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The Impact of New Drug Launches on Longevity Growth in Nine Middle Eastern and African Countries, 2007–2015

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Abstract:
This study provides econometric evidence about the impact that new chemical entity (NCE) launches had on premature mortality from 17 diseases in 9 Middle Eastern and African countries during the period 2007–2015. The greater the relative number of NCEs for a disease launched in a country, the greater the subsequent relative decline in premature mortality from that disease, controlling for the average rate of mortality decline in each country and from each disease.
An 8-year increase in the number of post-1992 NCEs ever launched is estimated to have reduced the number of years of potential life lost before age 75 (YPLL75) in 2015 by 9.5 %. This is approximately half of the 18.9 % reduction in YPLL75, and about one-third of the 29.7 % reduction in the premature mortality rate. In the absence of 8 previous years of NCE launches, 2.80 million additional YPLL before age 75 would have been lost in 2015. Expenditure on new drugs per life-year below age 75 gained in 2015 from the drugs was $US 834. According to the standards of the WHO's Choosing Interventions that are cost–effective project, new drugs launched in the nine ME&A countries were very cost–effective overall.

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1 Introduction

Premature mortality has been recognized by numerous analysts and organizations to be an important measure of a population's health. Premature mortality is usually measured by the number of Years of Potential Life Lost (YPLL) before a specified age. The calculation of YPLL involves summing up deaths occurring at each age and multiplying this by the number of remaining years to live up to a selected age limit. For example, if the selected age limit is 70,[1] and 20 people die at the age of 60, then those deaths would represent 200 (=20 × (70 − 60)) YPLL before age 70. YPLL emphasizes deaths of younger persons – many of which may be preventable – whereas statistics that include all mortality are dominated by deaths of the elderly. Previous authors have argued that "reducing premature mortality is a crucial public health objective" (Renard, Tafforeau, and Deboosere 2014), and that YPLL "should be considered when allocating research funds" (Burnet et al. 2005).

Previous studies (e. g. Lichtenberg 2016, 2017) have shown that pharmaceutical innovation – the introduction and use of new drugs – has reduced premature mortality in several OECD countries. Those studies were based on difference-in-differences research designs: they showed that diseases for which more new drugs were introduced in a country had larger subsequent reductions in premature mortality.

The purpose of this article is to assess the impact that new drug launches had on premature mortality in nine Middle Eastern and African countries[2] during the period 2007–2015. Premature mortality rates[3] declined substantially (by about 30–32 %) in these countries during this period. As shown in Figure 1, in 2007, the premature (before age 75) mortality rate in these countries was 2.44 times as high as the premature (before age 75) mortality rate in the USA; by 2015, this ratio had declined to 1.75.

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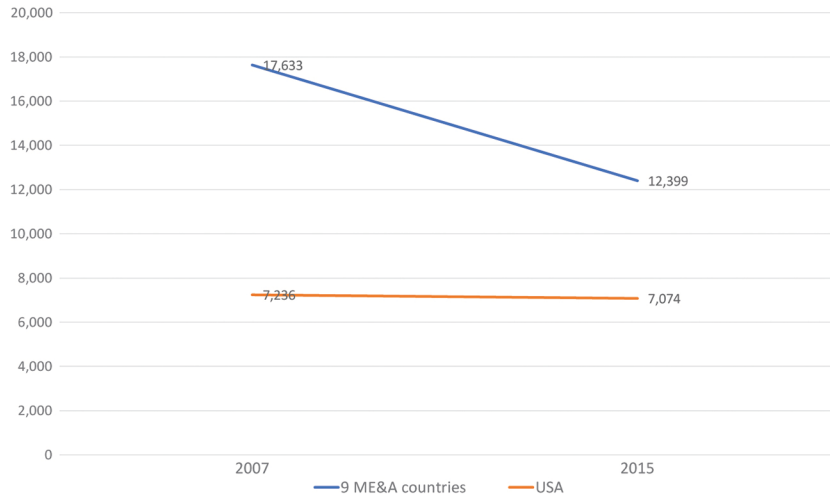

Figure 1: Premature (before age 75) mortality rate, all natural causes.
Source: Author's calculations, based on data from World Health Organization (2016) and U.S. Centers for Disease Control (2017).

I will estimate the number of life-years gained in 2015 from drugs previously launched in the nine countries. I will also estimate expenditure on these drugs in 2015. By combining these two estimates, I can calculate the overall cost-effectiveness of (or cost per life-year gained from) pharmaceutical innovation in the nine countries.

This study will employ a "triple-differences," or difference-in-difference-in-differences, research design: I will estimate the impact that new drug launches had on premature mortality from 17 diseases in 9 Middle Eastern and African countries during the period 2007–2015. This design enables me to control for the average rate of mortality decline in each country and from each disease. Pischke (2005, 11) observed that "triple differences may allow for a more credible analysis" than a difference-in-differences ("double difference") analysis. Similarly, Berck and Villas-Boas (2015) argued that:

> the difference-in-difference model measures the effect of policy by removing the effects of time and place. When the outcome variable is determined by policy, time, place and yet another variable, a triple difference strategy may reduce the bias in the estimate of the effect of the policy change.

Figure 2 shows the number of post-1992 new chemical entities (NCEs) launched in nine Middle Eastern and African countries during the period 1993–2015. South Africa had the largest number of NCE launches; Morocco had the smallest number. The triple-difference methodology is feasible because the *relative* number of NCEs launched to treat different diseases varied across countries. This variation is illustrated by Figure 3, which shows the number of post-1992 NCEs launched in each country for two diseases: cardiovascular diseases, and endocrine, blood, and immune disorders. In four countries (Jordan, Kuwait, Morocco, and Tunisia), the number of cardiovascular NCE launches was larger than the number of endocrine, blood, and immune disorder NCE launches; in the other five countries, the number of cardiovascular NCE launches was smaller than the number of endocrine, blood, and immune disorder NCE launches. I hypothesize that the difference between the decline in mortality from cardiovascular disease and the decline in mortality from endocrine, blood, and immune disorders was larger in Jordan than it was in Saudi Arabia. Instead of performing the analysis using just two diseases in two countries, I will perform the analysis on 17 diseases in 9 countries.

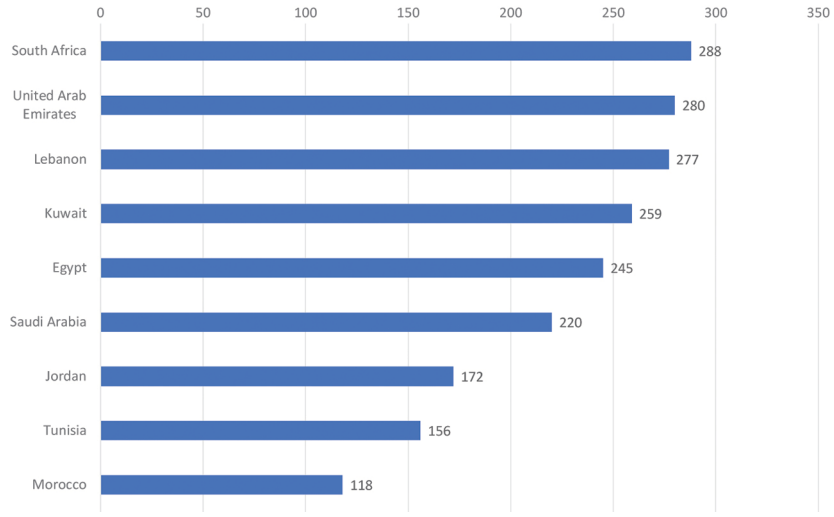

Figure 2: Number of post-1992 NCEs launched during 1993–2015, by country.
Source: Author's calculations, based on data from IMS Health New Product Focus database.

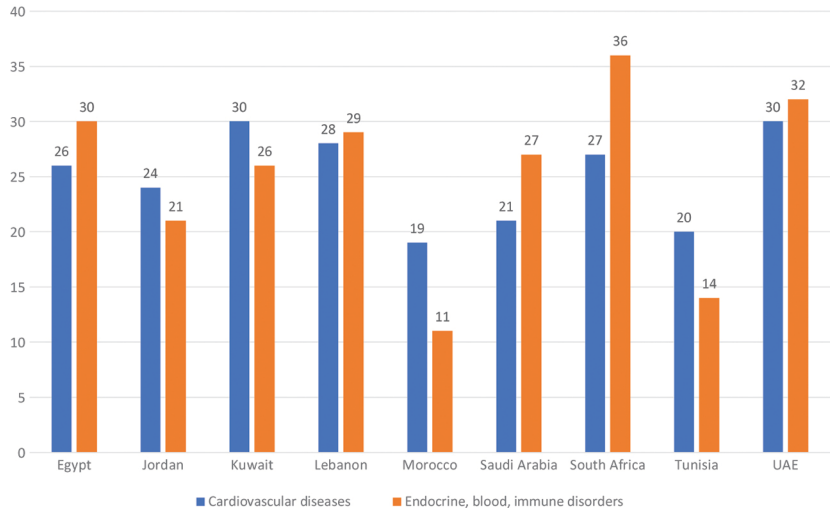

Figure 3: Number of post-1992 NCEs launched during 1993–2015 for 2 diseases, by country.
Source: Author's calculations, based on data from IMS Health New Product Focus and Theriaque databases.

In the next section, I will provide background and motivation for the econometric model of premature mortality, which is developed in Section 3. Data sources are discussed in Section 4. Empirical results are presented in Section 5. Implications of the results are discussed in Section 6. Section 7 concludes.

2 Background and Motivation

Before describing the econometric model I will use to estimate the effect of new drug launches on premature mortality, I will provide some theoretical and empirical background and motivation for the model, which can be summarized by Figure 4.

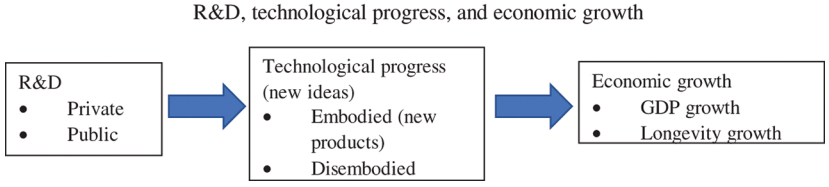

Figure 4: R&D, technological progress, and economic growth.

Starting on the right of this figure: longevity increase is a very important part of economic growth, broadly defined. Nordhaus (2005) argued that:

> improvements in health status have been a major contributor to economic welfare over the twentieth century. To a first approximation, the economic value of increases in longevity in the last hundred years is about as large as the value of measured growth in non-health goods and services.

(Murphy and Topel 2006) estimated that cumulative gains in life expectancy after 1900 were worth over $1.2 million to the representative American in 2000, whereas post-1970 gains added about $3.2 trillion per year to national wealth, equal to about half of GDP. The United Nations' Human Development Index, which is used to rank countries into four tiers of human development, is a composite statistic of life expectancy, income per capita, and education (United Nations 2017).

There is a consensus among macroeconomists that technological progress is the principal source of GDP growth. Romer (1990) argued that "growth…is driven by technological change that arises from intentional investment decisions made by profit-maximizing agents" (S71). Jones argued that "long-run growth is driven by the discovery of new ideas throughout the world."[4] And Chien (2015) said that "it has been shown, both theoretically and empirically, that technological progress is the main driver of long-run growth."

Since technological progress, or the discovery of new ideas, is the fundamental source of one of the major components – GDP growth – of "human development," or economic growth, broadly defined, it is quite plausible that the discovery of new ideas has also played a major role in longevity growth. Some previous authors have suggested that this is the case. Fuchs (2010) 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, Deaton, and Lleras-Muney (2006) 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.

In general, measuring the number of ideas is challenging. One potential measure is the number of patents, but Patterson (2012, 8) noted that only 1 % of patent applications made by Bell Labs "generated [commercial] value." Fortunately, measuring pharmaceutical "ideas" is considerably easier than measuring ideas in general. The measure of pharmaceutical ideas I will use is the number of new molecular entities used to treat a disease launched in a country. Since we have precise information about when those ideas reached the market and the diseases to which they apply, we can assess the impact of those ideas on longevity in a triple differences framework.

Technological change may be either disembodied or embodied. Suppose firm X invests in R&D, and that this investment results in a valuable discovery. If the technological advance is disembodied, consumers and other firms could benefit from the discovery without purchasing firm X's goods or services; they could benefit just by reading or hearing about the discovery. However, if the technological advance is embodied, consumers and other firms must purchase firm X's goods or services to benefit from its discovery. Solow (1960) 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…[5]

Romer (1990) also assumed that technological progress is embodied in new goods: "new knowledge is translated into goods with practical value," and "a firm incurs fixed design or research and development costs when it creates a new good. It recovers those costs by selling the new good for a price that is higher than its constant cost of production." Grossman and Helpman (1993) 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 (1996) stated simply that "new goods are at the heart of economic progress," and Bils (2004) said that "much of economic growth occurs through growth in quality as new models of consumer goods replace older, sometimes inferior, models." Hercowitz (1998, 223) concluded that "'embodiment' is the main transmission mechanism of technological progress to economic growth."

Most scholars agree with Jones' (1998, 89–90) statement that "technological progress is driven by research and development (R&D) in the advanced world." In 1997, the medical substances and devices sector was the most R&D-intensive[6] major industrial sector: 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. (National Science Foundation 2017). In 2007, 89 % of private biomedical research expenditure was funded by pharmaceutical and biotechnology firms; the remaining 11 % was funded by medical device firms (Dorsey 2010).

A U.S. government institute (the National Cancer Institute (NCI)) has also played an important role in cancer drug discovery and development.[7] Frequently, NCI's drug development efforts focus on unmet needs that

are not being adequately addressed by the private sector. NCI's cancer drug discovery and development activities originated from a congressionally mandated initiative known as the Cancer Chemotherapy National Service Center (CCNSC), which, in 1955, established a national resource to facilitate the evaluation of potential anticancer agents. In 1976, the CCNSC's functions were incorporated into the Developmental Therapeutics Program in NCI's Division of Cancer Treatment and Diagnosis (National Cancer Institute 2017).

3 Econometric Model of Premature Mortality

To investigate the impact that new chemical entity (NCE) launches had on the number of YPLL at different ages and other mortality measures, I will estimate models based on the following triple-differences model:

$$\text{MORT}_{ict} = \beta_k \ln\left(\text{CUM\_NCE}_{ic,t-k}\right) + \alpha_{ic} + \delta_{it} + \pi_{ct} + \varepsilon_{ict} \quad (1)$$

where MORT_{ict} is one of the following variables:

$\ln(\text{YPLL75}_{ict})$	= the log of the number of YPLL before age 75 due to disease i in country c in year t (y = 2007, 2015)[8]
$\ln(\text{YPLL65}_{ict})$	= the log of the number of YPLL before age 65 due to disease i in country c in year t
$\ln(\text{N\_DEATHS}_{ict})$	= the log of the number of deaths due to disease i in country c in year t
AGE_DEATH_{ict}	= mean age at death due to disease i in country c in year t

and

$\text{CUM\_NCE}_{ic,t\text{-}k}$	= $\sum_m \text{IND}_{mi}\,\text{LAUNCHED}_{mc,t\text{-}k}$ = the number of post-1992 NCEs to treat disease i that had been launched in country c by the end of year t-k[9]
IND_{mi}	= 1 if NCE m is used to treat (indicated for) disease i = 0 if NCE m is not used to treat (indicated for) disease i
$\text{LAUNCHED}_{mc,t\text{-}k}$	= 1 if NCE m had been launched in country c by the end of year t-k = 0 if NCE m had not been launched in country c by the end of year t-k
α_{ic}	= a fixed effect for disease i in country c
δ_{it}	= a fixed effect for disease i in year t
π_{ct}	= a fixed effect for country c in year t[10]

Eq. (1) will be estimated using data on 17 major diseases comprising the disease classification used in World Health Organization (2017).

Due to data limitations, the number of NCEs is the only country- and disease-specific and time-varying explanatory variable in eq. (1). But both a patient-level U.S. study and a longitudinal country-level study have shown that controlling for numerous other potential determinants of longevity does not reduce, and may even increase, the estimated effect of pharmaceutical innovation. The study based on patient-level data (Lichtenberg 2013) found that controlling for race, education, family income, insurance coverage, Census region, BMI, smoking, the mean year the person started taking his or her medications, and over 100 medical conditions had virtually no effect on the estimate of the effect of pharmaceutical innovation (the change in drug vintage) on life expectancy. The study based on longitudinal country-level data (Lichtenberg 2014a) found that controlling for ten other potential determinants of longevity change (real per capita income, the unemployment rate, mean years of schooling, the urbanization rate, real per capita health expenditure (public and private), the DPT immunization rate among children ages 12–23 months, HIV prevalence and tuberculosis incidence) *increased* the coefficient on pharmaceutical innovation by about 32 %.

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 two reasons. First, more than half of U.S. funding for biomedical research came from pharmaceutical and biotechnology firms (Dorsey 2010). Much of the rest came from the federal government (i. e. the NIH), and new drugs often build on upstream government research (Sampat and Lichtenberg 2011). The National Cancer Institute (2017) says that it "has played a vital role in cancer drug discovery and development, and, today, that role continues." Second, previous research based on U.S. data (Lichtenberg 2014a, 2014b) indicates that non-pharmaceutical medical innovation is not positively correlated across diseases with pharmaceutical innovation.

Estimates of eq. (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. 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. (2007) argued that "mental disorders increase risk for communicable and non-communicable diseases, and contribute to unintentional and intentional injury. Conversely, many health conditions increase the risk for mental disorder, and comorbidity complicates help-seeking, diagnosis, and treatment, and influences prognosis."

My data on drug launches are left-censored: I only have data on drugs launched after 1992. I therefore define $\text{CUM\_NCE}_{ic,t\text{-}k}$ as the number of post-1992 NCEs (i. e. NCEs first launched anywhere in the world after 1992) used to treat disease i that had been launched in country c by the end of year t-k. Consequently, this measure is subject to error, because $\text{CUM\_NCE}_{ic,t\text{-}k}$ will not (but should) include pre-1993 NCEs that were first launched in country c after 1992. If this measurement error is random, it is likely to bias estimates of β_k toward zero.

Eq. (1) includes a large number of parameters, mainly due to 153 (17 diseases × 9 countries) disease/country fixed effects (α_{ic}'s). These "nuisance" parameters are not of interest to us, and estimation of a (simpler) "difference-in-differences" model, which can be derived from the triple-difference model (eq. (1)), is less computationally burdensome. Setting $\text{MORT}_{ict} = \ln(\text{YPLL75}_{ict})$, and t equal to 2007 and 2015, yields eq. (2) and eq. (3), respectively:

$$\ln\left(\text{YPLL75}_{ic,2007}\right) = \beta_k \ln\left(\text{CUM\_NCE}_{ic,2007-k}\right) + \alpha_{ic} + \delta_{i,2007} + \pi_{c,2007} + \varepsilon_{ic,2007} \tag{2}$$

$$\ln\left(\text{YPLL75}_{ic,2015}\right) = \beta_k \ln\left(\text{CUM\_NCE}_{ic,2015-k}\right) + \alpha_{ic} + \delta_{i,2015} + \pi_{c,2015} + \varepsilon_{ic,2015} \tag{3}$$

Subtracting eq. (2) and eq. (3), yields:

$$\Delta \ln\left(\text{YPLL75}_{ic}\right) = \beta_k \Delta \ln\left(\text{CUM\_NCE\_}k_{ic}\right) + \delta'_i + \pi'_c + \varepsilon'_{ic} \tag{4}$$

where

$\Delta\ln(\text{YPLL75}_{ic})$	$= \ln(\text{YPLL75}_{ic,2015}) - \ln(\text{YPLL75}_{ic,2007})$ = the log change from 2007 to 2015 in the number of YPLL before age 75 due to disease i in country c
$\Delta\ln(\text{CUM\_NCE\_k}_{ic})$	$= \ln(\text{CUM\_NCE}_{ic,2015-k}) - \ln(\text{CUM\_NCE}_{ic,2007-k})$ = the log change from 2007 − k to 2015 − k in the number of post-1992 NCEs for disease i that had ever been launched in country c
δ'_i	$= \delta_{i,2015} - \delta_{i,2007}$ = the difference between the 2007 and 2015 fixed effects for disease i
π'_c	$= \pi_{c,2015} - \pi_{c,2007}$ = the difference between the 2007 and 2015 fixed effects for country c

More generally,

$$\Delta\text{MORT}_{ic} = \beta_k \Delta \ln\left(\text{CUM\_NCE\_k}_{ic}\right) + \delta'_i + \pi'_c + \varepsilon'_{ic} \tag{5}$$

where

$$\Delta\text{MORT}_{ic} = \text{MORT}_{ic,2015} - \text{MORT}_{ic,2007}$$

To address the issue of heteroskedasticity,[11] eq. (5) will be estimated by weighted least squares, using the following weights:

Dependent variable	Weight
$\Delta\ln(\text{YPLL75}_{ic})$	$(\text{YPLL75}_{ic,2007} + \text{YPLL75}_{ic,2015})/2$
$\Delta\ln(\text{YPLL65}_{ic})$	$(\text{YPLL65}_{ic,2007} + \text{YPLL65}_{ic,2015})/2$
$\Delta\ln(\text{N\_DEATHS}_{ic})$	$(\text{N\_DEATHS}_{ic,2007} + \text{N\_DEATHS}_{ic,2015})/2$
$\Delta\text{AGE\_DEATH}_{ic}$	$(\text{N\_DEATHS}_{ic,2007} + \text{N\_DEATHS}_{ic,2015})/2$

The disturbances of eq. (5) will be clustered in a two-way cluster on country and disease.

Eq. (5) will be estimated for different values of *k:* $k = 0, 1, \ldots, 5$. A separate model is estimated for each value of *k*, rather than including multiple values ($CUM\_NCE_{i,t}$, $CUM\_NCE_{i,t-1}$, $CUM\_NCE_{i,t-2}$, ...) in a single model because CUM_NCE is highly serially correlated (by construction), which would result in extremely high multicollinearity if multiple values were included.

The lag structure of the relationship between $MORT_{ict}$ and $CUM\_NCE_{ic,t-k}$ (e. g. whether the magnitude of β_5 ($|\beta_5|$) is larger or smaller than the magnitude of β_0) is likely to depend on several factors. New drugs diffuse gradually – they aren't used widely until some years after launch; this would cause $|\beta_5| > |\beta_0|$. But the effect of a drug's launch on mortality is likely to depend on the *quality* as well as on the *quantity* of the drug. Indeed, it is likely to depend on the *interaction* between quality and quantity: a quality improvement will have a greater impact on mortality if drug utilization (quantity) is high. If newer drugs tend to be of higher quality than older drugs (see Lichtenberg 2014b), this would cause $|\beta_5| < |\beta_0|$. Also, because our data on drug launches are left-censored, $CUM\_NCE_{ic,t-k}$ is subject to greater measurement error for large *k* (e. g. $k = 5$) than it is for small *k* (e. g. $k = 0$). Due to the potentially offsetting effects of utilization, quality improvement, and measurement error, the shape of the lag structure is theoretically indeterminate.

4 Data Sources

Mortality data. Data on the number of YPLL before ages 75 and 65 and the number of deaths and mean age at death, by disease (coded by ICD-10), country, and year, were constructed from data obtained from the WHO's Global Health Estimates 2015 (World Health Organization 2016). That source provides data on the number of deaths by 5-year age group, disease, country, 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. Data on the number of YPLL before age 75 in 2007 and 2015, by country and cause, are presented in Table 1.

Table 1: Thousands of years of potential life lost before age 75, by country and cause, 2007 and 2015.

	Egypt		Jordan		Kuwait		Lebanon		Morocco		Saudi Arabia		South Africa		Tunisia		UAE		TOTAL	
	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015	2007	2015
20 Infectious and parasitic diseases	626	567	20	19	2	3	10	9	350	233	79	55	12,796	6,167	32	26	6	8	13,921	7,087
380 Respiratory infections	835	769	32	32	5	9	5	5	300	220	117	99	1,149	885	48	39	5	7	2,495	2,065
420 Maternal conditions	36	37	4	5	0	0	1	1	39	24	5	5	53	65	5	6	0	0	143	141
490 Neonatal conditions	1,994	2,092	135	132	16	14	22	30	923	768	373	298	1,098	852	117	105	22	22	4,699	4,311
540 Nutritional deficiencies	66	48	1	1	0	0	0	0	16	12	2	1	266	179	1	1	0	0	352	243
610 Malignant neoplasms	951	1,129	54	67	11	15	47	62	323	378	158	201	741	870	91	103	21	37	2,397	2,863
790 Other neoplasms	42	58	2	3	0	0	2	3	17	23	6	10	17	20	4	5	0	0	90	122
800 Diabetes mellitus	148	177	10	13	2	3	7	11	107	95	15	19	270	306	32	42	4	9	594	676
810 Endocrine, blood, immune disorders	202	237	7	8	1	2	2	3	21	17	29	28	139	156	11	12	3	4	414	467
820 Mental and substance use disorders	48	56	2	3	0	1	1	2	38	26	5	10	39	38	6	8	4	6	143	152
940 Neurological conditions	65	83	5	8	2	3	3	5	38	31	28	30	120	144	13	16	4	6	279	326
1100 Cardiovascular diseases	1,813	2,089	59	82	29	54	63	90	454	382	298	359	673	726	126	152	50	107	3,565	4,042
1170 Respiratory diseases	157	161	6	7	1	2	5	7	62	52	24	27	191	180	21	23	12	19	478	478
1210 Digestive diseases	737	806	9	11	2	5	6	8	87	69	29	34	178	180	24	29	5	9	1,077	1,151
1260 Genitourinary diseases	236	258	11	15	2	4	5	8	75	62	51	63	116	134	20	23	7	12	522	579
1330 Skin diseases	4	5	0	0	0	0	0	0	4	4	3	4	25	30	1	2	0	0	38	46
1340 Musculoskeletal diseases	6	8	2	3	0	0	0	1	5	3	5	5	12	15	2	3	0	1	32	38
1400 Congenital anomalies	911	1,117	61	69	21	19	15	20	214	209	241	222	292	292	64	61	15	17	1,833	2,026
Total	8,875	9,696	419	477	96	134	192	267	3,071	2,608	1,468	1,471	18,173	11,238	618	656	159	265	33,072	26,812

Source: Author's calculations, based on data from World Health Organization (2016).

Population data. Data on population by country, age group, and year (needed to compute premature mortality *rates*), were obtained from United Nations World Population Prospects 2017.

Drug launch data. Data on new chemical entity launches, by country and year (1993–2015),[12] were obtained from the IMS Health *New Product Focus* database (now known as QuintilesIMS Ark New Product Intelligence).

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 (2017). Data on the number of post-1992 NCEs launched during 1993–2015, by country and disease, are presented in Table 2.

Table 2: Number of post-1992 NCEs launched during 1993–2015, by country and disease.

Disease	Egypt	Jordan	Kuwait	Lebanon	Morocco	Saudi Arabia	South Africa	Tunisia	UAE	Average
20 Infectious and parasitic diseases	21	14	34	28	6	24	38	13	34	23.6
380 Respiratory infections	9	6	8	10	5	8	11	4	10	7.9
420 Maternal conditions	2	1	0	2	0	2	2	0	0	1.0
490 Neonatal conditions	0	0	0	0	0	0	0	0	0	0.0
540 Nutritional deficiencies	2	2	0	2	1	2	3	1	3	1.8
610 Malignant neoplasms	36	16	34	40	5	27	45	19	37	28.8
790 Other neoplasms	11	6	8	11	3	9	14	8	0	7.8
800 Diabetes mellitus	24	21	24	26	19	23	24	17	25	22.6
810 Endocrine, blood, immune disorders	30	21	26	29	11	27	36	14	32	25.1
820 Mental and substance use disorders	18	18	18	18	17	15	18	13	18	17.0
940 Neurological conditions	26	18	22	21	15	19	26	21	23	21.2
1100 Cardiovascular diseases	26	24	30	28	19	21	27	20	30	25.0
1170 Respiratory diseases	12	11	12	13	9	10	12	9	13	11.2
1210 Digestive diseases	10	7	10	9	3	10	9	10	10	8.7
1260 Genitourinary diseases	16	15	15	16	8	17	19	10	17	14.8
1330 Skin diseases	17	9	0	17	6	15	18	12	15	12.1
1340 Musculoskeletal diseases	20	14	0	19	10	18	20	14	20	15.0
1400 Congenital anomalies	1	1	1	1	1	0	1	1	1	0.9
Average	15.6	11.3	13.4	16.1	7.7	13.7	17.9	10.3	16.0	13.6

Source: Author's calculations, based on data from IMS Health New Product Focus and Theriaque databases.

Drug utilization data. Annual data on the number of standard units of drugs sold, by molecule, country, and year (1999–2010) were obtained from the IMS Health MIDAS database.

Disease classification. The disease classification used for the analysis of premature mortality is the one used in the World Health Organization (2017).

5 Empirical Results

Estimates of β_k parameters from eq. (5) are presented in Table 3. Each estimate is from a separate model. In rows 1–6, the dependent variable is the log of the number of YPLL before age 75. In row 1, the lag(k) equals zero. The estimate of β_0 is negative and significant (p-value = 0.0138). The point estimate indicates that a 10 % increase in the number of post-1992 NCEs ever launched resulted in a 1.8 % contemporaneous reduction in the number of YPLL before age 75. In lines 2–6, the lag length is 1, 2, ..., 5 years, respectively. Four of the five estimates are statistically significant (p-value < 0.02). The largest point estimate (in row 4) corresponds to a lag of 3 years; the most significant estimate (in row 5) corresponds to a lag of 4 years. There is no apparent trend in the lag

structure of the β_k parameters; as noted above, this may be due to the potentially offsetting effects of utilization, quality improvement, and measurement error.

Table 3: Estimates of β_k parameters of eq. (5), $\Delta\text{MORT}_{ic} = \beta_k \Delta \ln(\text{CUM\_NCE\_k}_{ic}) + \delta_i' + \pi_c' + \varepsilon_{ic}'$.

Row	Parameter	k (lag)	Estimate	Std. Err.	Z	Pr > |Z|
	$\Delta\text{MORT}_{ic} = \ln(\text{YPLL75}_{ic,2015}) - \ln(\text{YPLL75}_{ic,2007})$					
1	β_0	0	−0.178	0.072	−2.46	0.0138
2	β_1	1	−0.218	0.068	−3.21	0.0013
3	β_2	2	−0.076	0.054	−1.39	0.1633
4	β_3	3	−0.242	0.085	−2.84	0.0046
5	β_4	4	−0.206	0.053	−3.86	0.0001
6	β_5	5	−0.161	0.050	−3.22	0.0013
	$\Delta\text{MORT}_{ic} = \ln(\text{YPLL65}_{ic,2015}) - \ln(\text{YPLL65}_{ic,2007})$					
7	β_0	0	−0.224	0.089	−2.50	0.0123
8	β_1	1	−0.262	0.083	−3.15	0.0016
9	β_2	2	−0.067	0.069	−0.98	0.3281
10	β_3	3	−0.263	0.096	−2.73	0.0064
11	β_4	4	−0.230	0.070	−3.30	0.0009
12	β_5	5	−0.188	0.065	−2.92	0.0035
	$\Delta\text{MORT}_{ic} = \ln(N\_\text{DEATHS}_{ic,2015}) - \ln(N\_\text{DEATHS}_{ic,2007})$					
13	β_0	0	−0.039	0.027	−1.44	0.1485
14	β_1	1	−0.065	0.026	−2.51	0.0121
15	β_2	2	−0.015	0.030	−0.50	0.6197
16	β_3	3	−0.098	0.047	−2.09	0.0365
17	β_4	4	−0.093	0.029	−3.20	0.0014
18	β_5	5	−0.057	0.021	−2.67	0.0077
	$\Delta\text{MORT}_{ic} = \text{AGE\_DEATH}_{ic,2015} - \text{AGE\_DEATH}_{ic,2007}$					
19	β_0	0	0.839	0.335	2.50	0.0123
20	β_1	1	0.885	0.360	2.46	0.0139
21	β_2	2	0.598	0.267	2.24	0.0250
22	β_3	3	0.867	0.580	1.49	0.1351
23	β_4	4	0.714	0.326	2.19	0.0284
24	β_5	5	0.576	0.234	2.46	0.0138

There are 153 (17 diseases × 9 countries) disease-country pairs in our sample, but as indicated by the data in Table 1, one disease in one country – infectious and parasitic diseases in South Africa – accounts for almost a third of mean YPLL75: 10.1 million out of 31.0 million. (The disease-country pair with the second-highest mean YPLL75 (2.2 million) is neonatal conditions in Egypt.) It seems prudent to check the sensitivity of the estimates to the inclusion or exclusion of this potentially highly influential observation. I therefore estimated eq. (1) for $\text{MORT}_{ict} = \text{YPLL75}_{ict}$ and $k = 4$ when two different exclusion criteria were imposed: (1) South Africa was excluded, and (2) infectious and parasitic diseases were excluded. When South Africa was excluded, the estimate of β_4 was −0.160 ($Z = 4.05$; p-value < 0.0001). When infectious and parasitic diseases were excluded, the estimate of β_4 was −0.146 ($Z = 4.54$; p-value < 0.0001). There is a highly significant inverse relationship between cumulative NCE launches and YPLL75, whether we include or exclude a country or a disease accounting for a substantial share of premature mortality in the nine countries.

Another way to describe the relationship between cumulative NCE launches and premature mortality is to divide the observations into three groups (low, medium, and high innovation) based on their relative (to both country and disease average) growth in cumulative NCEs, and then to compute the (weighted) mean 2007–2015 change in ln(YPLL75) for each group.[13] The results of this calculation are shown in Figure 5. Mean relative (to disease and country average) 2007–2015 growth in YPLL75 of disease-country pairs with low relative cumulative NCE growth was 6.6 %, whereas mean relative 2007–2015 growth in YPLL75 of disease-country pairs with high relative cumulative NCE growth was −2.9 %.

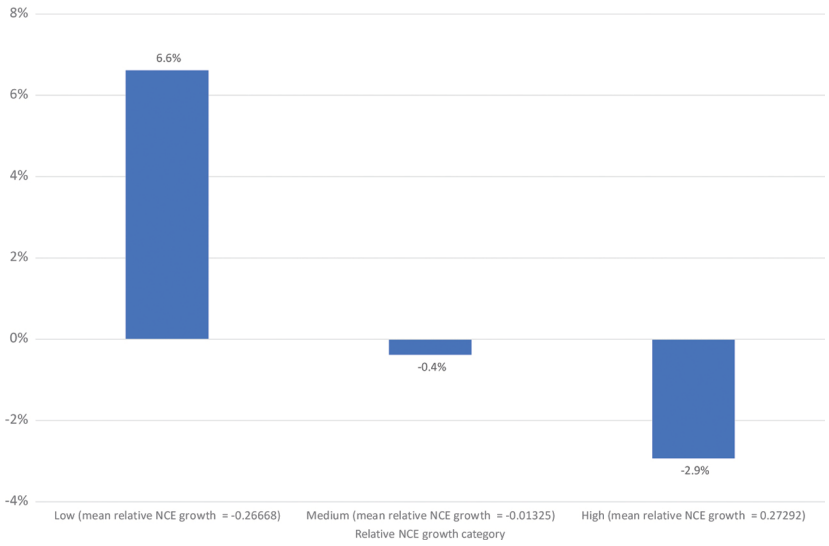

Figure 5: Mean 2007–2015 growth in YPLL75, by relative NCE growth category.

Now I will describe the remainder of the estimates in Table 2, which are estimates of β_k parameters from eq. (1) for additional mortality measures. In rows 7–12, the dependent variable is the log of the number of YPLL before age 65. Estimates of the effect of NCE launches on YPLL65 are similar to, but generally slightly larger than, estimates of the effect of NCE launches on YPLL75.

In rows 13–18, the dependent variable is the log of the number of deaths. All of the estimates are negative, and four of them are statistically significant (p-value < 0.04). The most significant estimate indicates that a 10 % increase in the number of post-1992 NCEs ever launched for a disease resulted in a 0.93 % reduction in the number of deaths 4 years later.

In rows 19–24, the dependent variable is mean age at death. All of the estimates are positive, and five of them are statistically significant (p-value < 0.03). These estimates imply that 8 years of NCE launches increased mean age at death by about 6 months.

Since Table 3 has four dependent variables, and for each variable six different hypotheses are tested, 24 different hypotheses were tested in Table 3, which might lead to false discoveries. According to Bland and Altman (1995), we can use the Bonferroni method to correct for multiple outcomes (and avoid false discoveries). The Bonferroni method can be implemented "by multiplying the observed p-value from the significance tests by the number of tests, k, any kP which exceeds one being ignored. Then *if any kP is less than 0.05 the [treatment effect is] significant at the 0.05 level*" (emphasis added). Six of the 24 kP's in Table 3 are less than 0.05. Consequently, the hypothesis that new drug launches reduced mortality is confirmed when we correct for multiple outcomes.

6 Discussion

Now I will use the estimates of the β_k parameters from eq. (1) presented in Rows 1–6 of Table 3 to estimate the number of life-years before age 75 gained in 2015 from drugs previously launched in the nine ME&A countries. Then I will estimate expenditure on these drugs in 2015, and combine these two estimates to calculate the overall cost-effectiveness of (or cost per life-year gained from) pharmaceutical innovation in those countries.

Table 4 shows the calculation of the 2007–2015 log change in YPLL75 attributable to new drug launches. Column 1 shows the lag length, k (k = 0, 1, …, 5). Column 2 shows the estimates of β_k from Rows 1–6 of Table 3. Column 3 shows the weighted mean value of $\Delta\ln(\text{CUM\_NCE\_}k)$ for the nine ME&A countries, weighted by average YPLL75. Column 4 shows the product of column 2 and column 3, which is the estimated 2007–2015 log change in YPLL75 attributable to the increase in the number of post-1992 NCEs ever launched k years earlier. As shown in row 7, the mean of the six estimates of ($\beta_k \times \text{mean}(\Delta\ln(\text{CUM\_NCE\_}k))$) is −0.099. This indicates that an 8-year increase in the number of post-1992 NCEs ever launched reduced YPLL75 in 2015 by 9.5 % (=1 − exp(−0.099)). This is approximately half of the 18.9 % reduction in YPLL75, and about one-third of the 29.7 % reduction in the premature mortality rate.

Table 4: Calculation of the 2007–2015 log change in YPLL75 attributable to new drug launches.

Column:	1	2	3	4

Row	k	β_k	mean(Δln(CUM_NCE_k))	β_k × mean(Δln(CUM_NCE_k))
1	0	−0.178	0.386	−0.069
2	1	−0.218	0.443	−0.097
3	2	−0.076	0.471	−0.036
4	3	−0.242	0.579	−0.140
5	4	−0.206	0.693	−0.142
6	5	−0.161	0.702	−0.113
7	average			−0.099

This estimate implies that if the number of post-1992 NCEs ever launched had not increased for 8 years, YPLL75 would have been 10.5 % (=exp(0.099) − 1) higher than it actually was. As shown in Table 1, in 2015 26.8 million YPLL before age 75 were lost from all diseases in the nine countries. In the absence of eight previous years of NCE launches, 2.80 million (=10.5 % × 26.8 million) additional YPLL before age 75 would have been lost in 2015.

To estimate expenditure in 2015 on new drugs (e. g. drugs launched during 2004–2013) by people below age 75 (NEW_DRUG_EXPEND_AGE < 75), I will use the following formula:

$$\text{NEW\_DRUG\_EXPEND\_AGE} < 75 = \text{AGGREGATE\_DRUG\_EXPEND}^* \text{NEW\_DRUG\_EXPEND\_\%}^* \text{DRUG\_EXPEND\_AGE} < 75\_\% \quad (6)$$

where

AGGREGATE_DRUG_EXPEND	= aggregate prescription drug expenditure in the 9 ME&A countries in 2015
NEW_DRUG_EXPEND%	= the fraction of drug expenditure that was on new drugs (e. g. drugs launched in the previous 10 years)
DRUG_EXPEND_AGE< 75%	= the fraction of drug expenditure that was for people below age 75

Data on aggregate prescription drug expenditure in 2015 are not available, but the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) has published 2014 data (whose source is given as Business Monitor International). These data, which are shown in Table 5, indicate that prescription drug expenditure in the 9 ME&A countries in 2014 was $19.4 billion.

Table 5: Pharmaceutical Expenditure in 9 Middle Eastern and African countries, 2006 and 2014.

Country	Total pharmaceutical expenditure $US millions at exchange rate, 2006	Total pharmaceutical sales (USD million), 2014	Pharmaceutical sales–prescription drugs (USD million), 2014
Egypt	$2,062	$4,170	$3,410
Jordan	$316	$910	$740
Kuwait	$303	$1,010	$850
Lebanon	$464	$1,530	$1,210
Morocco	$948	$1,490	$1,040
Saudi Arabia	$2,136	$7,160	$6,230
South Africa	$2,965	$3,670	$3,220
United Arab Emirates	$664	$2,200	$1,860
Tunisia	$1,077	$940	
TOTAL	$10,936	$23,080	$19,348

Sources: 2006 data: World Health Organization (2011). World Medicines Situation 2011 – Medicine Expenditures, http://apps.who.int/medicinedocs/en/m/abstract/Js20052en/ 2014 data: International Federation of Pharmaceutical Manufacturers & Associations (2017). THE PHARMACEUTICAL INDUSTRY AND GLOBAL HEALTH: FACTS AND FIGURES. 2017, Annex 2, Pharmaceutical Market, 2014, https://www.ifpma.org/wp-content/uploads/2017/02/IFPMA-Facts-And-Figures-2017.pdf.

To estimate NEW_DRUG_EXPEND_%, I will use annual 1999–2010 data[14] on expenditure by molecule from the IMS Health MIDAS database for four market segments: Egypt retail, Morocco retail, South Africa total market, and Saudi Arabia retail.[15] Those data indicate that 12.5 % of 2010 prescription drug expenditure ($US 14.7 billion) in the four market segments was on products containing molecules that had zero sales in 1999. I will

assume that 12.5 % of 2015 drug expenditure in the 9 ME&A countries was on products containing molecules that had zero sales in 2004, i. e. that were launched after 2004.

Data on drug expenditure by age group for the 9 ME&A countries are not available, but data for the U.S. indicate that, in the U.S. in 2014, people 75 years of age and older accounted for 6.5 % of the population and 13.8 % of outpatient drug expenditure, i. e. that their share of outpatient drug expenditure was 2.13 times their population share.[16] In the 9 ME&A countries in 2015, people 75 years of age and older accounted for 1.7 % of the population, so I will assume that they accounted for 3.6 % (=2.13 × 1.7 %) of drug expenditure. Hence, I estimate that people below age 75 accounted for 96.4 % of drug expenditure.

Substituting these estimates into eq. (6) implies that expenditure in 2015 on new drugs by people below age 75 was $US 2.34 billion (=$US 19.4 billion × 12.5 % × 96.4 %). Combining this estimate with my estimate of the reduction in YPLL75 from all natural causes in 2015 from previous new drug launches (2.80 million), the estimated expenditure on new drugs per life-year below age 75 gained in 2015 from the drugs was $US 834 (=$US 2.34 billion/2.80 million life-years).

As noted by Bertram et al. (2016), authors writing on behalf of the WHO's *Choosing Interventions that are Cost–Effective* project (WHO-CHOICE) suggested in 2005 that:

> interventions that avert one DALY [disability-adjusted life-year] for less than average per capita income for a given country or region are considered very cost–effective; interventions that cost less than three times average per capita income per DALY averted are still considered cost–effective.[17]

Population-weighted average per capita income (GDP) in the nine ME&A countries in 2015 was $US 7929,[18] so my estimates indicate that the new drugs launched there were very cost–effective overall, even if they did not reduce other medical costs or increase productivity.

But evidence from other countries suggests that new drug launches reduce other medical costs and increase productivity. Lichtenberg (2014b) showed that in the U.S., new drugs tend to "crowd out" old drugs, and that about 25 % of new drug cost is offset by reduced expenditure on old drugs. If that also applies to the nine ME&A countries, the *net* increase in pharmaceutical expenditure per life-year before age 75 gained was $US 626 (=75 % × $US 834). Lichtenberg (2014b) also showed that, in the U.S., pharmaceutical innovation resulted in substantial reductions in hospital expenditure, work-loss days, and school-loss days.

7 Summary and Conclusions

This study has provided econometric evidence about the impact of new drug launches on premature mortality from 17 diseases in nine ME&A countries during the period 2007–2015. A "triple-differences" research design was used, enabling me to control for the average rate of mortality decline in each country and from each disease.

Overall, the estimates were highly consistent with the hypothesis that the greater the relative number of drugs for a disease launched in a country, the greater the subsequent relative decline in premature mortality from that disease. There is a highly significant inverse relationship between cumulative NCE launches and YPLL75, whether we include or exclude a country (South Africa) or a disease (infectious and parasitic diseases) accounting for a substantial share of premature mortality in the nine countries.

Mean relative 2007–2015 growth in YPLL75 of disease-country pairs with low relative cumulative NCE growth was 6.6 %, whereas mean relative 2007–2015 growth in YPLL75 of disease-country pairs with high relative cumulative NCE growth was −2.9 %. One estimate indicated that a 10 % increase in the number of drugs ever launched resulted in a 2.4 % reduction in the number of YPLL before age 75 three years later.

An 8-year increase in the number of post-1992 NCEs ever launched reduced YPLL75 in 2015 by 9.5 %. This is approximately half of the 18.9 % reduction in YPLL75, and about one-third of the 29.7 % reduction in the premature mortality rate. In the absence of 8 previous years of NCE launches, 2.80 million additional YPLL before age 75 would have been lost in 2015. Estimated expenditure in 2015 on new drugs by people below age 75 was $US 2.34 billion, so expenditure on new drugs per life-year below age 75 gained in 2015 from the drugs was $US 834. According to the standards of the WHO's *Choosing Interventions that are Cost–Effective* project, new drugs launched in the nine ME&A countries were very cost–effective overall, even if they hadn't reduced other medical costs or increased productivity.

But evidence from other countries suggests that new drug launches reduce other medical costs and increase productivity. A previous study based on U.S. data showed that about 25 % of new drug cost is offset by reduced expenditure on old drugs, so the *net* increase in pharmaceutical expenditure per life-year before age 75 gained in 2015 may have been $US 626, and that pharmaceutical innovation resulted in substantial reductions in hospital expenditure, work-loss days, and school-loss days.

Notes

1 Age 70 is used in OECD Health Statistics. A U.S. Centers for Disease Control website allows calculation of U.S. premature mortality for five different age limits (65, 70, 75, 80, and 85).
2 The nine countries (chosen on the basis of data availability) are Egypt, Jordan, Kuwait, Lebanon, Morocco, Saudi Arabia, South Africa, Tunisia, and the United Arab Emirates.
3 The premature (before age 75) mortality rate is the number of years of potential life lost before age 75 per 100,000 population below age 75.
4 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. As noted by Jovanovic and Yatsenko (2012), in "the Spence–Dixit–Stiglitz tradition…new goods [are] of higher quality than old goods."
5 We hypothesize that innovations may be embodied in nondurable goods (e. g. drugs) and services as well as in durable equipment.
6 R&D intensity is the ratio of R&D to sales.
7 Sampat and Lichtenberg (2011) showed that government funding has played an indirect role – for example, by funding basic underlying research that is built on in the drug discovery process – in almost half of the drugs approved and in almost two-thirds of priority-review drugs.
8 The nine countries included in the sample are those for which data on NCE launches beginning in 1993 are available. For three countries (Egypt, Saudi Arabia, South Africa), drug launch data are available beginning in 1982; for Morocco, drug launch data are available beginning in 1986; for Jordan, Kuwait, Lebanon, Tunisia, and UAE, drug launch data are available beginning in 1993.
9 For reasons discussed below, I will allow (but not impose) the effect of cumulative drug launches on mortality to be subject to a lag of k years ($k = 0, 1, \ldots, 5$).
10 π_{ct} controls for country- and year-specific macroeconomic variables such as GDP, mean per capita health expenditure, and the unemployment rate.
11 In eq. (4), the dependent variable is essentially the percentage change between 2007 and 2015 in YPLL75. Percentage changes of disease-country observations with low average mortality exhibit much greater variance and volatility than disease-country observations with high average mortality.
12 Coverage of drug launches in my version of the IMS Health *New Product Focus* database ended on 1 November 2015.
13 This calculation is performed as follows. (1) Compute the residuals from the (weighted) regression of $\Delta\ln(\text{CUM\_NCE\_4}_{ic})$ on disease and country dummy variables. (2) Divide the residuals into three groups: low, medium, and high residuals. (3) Compute the residuals from the (weighted) regression of $\Delta\ln(\text{YPLL75}_{ic})$ on disease and country dummy variables. (4) Compute the mean value of the $\Delta\ln(\text{YPLL75}_{ic})$ residuals for the low, medium, and high $\Delta\ln(\text{CUM\_NCE\_4}_{ic})$ residual groups.
14 More recent IMS data are not available.
15 According to Table 5, these four countries accounted for 72 % of prescription drug expenditure in the nine ME&A countries in 2014.
16 The share of the elderly in total (outpatient + provider-administered) drug expenditure may be higher than their share in outpatient drug expenditure alone. A substantial fraction of provider-administered drug expenditure is on cancer chemotherapy, and cancer is predominantly a disease of the elderly.
17 Lichtenberg (2009) showed that the number of DALYs gained could be either less than or greater than the number of life-years gained.
18 Morocco had the lowest per capita GDP: $2,919.

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