STATIC AND DYNAMIC EFFECTS OF HEALTH POLICY: EVIDENCE FROM THE VACCINE INDUSTRY*

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Public policies designed to increase utilization of existing technologies may also affect incentives to develop new technologies. This paper investigates this phenomenon by examining policies designed to increase usage of preexisting vaccines. I find that these policies were associated with a 2.5-fold increase in clinical trials for new vaccines. For several diseases, the induced innovation is socially wasteful, though small in magnitude. In one case, however, the "dynamic" social welfare benefits from induced innovation exceed the policies' "static" benefits from increasing vaccination with existing technology. These findings underscore the importance of including technological progress in economic analysis of public policy.

This paper compares the static and dynamic welfare effects of public policies. Public policies designed for the "static" purpose of increasing utilization of an existing technology may also affect incentives to develop new technologies. Recognition of such policies' "dynamic" effects on the development of new technologies may substantially alter the analysis of optimal policy, as well as the welfare impact of any given policy.

Whether or not it is important to consider policy-induced innovation when evaluating the welfare effects of policies designed for "static" purposes depends, first and foremost, on whether such policies have a substantial effect on innovation. This key unknown parameter of the investment response is the main focus of the empirical analysis in the paper.

I look within the medical sector, where rapid technological progress has been a defining feature of the industry over the last century. Technological progress has been a key contributor to the dramatic health improvements of the twentieth century. It is also widely viewed as the driving force behind the rapid growth in the real cost of medical care [Newhouse 1992]. Yet we know remarkably little about the determinants of the developments of these

new technologies. Perhaps relatedly, almost all empirical economic analysis of health policy has focused on its static effects on utilization of existing medical technologies, and ignored its dynamic effects on the development of new medical technologies.

A major role for economic incentives in affecting technological changes seems a natural proposition [Schmookler 1966], and the medical sector is no exception [Weisbrod 1991]. It is considerably less clear, however, whether investment responds to the economic incentives embodied in *current health policy*. The long lags in the R&D pipeline combined with the uncertainty about future health policy suggest that it might not be optimal to make current investment decisions based on current policy. Moreover, to the extent that health care policy responds endogenously to technological change—from either political pressure for public insurance to cover a new technology or the ex post temptation to hold up the developer of a new technology—this will further weaken the incentive for developers to heed the current policy climate in making investment decisions.

I provide what is, to my knowledge, the first empirical evidence that health policies aimed at affecting health care utilization also have large effects on technological change. I examine the introduction of three different public health policies designed to increase vaccination rates against six specific diseases; an ancillary consequence of these policies was to increase the expected return to developing new vaccines against these diseases. I estimate the change in investment in vaccines against the six diseases affected by the policies, using changes in investment for vaccines against carefully selected diseases that were not affected by the policies to control for underlying secular trends in R&D in the vaccine industry.

I find robust evidence that the policies I study are associated with a statistically significant, 2.5-fold increase in the number of new vaccine clinical trials for the affected diseases. These estimates imply that a $1 increase in annual expected market revenue for vaccines against a particular disease stimulates an additional 6 cents in annual present discounted value investment in that vaccine. The investment response appears to persist in the long run, at least as measurable in the data, and to be ultimately associated with an increase in new vaccine approvals for the affected diseases. However, my results also suggest potential limits to the effect of health policy on technological change; I am unable to find evidence of an effect of the policies on more funda-

mental aspects of research and development, as measured by the start of new preclinical trials or the filing of ultimately successful patent applications.

Given the evidence of a substantial investment response, I demonstrate how recognition of this investment response can affect one's conclusion about the overall welfare implications of these policies. For most of the affected diseases, I find that the induced innovation is entirely socially wasteful business stealing, although the magnitude of the dynamic social costs is small. In one case, however, I estimate that the "dynamic" welfare benefits from the induced innovation are not only positive, but also larger than the "static" welfare benefits from the policy's effect on vaccination with the preexisting technology. These findings underscore the inadequacy of the near-exclusive focus in economic evaluations of health policy on the policy's "static" effects.

The rest of the paper proceeds as follows. Section I outlines a simple economic framework to illustrate the importance of considering the potential technological response to policies aimed at changing utilization of the existing technology. Section II describes the particular public health policies used in the empirical analysis. Section III presents the data and empirical framework. Section IV presents the estimates of the investment response to these policies. Section V estimates the welfare impact of this induced investment, using the conceptual framework outlined in Section I. The last section concludes.

I. Static and Dynamic Effects of Policy

In this section I illustrate how consideration of the dynamic effects of policies on incentives to innovate may substantially alter—in either direction—the policy's overall welfare impact. Consider the standard analysis of the optimal subsidy in the presence of positive consumption externalities. Figure I illustrates the standard setup for the monopoly case. The initial private market equilibrium (Q_0) is below the social optimum (Q^*). The traditional static, or one-period, analysis would set the "optimal" Pigouvian subsidy at the level that moves the demand curve from D_0 to D_1 and thus the equilibrium quantity to the social optimum Q^*. Welfare gains would be given by the area of triangle abc, minus the cost of public funds associated with the subsidy.

In a dynamic, multiperiod setting, however, the subsidy will
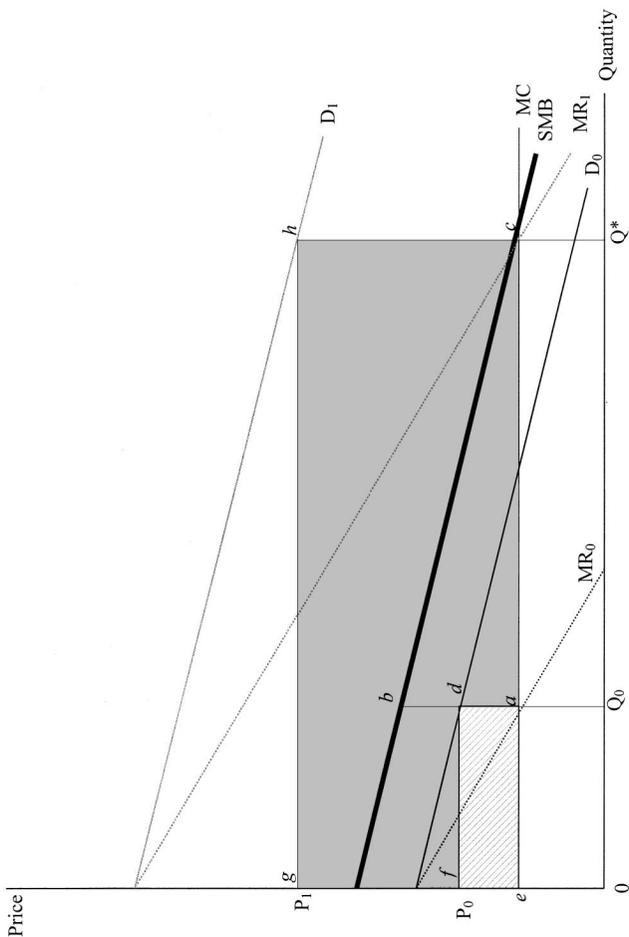
FIGURE I

also alter incentives to develop new technologies. Figure I shows that the subsidy increases the current monopolist's profits from the small shaded rectangle *eadf* to the large gray rectangle *echg*. It may therefore increase the incentives to develop an improved technology of both would-be entrants and the current monopolist (to stave off potential entrants).[1] This incentive effect applies generally to any product market exhibiting prices above marginal costs, and thus positive expected returns to innovation; the monopoly case was chosen simply for ease of exposition.

The net social welfare effect of any induced innovation may be either positive or negative. There are two main potential sources of social welfare benefits from any induced innovation.[2] The innovation may have a direct positive effect on social welfare at a given level of demand by producing a higher "quality" product (i.e., increased social marginal benefit or decreased social marginal cost). The innovation may also have an indirect positive effect on social welfare by increasing private demand, if the static effect of the policy on demand is insufficient to reach the social optimum; innovation may increase demand if it increases price competition or if it produces a higher "quality" product. The social costs of any induced innovation include the (up-front) R&D expenditures. They also include any overconsumption the innovation induces relative to the social optimum; induced innovation can induce overconsumption if it further increases demand via enhanced price competition.

The extreme case in which all of the induced innovation is pure business stealing with no social welfare benefits can be illustrated in Figure I, where the subsidy is sufficient (at the existing technology) to achieve the social optimum Q^*. If we also assume that there is no technological potential for quality-improving innovations (i.e., increasing SMB or decreasing MC), then any induced innovation simply imposes a social cost equal to the R&D expenditures and any overconsumption it might induce.

Figure II illustrates the other extreme case in which potential social welfare benefits from induced innovation are large and positive; for visual clarity, the private demand curves are not drawn. The static impact of the subsidy (holding technology con-

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1. Of course, if the main incentive for innovation is to increase private demand, the policy might instead *decrease* incentives to innovate. This is ultimately an empirical question, and one that I investigate below.
2. I ignore other potential social benefits such as research spillovers, since these are extremely difficult to estimate.
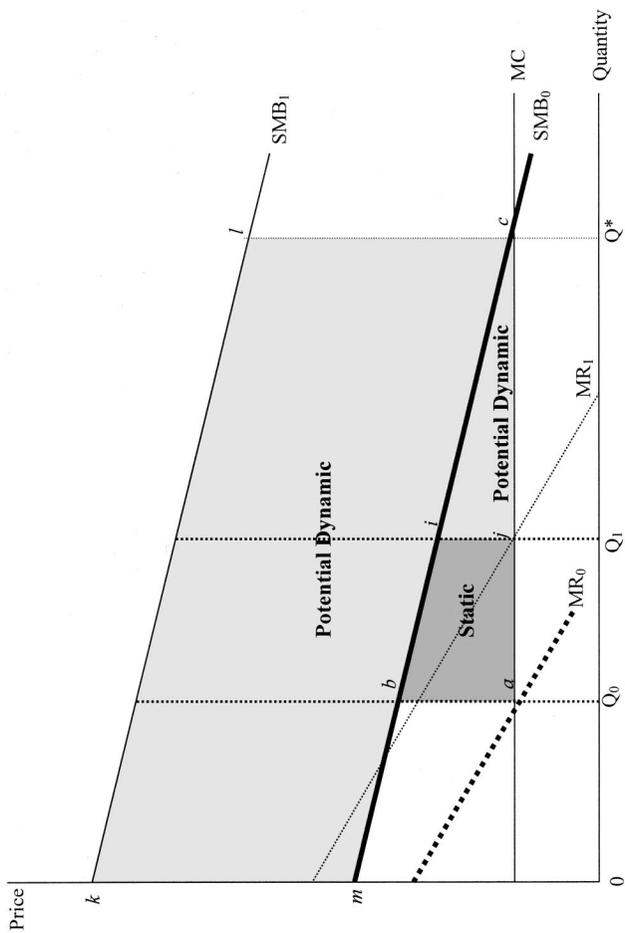
FIGURE II

stant) produces an equilibrium quantity (Q_1) that is substantially below the social optimum Q^*. Innovation that increases demand to the social optimum Q^* would produce social welfare benefits given by triangle jic. In addition, quality-improving innovation that shifts the social marginal benefit curve out from the current curve (SMB_0) to the potential curve (SMB_1) would produce social benefits given by parallelogram $mclk$.[3] These total dynamic benefits (shown in light gray) may exceed both the costs of the induced innovation and the static welfare benefits of the policy (shown by the dark gray area $ajib$).

Whether or not it is important to consider these dynamic effects in evaluating or designing policy depends on whether, in fact, there is a substantial innovation response to the economic incentives embodied in public policies. I investigate this question empirically in the specific context of vaccines. Vaccines are a particularly interesting area to study the innovation response to public policy since the government plays a central role in determining vaccine demand.[4] In addition, theoretical work by Kremer [2001] has suggested that increasing the expected market revenue from vaccine development may be better suited to encouraging targeted vaccine development than traditional subsidies to R&D.

The large public health benefits from vaccinations make vaccines of substantial interest in their own right. However, they also suggest that the negative social welfare costs of induced innovation are likely to be less important for vaccines than for other health technologies. Since the benefit-cost ratio from vaccination is at the extreme high end of health technologies, any dynamic social costs are likely to be much smaller relative to the static benefits of the policy than for other health technologies. Moreover, since socially optimal vaccination rates are often close to 100 percent, the dynamic social costs of induced vaccine innovation are limited to the R&D expenditures. However, for other health products, these costs also include any socially wasteful overconsumption induced by the innovation. Any induced overconsumption is particularly costly in the health sector relative to

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3. Changes in product quality may also change the social optimum Q^*. For simplicity, this is not shown in Figure II.
4. In the United States, the government's recommended immunization schedule is the primary determiner of vaccine demand [Schwartz and Orenstein 2001]. The government is also a direct purchaser of at least half of the childhood vaccines administered each year (data provided by Bob Snyder of the CDC).

other sectors of the economy, since health insurance already induces overconsumption.

The magnitude of any innovation response I estimate for vaccines is likely to be suggestive of the response of other pharmaceuticals; both involve for-profit companies making large sunk investments in products that require FDA approval. It may be less informative of the innovation response of other health technologies, such as surgical procedures, which involve different actors and a different development process.

II. THE SETTING FOR THE EMPIRICAL ANALYSIS: VACCINE POLICY AND VACCINE DEVELOPMENT

The empirical strategy is to study the investment response to vaccine policies that meet four essential criteria. First, they had to occur at a discrete point in time; the impact on innovation of slow-moving trends (such as the growth in managed care) is difficult to distinguish from concurrent technological developments. Relatedly, the policies could not have been anticipated by the industry, or it would be difficult to identify the point in time at which the innovation response is expected. Second, the policies had to be expected to have a substantial effect on the expected return to vaccine development. I therefore focus on U. S. policies, since the United States is the single largest pharmaceutical market and accounts for over two-fifths of global pharmaceutical spending [PhrMA 2000].

Third, the policies had to affect economic incentives for developing vaccines against an *identifiable, and limited,* set of diseases. The key challenge of the empirical work is to distinguish the investment effect of the policies from changes in investment due to exogenous technological advances. The common technological basis for vaccine development [Ellis 1999; NIH 1998] provides the opportunity to use vaccines against diseases that were not affected by the policies to try to control for such exogenous changes. Finally, the policies could not have been prompted by technological developments; it is difficult to distinguish the effect of such policies from the investment that would otherwise have occurred in response to the changing technology.

I identified three different policy changes—affecting vaccines against six different diseases—that met all of these criteria and occurred during the period in which the investment data (described in Section III) are available. Two of the policies increased

the economic return to vaccine development by enlarging the expected market for the vaccine. These are the 1991 CDC recommendation that all infants be vaccinated against Hepatitis B, and the 1993 decision for Medicare to cover (without any copayments or deductibles) the cost of influenza vaccination for Medicare recipients. The change in Medicare coverage was coordinated with a Federal information campaign designed to encourage Medicare beneficiaries to use this new benefit [CDC 1994].

The third policy, the introduction of the Vaccine Injury Compensation Fund (VICF) in 1986, indemnified manufacturers from lawsuits stemming from potentially adverse reactions to childhood vaccines against polio, diphtheria-tetanus (DT), measles-mumps-rubella (MMR), and pertussis. In return for an excise tax levied on the affected vaccines, the government administered a no-fault compensation system. The VICF increased incentives for vaccine development primarily by reducing expected liability costs; the compensation schedule that was set for successful claims was considerably below the average from the tort system [GAO 1999; HRSA 2002].

At the time of their enactment, the industry expected these policies to substantially increase the return to developing vaccines against the affected diseases. However, this was not part of the objective of the policies, which was to increase vaccination rates. This increase was expected to occur through recommending that children be vaccinated (Hepatitis B policy), reducing the out-of-pocket cost of the vaccine and promoting greater awareness of its benefits (Influenza policy), or ensuring an available supply of existing vaccines (the VICF). Appendix 1 provides more detail and evidence on these points.

Perhaps the most critical issue in selecting policies is to verify that these policies were not themselves a response to technological change. One concern is that companies may lobby for policies that benefit vaccines that they have just developed or are on the verge of developing. Appendix 1 provides detailed qualitative evidence on the rationale and timing for each policy that assuages this concern. I also ascertained, using data from Hoyt [2002], that none of the policies immediately followed a new vaccine approval for an affected disease. Finally, in the empirical analysis below, I do not find evidence of increased investment activity for the affected diseases prior to enactment of the policy. This suggests that the policies were not a response to an increase in perceived technological possibilities for the affected diseases. It

also suggests that the policies were not anticipated by the industry prior to their enactment.

It is worth noting that, by their very nature, the policies affected diseases which already had existing vaccines. The paper therefore analyzes the investment response to increased incentives to develop improved versions of existing vaccines. Improvements to existing vaccines may require fundamental scientific advances and encouraging such improvements is a top domestic health priority. Improved vaccines may have substantial direct health benefits by increasing a vaccine's efficacy or reducing its side effects. They may also produce indirect health benefits by encouraging vaccination [Institute of Medicine 2001].

III. Data and Empirical Framework

III.A. Data and Descriptive Statistics

I investigate the investment response to the policies at four sequential stages of the R&D pipeline: basic research (which may result in a patent), preclinical trials (testing in animals), clinical trials (testing in humans), and FDA approval. All of these activities are increasing over the 1980s and 1990s.

As a compound moves from basic research to clinical trials, there is an increase in the time and monetary costs of development, the probability of success, and the share of the activity carried out in for-profit companies. The primary focus of the empirical work is on the effect of the policies on the decision to start new clinical trials, the last and most expensive stage of development. Development times and success rates from the start of clinical trials are comparable for vaccines to those for other pharmaceuticals [Struck 1996; DiMasi et al. 1991].

The business publication, *The NDA Pipeline,* provides annual data from 1983 through 1999 on new preclinical trials, new clinical trials, and new approvals in the United States for vaccines against specific diseases. These data are both comprehensive and very high quality for new clinical trials and approvals, but considerably less so for new preclinical trials. The USPTO's on-line database provides the filing date of ultimately successful patent applications from 1976 through 1996. These data are extremely accurate; however, they are a noisy measure of basic vaccine research, since a relatively low proportion of successful basic

research in vaccines is patented. Appendix 2 provides more detail on these points and on the data.

The data include all prophylactic vaccines against infectious diseases in humans, except HIV/AIDS. This is excluded because public policy toward this disease was in constant flux over the time period studied. There are 32 different diseases with new vaccine clinical trials in the data, of which six were affected by the policies.

The main empirical finding that the policies are associated with an increase in new vaccine clinical trials is readily apparent in the descriptive statistics in the top panel of Table I. This shows the number of new clinical trials per year for vaccines against each of the diseases affected by a change in policy. For four of the six affected vaccines—Pertussis, Diphtheria-Tetanus, Hepatitis B, and the Flu—the data reveal a substantial increase in the number of new vaccine clinical trials per year after the introduction of the policy.[5] This increase occurs with about a one-year lag after the policy's introduction, and persists through the latest years of available data. The one-year lag is consistent with industry opinion that it would take six to eighteen months to get a new clinical trial going (e.g., Sanyour [interview]).

III.B. Econometric Framework

A central limitation to the simple time series analysis in the top panel of Table I is that the entire time period is one of increasing R&D. To distinguish any potential effect of the policies from the increase in new clinical trials that would have occurred without these policies, I compare changes in the number of new vaccine clinical trials for affected diseases after the policy goes into effect with changes in the number of new vaccine clinical trials for diseases that were not affected by the policies.

The basic estimating equation for a sample of affected and control diseases is

$$(1) \qquad \text{Newtrials}_{it} = \alpha_i + \gamma_t + \lambda \text{ADOPT}_{it} + \varepsilon_{it}.$$

Newtrials_{it} is the number of new vaccine clinical trials for disease

5. I date the policy's introduction as the first full year the policy is in effect. For the VICF, which was announced in 1986 but effective in 1988, I date the policy's introduction as 1987, the first full year that the policy was anticipated.

TABLE I
NUMBER OF NEW VACCINE CLINICAL TRIALS PER YEAR

Disease	Year clinical trial started																
	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
Affected diseases																	
Pertussis	1	1	1	0	0	5	4	5	1	1	3	4	5	1	0	2	6
Measles-Mumps-Rubella	0	0	1	0	0	1	0	1	0	0	0	0	0	1	0	0	0
Diphtheria-Tetanus	1	0	0	0	0	3	1	3	0	1	2	1	5	2	0	2	7
Polio	0	0	0	2	1	2	1	0	0	0	1	0	1	1	0	0	2
Hepatitis B	1	0	3	1	0	1	0	1	0	0	2	2	5	3	1	5	5
Flu	0	0	0	0	0	0	0	2	1	0	1	2	1	3	2	4	3
Control diseases																	
"Any clinicals"	0.04	0.00	0.12	0.19	0.04	0.42	0.15	0.19	0.04	0.19	0.35	0.46	0.38	0.42	0.42	0.81	0.73
"Early clinicals"	0.14	0.00	0.43	0.71	0.14	1.29	0.57	0.57	0.14	0.42	0.14	0.71	1.00	0.71	0.43	0.29	0.70
"Prior approvals"	0.00	0.00	0.00	0.43	0.00	0.14	0.00	0.00	0.00	0.29	0.86	0.71	0.29	0.57	0.29	0.71	0.71
"Technology"	0.11	0.00	0.22	0.11	0.11	0.56	0.11	0.44	0.11	0.33	0.22	0.44	0.89	0.56	0.44	0.56	0.78

The switch from gray to white background demarcates the start of a new policy. Entries for control groups represent average number of new clinical trials per year. Table II provides a list of the diseases included in each of the control groups; see text for further details.

i in year t.[6] α_i is a disease-specific fixed effect that controls for any fixed differences across diseases in average investment. γ_t is a year fixed effect; it controls flexibly for any secular trend in investment that is common across all diseases.

ADOPT$_{it}$ is the key variable of interest. It is an indicator variable for whether a policy is in place in year t for disease i. The coefficient on ADOPT$_{it}$, λ, measures the average annual change in the number of new clinical trials for affected diseases relative to the change for the control diseases, after controlling flexibly for common secular changes and for disease-specific fixed effects.

The choice of appropriate control diseases is an important and difficult one. The key is to control for factors that affect the trend in vaccine development, particularly exogenous changes in technology. The common technological basis for vaccines suggests the selection of a control group from among vaccines against diseases not affected by the policies. I try a number of different approaches to defining the control group, all of which produce similar results.

The "any clinicals" control group includes as control diseases all 26 unaffected diseases for which there was at least one new clinical trial during the 17 years of data. However, these 26 control diseases are not necessarily well-matched to the affected diseases on characteristics that may be related to the rate of new vaccine clinical trials. I therefore define three alternative control groups that are strict subsets of the "any clinicals" control group and are designed to better match the affected diseases on characteristics that are potentially related to the trend in new vaccine clinical trials for those diseases.

The "early clinicals" control group consists of the seven diseases in "any clinicals" that had at least one new vaccine clinical trial between 1983 and 1986; its average number of new clinical trials per year per disease in this preperiod (0.32) thus better matches the affected diseases (0.46) than the "any clinicals" sample does (0.09). The "prior approvals" control group consists of the seven diseases in "any clinicals" that, like all of the affected

6. Twenty percent of the new clinical trials in the data are for "combination vaccines" which provide immunization against multiple diseases. In general, I record a new vaccine clinical trial for each disease in the combination. However, to avoid overcounting of clinical trials for the affected diseases, I group five of the affected diseases into two "disease categories:" measles, mumps, and rubella (MMR) and diphtheria and tetanus (DT). Vaccines for these diseases are almost always produced in these combinations.

diseases, had an approved vaccine in existence by the start of the data.

A key concern is that estimates of the policy-induced investment will be biased upward if the affected diseases have systematically higher innate technological potential than the control diseases. The "technology" control group therefore selects the nine diseases in "any clinicals" which the Institute of Medicine [1985a] judged to have high innate technological potential for further development.[7]

Table II describes the diseases included in each of the four control groups. Control diseases that match the affected diseases on one feature do not necessarily match on another; moreover, not all of the affected diseases themselves meet the criteria for eligibility in each of the control groups. As a result, I estimate equation (1) separately for each definition of the control group. I also estimate a weighted version of equation (1) with the weights based on each disease's propensity score, or probability for inclusion in the treatment group; the propensity scores are estimated as a function of whether the disease meets the criteria for inclusion in the early clinicals, prior approvals, or technology control group. Each affected disease is weighted by the inverse of its propensity score, and each control disease is weighted by the inverse of one minus its propensity score.

Of course, if the new vaccine investment in the affected diseases crowds out investment that would otherwise have occurred in the control diseases, this would undermine the validity of the empirical strategy. It would also affect the substantive interpretation of the results, suggesting that the policies may affect the *allocation* but not the overall *rate* of R&D. In practice, however, crowd-out is unlikely to be an issue for the analysis. While the supply of scientists or doctors may be inelastic in the short run [Goolsbee 1998], an increase in the number of new clinical trials primarily requires increased financing—which in the capital-rich pharmaceutical industry is unlikely to be constrained—and an increase in human test subjects, who are relatively elastically supplied. The data are also not suggestive of crowd-out. The bottom half of Table I shows an *upward* trend in the average number of new clinical trials per year for each of the

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7. To be included in this category, the Institute of Medicine also required that the further development be expected to convey substantial health benefits in the United States. Three of the six affected diseases also made the cut (see Table II).

TABLE II

DESCRIPTION OF THE DISEASES IN THE VACCINE SAMPLE

| Disease name | Included in restricted control groups? | | | Average number of new clinical trials per year per vaccine | | Year vaccine first approved |
	"Early clinicals"	"Prior approvals"	"Technology"	1983–1986	1996–1999	
Treated Diseases						
Hepatitis B	✓	✓	✓	1.25	3.25	1981
Influenza		✓	✓	0	3	1945
Polio	✓	✓		0.5	0.75	1955
Diphtheria, Tetanus (DT)	✓	✓		0.25	2.75	1949
Measles, Mumps, Rubella (MMR)	✓	✓		0.25	0.25	1971
Pertussis	✓	✓	✓	0.5	2.25	1914
Control diseases ("Any clinicals")						
Varicella (Chicken Pox)	✓			0.25	0.75	1995
Malaria	✓			0.25	1	Not yet
Cholera	✓	✓		0.25	0	1914
Haemophilus Influenza B (HIB)	✓		✓	0.5	1.25	1985
Parainfluenza	✓		✓	0.25	0.5	Not yet
Gonorrhea	✓		✓	0.25	0	Not yet
Typhoid	✓	✓		0.5	0.5	1914
Tuberculosis (BCG)		✓		0	0	1950
Meningitis		✓		0	2	1974
Yellow Fever		✓		0	0.25	1953
Streptococcus		✓	✓	0	1	1952
Pneumonia		✓		0	0.25	1977
Hepatitis A			✓	0	0.25	1995
Herpes			✓	0	0.25	Not yet
Rotavirus			✓	0	0.25	1998
Cytomagalovirus			✓	0	0	Not yet
Respiratory Syncytial Virus			✓	0	1.5	Not yet
Hepatitis C				0	0.75	Not yet
Lyme Disease				0	0.5	1998
Chlamydia				0	0.25	Not yet
Japanese Encephalitis				0	0.5	1992
Epstein-Barr Virus				0	0.25	Not yet
E. Coli				0	0.75	Not yet
Helicobacter pylori				0	0.5	Not yet
Human Papilloma Virus				0	0.75	Not yet
Otitis Media				0	1.25	Not yet

Listed control diseases consist of all 26 diseases included in the "any clinicals" control group. The first three columns show which of these diseases meet the more restricted control group definitions; for the treated diseases they indicate which of the treated diseases would also meet these definitions. "Early clinicals" consists of diseases that have at least one new clinical trial prior to 1987. "Prior approvals" consists of diseases for which an approved vaccine exists prior to 1983 (the start of the data). "Technology" consists of diseases that are listed by the Institute of Medicine [1985a] as having the potential to develop new or improved vaccine within the decade that would convey substantial health benefits within the United States. Data source for all columns but the last one is *The NDA Pipeline*. Hoyt [2002] provided the approval dates.

four control groups. I also find no evidence that any of the policies are associated with a break in trend for the number of new vaccine clinical trials per year for any of the control groups.

IV. ESTIMATES OF THE VACCINE INVESTMENT RESPONSE TO THE HEALTH POLICIES

IV.A. *The Investment Response of New Clinical Trials*

Table III reports the results from estimating equation (1) by OLS. I report unadjusted standard errors and p-values; I also report the adjusted p-value computed using the randomized inference approach developed by Bertrand, Duflo, and Mullainathan [2004] to account for possible serial correlation over time in investment for a given disease. The results indicate that—across all specifications—the policies are associated with a statistically significant increase of 1.2 to 1.3 new vaccine clinical trials per year for each affected disease. Between 1983 and 1986, each affected disease had on average 0.5 new clinical trials per year. The results therefore suggest that the policies are associated with about 2.5 times more new vaccine clinical trials per year per affected disease. Moreover, the OLS estimates imply that the economic incentives embodied in these three policies alone account for almost one-third of the 260 total new vaccine clinical trials for *all* diseases during the *entire* seventeen-year period.

TABLE III

EFFECT OF POLICIES ON NUMBER OF NEW CLINICAL TRIALS

	Any clinicals	Early clinicals	Prior approvals	Technology	Propensity score weighting
ADOPT	**1.210***	**1.307***	**1.233***	**1.212***	**1.192***
	(0.184)	**(0.273)**	**(0.263)**	**(0.242)**	**(0.248)**
Unadjusted p-value	<0.01	<0.01	<0.01	<0.01	<0.01
Adjusted p-value	<0.01	<0.01	<0.01	<0.01	<0.01
Mean dependent variable	0.48	0.87	0.75	0.73	0.54
Number of diseases	32	13	13	15	32
N	544	221	221	255	544

Results are from OLS estimates of equation (1). Top row indicates the control group used; these are defined in Table II. All regressions include year and disease fixed effects. Unadjusted standard errors are in parentheses. Adjusted p-values are calculated using the randomized inference approach of Bertrand, Duflo, and Mullainathan [2004]. ***, **, and * indicate significance at the 1 percent, 5 percent, and 10 percent level, respectively, using the unadjusted p-values.

The Hepatitis B and Flu policies were associated with an annual increase in expected market revenue of $518 million and $98 million, respectively.[8] Each new clinical trial represents $16.2 million in expected present discounted value expenditures.[9] Applying the point estimates in Table III, these numbers suggest that for every $1 permanent increase in expected annual market revenue from vaccines against a particular disease, the pharmaceutical industry will spend an additional 6 cents annually in present discounted value on R&D for vaccines against that disease.[10] One reason for an investment response to the policies that is much lower than the expected change in market revenue may be that there are a limited number of products than can easily and cheaply be put through clinical trials in response to an increase in economic incentives. In addition, it is important to remember that new vaccine clinical trials enjoy only a 40 percent approval rate [Struck 1996] and that a successful approval does not capture the entire market [Merck 2000].

To examine the time pattern of the investment response, I replaced the single ADOPT indicator variable in equation (1) with a series of mutually exclusive indicator variables for different periods relative to the implementation of the policies:

$$(2) \quad \text{Newtrials}_{it} = \alpha_i + \gamma_t + \lambda_1 \text{ADOPT}_{it,(-7+)} + \lambda_2 \text{ADOPT}_{it,(-6 \text{ to } -4)}$$
$$+ \lambda_3 \text{ADOPT}_{it,(1 \text{ to } 3)} + \lambda_4 \text{ADOPT}_{it,(4 \text{ to } 6)}$$
$$+ \lambda_5 \text{ADOPT}_{it,(7+)} + \varepsilon_{it}.$$

These indicator variables indicate, respectively, 7 or more years prior to the policy, 4−6 years prior to the policy, 1–3 years of the policy in effect, 4−6 years of the policy in effect, and 7 or more years of the policy in effect. The omitted reference category is 1 to 3 years prior to the policy.

Figure III graphs the pattern of λ coefficients when the "any

8. Estimates based on the revenue per person vaccinated [Merck 2000; CDC 2002c, 2002b] and the expected impact of the policy on vaccination rates (see Appendix 1). Estimates are based on the U. S. market only, since it is not standard practice for other countries to follow U. S. vaccine policy [Sanyour interview]. I do not include the VICF in this analysis since there is little evidence with which to gauge its impact on the expected change in liability costs.

9. DiMasi et al [1991], updated to 1999 dollars using the CPI-U. All estimates in this paper are in 1999 dollars.

10. To verify the robustness of this estimate, I reestimated equation (1) restricting the analysis to just the Hepatitis B and Flu policies and transforming the left-hand variable into new spending and the ADOPT variable into the change in expected annual market revenue. The estimates ranged from 5 to 6 cents and were statistically significant at the 1 percent level.
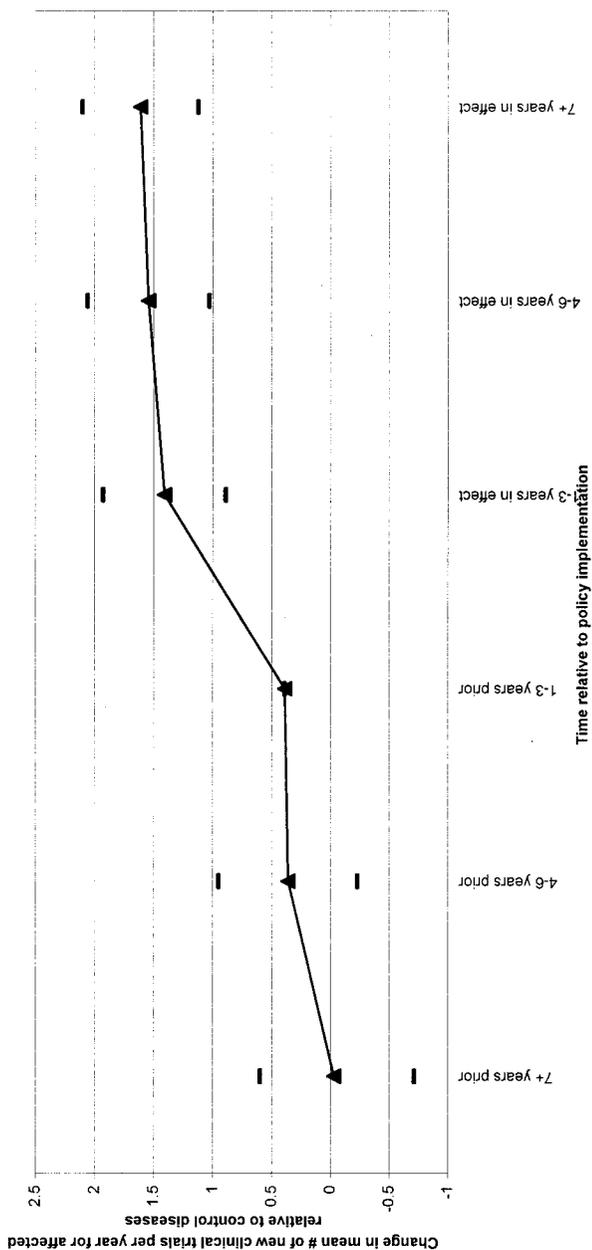
FIGURE III

Timing of Effect of Policies on New Clinical Trials

Figure III graphs the coefficients on the ADOPT variables from estimating equation (2) using the "any clinicals" control group; the regression includes year and disease fixed effects. The reference period (1–3 years prior to adoption) is set at the mean of the dependent variable for the affected diseases in that period. The dotted lines represent the 95 percent confidence intervals for these coefficients, based on the unadjusted standard errors. The adjusted and unadjusted *p*-values (not shown) are comparable.

clinicals" control group is used; results for other control groups (not shown) are similar. There is no evidence of a substantive or statistically significant change in the number of new clinical trials for affected diseases relative to control diseases in periods prior to the policies. This is supportive of the identifying assumption that, absent the policies, affected and control diseases would have had similar trends in the number of new clinical trials per year. It also suggests that the policies were not anticipated prior to their adoption, nor were they endogenous to increasing investment activity in the affected diseases. There is also no evidence of an increase prior to the policies in the number of new approvals, new preclinical trials, or new patent filings for the affected diseases when equation (2) is reestimated for these different dependent variables (not shown).

Figure III also indicates that the increase in new vaccine trials persists throughout the time period that I observe. This suggests that the induced investment represents investment in technologies that would not otherwise have been developed, rather than merely a movement forward in time of planned investment.

I explored the nature of the investment response by exploiting the distinction between solo vaccines, which provide immunization against a single disease, and combination vaccines, which combine separate vaccines against different diseases into a single vaccine against multiple diseases. The development of either type of vaccine can have important public health benefits [Decker and Edwards 1999; American Academy of Family Physicians 2000]. However, the development of a solo vaccine represents a technologically greater advance, as it commercializes a technology not previously used for immunization against a particular disease [Greenberg interview; Wolters interview]. I find that the policies are associated with statistically significant increases in the number of both types of clinical trials, with the increase in new solo vaccine trials representing about one-third to two-fifths of the total increase.

Finally, I examined whether the induced new clinical trials are ultimately associated with an expansion of the available product space, as measured by vaccine approvals. The average lag between the start of a new vaccine clinical trial and an approval is seven to eight years [Struck 1996]. I therefore estimate a modified version of equation (1) in which the ADOPT indicator is replaced by two mutually exclusive indicators: $ADOPT_{(1-6)}$ is an

indicator variable for the first 1 to 6 years that the policy is in place and ADOPT$_{7+}$ is an indicator variable for 7 or more years since the policy is in place. The dependent variable is the number of new vaccine *approvals* in year t for disease i. Table IV reports the results. There is no evidence of a change in approvals after a policy has been in place for 1–6 years, but a statistically significant increase of 0.3 to 0.4 new vaccine approvals per year per affected disease after the policy has been in place for 7 or more years. These estimates suggest that the 1.2 to 1.3 induced new clinical trials per year per affected disease had about a one-quarter to one-third approval rate; this is statistically indistinguishable from the average approval rate for new vaccine clinical trials of 0.4 [Struck 1996].

   The above evidence of the investment response of new clinical trials is remarkably robust. The working paper version of the paper [Finkelstein 2003] reports the results from a barrage of sensitivity tests, none of which substantively affects the findings. These include the addition of disease-specific linear or quadratic trends to equation (1), and, because of the count nature of the

<div align="center">

TABLE IV

EFFECT OF POLICIES ON NUMBER OF NEW APPROVED VACCINES

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	Any clinicals	Early clinicals	Prior approvals	Technology	Propensity score weighting
ADOPT$_{(1-6)}$ (Policy in place 1–6 years)	**−0.051**	**−0.081**	**−0.050**	**−0.083**	**−0.057**
	(0.072)	(0.101)	(0.092)	(0.102)	(0.060)
Unadjusted p-value	0.48	0.42	0.59	0.42	0.34
Adjusted p-value	0.41	0.40	0.38	0.48	0.32
ADOPT$_{(7+)}$ (Policy in place 7+ years)	**0.364*****	**0.346*****	**0.409*****	**0.305****	**0.348****
	(0.084)	(0.127)	(0.115)	(0.126)	(0.136)
Unadjusted p-value	<0.01	<0.01	<0.01	0.02	0.02
Adjusted p-value	<0.01	0.01	<0.01	0.05	0.02
Mean dependent variable	0.07	0.12	0.10	0.11	0.08
Number of diseases	32	13	13	15	32
N	576	234	234	270	576

   Dependent variable is number of approved vaccines against a given disease in a given year. Results are from OLS estimates of equation (1) but where the indicator ADOPT has been replaced by two mutually exclusive indicator variables for a policy being in effect for 1–6 years (ADOPT$_{(1-6)}$) and for a policy being in effect 7 or more years (ADOPT$_{(7+)}$). Top row indicates the control group used. See notes to Table III for more details.

dependent variable which ranges from 0 to 7, reestimation of equations (1) and (2) using a conditional negative binomial fixed effects model. As another specification check, I also ascertained that the *private* benefits to the industry from the induced innovation were positive.[11]

IV.B. Investment Response at Earlier Stages of the R&D Pipeline

To investigate whether there is an investment response at earlier stages of the R&D pipeline, I reestimate equation (1) for two different dependent variables: the number of new preclinical and the number of new (ultimately successful) patents filings. Table V reports the results. Since only 60 percent of the patent filings are made by for-profit companies—compared with more than 99 percent of the new preclinical and clinical trials—Table V reports results for new patent filings separately for for-profit companies and nonprofit entities. To conserve space, I only report

TABLE V
EFFECT OF POLICIES ON INVESTMENT AT EARLIER STAGES OF THE R&D PIPELINE

	Number of new preclinical trials		Number of new patents filed by for-profit companies		Number of new patents filed by nonprofit entities	
	Any clinicals (1)	Propensity score (2)	Any clinicals (3)	Propensity score (4)	Any clinicals (5)	Propensity score (6)
ADOPT	**0.115**	**0.184**	**0.198**	**0.260**	**0.120**	**0.097**
	(0.173)	**(0.234)**	**(0.126)**	**(0.205)**	**(0.103)**	**(0.142)**
Unadjusted *p*-value	0.51	0.44	0.12	0.21	0.25	0.50
Adjusted *p*-value	0.56	0.68	0.11	0.12	0.40	0.41
Mean dependent variable	0.46	0.47	0.27	0.29	0.19	0.19
Number of diseases	32	32	32	32	32	32
N	544	544	672	672	672	672

The dependent variable is given in the top row; the next row indicates the control group used. Results are from OLS estimation of equation (1). See notes to Table III for more details.

11. Data on revenues from affected vaccines are from Merck [2000]. Mercer [2000] provides estimates of marginal production costs. Estimated development costs are calculated based on DiMasi et al. [1991] and Struck [1996].

results for the "any clinicals" control group and the propensity-score weighting; results for other control groups (not shown) are similar.

Issues with the preclinical and patent data discussed in Section III suggest that these results should be interpreted with caution. Nevertheless, they suggest that we cannot reject the null hypothesis that there was no change in either investment activity associated with the policies. The point estimates tend to be small in magnitude and statistically insignificant.[12] Nor is there any evidence of an investment response even after allowing for lags of as long as ten years (not shown). It may be that the longer lags between investment in these earlier stages and product licensure make the uncertainty about future health policy more of a deterrent to an investment response on these earlier margins. An unanswered question—and a fruitful avenue for further research—is whether larger or differently structured economic incentives would have an effect on these more fundamental aspects of R&D.

Given these findings, it is interesting to revisit the evidence of a relatively quick response of new clinical trials to the policies, as well as a persistence of this response in the years after the policy decision (see Table I and Figure III). The quick initial response suggests the existence of a substantial reservoir of technologically feasible products on the shelf for whom the decision to begin clinical trials is responsive, on the margin, to increases in the expected economic return to the clinical trial.[13] Consistent with this, I find that almost all of the investment response in the first three years that the policy has been in place is from established firms (defined as those with at least one vaccine on the market).[14] Such firms are more likely than less established firms to have products sitting on the shelf that can quickly be used in new clinical trials. By contrast, after the policy has been in place for seven or more years, I find that it is now less established firms (i.e., those that do not already have a vaccine on the market) that

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12. In addition, although all of the OLS estimates in Table V are positive, estimates using the negative binomial model tend to have the opposite sign, although they are small and insignificant; see results in Finkelstein [2003].

13. Conversations with individuals in the pharmaceutical industry confirm that vaccine projects are routinely shelved after preclinical trials when the results indicate that the product is not commercially viable.

14. Data on what firms have on the market each year are from annual editions of the *Physician's Desk Reference*. The vaccine manufacturing market is substantially more concentrated than the vaccine development market.

account for more of the investment response. The source of the investment response from these latecomers may also be off-the-shelf projects; it may simply take the less-established firms more time to assemble the financing to start new clinical trials. Alternatively, the source for the later investment response may come from successful new preclinical trials completed since the policy went into effect.[15]

V. Welfare Analysis

Given the evidence of a substantial investment response to the vaccination policies, I now apply the conceptual framework developed in Section I to illustrate how consideration of the policies' dynamic consequences affects their overall social welfare implications. I begin with the traditional static welfare analysis, which ignores endogenous technological change. The first step is to estimate the static policy effect on vaccination rates. Since a new vaccine approval will take on average 7–8 years after the start of a new clinical trial, a reasonable estimate of the static impact of the 1991 Hepatitis B recommendation and the 1993 Flu policy is the increase in vaccination rates for the affected disease over the 8 years after the introduction of the policy, less the expected increase in vaccination rates due to underlying secular trends. The VICF is excluded from this analysis as it was a preemptive measure to prevent anticipated decreases in vaccination rates; its static effect is therefore very difficult to estimate.

Figures IV and V illustrate the static impact of the Hepatitis B and Flu policies, respectively. The Hepatitis B recommendation appears to have had a substantial static impact. Vaccination rates, which were essentially zero prior to the 1991 policy [Woodruff et al. 1996], increased sharply following the policy, and by 2000 had reached 90 percent. Over the same period, vaccination rates for other childhood vaccines exhibited only a slight upward trend (the trend in MMR vaccination rates is shown by way of example). By contrast, Figure V suggests that the static impact of the Flu policy was at most the 15 percentage point postpolicy increase in vaccination rates and more likely close to

15. In this context, it is important to emphasize that the lack of evidence of an *increase* in new patents or preclinical trials associated with the policies should not be confused with the lack of *any* steady state R&D activity at these earlier stages. Indeed, the rate of new patent filings and preclinical trials is higher for the affected diseases than for the control diseases.
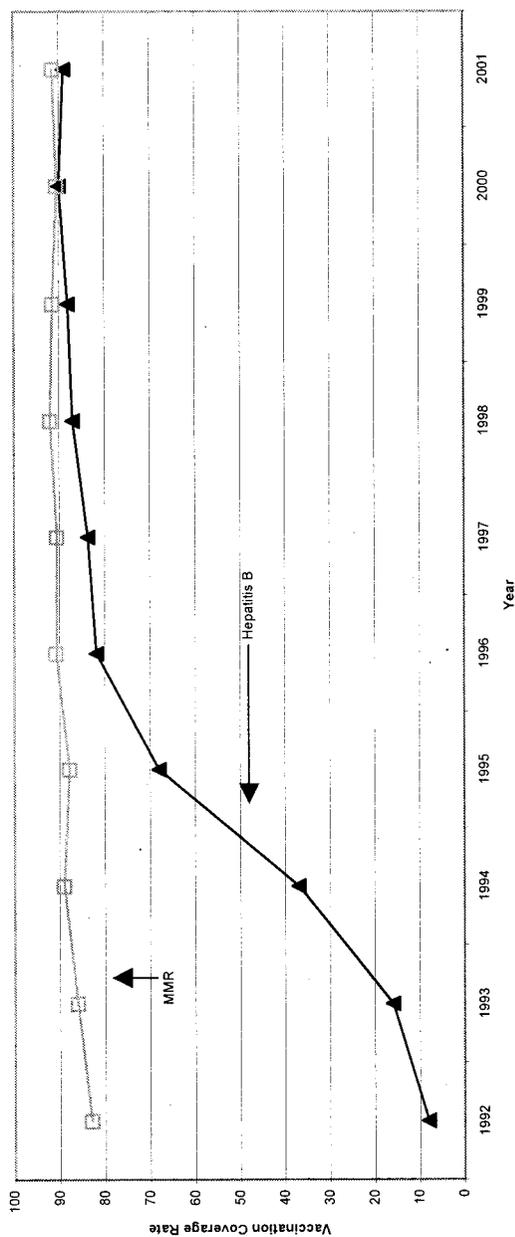
FIGURE IV

Vaccination Coverage Levels among Children 19–35 Months

Data on vaccination rates are from National Health Interview Surveys as reported in CDC [1995a, 1997, 1998, 2001, 2002c].
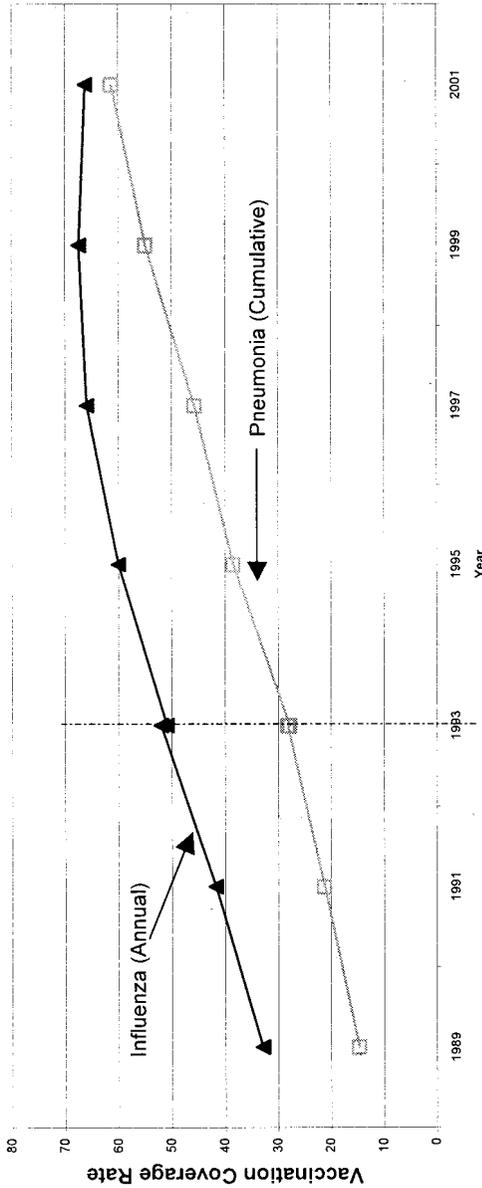
FIGURE V

Trends in Vaccination Rates for Ages 65+

1989–1993 data are from National Health Interview Surveys as reported in CDC [1995b].
1993–1999 data are from Behavioral Risk Factor Surveillance System and reported in CDC [2002b].

TABLE VI
DOLLAR VALUE OF HEALTH BENEFITS FROM STATIC IMPACT OF POLICIES

	Estimated static impact on vaccination rate (1)	Dollar value of static impact on vaccination rate (2)	Costs of static policy impact (3)	Dollar value of *net* static impact on vaccination rate (4)
Hepatitis B recommendation	0.90	$7,524	$326	$7,198
Medicare covers Flu	0 to 0.15	0 to $2,775	$60 to $111	−$60 to $2,664

All estimates are annual and all dollar amounts are in millions. See text for more details.

zero; the upward trend in Flu vaccination rates after the policy is comparable to the trend prior to the policy and to the trend in vaccination rates for pneumonia, which is also routinely recommended for the elderly.[16] In the analysis, I therefore assume that the static effect of the Hepatitis B policy was to increase vaccination rates by 90 percentage points, and that the static effect of the Flu policy was to increase vaccination rates by between 0 and 15 percentage points. These estimates are summarized in column (1) of Table VI.

Column (2) of Table VI shows the dollar value of the annual health benefits from this increase in vaccination rates. These are given by

$$(3) \qquad\qquad \Delta V * E_0 * \bar{H},$$

where ΔV denotes the static policy impact on vaccination rates, $\bar{H}$ denotes the dollar value of the annual social health benefits from complete vaccination of the target population with a 100 percent efficacious vaccine, and E_0 denotes the maximal efficacy of the existing vaccines at the time of the policy. For $\bar{H}$, I use estimates of $31.9 billion for the Flu and $8.8 billion for Hepatitis B.[17] For E_0, I use estimates of 58 percent for Flu [Kilburn and Arden 1999] and 95 percent for Hepatitis B [Mahoney and Kane 1999].

16. As described in more detail in Appendix 1, the investment response to the Flu policy was based on its ex ante expected impact, which was considerably higher than even liberal estimates of its actual impact.

17. The Institute of Medicine [1985a] presents estimates of $\bar{H}$ in terms of infant mortality equivalents. I convert these estimates to a dollar metric using the $3 million value per infant life from Cutler and Richardson [1999].

Column (3) shows the estimated static costs of the policy. These include the production costs associated with the induced increase in vaccination rates, as well as the cost of public funds associated with the policy (which will depend on overall vaccination levels).[18] Column (4) combines the results in columns (2) and (3) to show that the net static social welfare benefits of the policies. These are large and positive, on the order of $7 billion per year for the Hepatitis B policy, and up to $2.7 billion per year for the Flu policy.

I next consider how the policies' dynamic consequences would alter this traditional static welfare analysis. Given the 7–8 year lag from the start of a clinical trial to approval, the dynamic benefits of these policies are only beginning to be realized. Therefore, I compute both the maximum *potential* dynamic benefit and the *actual* dynamic benefits induced by the policies to date; these represent, respectively, upper- and lower-bound estimates of the policies' dynamic benefits. For both sets of estimates, I follow the analytical framework developed in Section I and consider two types of potential dynamic social benefits from the induced investment: increases in vaccination rates (via increased product quality or increased price competition) and increases in vaccine product quality. Table VII summarizes the results.

Column (1) shows the dynamic effect on vaccination rates; the maximum potential effect is the difference between the maximum achievable vaccination level (set conservatively at 90 percent) and the vaccination rate reached after the static effect of the policy. For Hepatitis B, the static effect of the policy was sufficient to achieve this maximum feasible vaccination rate. For the Flu, however, vaccination rates had only reached 67 percent after the policy had been in place for eight years, leaving a potential dynamic impact on vaccination rates of up to 23 percentage points. However, since no new Flu approvals occurred prior to June 2003, there have been no actual dynamic effects on vaccination rates to date. Column (2) shows the dollar value of the dynamic effects on vaccination rates. These are estimated using the formula in equation (3) and discounted back eight years (using a 3 percent annual discount rate) to reflect the earliest these potential benefits may accrue.

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18. Estimates of production costs are derived from Mercer [2000] and the CDC Survey of Biologics 1999 data. I assume that all vaccine purchases are paid for by public funds and that the marginal cost of public funds is 1.4; Merck [2000] provides data on annual vaccine expenditures.

TABLE VII
DOLLAR VALUE OF HEALTH BENEFITS FROM DYNAMIC IMPACT OF POLICIES

	Increase in vaccination rate (1)	Dollar value of increase in vaccination rate (2)	Increase in efficacy (3)	Dollar value of increase in efficacy (4)	Costs of dynamic policy impact (5)	Dollar value of *net* dynamic impact (6)
Upper-bound estimate (maximum potential benefit)						
Hepatitis B recommendation	0	0	0	0	$20	−$20
Medicare covers Flu	0.23	$3,395	0.27	$6,104	$20	$9,479
Lower-bound estimate (actual benefits to date)						
Hepatitis B recommendation	0	0	0	0	$20	−$20
Medicare covers Flu	0	0	0.27	$4,307	$20	$4,287

All estimates are annual, and all dollar amounts are in millions. Dollar value of dynamic benefits are discounted using a 3 percent annual discount rate. See text for more details.

Increases in vaccine product quality can arise from increases in vaccine efficacy or decreases in vaccine side effects (marginal costs of production are trivial). At the time of the Hepatitis B policy, there was little potential for improvement in vaccine quality, as vaccines with few side effects and very high efficacy rates already existed [Mahoney and Kane 1999]. However, the best existing Flu vaccine at the time of the 1993 policy had an efficacy rate 27 percentage points below the 85 percent efficacy rate that was considered technologically feasible [Institute of Medicine 1985a; Kilburn and Arden 1999]. There is some evidence that policy-induced innovation achieved this increase in efficacy. Out-of-sample extrapolation of the approval estimates in Section IV suggests that the 1993 Flu policy was responsible for the 2003 approval of the first new Flu vaccines since 1978. This new vaccine—the first ever intranasal Flu vaccine—has an 85 percent efficacy rate in healthy adults [CDC 2003].[19] Column (3) summarizes these potential and actual increases in efficacy.

Column (4) shows the associated dollar value of these increases in efficacy. This is given by

19. As of January 2004, FDA approval for use by the elderly had not yet occurred but is expected. The estimate of "actual benefits" for the Flu policy in columns (4) and (6) assumes that this approval occurs and that all Flu vaccinations for the elderly are done with the new vaccine.

(4) $$\Delta E * V * \bar{H},$$

where V denotes the vaccination rate, ΔE denotes the maximum potential increase in efficacy, and $\bar{H}$ denotes the dollar value of the annual social health benefits from complete vaccination of the target population with a 100 percent effective vaccine. The difference in Table VII between the maximum potential dollar value and the actual dollar value of the increase in efficacy for the Flu vaccine reflects the fact that the former uses the maximum possible vaccination rate of 90 percent, while the latter uses the current vaccination rate of 67 percent. In addition, the maximum benefits are discounted by eight years (the minimum time for a new approval), while the actual benefits are discounted by ten years (the time between the 1993 policy and the 2003 new vaccine approval); in both cases, a 3 percent annual discount rate is used.

The dynamic costs of the induced R&D in new vaccines is limited to the induced R&D expenditures; it does not include any costs from induced overconsumption of the new technologies since optimal vaccination rates are essentially 100 percent for existing vaccines. Column (5) shows the estimated dynamic costs of $20 million per year in induced EPDV R&D expenditures; these are based on the estimated 1.2 induced new vaccine clinical trials per year and the $16.2 million EPDV cost of each clinical trial [Di-Masi et al. 1991]. Column (6) combines the estimates in columns (2), (4), and (5) to show the *net* dynamic impact of the policy. It reveals that the two policies represent polar opposite cases of the welfare consequences of induced investment.

For Hepatitis B, the dynamic welfare impact of the policy corresponds to the case illustrated previously in Figure I in which there is no technological potential for improvement in product quality and the static effect of the policy is sufficient to achieve the socially optimal quantity. As a result, all of the induced innovation is socially wasteful business stealing. Most of the investment induced by the VICF was probably similarly socially wasteful. The affected diseases were all at the socially optimal feasible vaccination rate prior to any postpolicy technological change. In addition, for three of the four diseases, very high quality vaccines already existed [Institute of Medicine 1985a]. However, recognition of the socially wasteful induced innovation does little to alter the overall welfare implications of either policy. The socially wasteful induced investment of $20 million per year pales in comparison to the net static benefits from the Hepatitis

B policy of over $7 billion per year. Even a very small static impact of the VICF would similarly dwarf the $20 million per year in induced R&D expenditures for each of these diseases, since the net social welfare benefits from childhood vaccination are very high. As noted in Section I, the magnitude of any negative social welfare costs from induced innovation is likely to be small and less important for vaccines relative to other health technologies since the social costs are limited to induced R&D expenditures and vaccines have an extraordinarily high benefit-cost ratio.

For the Flu policy, however, the dynamic welfare impact corresponds to the case illustrated previously in Figure II in which there is substantial potential both for development of a higher quality product and for the induced innovation to increase demand to the socially optimal level. Indeed, Table VII shows dynamic benefits that are not only positive, but also larger than the static benefits. The upper-bound estimate of the dynamic benefits of the Flu policy is about $9.5 billion per year. This is larger than the Flu policy's maximum potential static benefits, which I estimate are only $7.2 billion per year.[20] The lower-bound estimate from Table VII of the annual dynamic benefits from the flu policy ($4.3 billion) already exceeds the upper-bound estimate from Table VI of the actual annual static benefits from the Flu policy ($2.7 billion). Estimates of the dynamic benefits assume that any induced new Flu vaccine is used only in the United States; to the extent that other countries also adopt the new vaccine, the dynamic benefits will be even higher than what I have estimated.

VI. Conclusion

This paper provides empirical evidence that the economic incentives embodied in health policies can affect the rate of technological change in medicine. I find robust evidence of a substantial and sustained increase in new vaccine clinical trials (and ultimately in new vaccines) associated with health policies that increased the expected return to developing these new vaccines. However, I find no evidence of an increase in more basic inventive

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20. This is calculated based on equation (3), a prepolicy efficacy of 58 percent [Kilburn and Arden 1999] and a maximum increase in vaccination rates from the 51 percent level in 1991 [CDC 2002b] to 90 percent.

activities, such as preclinical trials or patent filings, associated with the policies. This suggests that the relative roles of the state of science and economic incentives in affecting technological progress may be systematically different at different stages in the innovation process.

The evidence of a substantial innovation response to policies designed to increase utilization of existing vaccine technology raises the question of the impact of the induced innovation on the overall welfare consequences of the policies. For most of the affected diseases, I find that the policies induced socially wasteful investment in business stealing, but that the magnitude of the dynamic welfare costs is small relative to the static welfare gains of the policies' effect on vaccination rates. However, in the case of the Flu vaccine, I estimate that the "dynamic" social welfare benefits from the induced innovation are not only positive, but also larger than the "static" social welfare benefits of the Flu policy from increasing utilization of the existing vaccines. An important avenue for further work is to consider more systematically how recognition of the induced investment response to health policy affects the assessment of optimal health policy intervention.

APPENDIX 1: DETAILED DESCRIPTION OF POLICY CHANGES

1. CDC Recommendation of Universal Hepatitis B Vaccination for Infants (July 1991)

Rationale. Although a Hepatitis B vaccine had existed since 1981 and had been recommended for use in high-risk groups since 1982, it quickly became clear that the health care system was not successful at vaccinating the at-risk population, which consisted of homosexuals, intravenous drug users, promiscuous heterosexuals, and health care workers [CDC 2002a; Institute of Medicine 1985a]. A long political battle ensued over the relative benefits of reaching the at-risk population by prophylactically vaccinating the entire birth cohort, compared with the risk that adding a nonchildhood disease to the childhood immunization schedule would only enhance the difficulty of getting parents to comply with the existing schedule [Snyder interview; Grady interview;

Kaye interview]. Prior to the Hepatitis B recommendation, there were no vaccines against nonchildhood diseases included in the recommended childhood immunization schedule.

Was the timing the result of technological developments? The 1991 recommendation for universal Hepatitis B vaccination was the outcome of an uncertain, decade-long, political battle that followed the approval of the first Hepatitis B vaccine in 1981 and the failure to vaccinate the at-risk population (see above). There is no indication either in the records of the Advisory Committee on Immunization Practices [CDC 1991] or in conversations with policy-makers (e.g., Snyder [interview]) that any technological changes in the nature of the Hepatitis B vaccine influenced the decision. Furthermore, since the political battle was long and its outcome uncertain until the end, it is hard to argue that the policy's ultimate adoption, much less its timing, was anticipated by vaccine developers.

Expected impact of the policy. The policy was expected to dramatically increase the market size, going from failed efforts to vaccinate a small subsection of the population to a guaranteed annual cohort of the 4 million live births per year.[21] Industry members said they were optimistic at the time of the policy that the policy would result in essentially complete vaccination of the birth cohort [Sanyour interview; Piron interview]. Indeed, subsequent evidence was consistent with these expectations (see Figure IV).

Three main mechanisms translate a CDC recommendation into dramatic changes in standard immunization practices. First, public programs, which account for over half of childhood immunizations in the United States, follow the recommendations of the CDC [Snyder interview; Woodruff et al. 1996]. Second, for liability reasons, pediatricians' private practice also tends to follow the CDC recommendation [Grady interview]. Indeed, the American Academy of Pediatrics officially endorsed the CDC's recommendation the following year. Third, states follow the CDC recommendation in determining the required vaccinations for school attendance [Alfona interview]; these requirements have a large effect on vaccination rates (see, e.g., Orenstein and Hinman [1999]).

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21. As one pharmaceutical executive put it memorably: "trying to sell a vaccine for which there isn't a [CDC] recommendation for universal or near universal coverage of the birth cohort is like pissing in the wind."

2. Medicare Coverage of Influenza Vaccine and Federal Information Campaign (May 1993)

Rationale. The decision for Medicare to cover the Flu vaccine followed a five-year, congressionally mandated series of demonstration projects which concluded that providing Flu vaccines to Medicare beneficiaries was cost-effective. Medicare coverage was accompanied by a HCFA-initiated information campaign designed to promote use of the new benefit [CDC 1994].

Was the timing the result of technological developments? The timing of the congressional decision to evaluate the cost-effectiveness of covering Flu vaccines for Medicare beneficiaries was not the result of the development of new Flu vaccines, as the most recent Flu vaccine prior to these demonstration projects has been on the market since 1978 [Hoyt 2002]. In addition, it does not appear that the policy was anticipated prior to the decision [Piron interview; Sanyour interview].

Expected impact of the policy. The CDC's vaccine target population for the Flu consists of individuals over age 65 as well as individuals with certain health problems that put them at risk of vaccine complications [Institute of Medicine 1985a]. As a result, substantial changes in Flu vaccination rates for the elderly would constitute a substantial absolute and proportional change in sales of Flu vaccines.

Conversations with people in the pharmaceutical industry reveal that the Medicare reimbursement decision was noticed and expected to have a dramatic market impact [Sanyour interview; Kay interview].[22] The vaccine industry was not alone in forecasting large increases in Flu immunization associated with the policy; the results from demonstration projects studying the impact of Medicare coverage of the Flu vaccine also forecast substantial increases in immunization (see, e.g., Schmitz et al. [1993]). In practice, the effect of the policy on coverage rates turned out to be considerably less dramatic than expected (see Figure V); however, it is the expected response that matters for investment decisions.

Three primary mechanisms were behind the industry's belief that Medicare coverage would result in increased profitability of

22. As one person in the industry put it: "it changed the forecast assumptions . . . our market forecasters saw Medicare reimbursement and forecasted close to 100 percent coverage. A number of decisions were made based on this false premise."

the Flu vaccine. First, it was believed—in part based on the demonstration projects—that vaccination rates among the elderly would be extremely responsive to Medicare coverage and information campaigns. Second, there is a general sense among individuals in the industry that doctors are more willing to adopt new, more expensive vaccines if insurance will cover vaccination. Third, there is believed to be a multiplier effect from Medicare policy to private insurance policies, private physician practices, government vaccination practices, and state mandates [Grady interview; Alfona interview].

3. Vaccine Injury Compensation Fund (VICF) (1986)

Rationale. The 1986 enactment of the VICF was a response to a surge in product liability lawsuits in the early 1980s. This prompted large-scale exit of manufacturers of childhood vaccines and raised concerns about the continued availability of childhood vaccines [Kitch et al. 1999; Institute of Medicine 1985a, 1985b; GAO 1999].

Was the timing the result of technological developments? The pharmaceutical industry had been lobbying for the policy for well over a decade; the exact timing seems to have been prompted by the surge in lawsuits and the withdrawal of manufacturers, not any technological developments [Kitch et al. 1999]. Again, the enactment of the policy does not appear to be anticipated, since the outcome of the lobbying efforts remained uncertain (e.g., Piron [interview]).

Expected impact of the policy. Individuals in the vaccine industry are quick to point to this policy as a huge boost to the industry, and one that was viewed as such at the time of enactment. The industry is almost hyperbolic in describing its benefits to the industry [Kaye interview; Michael interview; Manning interview]. In addition, the vaccine industry's lobbying for similar indemnification for the anthrax vaccine in the wake of September 11 is indicative of this being deemed beneficial to the industry.

APPENDIX 2: DATA

The NDA Pipeline Data

The NDA Pipeline is an annual business publication which has been published since 1982 by F-D-C Reports, a well-regarded, long-established, research firm that covers the pharmaceutical

industry.[23] The publication contains a listing, for each company or research organization, of all of its pharmaceutical products in development at the end of the calendar year, a brief description of each product, and each product's stage in the R&D pipeline.

The publication aims to cover all companies with a presence in the United States, and to report on any products anywhere in the pipeline from preclinical trials through approvals. It collects similar information from high-profile, nonprofit, research organizations in the United States. Data are collected from four primary sources. These include any information publicly released by the company (for example, to potential investors and stock analysts, required disclosures to the SEC, or at scientific conferences), information released by the FDA, company responses to the F-D-C's annual survey of each company's pipeline, and specific contacts in the various firms. The F-D-C sends the initial description of each company's pipeline to the company for verification.

Interviews with people who work in the industry or use the reports indicate that these are thought to be reliable and high quality data. While probably not completely comprehensive, the collection method is believed to capture the vast majority of compounds in clinical trials. I was able to verify the general quality of the data by ascertaining that any product that I knew had been in clinical trial or approved was indeed in the data, and by observing the continuity from year to year in a product's description, and its movement through the phases of the clinical trials.

The data's primary disadvantage is that they rely heavily on self-reported information. Companies are, in general, eager to report on projects in clinical trials, for this attracts positive publicity and potential investor support. In addition, since much of the information on clinical activity has already been released to certain segments of the public, and *The NDA Pipeline* is widely read in the industry, companies respond to the F-D-C surveys to ensure the accuracy of the reported information. Because companies are less likely to publicize information on preclinical trials, the data are considered—both by industry members and the F-D-C staff—substantially more reliable for measuring clinical activity than preclinical activity.

I use eighteen volumes of the publication, from the earliest volume (1982) through 1999, to compile seventeen years of data

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23. Additional information about the company and its publication can be found at http://www.fdcreports.com.

on new vaccine clinical trials and preclinical trials. I construct the date of a compound's entry into preclinical or clinical trials by using the name of the company(ies) developing the product and the product description to follow it from year to year. While several other data sources provide a snapshot of the pipeline in a recent year, *The NDA Pipeline* is the only source that permits this retrospective construction of when a product entered the clinical or preclinical pipeline. I also compile an eighteen-year repeated cross section on product approvals.

The Patent Data

I use the U. S. Patent and Trademark Office's comprehensive on-line database of all approved patents from 1976 through 2001 to create a database of the filing date of (ultimately) successful patent applications. Since patents only enter the database once they are approved, the data will produce an underestimate of successful patent filings in more recent years. Since 98 percent of the patents approved between 1980 and 1996 were approved within five years or less, I keep in the sample all patents approved within five years or less and am thus able to create a consistent 21-year time series on successful patents filed from 1976 through 1996. I do not include patents filed before 1976 since only the subset approved in 1976 or later are in the data.

While an extremely accurate measure of patent filings, the data are probably a noisy measure of basic vaccine research, since a lower proportion of successful basic research is patented for vaccines than for other pharmaceuticals. The key form of intellectual property in vaccine development is the exact process used to produce the immunizing agent; this is difficult to mimic, making the need for official patent protection lower than in pharmaceuticals, where the intellectual property is more likely to be the molecular structure of a compound [Sanyour interview]. The lack of generic competition in vaccines underscores this point.

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