disease burden.

From the difference-in-differences model of the level of disease burden, we can easily derive the following simple cross-sectional model of the growth of disease burden:

\begin{equation}
\Delta \ln (\text{BURDEN}_{d}) = \beta_1 \Delta \text{CUM NCE}_{d,k} + \delta' + \epsilon'_{d} \quad (2)
\end{equation}

where

\begin{equation}
\Delta \ln (\text{BURDEN}_{d}) = \ln (\text{BURDEN}_{d,2015}) - \ln (\text{BURDEN}_{d,2000})
\end{equation}

= the log change from 2000 to 2015 in the burden of disease \textdollar; \Delta \text{CUM NCE}_{d,k} = \text{CUM NCE}_{d,2015,k} - \text{CUM NCE}_{d,2000,k} \end{equation}

= the number of post-1981 NCEs launched between 2000-k and 2015-k, \delta' = \delta_{2015} - \delta_{2007} \quad = the difference between the 2015 and 2000 fixed effects.

To address the issue of heteroskedasticity (In equation (2), the dependent variable is essentially the percentage change between 2000 and 2015 in BURDEN. Percentage changes of observations with low average disease burdens exhibit much greater variance and volatility than percentage changes of observations with high average disease burdens), equation (2) will be estimated by weighted least squares, weighting by \((\text{BURDEN}_{d,2000} + \text{BURDEN}_{d,2015})/2\).

The data sources used to construct the variables in equation (2) are described in Appendix A.

Results

Estimates of \(\beta_k\) parameters of equation (2), where the burden of disease is measured by the number of years of potential life lost before different ages, are presented in Table 1. Rows 1–10 show estimates when the YPLL age threshold is 70 (70 is the YPLL age threshold used in the OECD Health Statistics database), and the lag length \((k)\) varies between 0 (row 1) and 18 years (row 10). The estimates in rows 1–7 are not statistically significant, indicating that \(YPLL_{70}\) is not significantly related to the cumulative number of NCEs launched 0–12 years earlier. However, the estimates in rows 8–10 are negative and significant (\(P\)-value < 0.04), indicating that \(YPLL_{70}\) is significantly inversely related to the cumulative number of NCEs launched 14–18 years earlier. The finding that \(YPLL_{70}\) is significantly inversely related only to the cumulative number of NCEs launched 14–18 years earlier is consistent with the fact that utilization of recently launched drugs tends to be much lower than utilization of drugs launched many years earlier, and that some drugs may have to be consumed for a sustained period to achieve full effectiveness. The estimate of \(\beta_{18}\) in row 10 indicates that, on average, the launch of a drug for a disease reduced \(YPLL_{70}\) from that disease 18 years later by about 2.0\%.

We can estimate the overall reduction in \(YPLL_{70}\) in 2015 attributable to drug launches during 1983–1997 by multiplying \(\beta_{18}\) by the weighted mean number of drugs launched during that period. As shown in the last column of row 10, drug launches during 1983–1997 are estimated to have reduced \(YPLL_{70}\) by 12\% in 2015. During the period 2000–2015, aggregate \(YPLL_{70}\) declined by about 23\%. The population below age 70 increased by about 20\%, so \(YPLL_{70}\) per 100 000 population below age 70 decreased by 36\%. Drug launches during 1983–1997 account for about one-third of the 2000–2015 decline in \(YPLL_{70}\) per 100 000 population below age 70.

Rows 11–20 of Table 1 show estimates when the YPLL age threshold is 75. The estimates based on this higher age threshold are larger and more significant. The estimates in rows 12–18 are negative and significant (\(P\)-value < 0.02), indicating that \(YPLL_{75}\) is significantly inversely related to the cumulative number of NCEs launched 12–18 years earlier. The estimate of \(\beta_{18}\) in row 20 indicates that, on average, the
launch of a drug for a disease reduced YPLL_75 from that disease 18 years later by about 2.5%. Drug launches during 1983–1997 are estimated to have reduced YPLL_75 by 15% in 2015.

Rows 21–30 of Table 1 show estimates when the YPLL age threshold is 80. Once again, the estimates based on this higher age threshold are larger and more significant. The estimates in rows 26–30 are negative and significant ($P$-value < 0.04), indicating that YPLL_80 is significantly inversely related to the cumulative number of NCEs launched 10–18 years earlier. The estimate of $\beta_{18}$ in row 30 indicates that, on average, the launch of a drug for a disease reduced YPLL_80 from that disease 18 years later by about 3.0%. Drug launches during 1983–1997 are estimated to have reduced YPLL_80 by 20% in 2015. Drug launches during 1983–1997 account for almost half of the 2000–2015 decline in YPLL_80 per 100 000 population below age 80.

Estimates of $\beta_k$ parameters of equation (2), where the burden of disease is measured by the number of disability-adjusted life years lost, are presented in Table 2. Rows 1–10 show estimates when the dependent variable is the log of DALYs lost at all ages (DALYS_AGE_0–99), and the

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Table 1 Estimates of $\beta_k$ parameters of equation (2): years of Potential Life Lost before ages 70, 75, and 80

| Row | Lag | Parameter | Estimate | Std. Error | t Value | Pr > | $|t|$ | wtd. Mean ($\Delta \text{Cum}_{\text{NCE}} k$) | $\beta_k$ * wtd. Mean ($\Delta \text{Cum}_{\text{NCE}} k$) |
|-----|-----|-----------|----------|------------|---------|-------|------|-----------------|---------------------|
|     |     | $\beta_0$ | 0.004    | 0.009     | 0.50    | 0.617 | 6.61 | 0.03            |
| 2   | 2   | $\beta_2$ | −0.001   | 0.008     | −0.10  | 0.919 | 6.85 | −0.01           |
| 3   | 4   | $\beta_4$ | −0.003   | 0.007     | −0.49  | 0.627 | 7.36 | −0.03           |
| 4   | 6   | $\beta_6$ | −0.003   | 0.007     | −0.37  | 0.715 | 7.86 | −0.02           |
| 5   | 8   | $\beta_8$ | −0.004   | 0.007     | −0.61  | 0.546 | 7.76 | −0.03           |
| 6   | 10  | $\beta_{10}$ | −0.005 | 0.007     | −0.75  | 0.453 | 7.45 | −0.04           |
| 7   | 12  | $\beta_{12}$ | −0.010 | 0.006     | −1.77  | 0.083 | 8.08 | −0.08           |
| 8   | 14  | $\beta_{14}$ | −0.013  | 0.006     | −2.13  | 0.037 | 7.60 | −0.10           |
| 9   | 16  | $\beta_{16}$ | −0.015  | 0.007     | −2.14  | 0.037 | 6.80 | −0.11           |
| 10  | 18  | $\beta_{18}$ | −0.020  | 0.009     | −2.33  | 0.024 | 5.89 | −0.12           |
|     |     | $\beta_0$ | 0.002    | 0.009     | 0.18   | 0.860 | 6.88 | 0.01            |
| 11  | 2   | $\beta_2$ | −0.005   | 0.008     | −0.64  | 0.525 | 7.10 | −0.04           |
| 12  | 4   | $\beta_4$ | −0.007   | 0.007     | −1.10  | 0.278 | 7.63 | −0.06           |
| 13  | 6   | $\beta_6$ | −0.006   | 0.007     | −0.90  | 0.370 | 8.11 | −0.05           |
| 14  | 8   | $\beta_8$ | −0.008   | 0.007     | −1.22  | 0.227 | 8.07 | −0.07           |
| 15  | 10  | $\beta_{10}$ | −0.010  | 0.007     | −1.41  | 0.163 | 7.76 | −0.08           |
| 16  | 12  | $\beta_{12}$ | −0.014  | 0.006     | −2.59  | 0.012 | 8.44 | −0.12           |
| 17  | 14  | $\beta_{14}$ | −0.017  | 0.006     | −2.98  | 0.004 | 7.99 | −0.14           |
| 18  | 16  | $\beta_{16}$ | −0.020  | 0.007     | −2.92  | 0.005 | 7.15 | −0.14           |
| 19  | 18  | $\beta_{18}$ | −0.025  | 0.008     | −3.08  | 0.003 | 6.22 | −0.15           |
| 21  | 0   | $\beta_0$ | −0.001   | 0.009     | −0.17  | 0.863 | 7.06 | −0.01           |
| 22  | 2   | $\beta_2$ | −0.009   | 0.008     | −1.19  | 0.240 | 7.29 | −0.07           |
| 23  | 4   | $\beta_4$ | −0.011   | 0.007     | −1.69  | 0.096 | 7.86 | −0.09           |
| 24  | 6   | $\beta_6$ | −0.010   | 0.007     | −1.44  | 0.156 | 8.32 | −0.08           |
| 25  | 8   | $\beta_8$ | −0.012   | 0.007     | −1.86  | 0.067 | 8.34 | −0.10           |
| 26  | 10  | $\beta_{10}$ | −0.014  | 0.007     | −2.12  | 0.038 | 8.02 | −0.11           |
| 27  | 12  | $\beta_{12}$ | −0.018  | 0.005     | −3.52  | 0.001 | 8.82 | −0.16           |
| 28  | 14  | $\beta_{14}$ | −0.021  | 0.005     | −3.95  | 0.000 | 8.39 | −0.18           |
| 29  | 16  | $\beta_{16}$ | −0.025  | 0.006     | −3.85  | 0.000 | 7.52 | −0.18           |
| 30  | 18  | $\beta_{18}$ | −0.030  | 0.007     | −3.99  | 0.000 | 6.55 | −0.20           |
lag length \((k)\) varies between 0 (row 1) and 18 years (row 10). These estimates are plotted in Fig. 1. The estimates in rows 2–10 are negative and statistically significant, indicating that DALYS_AGE_0–99 is significantly inversely related to the cumulative number of NCEs launched 2–18 years earlier. However, recently launched drugs have smaller marginal effects on DALYS_AGE_0–99 than drugs launched longer ago, presumably due to much higher utilization of the latter. Drug launches during 1983–1997 are estimated to have reduced DALYS_AGE_0–99 by 18.1% \(= 1 - \exp(-0.20)\) in 2015. This is almost exactly equal to the actual (17.5%) reduction in DALYS_AGE_0–99 per capita. Hence drug launches during 1983–1997 account for all of the 2000–2015 per capita decline in DALYS_AGE_0–99.

Table 2: Estimates of \(\beta_k\) parameters of equation (2): Disability-adjusted life years lost, total and by age group

| Row | Lag | Parameter | Estimate | Std. Error | t Value | Pr > |t| | wtd. Mean \((\Delta CUM_N C E_k)\) | \(\beta_k \times\) wtd. Mean \((\Delta CUM_N C E_k)\) |
|------|-----|-----------|----------|------------|---------|-------|----------------|----------------|----------------|
| 1    | 0   | \(\beta_0\) | -0.010   | 0.006      | -1.73   | 0.088 | 6.38          | -0.07          |
| 2    | 2   | \(\beta_2\) | -0.012   | 0.005      | -2.13   | 0.036 | 7.09          | -0.08          |
| 3    | 4   | \(\beta_4\) | -0.010   | 0.005      | -2.10   | 0.038 | 8.00          | -0.08          |
| 4    | 6   | \(\beta_6\) | -0.010   | 0.005      | -2.06   | 0.043 | 8.31          | -0.08          |
| 5    | 8   | \(\beta_8\) | -0.013   | 0.005      | -2.68   | 0.009 | 8.36          | -0.11          |
| 6    | 10  | \(\beta_{10}\) | -0.015   | 0.005      | -2.99   | 0.004 | 8.15          | -0.12          |
| 7    | 12  | \(\beta_{12}\) | -0.018   | 0.004      | -4.50   | <0.0001 | 9.23          | -0.16          |
| 8    | 14  | \(\beta_{14}\) | -0.021   | 0.004      | -5.15   | <0.0001 | 8.64          | -0.18          |
| 9    | 16  | \(\beta_{16}\) | -0.024   | 0.005      | -5.06   | <0.0001 | 7.64          | -0.18          |
| 10   | 18  | \(\beta_{18}\) | -0.030   | 0.005      | -5.59   | <0.0001 | 6.56          | -0.20          |
| 11   | 18  | \(\beta_{18}\) | -0.007   | 0.013      | -0.52   | 0.604 | 3.06          | -0.02          |
| 12   | 18  | \(\beta_{18}\) | 0.000    | 0.009      | 0.01    | 0.995 | 4.86          | 0.00           |
| 13   | 18  | \(\beta_{18}\) | -0.003   | 0.008      | -0.40   | 0.690 | 4.91          | -0.02          |
| 14   | 18  | \(\beta_{18}\) | -0.015   | 0.006      | -2.48   | 0.015 | 5.26          | -0.08          |
| 15   | 18  | \(\beta_{18}\) | -0.031   | 0.006      | -5.51   | <0.0001 | 6.13          | -0.19          |
| 16   | 18  | \(\beta_{18}\) | -0.037   | 0.005      | -7.01   | <0.0001 | 6.78          | -0.25          |
| 17   | 18  | \(\beta_{18}\) | -0.046   | 0.007      | -7.00   | <0.0001 | 7.96          | -0.37          |

Rows 11–17 show estimates of equation (2) when the dependent variable is the change in the log of DALYs lost in different age groups (0–4, 5–14, 15–29, 30–49, 50–59, 60–69, 70+), and the lag length \((k)\) equals 18 years. (As shown in Appendix Table A2, with the exception of the lowest age group (age 0–4), the number of DALYs per person increases with age.) Estimates of \(\beta_{18}\) are not statistically significant for the 3 lowest age groups, i.e. for people below age 30, but they are significant for the 4 highest age groups. The implied percentage reduction in DALYs lost is largest for the highest age group. NCE launches during 1983–1997 are estimated to have reduced the number of DALYs lost by people of age 30–49 by 7.6%, and the number of DALYs lost by people above age 69 by 30.7%. As shown in Appendix Table A2, with the exception of the lowest age group (age 0–4), there is a strong positive correlation across age groups between the actual and predicted 2000–2015 log change in DALYs lost per person.
Fig. 1 Estimates of $\beta_k$ parameters of equation (2), $\Delta \ln(DALYS_{AGE\_0-99d}) = \beta_k \Delta CUM\_NCE_{kd} + \delta^* + \epsilon^* d$.

Vertical scale is inverted.
Dashed lines represent 95% confidence intervals; solid markers represent significant (p-value < .05) estimates; hollow marker represents insignificant (p-value > .05) estimate.

Fig. 2 Relationship across diseases between the number of post-1981 new chemical entities launched during 1983–1997 and the 2000–2015 log change in the number of disability-adjusted life years lost at all ages.

Bubble area is proportional to mean number of disability-adjusted life years lost at all ages.

Fig. 2 Relationship across diseases between the number of post-1981 new chemical entities launched during 1983–1997 and the 2000–2015 log change in the number of disability-adjusted life years lost at all ages.
Discussion

Main finding of this study

As discussed above, the estimate of β18 in row 10 of Table 2 indicates that, in the absence of drug launches during 1983–1997, DALYS_AGE_0–99 would have been 22.1% (= (1/exp(−0.20)) −1) higher in 2015. As shown in Appendix Table A2, the total number of DALYs in 2015 was 1.062 million, so drug launches during 1983–1997 are estimated to have reduced the total number of DALYs in 2015 by about 234 600 (= 22.1% × 1.062 million).

Calculations based on data from the IQVIA New Product Focus and MIDAS databases indicate that expenditure in 2015 on drugs launched during 1983–1997 was $296 million. (This represents 13% of IQVIA’s estimate of total pharmaceutical expenditure of $2.32 billion. According to the OECD Health Statistics database, total pharmaceutical sales in Ireland in 2015 in US dollars valued at the exchange rate was $2.20 billion. According to the International Federation of Pharmaceutical Manufacturers & Associations,18 total pharmaceutical sales in Ireland in 2014 were $3.16 billion.) This expenditure estimate, along with our estimate of the reduction in DALYs lost, implies that pharmaceutical expenditure per DALY gained in 2015 from drugs launched during 1983–1997 was $1263 (= $296 million/234 600 DALYs).

As noted by Bertram et al.,19 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 DALY for less than average per capita income for a given country or region are considered very cost–effective’. Ireland’s per capita GDP was $60 664 in 2015.

What is already known on this topic

The fact that the health status of the Irish people improved during the period 2000–2015 was previously known. But the factors responsible for this improvement in health status had not been established.

What this study adds

By using a difference-in-differences (or two-way fixed effects) research design, thereby investigating whether diseases for which more new drugs were launched had larger subsequent reductions in mortality, we assessed econometrically the role that pharmaceutical innovation—the introduction and use of new drugs—has played in improving the health of Irish people. This design controls for the effects of general economic and societal factors (e.g. income, education, and behavioral risk factors), to the extent that those effects are similar across diseases, e.g. smoking increases mortality from respiratory and cardiovascular disease as well as lung cancer, and education reduces mortality from all diseases.

Limitations of this study

Due to data limitations, we were unable to control for other potential determinants of the burden of disease (e.g. disease incidence, and the number of non-pharmaceutical medical innovations (e.g. medical device innovations) that had been launched in Ireland. Also, our estimates provide evidence about the impact of the launch of drugs for a disease on mortality from that disease, but they do not capture possible spillover effects of the drugs on mortality from other diseases.

Summary

We have performed an econometric assessment of the impact that pharmaceutical innovation had on the burden of disease in Ireland, using a difference-in-differences (or two-way fixed effects) research design: we investigated whether diseases for which more new drugs were launched had larger subsequent reductions in mortality.

Our estimates indicated that New Chemical Entities launched during 1983–1997 reduced the total number of disability-adjusted life years lost in 2015 by about 234 600. Pharmaceutical expenditure per DALY gained in 2015 from drugs launched during 1983–1997 was €1137.

NCE launches caused substantial reductions in the burden of disease in Ireland during the period 1994–2015, but perhaps the reductions could have been even larger, for 2 reasons. First, the number of post-1981 NCEs launched in Ireland during 1982–2015 was more than 12% lower than the number launched in 4 other European countries (Germany, Italy, Austria, and the UK), and Irish patients have access to only 20% of new oncology medicines launched since 2016.20 Second, utilization of NCEs 2 years after launch is only 20% as great as it is 10 years after launch.

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Appendix A. Data sources

Mortality data. Data on the number of deaths and the number of years of potential life lost before various ages, by disease and year (2000 and 2015), were constructed from data obtained from the World Health Organization’s Cause-Specific Mortality Database (World Health Organization22). That source provides data on the number of deaths by 5-year age group, disease, and year. I assume that all deaths in an age group occur at the midpoint of the age group, e.g. deaths in age group 65–69 occur at age 67.5.

DALYS data. Data on the number of DALYS lost in various age groups, by disease and year, were obtained from the World Health Organization’s Disease Burden Database (World Health Organization22). The disease classification used in the Cause-Specific Mortality Database and the Disease Burden Database is described in Annex Table A of World Health Organization (2018d).

Drug launch data. Data on post-1981 NCE launches were obtained from the IQVIA New Product Focus database. (Coverage of drug launches in my version of the IMS Health New Product Focus database ended on 1 November 2015.)

Drug indications data. Data on drug indications (coded by ICD-10) were obtained from Theriaque, a database produced by the French Centre National Hospitalier d’Information sur le Médicament.23 (While these data appear to be the best that are available, they may be incomplete, in two respects. First, only drugs that have been launched in France are covered. During the period 1982–2015, 610 post-1981 NCEs were launched in France, but 760 were launched in Japan and 758 were launched in Germany. 587 were launched in Ireland.) Second, Theriaque provides data only on labeled indications; it does not provide data on off-label indications.)

Data on the number of post-1981 NCEs ever launched and the number of DALYS, by disease, are presented in Appendix Table A1.

Drug utilization and expenditure data. Data on the quantity (number of standard units) and value (in USD) of drugs sold, by molecule and year (2007–2017) were obtained from the IQVIA MIDAS database.
Appendix Fig. A1  Number of post-1981 New Chemical Entities used to treat 4 diseases ever launched in Ireland, 2000–2015.

Source: author’s calculations based on data contained in IQVIA New Product Focus database and Theriaque database.

Appendix Fig. A2  Mean annual number of standard units sold, by number of years since launch.

Source: author’s calculations based on data contained in IQVIA New Product Focus and MIDAS databases.
Appendix Table A1  Number of post-1981 NCEs ever launched and number of DALYs, by disease

| Disease                                        | CUM_NCE | DALYS (thousands) |
|------------------------------------------------|---------|-------------------|
|                                                | 1990    | 1995  | 2000  | 2005  | 2010  | 2015  | 2000 | 2015 |
| 30 Tuberculosis                                | 0       | 0     | 0     | 0     | 1     | 2     | 1.1  | 0.5  |
| 70 Gonorrhea                                   | 4       | 4     | 4     | 4     | 4     | 4     | 0.1  | 0.1  |
| 85 Genital herpes                              | 0       | 1     | 2     | 2     | 2     | 2     | 0.1  | 0.1  |
| 90 Other STDs                                  | 0       | 0     | 1     | 1     | 1     | 1     | 0.1  | 0.1  |
| 100 HIV/AIDS                                   | 2       | 4     | 13    | 21    | 26    | 28    | 0.6  | 0.9  |
| 110 Diarrhoeal diseases                        | 2       | 2     | 2     | 2     | 2     | 3     | 1.7  | 2.0  |
| 170 Meningitis                                 | 3       | 4     | 4     | 5     | 5     | 7     | 2.3  | 0.6  |
| 190 Acute hepatitis B                          | 2       | 2     | 3     | 6     | 8     | 8     | 0.3  | 0.3  |
| 200 Acute hepatitis C                          | 2       | 2     | 3     | 4     | 5     | 5     | 0.0  | 0.0  |
| 220 Malaria                                    | 1       | 2     | 2     | 2     | 2     | 2     | 0.0  | 0.0  |
| 370 Other infectious diseases                  | 10      | 18    | 24    | 30    | 35    | 35    | 3.1  | 2.5  |
| 390 Lower respiratory infections               | 9       | 12    | 17    | 21    | 22    | 23    | 34.8 | 14.2 |
| 400 Upper respiratory infections               | 7       | 9     | 12    | 13    | 13    | 13    | 4.6  | 5.5  |
| 410 Otitis media                               | 5       | 6     | 6     | 6     | 6     | 6     | 1.4  | 1.5  |
| 420 Maternal conditions                        | 0       | 0     | 0     | 0     | 2     | 2     | 0.4  | 0.4  |
| 500 Preterm birth complications                | 1       | 1     | 1     | 1     | 1     | 1     | 9.4  | 8.0  |
| 530 Other neonatal conditions                  | 0       | 0     | 0     | 0     | 0     | 0     | 2.6  | 2.1  |
| 580 Iron-deficiency anaemia                    | 1       | 1     | 1     | 2     | 4     | 4     | 1.9  | 1.7  |
| 620 Mouth and oropharynx cancers               | 0       | 0     | 1     | 3     | 8     | 9     | 37.5 | 41.4 |
| 630 Oesophagus cancer                          | 1       | 1     | 2     | 2     | 2     | 2     | 3.5  | 4.7  |
| 640 Stomach cancer                             | 2       | 2     | 4     | 5     | 5     | 6     | 8.1  | 9.0  |
| 650 Colon and rectum cancers                   | 0       | 0     | 2     | 6     | 7     | 9     | 21.5 | 22.7 |
| 660 Liver cancer                               | 1       | 1     | 1     | 1     | 2     | 3     | 4.6  | 6.3  |
| 670 Pancreas cancer                            | 2       | 2     | 2     | 4     | 6     | 7     | 10.1 | 10.6 |
| 680 Trachea, bronchus, lung cancers            | 1       | 1     | 3     | 8     | 9     | 15    | 37.5 | 41.4 |
| 691 Malignant skin melanoma                    | 2       | 2     | 2     | 2     | 2     | 2     | 4.0  | 4.4  |
| 692 Non-melanoma skin cancer                   | 0       | 0     | 0     | 1     | 1     | 1     | 1.0  | 1.3  |
| 700 Breast cancer                              | 2       | 4     | 10    | 16    | 19    | 22    | 19.9 | 20.9 |
| 710 Cervix uteri cancer                        | 0       | 0     | 1     | 2     | 2     | 2     | 3.1  | 3.0  |
| 730 Ovary cancer                               | 1       | 1     | 2     | 4     | 5     | 7     | 6.3  | 6.8  |
| 740 Prostate cancer                            | 3       | 5     | 6     | 6     | 8     | 11    | 8.9  | 9.7  |
| 745 Kidney cancer                              | 1       | 1     | 1     | 2     | 3     | 4     | 5.1  | 5.9  |
| 750 Bladder cancer                             | 1       | 1     | 1     | 1     | 1     | 2     | 3.7  | 4.3  |
| 751 Brain and nervous system cancers           | 0       | 0     | 1     | 1     | 1     | 2     | 9.1  | 9.5  |
| 752 Gallbladder and biliary tract cancer       | 0       | 0     | 0     | 0     | 0     | 0     | 0.9  | 1.1  |
| 754 Thyroid cancer                             | 0       | 0     | 0     | 0     | 1     | 2     | 0.5  | 0.8  |
| 755 Mesothelioma                               | 1       | 1     | 1     | 1     | 4     | 4     | 0.7  | 0.9  |
| 761 Hodgkin lymphoma                           | 1       | 1     | 1     | 1     | 1     | 3     | 0.7  | 0.8  |
| 762 Non-Hodgkin lymphoma                       | 5       | 5     | 6     | 9     | 12    | 18    | 6.3  | 6.5  |
| 763 Multiple myeloma                           | 2       | 2     | 2     | 3     | 4     | 6     | 3.1  | 3.7  |
| 770 Leukaemia                                  | 5       | 5     | 8     | 10    | 13    | 19    | 6.7  | 6.6  |
| 800 Diabetes mellitus                          | 3       | 6     | 14    | 21    | 29    | 30    | 18.5 | 23.3 |
| 830 Depressive disorders                       | 4       | 7     | 11    | 13    | 13    | 13    | 28.4 | 33.5 |
| 840 Bipolar disorder                           | 1       | 2     | 4     | 5     | 5     | 6     | 6.1  | 7.2  |
| Disease                                      | CUM_NCE (thousands) | DALYS (thousands) |
|---------------------------------------------|---------------------|-------------------|
| 850 Schizophrenia                           | 0 1 3 5 6 7         | 7.1 9.5           |
| 860 Alcohol use disorders                   | 0 0 0 0 0 1         | 12.9 13.9         |
| 880 Anxiety disorders                       | 3 5 7 10 10 10      | 19.9 24.4         |
| 890 Eating disorders                        | 1 1 1 1 1 1         | 3.1 3.8           |
| 911 Attention deficit/hyperactivity syndrome| 0 0 0 1 1 1         | 0.4 0.5           |
| 912 Conduct disorder                        | 0 1 1 1 1 1         | 3.3 3.4           |
| 920 Idiopathic intellectual disability      | 0 1 1 1 1 1         | 1.8 2.0           |
| 930 Other mental and behavioural disorders  | 2 3 10 14 16 18     | 6.0 7.5           |
| 950 Alzheimer disease and other dementias   | 0 0 1 1 1 1         | 13.3 32.6         |
| 960 Parkinson disease                       | 1 1 6 7 8 8         | 2.4 5.4           |
| 970 Epilepsy                                | 2 3 8 10 13 15      | 6.4 5.7           |
| 980 Multiple sclerosis                      | 2 4 7 9 10 14       | 2.4 4.0           |
| 990 Migraine                                | 0 0 2 5 7 7         | 20.2 24.4         |
| 1000 Non-migraine headache                  | 0 0 0 1 2 2         | 4.3 5.4           |
| 1010 Other neurological conditions          | 0 2 10 10 13 14     | 7.3 9.0           |
| 1030 Glaucoma                               | 1 2 5 7 7 8         | 0.3 0.4           |
| 1050 Uncorrected refractive errors          | 0 0 0 2 4 4         | 0.5 0.6           |
| 1060 Macular degeneration                   | 1 1 2 4 6 6         | 2.2 2.5           |
| 1070 Other vision loss                      | 1 1 5 7 8 8         | 2.2 2.5           |
| 1090 Other sense organ disorders            | 5 7 9 10 10         | 3.7 5.1           |
| 1120 Hypertensive heart disease             | 11 16 23 27 29      | 3.7 2.8           |
| 1130 Ichaemic heart disease                 | 8 10 15 22 23       | 137.1 86.5        |
| 1140 Stroke                                 | 1 2 5 5 7 8         | 49.5 34.7         |
| 1150 Cardiomyopathy, myocarditis, endocarditis| 1 1 1 1 2 2     | 7.9 6.7           |
| 1160 Other circulatory diseases             | 10 12 23 32 39 43   | 38.9 32.3         |
| 1180 Chronic obstructive pulmonary disease  | 7 10 13 15 16       | 36.6 35.0         |
| 1190 Asthma                                 | 0 0 2 3 4 4         | 17.7 18.3         |
| 1200 Other respiratory diseases             | 9 13 16 19 20 24    | 9.6 9.9           |
| 1220 Peptic ulcer disease                   | 4 5 8 8 8 8         | 2.0 1.5           |
| 1230 Cirrhosis of the liver                | 1 1 1 4 6 6         | 8.2 11.5          |
| 1244 Inflammatory bowel disease             | 1 1 2 3 4 5         | 1.3 1.0           |
| 1248 Pancreatitis                           | 1 1 1 1 1 1         | 1.1 1.1           |
| 1250 Other digestive diseases               | 5 8 12 12 13        | 9.4 10.6          |
| 1270 Kidney diseases                        | 9 11 15 18 20       | 9.8 9.6           |
| 1280 Benign prostatic hyperplasia           | 1 3 4 6 7 7         | 2.3 3.2           |
| 1300 Other urinary diseases                 | 8 14 17 20 22 25    | 2.8 2.4           |
| 1310 Infertility                            | 0 0 2 3 3 3         | 0.9 1.2           |
| 1320 Gynecological diseases                 | 1 4 4 4 4 4         | 4.1 4.9           |
| 1330 Skin diseases                          | 13 18 28 38 42      | 10.7 12.7         |
| 1350 Rheumatoid arthritis                   | 4 4 11 13 17        | 5.0 6.2           |
| 1360 Osteoarthritis                         | 2 5 6 6 6 6         | 7.1 10.4          |
| 1370 Gout                                   | 0 0 0 0 0 0         | 1.0 1.4           |
| 1380 Back and neck pain                     | 1 1 5 7 9 9         | 34.5 45.6         |
| 1390 Other musculoskeletal disorders        | 6 6 13 20 25        | 13.5 16.4         |
| 1440 Congenital heart anomalies             | 0 0 1 1 1 1         | 5.8 4.2           |
| 1460 Other congenital anomalies             | 0 1 1 1 2 2         | 10.6 9.2          |
| 1502 Other oral disorders                   | 0 0 0 0 1 1         | 2.1 2.6           |
Scales are inverted.
The predicted 2000-2015 log changes in DALYs per person are the values of $\left[J_{18} \times \text{wtd. mean } \left\{ \Delta \text{CUM\_NCE}\_18 \right\} \right]$ reported in rows 11-17 of Table 2.

**Appendix Fig. A3** Correlation across age groups between actual and predicted 2000–2015 log change in DALYs per person.

**Appendix Table A2** Total DALYs and DALYs per capita in 2000 and 2015, by age group

| Age group | DALYs (000s) | POP (000s) | DALYs per capita |
|-----------|--------------|------------|------------------|
|           | 2000         | 2015       | 2000          | 2015          | 2000      | 2015      |
| 0–4       | 43.2         | 31.7       | 269.2         | 352.9         | 0.16      | 0.09      |
| 5–14      | 29.2         | 31.4       | 553.4         | 668.7         | 0.05      | 0.05      |
| 15–29     | 121.9        | 88.3       | 1005.8        | 819.6         | 0.12      | 0.11      |
| 30–49     | 194.7        | 222.5      | 1049.4        | 1427.8        | 0.19      | 0.16      |
| 50–59     | 134.5        | 147.0      | 412.3         | 564.2         | 0.33      | 0.26      |
| 60–69     | 162.9        | 180.6      | 274.6         | 459.1         | 0.59      | 0.39      |
| 70+       | 367.6        | 360.1      | 284.2         | 407.9         | 1.29      | 0.88      |
| Total     | 1054.0       | 1061.7     | 3848.8        | 4700.1        | 0.27      | 0.23      |