NBER WORKING PAPER SERIES

HEALTH POLICY AND TECHNOLOGICAL CHANGE: EVIDENCE FROM THE VACCINE INDUSTRY

Amy Finkelstein

Working Paper 9460
http://www.nber.org/papers/w9460

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
January 2003

I am grateful to Daron Acemoglu, David Autor, Pierre Azoulay, Ernie Berndt, Tim Bresnehan, Iain Cockburn, David Cutler, Glenn Ellison, Sara Ellison, Vic Fuchs, Jeff Furman, Jon Gruber, Rebecca Henderson, Jerry Hausman, Peg Hewitt, Kendall Hoyt, Seema Jayachandran, Melissa Schettini Kearney, John Kennedy, Michael Kremer, Margaret Kyle, Ben Olken, Jim Poterba, Steve Propper, Sarah Reber, Scott Stern, and seminar participants at Harvard, the Fed, Stanford GSB, and the NBER Summer Institute for helpful comments and discussions. Hogan Chen provided outstanding research assistance. The views expressed herein are those of the authors and not necessarily those of the National Bureau of Economic Research.

Health Policy and Technological Change: Evidence from the Vaccine Industry
Amy Finkelstein
NBER Working Paper No. 9460
January 2003
JEL No. I1, I18, O3

ABSTRACT

Rapid technological progress has been a defining feature of the medical sector over the last century, yet we know little about the determinants of the development of these new technologies. This paper examines whether and to what extent the demand-side incentives embodied in health policy affect the rate of technological change in the medical sector. Specifically, I estimate the effect on vaccine investment of discrete changes in health policy that increased the return to developing vaccines against specific diseases. I present robust evidence of an increase in vaccine investment associated with the increase in demand-side investment incentives. The induced investment represents 70% of the total subsequent vaccine investment in the affected diseases, and suggests that a $1 increase in annual market revenue for a vaccine is associated with 5 to 6 cents of additional investment in that vaccine''s development. However, this response appears limited to the last stage of the R&D pipeline – clinical trials – which represents the commercialization of existing technology; I am unable to detect evidence of an investment response at earlier stages – as measured by pre-clinical trials or patent filings – that represent more of an attempt to develop fundamentally new technologies. Finally, I present suggestive evidence that the potential dynamic health benefits from the technological change induced by the policies are at least as large as the static health benefits from the policies'' primary aim of increasing vaccination rates with the existing technology. These results suggest that the near-exclusive focus on static health benefits in empirical evaluations of health policies is inadequate.

Amy Finkelstein
National Bureau of Economic Research
1050 Massachusetts Avenue
Cambridge, MA 02138
afinkels@nber.org

Ever since Schmookler (1966), economists have debated the relative roles of demand factors and of the state of basic science in determining the rate and direction of technological progress. Modern growth theory emphasizes not only that technological change is the driving force behind economic growth, but also that this technological progress is endogenous to economic incentives.

In the medical sector, technological progress has been a defining feature of the industry over the last century. Advances in medical technology have been an important component of the dramatic health improvements of the 20th century. They have also been the driving force behind the rapid growth in the real cost of medical care (Newhouse 1992). The potential role that demand-side factors, and in particular, health policy, may have played in affecting this technological progress has long been recognized (see e.g. Weisbrod (1991) for an in-depth discussion). More recently, and with a specific focus on encouraging the development of vaccines for developing countries, Kremer (2001) has suggested that demand-side incentives may be better suited to encouraging targeted vaccine development than traditional supply-side subsidies to inventive activity.

Yet despite the theoretical attention and importance attached to this issue, we have little empirical evidence on the role of demand in affecting the rate of technological progress.[1] Indeed, I know of no empirical evidence on the role of demand factors in affecting the development of new medical technologies. This paper presents the first such evidence.

The empirical approach of this paper is to examine three discrete policy changes that increased the demand-side incentives to develop new versions of vaccines against six particular diseases. Because they occur at discrete points in time, I can try to distinguish the effects of these policies from the secular increases in R&D in the vaccine industry over the time period studied. Because the policies affect only particular diseases, I can also use changes in investment in vaccines against other carefully-selected infectious diseases that are unaffected by the policies to try to control for other changes that may also have affected investment decisions.

[1] Most of the empirical work testing the induced-innovation hypothesis has been in the environmental literature (see e.g. Newell, Jaffe and Stavins, 1999).

The results shed light on three issues. First, I investigate the open empirical question of *whether* medical investment responds to the demand-side incentives embodied in health policy.[2] The response may be limited either by the existing state of technology, or by the combined impact of the long lags in the 15+ year R&D pipeline and uncertainty about future health care policy. Indeed, to the extent that health care policy responds endogenously to technological change – from either political pressure to provide public health insurance coverage for new breakthrough technologies or the ex-post temptation to hold-up the developer of an important new technology – this will weaken the incentive for developers to heed the current policy climate in making investment decisions.

I find robust evidence that the policies are associated with a statistically significant increase in the number of new vaccine clinical trials for the affected diseases. The central estimates indicate that the policies are associated with a 2.5-fold increase in the annual number of new vaccine clinical trials against these diseases. There is also suggestive evidence of an increase in approvals of new vaccines for the affected diseases, suggesting that the policies are associated with an expansion of the vaccine product space.

Second, I examine *which margins* of the process of R&D appear responsive to demand-side incentives. In particular, I investigate whether the induced investment involves attempts to create fundamentally new technologies or is limited to the commercialization of existing technologies through clinical trials. Here, the results point to potential limits to the ability of demand-side incentives to induce technological change. I am unable to find evidence of an effect of the demand-side incentives on more fundamental development efforts, as measured by the decision to start new pre-clinical trials, or the filing of ultimately successful patent applications.

Finally, I present two ways of interpreting the *magnitude* of the investment response. First, making additional assumptions about the expected revenue increase associated with the policies and about the costs of new vaccine clinical trials, I estimate that an increase of one dollar in the expected present

[2] See e.g. Pauly and Cleff (1996) on the open empirical question of "the link (if any) between profits from old vaccines and spending on R&D for new vaccines" (p.19-20).

discounted value of market revenue from vaccines against a particular disease stimulates 5 to 6 cents of present discounted value of investment in that vaccine. Second, the primary and stated purpose of all of the health policies studied was to increase utilization of existing vaccines. I perform a back of the envelope comparison of the potential health benefits from the dynamic effects of these policies on extending the technological frontier relative to the static health benefits from the increased utilization of the existing technology. Even under very conservative assumptions, the potential dynamic health benefits from the development of new technologies appear at least as large as the static health benefits from increasing use of existing technologies. This highlights the importance of considering not only the static, but also the dynamic consequences, of health policies when evaluating their likely impact on health.

The paper focuses on the R&D response of a sub-sector of the pharmaceutical industry, the vaccine industry. Two factors make vaccines a particularly compelling setting for studying the effects of health policy on technological change. First, the government plays a central role in affecting the demand for vaccines.[3] Second, further vaccine development has the potential to produce dramatic health benefits. This applies particularly to developing countries – where vaccines against many widespread diseases such as AIDS and malaria currently do not exist – but also to developed countries where the rising threat of bio-terrorism has increased the importance of developing improved versions of vaccines against diseases such as anthrax and small pox. In addition, because vaccines share key development features with the rest of the pharmaceutical industry – namely for-profit companies investing large sunk costs in long-term projects with uncertain outcomes – the results from this study should be viewed as suggestive, at least qualitatively, of the effects of demand-side incentives in the pharmaceutical industry more generally.

The rest of the paper proceeds as follows. Section two provides the relevant background on vaccine development. Section three describes the criteria for selecting policy changes to study, and provides a detailed description of the three policy changes selected based on these criteria. Two of these policies increased the expected market size for vaccines against two different diseases (hepatitis B and the flu).

[3] The government is both the major determinant of the set of standard immunizations administered to children (Schwartz and Orenstein 2001) and a major purchaser of vaccines. For example, in 1997, the U.S. government purchased 60% of all childhood vaccine doses administered in the U.S. (Bob Snyder of CDC provided these data).

The third policy – the Vaccine Injury Compensation Fund – introduced a government-run, no-fault product liability system that reduced the mean and variance of product liability costs associated with four childhood vaccines: polio, diphtheria-tetanus, measles-mumps-rubella, and pertussis.

Section four describes the new data set that I construct to measure annual investment activity in vaccines against different diseases during the time period studied, the 1980s and 1990s. Section five presents descriptive statistics of the time series pattern of new vaccine clinical trials for affected and control diseases, and develops the econometric framework for more formal analysis. The next three sections present the three main sets of results. Section six presents the econometric evidence of the basic investment response to the policies; it focuses on the effect of the policies on the decision to start new clinical trials but also presents suggestive evidence of their effect on vaccine approvals. Section seven delves deeper into the *nature* of the investment response by examining which margins of the investment process responded to the increased incentives. Section eight provides two ways of gauging the magnitude of the investment response. The last section concludes.

2. Background on vaccine development

In 2001, the pharmaceutical industry spent about $1.1 billion, or about 4% of total privately-financed R&D in pharmaceuticals, on R&D for "biologicals", a therapeutic class of drugs of which vaccines are the primary component (PhRMA 2001). The vaccine R&D pipeline – like that of other pharmaceutical products – can be roughly divided into three sequential stages: basic research (which may produce new patentable technologies), pre-clinical trials (testing in animals), and clinical trials (testing in humans) which, if successful, will secure FDA approval for a new product. As a compound moves through the pipeline, 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 pharmaceutical companies rather than in academic or government laboratories.[4] The decision to start a new clinical trial – the most expensive and time consuming component of the pipeline as well as the final step before product approval – will be the primary measure of investment used in the empirical work.

[4] For more detail, see Gelijns (1990), Mathieu (1997), and National Vaccine Advisory Committee (1997).

Vaccines offer a steady and reliable source of modest profits. Development times and success rates from the start of clinical trials through approval are comparable to those for other pharmaceutical products.[5] The central role of the government in determining vaccine demand reduces marketing costs and uncertainty about future market size; however, it also holds down prices.

For vaccines, but not for other pharmaceuticals, the FDA requires that companies begin building physical manufacturing capacity prior to product approval. This may explain the concentrated nature of the U.S. vaccine manufacturing market, in which the top four firms' market share is over 95%.[6] The market for vaccine *development* is substantially less concentrated; however, because successful development projects are almost always acquired by established companies prior to approval, product market concentration remains high (Pauly and Cleff 1996).

Much of vaccine development is aimed at developing improved versions of vaccines against diseases for which a vaccine already exists. Indeed, all of the diseases affected by the policies studied in this paper already had an existing vaccine. Improvements to existing vaccines include improving the vaccine's efficacy at disease prevention or reducing the vaccine's risk of adverse side effects. It can also involve the development of a vaccine that combines separate, existing vaccines against different diseases into a single vaccine; this can be very important for increasing vaccination rates by reducing the number of different shots and visits needed to complete an immunization schedule (Decker and Edwards (1999), American Academy of Family Physicians (2000)). Given this multi-dimensionality to vaccine "quality", there are often several different vaccines on the market against a given disease, and the latest generation vaccine does not necessarily capture the entire market.

Regardless of the disease, vaccine development shares several common technological components and has benefited generally from a series of technological advances in the 1980s and 1990s in biotechnology and in our understanding of the immune process (see e.g. Institute of Medicine 1985b, Ellis 1999 and NIH 1998). Not surprisingly, given these technological advances, vaccines have shared in

[5] See Struck (1996) for vaccines, and DiMasi et al. (1991) or OTA (1993) for comparable industry-wide statistics.
[6] This is true throughout the period studied. See e.g. Institute of Medicine (1985b) and Merck (2000).

the rapid growth in industry investment in pharmaceutical R&D (OTA 1993, Grabowski and Vernon 1997). It will be the key challenge of the empirical work to distinguish the investment effect of increases in demand-side incentives from changes in investment that would have arisen simply because of exogenous technological advances. The common technological basis of much of vaccine development provides the opportunity to use vaccines against diseases that were not affected by the policies to try to control for changes in vaccine investment that are driven by exogenous changes in the technological possibilities frontier.

3. The policies

The empirical approach of this paper is to identify discrete policy changes that affect the demand-side incentives for developing improved versions of vaccines against particular diseases. Unlike traditional supply-side incentives, such as the investment tax credit, that affect the (fixed) *investment costs* associated with developing a new vaccine, demand-side incentives affect the *marginal* net revenue from vaccine sales.

3.1 Criteria for choosing policies

I limit myself to policy changes that meet six essential criteria. First, they had to occur at an identifiable point in time; the effect of slow-moving secular trends – such as changing demographics or the growth in managed care – on investment is difficult to distinguish from concurrent technological developments. Second, they had to affect demand-side incentives for developing vaccines against an identifiable, but limited, class of infectious diseases; investment in developing vaccines against unaffected diseases can therefore potentially be used to control for changes in other factors that may also affect vaccine investment.

Third, the policies could not be prompted by technological developments, for it would be difficult to distinguish the effect of the demand-side incentives from the change in investment behavior that would otherwise have occurred in response to the changing technology. This requirement, in particular, eliminated many candidate policies. For example, the CDC recommendations for universal childhood vaccination against HIB in 1991 and chicken pox in 1996 were excluded from the set of candidate

policies because they were prompted by recent approvals of improved, or first-time, vaccines against these diseases (CDC 1991b, CDC 1996b).[7] Fourth the policies could not have been anticipated by the industry in advance of their enactment or we would not expect to see an investment effect at the time of the policy's announcement. A consequence of these four restrictions is that my estimates of the relative contribution of demand-side incentives to the determinants of vaccine development represent a lower-bound on the overall contribution of demand-side incentives to vaccine development, since changes in demand-side incentives that do not meet these four criteria are not incorporated into the analysis.

Fifth, the policies had to be expected to have a substantial effect on the demand-side incentives for developing a particular vaccine. This caused me, among other things, to focus exclusively on U.S. policies; the U.S. is the single largest market for pharmaceuticals, accounting for over two-fifths of world-wide spending on pharmaceuticals in 1998 (PhrMA 2000). Finally, the policies had to occur after 1983 and before 1999, since this is the period for which the investment data (described below) are available.

3.2 The policies that satisfy these criteria

I identified three different policy changes – affecting vaccines against a total of six different infectious diseases – that met all six of the above criteria. One was the 1991 recommendation of the CDC's Advisory Committee on Immunization Practices (ACIP) that all infants be vaccinated against hepatitis B. Another was the 1993 decision for Medicare Part B to cover (without any co-payments or deductibles) the cost of influenza vaccination for any Medicare recipient; this decision was coordinated with a HCFA information campaign to encourage Medicare beneficiaries to avail themselves of this new benefit (CDC 1994). Both of these policies were expected at the time of their introduction to increase demand-side investment incentives by substantially enlarging the market for the affected vaccine.

The third policy, the introduction of the Vaccine Injury Compensation Fund (VICF) in 1986, indemnified vaccine manufactures against product liability lawsuits stemming from potentially adverse health reactions to childhood vaccines. It covered the childhood vaccines that were then recommended by

[7] The estimated effect of the policies actually studied may be biased downward by the inclusion of such diseases among the controls. I do not automatically exclude them, however, since this would tend to remove diseases that benefited from technological advances from the controls, and thus bias upward the estimated effect of the policies.

the CDC for routine childhood immunization: polio, diphtheria-tetanus (DT), measles-mumps-rubella (MMR), and pertussis. In return for an excise tax levied on the affected vaccines, the government introduced a no-fault compensation system with a fixed payment schedule for claims. This benefited developers of these vaccines in two ways. First, it reduced their exposure to risk by removing the aggregate uncertainty concerning the potential magnitude of liability costs that was created by the uncertain legal environment for product liability in the 1980s.[8] Second, it reduced expected liability costs, since the program included several measures to limit payouts for successful claims below current average awards (GAO 1999; HRSA 2002). The VICF thus increased demand-side incentives by reducing the mean and the variance of product liability expenses; in an option-value investment model, this should produce increased investment (Dixit and Pyndick 1994).[9]

Qualitative evidence, based on documentary sources and lengthy conversations with individuals in the vaccine industry, policy-makers, and physicians establishes two key points.[10] First, at the time of their enactment, the industry expected each of these policies to substantially increase the expected return to developing new vaccines against the affected diseases. Second, the explicit objective of each of these policies was to increase vaccination rates, either through recommending (or requiring) that children be vaccinated (the CDC recommendation of hepatitis B vaccination), through reducing the cost to the individual of the vaccine and promoting greater awareness of its benefits (Medicare coverage of the flu vaccine), or through ensuring the continued manufacture and hence available supply of existing vaccines (the VICF). The empirical evidence thus points to the unintended consequences that policies designed to increase utilization of existing technology can have for technological change.

To examine whether the policies were a response to technological changes, I ascertained that none of

[8] In principle, the VICF may have also reduced each manufacturer's idiosyncratic risk of liability expenditures by pooling this risk across the different companies. I do not consider this a likely source of increased demand-side incentives, however, since there is no indication of any market failure preventing the four large vaccine manufacturers from pooling this risk prior to the introduction of the government pooling mechanism.

[9] The VICF constitutes a change in demand-side rather than supply-side incentives – based on the distinction defined above – because it did not change the *investment* costs associated with developing new vaccines.

[10] See Appendix A for a more detailed description of the qualitative evidence and its sources.

the policies followed – even with a several year lag – new vaccine approvals for the affected diseases.[11] In addition, in the empirical work below, I am unable to find any evidence that investment activity in any of the stages of vaccine development was increasing for the affected diseases relative to control diseases in periods prior to the adoption of the policies. This suggests that the policies were not a response to an increase in the perceived technological possibilities for the affected diseases. It also suggests that the policies were not anticipated by the industry prior to their enactment.

Qualitative evidence (described in more detail in Appendix A) on the reasons for the policies and their timing reinforces the notion that they were not a response to technological developments. The 1991 recommendation for universal hepatitis B vaccination was the outcome of an uncertain, decades-long, political battle that followed the approval of the first hepatitis B vaccine in 1981 and the failure to vaccinate the at-risk population, which consists primarily of homosexuals, intravenous drug users and promiscuous heterosexuals. The prolonged political battles concerned the relative benefits of reaching the at-risk population by prophylactically vaccinating the entire birth cohort, compared to the risk that adding a non-childhood disease to the childhood immunization schedule would only enhance the difficulty of achieving compliance with the existing schedule. The 1993 Medicare decision regarding the flu vaccine followed a five-year, congressionally mandated series of demonstration projects that concluded that providing flu vaccines to Medicare beneficiaries was cost-effective; the timing of the decision to conduct these demonstration projects was not itself 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. The enactment of the VICF – which the industry had lobbied for since the early 1970s – was a response to the surge in product-liability lawsuits in the early 1980s that prompted large-scale industry exit of manufacturers of childhood vaccines and raised concerns about the continued availability of these childhood vaccines.

4. The data

Data on pharmaceutical companies' R&D *expenditures* on particular projects are unavailable. Indeed, at very early stages in the R&D pipeline they may not even exist, as researchers may not yet know the

[11] Information on vaccine approvals comes from Hoyt (2002).

therapeutic attributes of the compound under study. Instead, I measure four outcomes of the underlying expenditure decisions that capture increasingly late stages of the R&D pipeline: the filing of an (ultimately successful) patent application, the start of a new pre-clinical trial, the start of a new clinical trial, and FDA approval of a new vaccine. I draw on a novel data set to construct measures of the last three activities in each year for each disease.

4.1 Data on new pre-clinical trials, new clinical trials, and approvals.

These data come from an annual business publication, The NDA Pipeline, which has been published since 1982.[12] It is published by F-D-C Reports, a well-regarded, long-established, research firm that covers the pharmaceutical industry.[13] 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 pre-clinical trials through approvals. It collects similar information from high-profile, non-profit, research organizations in the U.S. 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.[14]

Interviews with people who work in the industry or use the reports indicate that these are thought to be reliable 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

[12] The complete collection of volumes is available at the Tufts Center for Drug Development in Boston. I am extremely grateful to the Center and its staff for allowing me access to the library.
[13] Additional information about the company and its publication can be found at http://www.fdcreports.com.
[14] Based on conversations with individuals in the research division and customer service division of F-D-C Reports.

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.[15]

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 pre-clinical trials, the data are considered – both by industry members and the F-D-C staff – substantially more reliable for measuring clinical activity than pre-clinical activity. [16] Partly for this reason – as well as the fact that clinical trials represent the last and most expensive stage of development – the primary focus of the empirical work is on the effect of the policies on the decision to start new clinical trials; however, I also present suggestive evidence of the effect on new preclinical trials.

I use all 18 volumes of the publication, from 1982 through 1999, to compile 17 years of data on new vaccine clinical trials and new vaccine pre-clinical trials.[17] I also compile an 18-year repeated cross-section on product approvals. I include in the sample all prophylactic vaccines for humans against infectious diseases, except for HIV/ AIDS, which I exclude because the changing public policies toward this disease – on both the demand and supply side – make it useful neither as a treatment nor as a control vaccine. I also exclude vaccines designed to treat, rather than to prevent, a disease. Figure 1 shows the number of new clinical trials per year for the entire sample; it reflects the general increase in R&D

[15] I do not have enough power to perform a separate analysis on the effect of the policies on transitions between the different phases of clinical trials. In addition, the lack of formal demarcating boundaries between these phases (DiMasi et al. 1991) makes any attempt to analyze transition probabilities between phases problematic.

[16] The preceding information was independently corroborated in conversations with people at Merck, the staff of the F-D-C reports, and Dr. Joseph DiMasi, who is the Director of Economic Analysis of the Tufts Center for the Study of Drug Development and who has access to proprietary data on drug development.

[17] The data are available as a repeated cross-section that gives each compound's phase in the development pipeline in each year. I construct the date of a compound's entry into pre-clinical 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 pre-clinical pipeline.

activity over the 1980s and 1990s.

4.2 Data on new patents

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. I use the same sample definition described above. 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.[18]

Figure 2 shows the number of new pre-clinical trials and ultimately-successful patent applications per year for the entire sample period available for each series. As with the clinical trials, there is a general increase in these R&D activities over the time period.

5. Descriptive results and empirical framework

In this section, I begin by presenting some informative descriptive statistics on the time-series pattern of new vaccine clinical trials for the affected diseases. I then discuss the approach taken to constructing potential sets of control diseases, and compare the time-series pattern of new vaccine clinical trials for the various definitions of the control diseases to that for the affected diseases. Finally, I develop the formal econometric framework for analyzing the effect of the policies on vaccine investment. The subsequent two sections present the results from this econometric analysis.

5.1 The pattern in the time series

Table 1 contains the heart of the empirical evidence on the investment response to increased demand-side incentives. The top panel shows the number of new clinical trials per year for vaccines against each of the diseases affected by a change in policy.[19] I measure the beginning of a policy – denoted by the solid

[18] I do not include patents filed before 1976 since only the subset approved in 1976 or later are in the data.
[19] Although variants of the flu vaccine are developed each year, this does not require new clinical trials. A new clinical trial for a flu vaccine represents an attempt to develop a new inoculation mechanism that, if approved, will then be adapted annually based on that year's particular strain of the flu.

black line and the switch from gray to white background – as the first full year the policy was in effect.[20] For four of the six affected vaccines – pertussis, diphtheria-tetanus, hepatitis B and the flu vaccine – the data reveal a substantial increase, after the introduction of the policy, in the number of new vaccine clinical trials per year. There is no evidence, however, of an increase in new clinical trials for vaccines against the other two diseases –MMR and polio– associated with the policies.

For the four diseases for which the descriptive statistics suggest an investment response, two aspects of the response are worth noting. First, the increase in investment tends to occur after about a one-year lag following the introduction of the policy. This is consistent with industry opinion that it would take a year or two to translate a decision to engage in more clinical trials to translate into a new clinical trial (e.g. Sanyour interview). Second, the increase in investment persists through the latest years of available data.

5.2 Choosing appropriate control diseases

A central limitation to this time series analysis is that, as discussed above, the entire time period is one of increasing R&D. It is critical to distinguish any potential effect of the policies from the secular increase in new clinical trials that would have occurred without these policies. One approach – which I pursue in the formal empirical work below – is to estimate whether the policies are associated with a deviation from the trend for each affected disease in the number of new vaccine clinical trials per year. The other approach is a difference-in-differences approach. I use evidence from the number of new vaccine clinical trials per year for diseases that were not affected by the policies to try to control for other exogenous changes that may also have affected investment decisions. The primary candidate for confounding the effect of demand-side incentives is the investment effect of the technological advances the benefited vaccine development during the 1980s and 1990s.

The choice of appropriate control diseases is an important and difficult one. The key concern is to adequately control for other factors that may be affecting vaccine development, particularly exogenous changes in technology. The common technological basis for vaccines suggests the selection of a control

[20]In the case of the VICF, which was announced in 1986 but effective starting in 1988, I count 1987 as the first full year that the policy was "in effect" since this was the first full year in which it was anticipated. The results presented in subsequent sections are not sensitive to instead defining 1988 as the first full year that the VICF was in effect.

group from among vaccines against other infectious diseases not affected by the policies. However, the most inclusive possible control group – any other infectious disease in humans – would include a large number of diseases for which there were no vaccine clinical trials at any point in the data, such as anthrax, small-pox and leprosy. Since such diseases by definition experience *no* increase in the number of new clinical trials over the time period, their inclusion in a control group would bias the difference-in-differences estimates toward finding an effect of the policies.

I therefore use for the most inclusive control group all 26 unaffected diseases for which there was at least one new clinical trial during the 17 years of data. I call this the "any clinicals" control group. It includes a large number of diseases – such as lyme disease – for which there were no clinical trials in the first half of the data and whose development was made possible only by technological advances (Ellis 1999). The inclusion of such vaccines in the control group allows for a maximal possible role for technological change, a role that exceeds – at least in percentage terms – the effect of technological change on investment in the affected diseases.

One disadvantage of the "any clinicals" control group is that the included diseases are not necessarily well-matched to the affected diseases on characteristics that may be related to the rate of new vaccine clinical trials. In the empirical work, I can control for any fixed differences across affected and control diseases in the rate of new vaccine clinical trials. However, the difference-in-differences analysis will be contaminated if the affected and control diseases are on different trends in the number of new vaccine clinical trials per year.

I therefore define three alternative control groups that are strict subsets of the "any clinicals" control groups. These are designed to better match the affected diseases on characteristics that are potentially related to the trend in new vaccine clinical trials for that disease. Appendix B provides detailed information on each disease's characteristics and in which control groups it is included.

The "early clinicals" control group consists of the 7 diseases in "any clinicals" that had at least one new vaccine clinical trial in the pre-period (1983-1986) before any of the three policies. The average number of new clinical trials in the pre-period is substantially higher for this "early clinicals" group (0.32)

and better matches the treated group (0.46) than the "all clinicals" control group (0.09). The "early clinicals" group should therefore help alleviate the concern over the potential for bias in the difference-in-differences estimate that would arise if diseases with different rates of investment activity in early years were likely to experience different trends in growth in subsequent years. It also has the additional advantage over the "any clinicals" control group that it is selected based on the level of the dependent variable in the pre-period rather than over the entire sample.

The "prior approvals" control group is designed to match the treated diseases on their common characteristic that each has an approved vaccine in existence at the start of the time period studied. The "prior approvals" control group therefore consists of the 7 diseases in "any clinicals" that had a vaccine in existence prior to 1983. This should alleviate concerns about the potential for bias in the difference-in-differences estimate that would arise if diseases with existing vaccines experience different rates of investment growth than diseases for which vaccines do not exist.

Finally, the "technology" control group selects the diseases in "any clinicals" with high innate technological potential for further development at the start of the time period studied. In some regards, this may be the most important control group; the key concern with the difference-in-differences strategy is that estimates of the demand-induced investment will be biased upward if the treated diseases have systematically higher innate technological potential than the control diseases. Selection of diseases for the "technology" control group is based on an Institute of Medicine report (Institute of Medicine 1985a) that describes 14 diseases for which new or improved vaccines would have substantial health benefits in the United States and whose development is considered technologically feasible within the decade. I define the "technology" control group as the 9 diseases from this list that are not affected by the policies (3 of the diseases were) and had at least one new clinical trials during the period studied (this excludes another 2). This may underestimate the effect of the policies since only three of the affected diseases – pertussis, flu, and hepatitis B – are included in the Institute of Medicine's list. Whether the other three affected diseases are not included because they had low technological potential or because their development was not expected to convey substantial health benefits is unclear.

Table 2 provides summary statistics on the diseases included in each control group and in the treated group. It indicates that control diseases that match the treated diseases on one feature do not necessarily match on another. In addition, not all of the treated diseases themselves meet the criteria for eligibility in each of the three control groups that are subsets of "any clinicals." This suggests the development of an optimal weighting scheme for each treated and control disease based on the degree of matching across these various characteristics; I pursue this approach in the formal empirical work below.

The bottom half of Table 1 shows the trend in the number of new clinical trials per year for each of the four control groups. Consistent with the increases in vaccine R&D over this time period, all control groups show a slight upward trend in the mean number of new vaccine clinical trials per year.

Table 3 shows the change in the average number of new vaccine clinical trials per year after the introduction of the policy for each affected disease. The first column shows the simple "before and after" change. It indicates that, for each of the four diseases for which a response is observed, the policies are associated, on average, with about two new vaccine clinical trials per year. The other four columns show the basic difference-in-differences estimate of the change for the affected disease relative to each control group. Because of the slight upward trend in the average number of new clinical trials in each of the control groups, the difference-in-differences estimates are all slightly (about 0.2 new clinical trials) smaller than the simple (single) time differences. The difference-in-differences estimates are similar across the various choices for the control group.

I now develop the formal econometric framework for analyzing the effect of the policies.

5.3 Econometric framework

The unit of observation is a given disease in a given year. The main dependent variable ($Newtrials_{it}$) is the number of new vaccine clinical trials for disease i in year t. New clinical trials may be either for vaccines against individual diseases or for combination vaccines that provide immunization against multiple diseases; 20% of the new clinical projects started in the data are for combination vaccines. Since a combination vaccine has immunization value against all of the combined diseases, and since the firm chooses the diseases that make up the combination, I count a combination vaccine as a separate new

vaccine clinical trial for each disease in the combination. This introduces a potential difficulty in the difference-in-differences specification: if, for technological reasons, the treated diseases are most easily combined with control (treated) diseases, and the impact of the policies is to induce the development of combination versions of vaccines against the treated diseases, then the difference-in-difference estimation will underestimate (overestimate) the effect of the demand-side incentives.

In practice, the potential upward bias is likely to be small. It applies only to combinations that involve multiple diseases that are affected by a policy. I partially address the issue by grouping five of these affected diseases into two "disease categories" – measles, mumps and rubella (MMR), and diphtheria, tetanus (DT) – since vaccines against these diseases are almost always produced in these combinations. As a result, between 1983 and 1986, of the 10 new clinical trials against ultimately-affected diseases, only two involve combinations: one is a combination among two ultimately-treated vaccines (DT and pertussis), while the other involves a combination of an ultimately-treated vaccine and a control vaccine (MMR and chicken pox). In addition, in section seven, I look separately at the effect of the policies on new clinical trials for solo vaccines (i.e. vaccines that immunize against only one disease) and continue to find evidence of an investment effect of the policies there.

I pursue two empirical strategies: deviations from disease-specific trends, and difference-in-differences. In the former approach, I limit the sample to the six affected diseases and estimate:

$$\text{Newtrials}_{it} = \alpha_i + \gamma_t + \sum_i \beta_i * \text{year}_t + \lambda \text{ADOPT}_{it} + \varepsilon_{it} \qquad (1)$$

α_i is a disease-specific fixed effect; it controls for any differences in the mean level of new clinical trials across different affected diseases. γ_t is a year fixed effect; it controls flexibly for any secular trend in new vaccine clinical trials that is common to all of the affected diseases. Year_t measures the calendar year; β_i therefore allows for a disease-specific linear trend in the number of new clinical trials per year.

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 the affected diseases associated with the policies, after controlling for fixed differences across diseases and common year-to-year changes in the average number of new clinical trials, as well as a disease-specific linear trend in the number of new clinical trials; in the sensitivity analysis below, I add a disease-specific quadratic trend to the controls. The primary drawback to this approach is that it assumes a functional form for the trend in new clinical trials for vaccines against each disease. This trend must be estimated off of 4 to 11 years of pre-data, depending on the policy.

In the difference-in-differences approach, I instead estimate the following equation on a combined sample of affected diseases and the chosen control diseases:

$$\text{Newtrials}_{it} = \alpha_i + \gamma_t + \lambda \text{ADOPT}_{it} + \varepsilon_{it} \qquad (2)$$

λ now measures the 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. In the sensitivity analysis below, I add in controls for disease-specific linear and quadratic trends in equation (2).

A causal interpretation of λ in equation (2) relies on the identifying assumption that, absent the policies, the affected and control diseases would have had similar trends in the number of new vaccine clinical trials. Each alternative definition of the control group described above represents an attempt to construct a set of control diseases that match the treated diseases on a characteristic that may be related to the trend in new vaccine clinical trials. In the empirical work below, I also conduct a partial test of the identifying assumption by looking at whether the affected and control diseases had similar trends in the number of new vaccine clinical trials in periods prior to the implementation of the policy.

Since there are several alternative possible definitions of the control group, I pursue two approaches to defining the control group. One approach is to estimate equation (2) separately for each definition of the control group. This produces separate difference-in-differences estimates based on each control group.

The other approach is to estimate a weighted version of equation (2) with the weights on the various treatment and control diseases chosen to give more weight to treatment and control diseases that are likely

to have had similar trends in the dependent variable absent the policy intervention. With sufficient data prior to the enactment of the policies, I would estimate the relationship between the three characteristics used to refine the definition of the control group – new clinical trials in the pre-period, prior approvals, and technological potential – and trends in the dependent variable, and use this relationship to form a weighted control group that matches the treated group's pre-treatment trend in the dependent variable, as in Abadie and Gardeazabal (2001). Lacking sufficient data to implement this approach, I instead base the weights on each disease's propensity score (p_i) for inclusion in the treatment group. The propensity score indicates the probability that a given disease is included in the treatment group. It is predicted using the coefficients from the following regression:

$$\text{Treated}_i = \beta_1 \text{EarlyClinicals}_i + \beta_2 \text{PriorApprovals}_i + \beta_3 \text{Technology}_i + \varepsilon_i \quad (3)$$

where "Treated" is an indicator variable for whether the disease is ultimately-treated and the regressors are indicator variables for whether the disease meets the criteria for inclusion in each of the three control groups.[21] The propensity score is higher on average for the treated diseases than for the control diseases (0.56 vs. 0.14), but there is substantial overlap in their distribution; two-thirds of the treated diseases have propensity scores within the range of propensity scores for the control diseases. In estimating equation (2), each treated vaccine is weighted by $\frac{1}{p_i}$, and each control vaccine is weighted by $\frac{1}{1-p_i}$. Thus control diseases are given more weight if they have higher propensity scores (i.e. are more similar to the treated diseases), while treated diseases are given more weight if they have lower propensity scores (i.e. are more similar to the control diseases).[22]

A potential concern with the difference-in-differences strategy is that the induced new vaccine investment in the treated diseases may occur at the expense of vaccine investment that would otherwise

[21] I estimate the propensity scores using a linear probability model; the 19 diseases that are not treated and have no prior approvals have negative predicted propensity scores, which I re-assign to zero. The results from a propensity-score weighted estimation of equation (2) are similar if the propensity scores are instead estimated using a logit model and these 19 diseases – which are dropped from the logit estimation – are assigned a propensity score of zero. They are also similar if the propensity scores are estimated with the indicator variable "early clinicals" replaced by the actual number of new clinical trials between 1983 and 1986.

[22] See Hirano et al. (2000) for a description of this approach to propensity score weighting.

have occurred in the control diseases. Such crowd-out not only undermines the validity of the control strategy, but also affects the substantive interpretation of the results; in the limit, 100% crowd-out would suggest that the net effect of these policies was on the *direction* but not the overall *rate* of investment in R&D in the vaccine industry.

Three factors, however, mitigate against the likelihood of substantial crowd-out. First, in the capital-rich pharmaceutical industry, the key reason to suspect crowd-out would be from an inelastic supply of scientists or doctors in the short run (see e.g. Goolsbee 1998). However, increased numbers of new clinical trials primarily require an increase in financing and the supply of more human subjects, rather than an increase in doctors to run the trials. Second, doctors who conduct clinical trials may work on a given disease – or physiological mechanism – rather than focus exclusively on vaccines. The potential crowd-out of investment would thus apply to investment in all pharmaceutical products, of which investment in vaccine development represents less than 4% (PhRMA 2001). Third, while I cannot directly test the counter-factual of what investment in the controls would have been in the absence of the policies, two empirical facts are not suggestive of crowd-out: Table 1 shows an *upward* trend in the number of new vaccine clinical trials for the control diseases, and I find no evidence of substantively or statistically significant structural breaks in a linear or quadratic trend in the number of new vaccine clinical trials for control diseases associated with the introduction of the first policy, the VICF, which affected four of the six affected diseases.

The estimation approach is determined by the panel nature of the data, the sample size, and the distribution of the dependent variable, which ranges from 0-7.[23] I therefore estimate equations (1) and (2) using both a linear and a non-linear fixed effects model. The linear model's primary attraction is its small sample properties (namely, unbiasedness) and its consistency, regardless of the true distribution of the error term. The count nature of the dependent variable, however, suggests potential efficiency gains from the use of the conditional negative binomial fixed effects model introduced by Hausman, Hall and Griliches (1984). The limitation to this non-linear model is whether the sample size is sufficient for

[23] Depending on the sample, 56 to 73 percent of the observations are zero, and 80 to 89 percent are zero or one.

asymptotic inference; the data consist of a 17-year panel on between 6 and 32 different diseases, depending on the sample definition.[24]

To account for possible serial correlation over time in the number of new clinical trials for a given disease, I adjust the standard errors following the randomized inference approach described by Bertrand, Duflo and Mullainathan (2002). Specifically, I remove the six treated diseases from the sample, and from the remaining sample of control diseases, I draw at random from a uniform distribution six different diseases and designate them as "treated diseases." I then randomly draw three different years between 1985 and 1997; four of the "treated diseases" are assigned one of these years as the year in which their treatment began and the other two "treated diseases" are assigned each of the other two selected years.[25] I then re-estimate λ based on these assignments.[26] I repeat this 200 times and calculate the p-value for my original estimate of λ by comparing it to the empirical distribution of estimates of λ when treatment status is randomly assigned. For each regression, I report this "adjusted" p-value, in addition to the unadjusted standard error, and corresponding unadjusted p-value.[27] In general, the adjusted and unadjusted p-values are very similar.

6. Evidence of the basic investment response: new clinical trials and approvals

6.1 Results for new clinical trials

Table 4 reports the results from estimating equations (1) and (2). It shows a striking uniformity in

[24] Another potential concern with the non-linear model is that although I condition out the disease fixed effects, the inclusion of 17 separate year fixed effects may re-introduce the incidental parameters problem and thus produce inconsistent estimates. To investigate this issue, I tried replacing the year fixed effects in equations (1) and (2) with biannual fixed effects, and I also experimented with aggregating the data up to the biannual-disease level rather than the year-disease level. (With 17 years of data, one of the "biannual" time periods actually encompasses three years -- 1989, 1990, and 1991.) None of the results was sensitive to either the coarser time grouping or the data aggregation, which alleviated concerns about an incidental parameters problem in the non-linear model.

[25] The choice of six treated diseases with four affected in the same year and two affected in two different years mimics the timing and scope of the actual policies studied. I restrict the potential policy years to 1985-1997 to ensure a minimum of two years pre and post each possible policy.

[26] For equation (1), I use the full sample of control vaccines ("any clinicals") to randomly select six treated diseases; the results are not sensitive to this choice. For the propensity-score matching approach, I re-estimate the propensity scores for each random assignment of treated and control diseases.

[27] Because I perform only 200 random draws, I report unadjusted and adjusted p-values rounded to the nearest 0.01.

both magnitude and statistical significance across the eleven reported specifications.[28] The five linear estimates suggest that the policies are associated, on average, 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. Four out of the five negative binomial estimates are statistically significant at at least the five percent level; they suggest that the policies are associated with 1.9 to 3.1 times more new vaccine clinical trials per year per affected disease. The estimated proportional effect of the policies is therefore quite similar in the linear and in the negative binomial specification, even though the latter estimates a constant proportional effect of the policy while the latter estimates a constant level effect of the ADOPT variable.[29]

One way to gauge the magnitude of the estimated effect of the policies is to note that the linear estimate of 1.2 new vaccine clinical trials per affected vaccine-year implies that the policies induced 60% of the new investment in the affected diseases over the 17-year period, and 70% of the investment in affected diseases in years in which the policies were in place. More broadly, the identified demand-side incentives alone accounted for one-third of the total new vaccine clinical trials for *any* disease during the entire 17-year period.[30]

These results speak to the average investment response. I also examined whether the investment response to the risk-reducing Vaccine Injury Compensation Fund was different than the response to the market-expanding hepatitis B and flu policies. Both types of policies were separately associated with a statistically significant increase in the number of new clinical trials. However, the investment response to

[28] Results from estimating equation (1) are reported only for the linear fixed effects model. Asymptotic inference (required for interpretation of the results of the negative binomial model) is likely to be problematic when the sample consists of only six different diseases, and the model requires estimation of 17 year fixed effects and six disease-specific linear trends. In practice, however, estimating equation (1) with the conditional negative fixed effects binomial model produces estimates that are positive and statistically significant.

[29] In results not reported here, I also examined whether the policies were associated with a change in whether there are *any* new clinical trials in a given year for a given disease. I find consistent evidence of a positive effect on this extensive margin in both a linear fixed effects and a conditional fixed effects logit model, although the statistical significance of the results in the logit model is sensitive to the choice of control group.

[30] There were 66 disease-years affected by a policy, implying 79.2 (i.e. 1.2*66) clinical trials induced by the policy. This compares to a total of 114 new trials during these affected disease-years, 131 new trials for the affected diseases over the entire 17-year period, and 260 new clinical trials for any diseases over the entire 17-year period.

the Vaccine Injury Compensation Fund (0.77 to 0.84 new clinical trials per year per affected disease) was roughly half of the response to the market-expanding policies (1.6 to 1.8 new clinical trials).

In addition, I enriched equation (2) to look more carefully at the time pattern of the estimated effect of the policies. I replaced the single ADOPT indicator variable in equation (2) with a series of mutually exclusive indicator variables for different periods relative to the implementation of the policies:

$$\begin{aligned}\text{Newtrials}_{it} = {} & \alpha_i + \gamma_t + \lambda_1 \text{ADOPT}_{it,(-7+)} + \lambda_2 \text{ADOPT}_{it,(-6\text{ to }-4)} + \lambda_3 \text{ADOPT}_{it,(1\text{ to }3)} \\ & + \lambda_4 \text{ADOPT}_{it,(4\text{ to }6)} + \lambda_5 \text{ADOPT}_{it,(7+)} + \varepsilon_{it}\end{aligned} \tag{4}$$

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.[31] The omitted reference category is 1 to 3 years prior to the policy.

Figure 3 shows the estimation results using the linear fixed effects model and the "any clinicals" control group.[32] The figure graphs the pattern of λ coefficients. Since these coefficients identify only changes in the dependent variable relative to the omitted category, I normalize the level of the dependent variable to its mean for the affected diseases in the 1 to 3 years prior to the policy (the omitted category). The dotted lines represent the 95 percent confidence intervals for these coefficients, based on the unadjusted standard errors.[33]

Two important results emerge from this analysis. First, there is little 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 (after controlling for disease-specific fixed effects and common year effects). This is supportive of the identifying assumption that, absent the policies, affected and

[31] Depending on the policy, there are 4 to 11 years of data prior to the policy and 6 to 13 years of the policy in effect. I do not look more finely than these three-year groupings to preserve the power of the statistical tests.
[32] To conserve space, I do not report the results from the other three control groups or the propensity-score weighting; they are all similar. Results for the negative binomial also look similar, except for when the "any clinicals" control group is used where, as in Table 4, the results are no longer statistically significant.
[33] The adjusted and unadjusted p-values (not shown) are comparable to each other and indicate that there are no significant changes in the number of new clinical trials for the treated diseases relative to the control diseases between the 1 to 3 years prior to policy adoption and either of the other two periods prior to policy adoption. By contrast, the increase in vaccine clinical trials for treated diseases relative to control diseases in each of the three different periods *after* policy adoption relative to the 1 to 3 years prior to policy adoption is statistically significant at the 1 percent level.

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 themselves endogenous to increasing investment activity in the affected diseases. Re-estimation of equation (4) with the number of new pre-clinical trials or the number of new patent filings as the dependent variable also provides no evidence of increases in either activity relative to the control diseases in periods prior to the policy adoption. This further suggests that the policies were not endogenous to increasing investment activity or perceived technological potential among the affected diseases.

Second, consistent with the descriptive results in Table 1, the econometric results indicate that the effect of the policies persists throughout the time period that I observe. This suggests that the induced increase in clinical trials represents induced investment in technologies that would otherwise not have been economically attractive to develop, rather than merely a movement forward in time of the start of planned investment. The policies thus appear to have changed the stock of future technology, rather than simply the timing of its development.

The persistence of the increased investment response also points to the existence of a large reservoir of new technologies – at least for vaccines – that are technically feasible but marginally not economically feasible. That technologically feasible vaccines are not always developed is, of course, well-known (see e.g. Institute of Medicine 1985a and 1985b). What has not been known, and what the results in this paper suggest, is that the decision of whether to invest in developing these vaccines is responsive, on the margin, to policies that increase the return on such investment.

6.2 Sensitivity analysis

I explored the sensitivity of the core empirical results in Table 4 to a variety of alternative estimation approaches. Here, I briefly discuss three of the more important sensitivity tests.

First, I relaxed the identifying assumption in equation (2) that, absent the policies, the treated diseases would have had the same trend in the number of new vaccine clinical trials as the control diseases. Specifically, I added disease-specific linear trends or disease-specific quadratic trends to the estimating

equation. The results are reported in Table 5 for the linear fixed effects model.[34] All of the results remain significant at at least the 5% level, although the estimated magnitude of the effect of the policies declines somewhat in the difference-in-differences specifications from 1.2-1.3 to 0.81-1.0.

Second, I considered the sensitivity of the estimates to alternative ways of accounting for a 1997 change in the Vaccine Injury Compensation Fund; the set of indemnified products was expanded to include the three vaccines that had been added to the childhood immunization schedule in the intervening years and to specify that in the future, any vaccine added to the recommended childhood immunization schedule would be *automatically* covered by the VICF (Kitch et al. 1999). At the time of the original law, however, future additions were not obviously anticipated (e.g. Piron interview; Kitch et al. 1999). Because the childhood immunization schedule is increasingly likely to include non-childhood diseases,[35] this 1997 policy change did not meet the criteria for policy selection that the policy affect only a limited class of diseases, and was therefore not included among the policies studied in the main analysis.

However, to test the sensitivity of my results to this approach, I re-estimated equations (1) and (2) on a sample that excluded 1998 and 1999, the years when this "new policy" was in effect. All of the above results were robust to this restriction, although the magnitude of the estimated policy effect declined slightly; for example, the linear estimates on this restricted sample indicate a 0.91 to 0.98 increase in new vaccine clinical trials associated with the policy. An alternative approach is to view the 1997 law change as an additional policy (or "reverse experiment") that affected all diseases *except* for the four diseases already covered by the VICF. Once again, the core results were insensitive to this alternative approach; I do not adopt it as the primary specification however, because the availability of control diseases for this "reverse experiment" is limited to these four previously-covered diseases which do not necessarily match the affected diseases on the characteristics that may relate to the trend in new vaccine clinical trials.

[34] Once again, I do not report results from the negative binomial model since the inclusion of additional covariates (one or two per each disease in the sample) exacerbates the potential problem of asymptotic inference in this small sample setting. In practice, the results of the negative binomial model are not sensitive to the inclusion of disease-specific linear trends but, for some definitions of the control group, are not robust to the inclusion of disease-specific quadratic trends.

[35] See e.g. http://www.vaccine.chop.edu/schedule.shtml

Finally, I examined the potential for bias in the estimated effect of the policies if there were other demand-side changes that differentially affected demand for vaccines against the treated and control diseases.[36] In particular, five of the affected diseases are primarily children's diseases while the remaining affected disease (the flu) is primarily a (serious) disease of the elderly. If there were other demand-side changes that generally affected the demand for vaccines against childhood diseases or against diseases for the elderly, the estimated effect of the policies could be biased by the inclusion of non-childhood or non-elderly diseases among the controls.[37]

To investigate these issues, I re-estimate two different versions of equation (2). In one case, I restrict the sample to the affected flu disease and the control pneumonia disease. I chose pneumonia since it is the only other vaccine routinely recommended for the elderly; it is covered by Medicare throughout the time period of the data. In the other case, I restrict the sample to the five affected childhood diseases and other, unaffected, childhood diseases.[38] Once again, the estimated effect of the policy was not sensitive in either magnitude or statistical significance to these alternative definitions of the control group.[39]

6.3 Suggestive evidence on approvals

I briefly explore whether the policies are also associated with an expansion of the available product space, as measured by vaccine approvals. Two factors make this analysis more difficult than the analysis of the policies' effect on new clinical trials: approvals are a much rarer event than new clinical trials, and,

[36] To the extent that the demand-side changes are slow moving, smooth changes in the demand for particular diseases, they may have been adequately captured by the inclusion of disease-specific linear or quadratic trends in the difference-in-differences analysis (see Table 5).

[37] For example, the general aging of the population may have increased incentives to develop vaccines for the elderly. Similarly, it is possible that the introduction of the 1994 Vaccines For Children Program (a federal program that expanded children's eligibility for public vaccine coverage) may have affected incentives to develop childhood vaccines. Conversations with people in the industry suggest that the effect of the Vaccines for Children Program on demand-side incentives was unclear (Kaye interview, Piron interview, Manning interview). The program expanded efforts to immunize children but also increased the government share of childhood vaccine purchases and changed the mechanism by which public prices were set.

[38] The exact definition of "childhood diseases" is not clear. I experiment with a variety of choices such as all other diseases that were added to the childhood immunization schedule during the time period studied (HIB, chicken pox, and rotavirus), and all non-affected diseases considered by Mercer (1995) to be childhood diseases with existing vaccines (tuberculosis, HIB, hepatitis A, and chicken pox). The results are not sensitive to the definition.

[39] An exception is the estimate from the negative binomial model when only the flu and pneumonia are in the sample; the point estimate on ADOPT is similar to those in Table 4 but is not statistically significant. This may reflect the difficulty in using asymptotic inference with only two diseases in the sample.

given the average of 7 to 8 years from the start of a new vaccine clinical trial until approval (Struck 1996), any effect of the policies on approvals is expected to occur with a substantial lag. The results in this section are therefore necessarily more speculative in nature than the evidence on new clinical trials.

The dependent variable is now $NewApprovals_{it}$, the number of new vaccine approvals in year t for disease i. I use 18 years (1982-1999) of vaccine approval data. Because of the likely 7 to 8 year lag between the implementation of a policy and any increase in approvals, I estimate a modified version of equations (1) and (2) 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 results for the linear model are reported in Table 6. They show 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. The fact that the increase in vaccine approvals does not show up before 7 or more years after the policy – even in finer cuts of the first one to six years – may suggest that companies do not, in response to the increased demand-side incentives, devote substantially more resources per year to the clinical trial, which might be expected to speed up development times above the 7 to 8 year average. Since there are only six years of data after the introduction of the flu policy, this policy does not contribute to identifying the coefficient on $ADOPT_{7+}$; I ascertained that the results in Table 6 are not sensitive to excluding the flu vaccine from the sample. They are also not sensitive to making the dependent variable a binary measure of any new approvals for that disease in that year. However, there is no evidence of a statistically significant increase in approvals in the negative binomial model (not shown).

The above results speak to the number of vaccines approved; it is also interesting to consider whether the induced clinical trials enjoy a higher or lower approval *rate* than average. The theory yields ambiguous predictions. On the one hand, the increased return from developing a product suggests that firms should be willing to invest more in the success of the project. On the other hand, the increased return may have induced the start of marginally less successful projects. Given an average approval rate

for new vaccine clinical trials of 0.4 (Struck 1996), the induced 1.2 to 1.3 new vaccine clinical trials per year per affected disease should be expected to produce, if there are no other changes, about 0.5 new vaccine approvals per year per affected disease. We cannot reject the hypothesis that the estimated coefficients on $ADOPT_{7+}$ in Table 6 – which range from 0.31 to 0.46 – are equal to 0.5.[40]

7. Which investment margins are responsive?

The results in the previous section established the principal finding that investment in vaccine development responds to policies that increase the return on such investment. In this section, I employ two different approaches to gauging the extent to which the induced investment represents an extension of the technological frontier. First, I exploit the distinction between solo vaccines, which provide immunization against a single disease, and combination vaccines, which provide immunization against multiple diseases. The development of either type of vaccine can have important public health benefits.[41] 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. In contrast, combination vaccines are more likely to repackage technologies already used individually for immunizing against individual diseases into a single administration. Combination vaccines, often referred to within the industry as "mix and match", are also considered to be cheaper and lower risk to develop (see e.g. Greenberg interview, Wolters interview).

I re-estimate equations (1) and (2) on two separate dependent variables: the number of new solo vaccine clinical trials in year *t* for disease *i*, and the number of new combination vaccine clinical trials in year *t* for disease *i*. In results not reported here, I find that the policies are associated with statistically significant increases in the number of each type of new vaccine clinical trial; the increase in new solo vaccine clinical trials represent about one-third to two-fifths of the combined increase in solo and

[40] Unfortunately, the data are not well suited to a more rigorous failure rate analysis. It is difficult to estimate a failure rate in the pre-period, given the small size of the risk set. In addition, the presence of two negatively correlated risks (stopping a project and approving a project) makes application of standard competing risks frameworks, which assume independence of the competing risks, problematic.

[41] Combination vaccines can deliver substantial public health benefits by reducing the number of shots and doctor visits needed for immunization and hence increasing compliance with the vaccination schedule (Decker and Edwards 1999, American Academy of Family Physicians, 2000).

combination vaccine clinical trials. This suggests that at least a non-trivial proportion of the investment response represents attempts to commercialize previously unused vaccine technologies.

Second, I investigate whether there is an investment response to demand-side incentives at two earlier stages of the R&D pipeline than clinical trials: the decision to start new pre-clinical trials and the filing of ultimately successful patent applications. Investments in such earlier stages represent attempts to develop fundamentally new technologies; investments in new clinical trials, by contrast, represent attempts to commercialize existing technologies. As with new clinical trials, there is a general increase in these R&D activities over the time period.

There are two reasons to expect less of an investment response on these earlier margins. First, the uncertainty about future health policy may be more of a deterrent, given the longer lags between investment in these earlier stages of R&D and product licensure. Second, a much higher proportion of the actors involved in patentable research are in the non-profit rather than for-profit sector, and we might expect their investment decisions to be less responsive to changes in financial incentives. On the other hand, if there is more of a reserve of technologically-feasible but not-quite-economically-attractive ideas that could produce new patents or new pre-clinical trials than there is for new clinical trials, there could be a larger investment response on these earlier margins.

I re-estimate equations (1) and (2) with two different dependent variables: the number of new pre-clinical trials in year t for vaccines against disease i, and the number of new patents filed in year t for vaccines against disease i. For the difference-in-differences specification, I use, for consistency, the same groups of control diseases used for the analysis of new clinical trials.[42] As with new clinical trials, the average number of new pre-clinical trials or new patent filings is substantially higher for the ultimately-affected diseases in the pre-period than for the "any clinicals" control group, and this disparity is substantially reduced with the use of the "early clinicals" control group.

[42] The results are not sensitive to alternative definitions of the control diseases based on pre-clinical or patent activity. For example, defining the most inclusive control group (the analog of "any clinicals") to include dengue fever and rheumatoid arthritis – which had pre-clinical but not clinical trials during the data – and to exclude yellow fever – which had clinical but not pre-clinical trials– does not affect the estimates in this section or in section six.

Tables 7 and 8 report the results for new pre-clinical trials and new patent filings respectively. Since only 60% of the patent filings are made by for-profit companies – compared to more than 99% of the new pre-clinical and clinical trials in The NDA Pipeline data – Table 8 reports the effect of the policies on new patent filings separately for for-profit companies and non-profit entities.[43] The results do not suggest evidence of a substantively or statistically significant change in either investment activity. The estimates tend to be small in magnitude, and to have the opposite sign in the linear and negative binomial estimates.

The results are not sensitive to the alternative specifications described in detail in the sensitivity analysis in section six. Since the filing date of an ultimately successful patent may only capture with a lag any increase in investment in patentable processes, I also experimented with a variety of different ways of grouping the time periods after the policies had gone into effect. However, I was still unable to detect an effect of the policies, even after 10 or more years.

Issues with the data suggest that the results in Tables 7 and 8 should be interpreted with some caution. As discussed, the data on new pre-clinical trials are probably less comprehensive than the data on new clinical trials. And although the patent data are extremely accurate, they capture only a limited fraction of the basic research relevant for vaccines, since patent protection is less important for vaccines than for other pharmaceuticals.[44]

Nevertheless, the results suggest that we cannot reject the null hypothesis that there was no change in pre-clinical or patent investment associated with the increase in demand-side incentives. The point estimates from the negative binomial model are noisy, producing large confidence intervals. For the linear model, however, the difference-in-differences estimates indicate that across all of the various specifications and sample definitions, we can reject a decline in patent or pre-clinical activity or more than –0.2 trials (or filings) per year per affected disease. Across all the specifications and samples, we can also always reject an increase of more than 0.7 new trials (or filings) per year per affected disease (and

[43] I include the 6% of patent filings that were joint filings by for-profit and non-profit entities in the for-profit sample and exclude them from the non-profit sample; the results are not sensitive to this choice.

[44] Even without official patent protection it is often difficult to obtain a key component of the intellectual property in vaccine development: the exact process used to produce the immunizing agent (Sanyour interview). The lack of generic competition underscores this point.

sometimes an increase of more than 0.3), which is considerably lower than the *point* estimate of an increase of 1.2 to 1.3 new vaccine clinical trials associated with the policies.

The lack of strong evidence of a *decline* in these investment activities suggests that the increased investment in new clinical trials was probably not financed by a substitution away from investment in earlier stages of the R&D pipeline. The increase in new clinical trials associated with the policies therefore appears to represent a net increase in total investment.

The lack of any compelling evidence of *increased* investment in these earlier stages in the R&D pipeline suggests that the investment response may have been limited to commercializing existing – if previously unused – technologies, rather than to creating fundamentally new technologies. An unanswered question is whether larger economic incentives would generate a positive response on these earlier margins. If not, there might be a limit to the ability to sustain a long-run increase in new clinical trials in response to demand-side incentives. This depends on whether the baseline flow of new pre-clinical and patent activity (see e.g. Figure 2) is sufficiently high to maintain a stock of unused technologies available for new clinical trials, or whether the increase in new clinical trials associated with the policies would ultimately deplete this stock.

It is also worth emphasizing that the lack of any observed increased activity at these earlier stages is consistent with the evidence of an immediate and prolonged increase in vaccine clinical trials associated with the policies. Conversations with individuals in the pharmaceutical industry indicate that vaccine projects are routinely shelved after pre-clinical trials because the results indicate that the product is not commercially viable. There exists, therefore, a stock of products that can be re-evaluated and launched into clinical trials should the financial incentives change.[45]

8. Interpreting the magnitude of the investment response

The detectable investment response therefore appears to be on the decision to start new clinical trials. In this section, I present two alternative approaches to interpreting the magnitude of this response. Several

[45] For example, it may be discovered during pre-clinical trials that the product is less efficacious than originally thought, that a competitor has competitor has made progress on developing a competing product, or that the cost of producing the product in the form needed to be efficacious is greater than originally envisioned.

additional assumptions are required to parameterize the magnitude of the increase in demand-side incentives and the increase in investment. The results should therefore be viewed as more speculative in nature, but hopefully more interpretable as well, than the core empirical estimates in section six.

8.1 The monetary cost of stimulating investment through demand-side incentives

By making assumptions about the costs of vaccine clinical trials and the increase in expected market revenue associated with each policy, I can use the empirical framework to estimate the monetary investment stimulus per dollar increase in the expected market revenue for vaccines against a particular disease.[46] I estimate a modified version of equation (2) as follows:

$$\text{Spending}_{\text{it}} = \alpha_i + \gamma_t + \lambda(\Delta\text{ExpMktRev})_{\text{it}} + \varepsilon_{it} \qquad (5)$$

The new dependent variable $Spending_{it}$ is now the implied present discounted value of spending (in millions of 1999 dollars) associated with the number of new clinical trials started in year t for vaccines against disease i. DiMasi et al. (1991) estimate the average expected present discounted value of the cost of a new pharmaceutical clinical trial at $16.2 million.[47] Since there are no available cost estimates specific to vaccine clinical trials, I use these estimates from the industry as a whole; reassuringly, on the one development input – the average length of clinical trials –where comparison is possible, vaccines match the overall industry quite closely (Struck 1996; DiMasi et al. (1991), OTA (1993)). $Spending_{it}$ is therefore \$16.2* $Newtrials_{it}$.

Equation (5) substitutes the indicator variable ADOPT_{it} in equation (2) with $\Delta\text{ExpMktRev}_{\text{it}}$. $\Delta\text{ExpMktRev}_{\text{it}}$ denotes the change in expected annual market revenue associated with the policy (in millions of 1999 dollars). It is coded zero for disease-years in which a policy is not in effect. In estimating the expected increase in market revenue, I must limit the analysis to the market-expanding hepatitis B and flu policies. Inclusion of the Vaccine Injury Compensation Fund in the analysis makes interpretation of a meaningful magnitude more difficult, since, as discussed, it increased demand-side incentives by a different mechanism that market-expansion, namely the reduction of the mean and

[46] With close-to-zero marginal costs, the increase in expected revenue may proxy the increase in expected profits.
[47] Author's update of DiMasi et al's (1991) estimates in 1987 dollars to 1999 dollars using the CPI-U.

variance of product liability costs. Moreover, in practice, there is little systematic evidence with which to gauge the magnitude of the expected change in the mean or variance of liability costs. As a result, I exclude the four diseases affected by the VICF from the sample when estimating equation (5); the core empirical results shown thus far are not sensitive to this exclusion.

The expected change in market revenue associated with the policies depends on the expected change in market vaccination rate and the expected revenue per person vaccinated. I estimate the expected per-person revenue from vaccine using information on 1999 vaccination rates (see Appendix A) and 1999 market revenue for each vaccine (Merck 2000).[48] Estimates of the expected increase in market vaccination rates associated with the policies are based on vaccination rates at the time of the policies and interviews with people in the pharmaceutical industry on the expected vaccination rate after policy implementation; Appendix A provides more detail. These calculations imply that, in 1999 dollars, the hepatitis B recommendation increased expected annual market revenue by $518 million, while the flu policy increased expected market annual revenue by $98 million.[49] The advantage of using ΔExpMktRev instead of ADOPT as the key right hand side variable is that the former takes account of the marked differences in the policies' impact on expected market size.

The results from estimating equation (5) with a linear fixed effects model are shown in Table 9. The estimated coefficient on $\Delta ExpMktRev_{it}$ is statistically significant at the 1 percent level and robust in magnitude across specifications. Table 9 indicates that for every $1 permanent increase in the expected annual market revenue from vaccines against a particular disease, the pharmaceutical industry will spend an additional 5 to 6 cents annually in present discounted value on R&D for vaccines against that disease. By contrast, estimates of the investment response to more traditional supply-side subsidies such as R&D

[48] This assumes that revenue per-person vaccinated in 1999 was consistent with expectations at the time of the policies' introduction of the post-policy revenue per-person vaccinated. Unfortunately, there are no available estimates of market revenue for particular vaccines prior to the policies.

[49] The inputs to this calculation are as follows: For flu and hepatitis B, respectively, annual market revenue in 1999 was $480 million and $149, and vaccination rates were 0.88 and 0.67. At the time of each policy's implementation, flu and hepatitis B vaccination rates were 0.51 and 0 respectively. The pharmaceutical industry expected both policies to produce "complete" immunization of the target population. Given the self-limiting nature of vaccine demand (Geoffard and Philipson 1997), however, "complete" vaccination may not be a 100% vaccination rates; I use a 0.95 vaccination rate as a realistic achievable upper bound on vaccination rates (Institute of Medicine 1985a). See Merck (2000) and Appendix A for more information on the inputs and their sources.

tax subsidies or direct public spending suggest that a dollar spent in this manner produces between a dollar and a dollar and seven cents of increased R&D spending.[50] The induced investment response to demand-side incentives is thus an order of magnitude lower than that from supply-side subsidies to R&D.

In a simple model of deterministic investment with one investor whose successful product captures the entire market, the investment level is chosen so that the marginal revenue from investment equals the marginal cost of investment;[51] in this situation, a dollar increase in market revenue would be expected to generate an additional dollar of investment. Since, in fact, new vaccine clinical trials enjoy only a 40% approval rate (Struck 1996), this would lower the expected investment response to 40 cents per dollar of increased market revenue. I estimate a response of about one-eighth this size. One reason may be that the inventor of a successful vaccine does not, in fact, capture the entire market; for example, in 1999, there were three active products of varying vintages on the U.S. hepatitis B vaccine market and four on the flu vaccine market (Merck 2000). In addition, uncertainty about future health policy – and hence future vaccine revenue – would further depress the investment response for risk averse investors.

8.2 Static vs. dynamic health consequences of health policy

The results thus far have suggested substantial increases in inventive activity associated with policies whose primary purpose was to increase utilization of the existing medical technology. This section provides a back of the envelope comparison of the health benefits from the increased utilization of the existing technology induced by the policies ("static" consequences) to the expected health benefits from the induced investment in developing improved versions of the existing vaccine ("dynamic" consequences).

I again limit the analysis to the hepatitis B and flu policies, since it is possible to estimate the increase in vaccination (the key static benefit) associated with each of these policies. The Vaccine Injury Compensation Fund, however, was a pre-emptive attempt to prevent expected shortages – or eliminations – of vaccine supply; how great these shortages might have been is extremely difficult to say.

[50] See Hall (1996) and Hall and Reenan (2000) for surveys of the empirical evidence.
[51] This assumes that investment is a continuous variable, rather than their being discrete projects with fixed costs.

The calculation assumes that the induced investment is socially beneficial. The preponderance of empirical evidence suggests that, on average, the social returns to R&D greatly exceed the private returns (see e.g. Griliches (1992) or Jones and Williams (1998)); this seems particularly compelling for vaccine development given vaccines' substantial positive health externalities. Nevertheless, it is possible that some of the *marginal* investment induced by the policies represent attempts at business stealing that contain little social value. For example, Table 1 indicates high levels of new investment in both hepatitis B and flu vaccines as late as 1999. By this point, the Institute of Medicine (2001) judged their to be potential for substantial domestic health benefits from improved versions of the flu vaccine, but not from further improvements to the hepatitis B vaccine. To be conservative, therefore, I will assume that there were no potential dynamic health benefits from the induced investment in the hepatitis B vaccine.[52]

The formula for the ratio of dynamic to static benefits is given by the following equation:

$$\frac{\text{Dynamic Benefits}}{\text{Static Benefits}} = \frac{\left((V_D * E_D) - (V_S * E_0)\right) * \left(\sum_{t=7}^{9} \frac{0.5}{(1+r)^t} + \sum_{10}^{\infty} \frac{1}{(1+r)^t}\right)}{\sum_{t=1}^{S} \frac{(V_t - V_0) * E_0}{(1+r)^t} + \sum_{t=S+1}^{\infty} \frac{(V_S - V_0) * E_0}{(1+r)^t}} \qquad (6)$$

V_t and E_t denote, respectively, the vaccination and efficacy rates in year *t*. The time subscripts 0, S, and D denote, respectively, the year prior to the policy enactment, the first year in which the full static benefits have been realized, and a year in which the full dynamic benefits have been realized. The real discount rate is denoted by *r*.

The static health benefits depend on the increase in vaccination rates associated with the policy $(V_S - V_0)$, the timing of this increase, the efficacy of the vaccine at disease prevention (E_0), and the health benefits from successful vaccination.[53] I make generous assumptions about the increase in vaccination rates associated with the two policies, assuming that the policies are responsible for all of the

[52] This is a conservative assumption since, in 1992, when the hepatitis B policy went into effect, there were probably still potential health benefits from improved hepatitis B vaccines. In particular, it was only after 1992 that the first hepatitis B vaccines without thimerosal, a preservative feared to cause neuro-developmental disorders (Stratton et al. 2001), were approved.

[53] The health benefits from successful vaccination do not appear in equation (6) since they are not needed to compute the *ratio* of dynamic to static benefits. Estimates, however, are available, in Institute of Medicine (1985a).

subsequent time series increase in vaccination rates.[54] I also assume that the high vaccination rates observed by the end of the available data will persist in the long-run, which seems reasonable since Appendix Figure A1 indicates that vaccination rates had flattened out in the last few observed years.

There are at least five different mechanisms by which increased investment might produce dynamic health benefits. These include: spillovers from one type of inventive effort to others (see e.g. Griliches (1992)), the development of vaccines with reduced side effects, the development of new vaccines with higher efficacy, increases in vaccination rates from increased willingness to use the improved vaccines, and increases in vaccination for unaffected diseases if the improved vaccines reduce the general fear of vaccines or are produced in combination with vaccines against other diseases (see e.g. Institute of Medicine (1985a)). Of these five potential dynamic benefits, I can find reasonable estimates for only two: increases in efficacy $(E_D - E_0)$ and increases in utilization for the affected diseases $(V_D - V_S)$. I therefore ignore the potential dynamic benefits accruing from the other three mechanisms.

As discussed, I assume that there are no potential dynamic health benefits from the induced investment in the hepatitis B vaccine.[55] I use the Institute of Medicine's (1985a) estimates of the expected increase in efficacy and increase in vaccination rate associated with the development of a new flu vaccine.[56] The Institute of Medicine (1985a) assumes that this improved flu vaccine could be developed within 4 to 6 years. However, the empirical evidence in Table 6 indicates that it was, on average, 7 years after a policy before new approvals occurred and that, beyond this point, a policy was associated with on average one new approved product every 3 years. To be conservative, I therefore assume that it takes 10 years (i.e. two approvals) for the full benefits to be realized and that each new product conveys 1/2 of the total benefits; these assumptions are incorporated into the numerator of equation (6), which assumes that

[54] As the data in Appendix Figure A1 indicate, this ignores the existence of a pre-existing upward trend in influenza vaccination rates for Medicare beneficiaries. It also ignores the possibility that some of the increases in the hepatitis B vaccination rate may have resulted from the approval of new hepatitis B vaccines in 1996 and 1999.

[55] The Institute of Medicine (1985a) indicates that benefits from an improved hepatitis B vaccine would come in the form of decreased side effects and increased utilization. There are no good estimates of the former, however, and vaccination rates by 1999 had already reached the level that the Institute of Medicine deemed achievable in 1985 from an improved hepatitis B vaccine.

[56] These estimates are based on the development of particular types of flu vaccines that had not been developed as of 1994, when the flu policy went into effect (author's assessment based on approval data in Hoyt (2002)).

one-half of the dynamic benefits are available in years 7-9, and all are enjoyed in years 10 and later.

The sources and values for the inputs used in calculating equation (6) are reported in Table 10, along with the results of the calculation. I report results under two different assumptions about the real discount rates (r): 3% and 5% ; the latter is what the Institute of Medicine (1985a) uses in discounting potential benefits from future vaccine development. Note that, by assumption, the ratio of dynamic to static health benefits from the hepatitis B policy is zero. However, the results in Table 10 indicate that, for the flu policy, the conservatively estimated dynamic health benefits are about 2.5 times the generously estimated static benefits. Averaging across these two very disparate results suggests that, on average, a lower bound estimate of the dynamic health benefits is that they are at least as large as the static benefits.

Much of the existing empirical work that evaluates the effect of health policies on health outcomes limits itself to the policies' role in increasing utilization of existing medical technology. The results in Table 10 suggest that this approach may be quite incomplete. A more nuanced analysis of health policy must also consider its potential dynamic effects on health via its effect on the medical production possibilities frontier.

9. Conclusion

This paper provides empirical evidence of the consequences that health policy can have on the development of new medical technologies. I examine the investment response to three policies that increased the demand-side incentives for investing in vaccines against six particular diseases. I use evidence from vaccine investment in carefully chosen groups of diseases that were unaffected by the policies to try to control for other secular trends affecting the rate of investment in vaccine development.

The results indicate that the demand-side incentives embodied in health policy can – and do – affect the rate of development of new medical technology. The central estimates suggest that the policies were associated, on average, with a 2.5-fold increase in the number of new vaccine clinical trials for affected diseases. This induced increase in investment appears to persist in the long run, at least as measurable in the data; this suggests that the policies are associated with investment that would otherwise not have been

pursued, rather than merely a moving forward in time of planned investment. The estimates imply that for every one-dollar increase in the expected annual market revenue from vaccines against a particular disease, the vaccine industry will invest an additional 5 to 6 cents annually (in present discounted value) in developing improved versions of this vaccine. There is also some suggestive evidence that this increased investment is associated, after accounting for the lag in development times, with an increase in new vaccine approvals for affected diseases. Under conservative assumptions, the potential "dynamic" health benefits from the induced investment in vaccine development appear at least as large as the "static" health benefits from the policies' promotion of increased utilization of the existing vaccine technology.

However, the investment response appears limited to clinical trials, the latest stage of the development process. I am unable to find evidence of an increase in more basic inventive activities, such as pre-clinical trials or new patent filings, associated with the policies. An unanswered question – and a fruitful avenue for further research – is whether larger demand-side incentives would have an effect on these more fundamental aspects of R&D, or whether the investment response to demand-side incentives is limited to commercializing existing technologies through new clinical trials.

The evidence in this paper has important implications for both the economics of technological change and for health economics. The empirical evidence indicates that appropriation of the returns to pharmaceutical innovation is likely to reduce the rate of future innovation; this has important implications for public policies regarding the pricing of pharmaceuticals and the protection of intellectual property. The results also inform the debate over the relative roles of the state of science and of demand-side factors in affecting technological progress, suggesting that these roles may vary along the R&D pipeline. Finally, the results are relevant for the large empirical literature in health economics devoted to analyzing the health benefits of policies that increase access to or utilization of existing medical technology. All of the policies studied here were designed for this purpose, yet the results indicate that they also had a considerable impact on affecting the future medical production possibilities frontier. This suggests the importance of considering potential dynamic effects on technological development in any analysis of the impact of health policy.

One aspect of the investment response that the current paper has not addressed concerns the types of companies who were the source of the induced investment response. Of particular interest is whether the induced investment came from companies already involved in vaccine development, or whether new companies were induced to enter the market for vaccine development. Information on this margin would provide a first step toward thinking about whether demand-side incentives affect not only the level of investment but also the *distribution* of investment across potential actors, and hence the amount of competition in the R&D market. I regard this as a promising direction for future work.

Narrowly construed, the evidence in this paper indicates how demand-side incentives affect decisions to develop improved versions of existing vaccines. This is currently of considerable interest, given the interest in developing improved versions of vaccines against diseases such as small pox and anthrax in the face of increased fear of bio-terrorist attacks. The evidence may also be construed as broadly indicative of the potential for an investment response to demand-side incentives to develop the first versions of vaccines against such diseases as malaria and HIV, as well as incentives to develop non-vaccine pharmaceuticals such as AIDS drugs; this is particularly true for products for which there currently exists a stock of technologically feasible, but economically unattractive, technologies. It is less clear, however, whether the development of other medical technologies – such as new medical equipment or new surgical procedures – which involves different actors and a different development process – would exhibit a similar responsiveness to financial incentives. To the extent that it does not, changes in demand-side incentives may alter not only the *rate* of technological progress in the medical sector, but also the *composition* of care.

References

Books and articles

Abadie, Alberto and Javier Gardeazabal. 2001. "The economic costs of conflict: a case-control study for the Basque country." NBER Working Paper 8478.

American Academy of Family Physicians. 2000. "Combination Vaccines for Childhood Immunizations, Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians." http://www.aafp.org/clinical/chidimmun/combvacc.html

Center for Disease Control. 2001, 2000, 1997, 1996a. "National State and Urban Area Vaccination Coverage Levels Among Children Aged 19-35 Months – United States." *Morbidity and Mortality Weekly Report*, various issues.

Center for Disease Control. 2002b. "Behavioral Risk Factor Surveillance System; Trend Data." http://198.246.97.130/brfss/Trends/trendchart.asp?qkey=10120&state=US.

Center for Disease Control. 2002a. "Achievements in Public Health: Hepatitis B vaccination – United States, 1982- 2002." *Morbidity and Mortality Weekly Report* 51(25):

Center for Disease Control. 1996b. "Prevention of Varicella: Recommendations of the Advisory Committee on Immunization Practices." *Morbidity and Mortality Weekly Report* 45 (RR11): 1-25.

Center for Disease Control. 1994. "Implementation of the Medicare influenza vaccination benefit – United States, 1993." *Morbidity and Mortality Weekly Report* 43(42): 771-3.

Center for Disease Control. 1991b. "Haemophilus b Conjugate Vaccines for Prevention of Haemophilus influenzae Type b Disease Among Infants and Children Two Month of Age and Older: recommendations of the ACIP." *Morbidity and Mortality Weekly Report* 40(RR01): 1-7.

Center for Disease Control. 1991a. "Hepatitis B Virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: recommendations of the Immunization Practices Advisory Committee (ACIP)." *Morbidity and Mortality Weekly Report* 40(RR-13);1-19. July 22.

Decker, Michael and Kathryn Edwards. 1999. "Combination Vaccines" in Plotkin and Orenstein (eds). Vaccines, 3rd Edition. W.B. Saunders Company: Philadelphia

DiMasi, Joseph, Ronald Hansen, Henry Grabowski and Louis Lasagna. 1991. Cost of innovation in the pharmaceutical industry. *Journal of Health Economics*

DiMasi, Joseph, Ronald Hansen, Henry Grabowski and Louis Lasagna. 1995. "Research and Development Costs for New Drugs by Therapeutic Category." *PharmacoEconomics* 7(2): 152-169.

Dixit and Pyndick. 1994. Investment under uncertainty.

Ellis, Ronald. 1999. "New Technologies for Making Vaccines" in Plotkin and Orenstein (eds). Vaccines, 3rd Edition. W.B. Saunders Company: Philadelphia

Gelijns, Annetine C. 1990. "Comparing the Development of Drugs, Devices, and Clinical Procedures" in Modern Methods of Clinical Investigation, Annetine C. Gelijins (ed). Committee on Technological Innovation in Medicine. National Academy Press, Washington D.C.

General Accounting Office. 1999. "Vaccine Injury Compensation". GAO / HEHS-00-8.

Grabowski and Vernon. 1997. The Search for New Vaccines. American Enterprise Institute.

Geoffard, Pierre-Yves and Tomas Philipson. 1997. "Disease eradication: private versus public vaccination." *American Economic Review*, 87(1):222-230.

Griliches, Zvi. 1992. "The search for R&D spillovers." *Scandinavian Journal of Economics* (94): ppS29-S47.

Goolsbee, Austan. 1998. "Does government R&D policy mainly benefit scientists and engineers?" *American Economic Review*, May.

Hall, Bronwyn. 1996. "The Private and Social Returns to Research and Development." In Technology, R&D, and the Economy, Bruce Smith and Claude Barfield (eds). The Brookings Institution, Washington D.C.

Hall, Bronwyn and John van Reenen. 2000. "How effective are fiscal incentives for R&D? A review of the evidence." *Research Policy* (29) pp. 449-469.

Hausman, Jerry, Bronwyn Hall, and Zvi Griliches. 1984. "Econometric models for count data with an application to the patents-R&D relationship." *Econometrica* 52(4): 909-938.

Health and Human Services. 1996. "First acellular pertussis vaccine approved for infants." http://www.hhs.gov/news/press/1996pres/960731b.html

Health Resources and Services Administration. 2002. "Background information on VICP." http://www.hrsa.gov/osp/vicp/abdvic.htm

Hirano, Keisuke, Guido Imbens and Geert Ridder. "Efficient estimation of average treatment effects using the estimated propensity score." NBER Technical Working Paper 251.

Hoyt, Kendall. 2002. "The Role of Military-Industrial Relations in the History of Vaccine Innovation" unpublished doctoral dissertation, MIT, May.

Institute of Medicine. 2001. Vaccines for the 21st Century: A tool for Decision Making. National Academy Press, Washington DC.

Institute of Medicine. 1985a. New Vaccine Development: Establishing Priorities, Volume 1: Diseases of Importance in the United States. National Academy Press, Washington D.C.

Institute of Medicine. 1985b. Vaccine Supply and Innovation. National Academy Press, Washington D.C.

Jones, Charles and John Williams. 1998. "Measuring the social return to R&D." *Quarterly Journal of Economics*, November, pp.1119-1135.

Kilburn and Arden. 1999. "Inactive influenza vaccines" in Plotkin and Orenstein (eds). Vaccines, 3rd

Edition. W.B. Saunders Company: Philadelphia

Kitch, Edmund, Geoffrey Evans, and Robyn Gopin. 1999. "U.S. Law" in Plotkin and Orenstein (eds). Vaccines, 3rd Edition. W.B. Saunders Company: Philadelphia

Kremer, Michael. 2001. "Creating Markets for new vaccines – Part I: Rationale" in Jaffe, Lerner and Stern (eds). Innovation policy and the economy.

Mathieu. 1997. New Drug Development: A Regulatory Overview. Fourth Edition. PARAXEL International Corporation, Waltham MA.

Mercer Management Consulting. 1995. *Report on the United States Vaccine Industry.*

Merck. 2000. "Value of the 1999 Vaccine Market." *MVD Business Research,* presented to SMAG, July 20, 2000.

National Vaccine Advisory Committee. 1997. "United States Vaccine Research: A delicate fabric of public and private collaboration." *Pediatrics*, 100: 1015-1020.

Newell, Richard, Adam Jaffe and Robert Stavins. 1999. "The induced innovation hypothesis and energy-saving technological change." *Quarterly Journal of Economics*, August, pp.941-975.

Newhouse, Joseph. 1992. "Medicare Care Costs: How Much Welfare Loss?" *Journal of Economic Perspectives*, 6(3): 3-21.

NIH. 1998. "Understanding Vaccines." NIH Publication No. 98-4219.

Office of Technology Assessment. 1993. "Pharmaceutical R&D: Costs, Risks and Rewards" OTA-H-522. Washington, DC: U.S. Government Printing Office, February 1993. U.S. Congress,

Orenstein, WA and AR Hinman. 1999. "The immunization system in the United States – the role of school immunization laws." *Vaccine*, 17 Suppl 3: S19-24.

Pauly, Mark and Bridget Cleff. 1996. "The Economics of Vaccine Policy," in Mark Pauly, Chester Robinson, Stephen Sepe, Merrile Singe and Mary William (eds) Supplying Vaccines: an economic analysis of critical issues IOS Press, Washington DC.

PhRMA (2001): Industry Profile 2001.http://www.phrma.org/publications/publications/profile01/

PhRMA (2000): Industry Profile 2000.http://www.phrma.org/publications/publications/profile00/

Stratton, Kathleen, Alicia Gable and Marie McCormick (eds). 2001. Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. National Academy Press, Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention

Romer, Paul. 2001. "Should the government subsidize supply or demand in the market for scientists and engineers?" Jaffe, Lerner, and Stern (eds) Innovation Policy and the Economy.

Schwartz, B and WA Orenstein. 2001. "Vaccination policies and programs: the federal government's role in making the system work." *Primary Care* 28(4): 697-711.

Schmitz R, D Kidder, A Schwartz, and P Cook. 1993. "Final results: Medicare influenza vaccine demonstration – selected states, 1988-1992." *Morbidity and Mortality Weekly Review,* 42(31): 601-604.

Schmookler, Jacob. 1966. Invention and Economic Growth. Cambridge, Harvard University Press.

Struck, Mark M. 1996. "Vaccine R&D success rates and development times." *Nature Biotechnology* (14): 591-593.

Weisbrod, Burton. 1991. "The health care quadrilemma: An Essay on Technological Change, Insurance, Quality of Care, and Cost Containment" *Journal of Economic Literature* Vol XXIX (June): pp. 523-552

Woodruff, BA, Stevenson J, Yusuf H, Kwong SL, Todoroff KP, Hadler MA, and Mahoney FJ. "Progress toward integrating hepatitis B vaccine into routine infant immunization schedules in the United States, 1991 through 1994." *Pediatrics* 97 (6 Pt 1): 798-803.

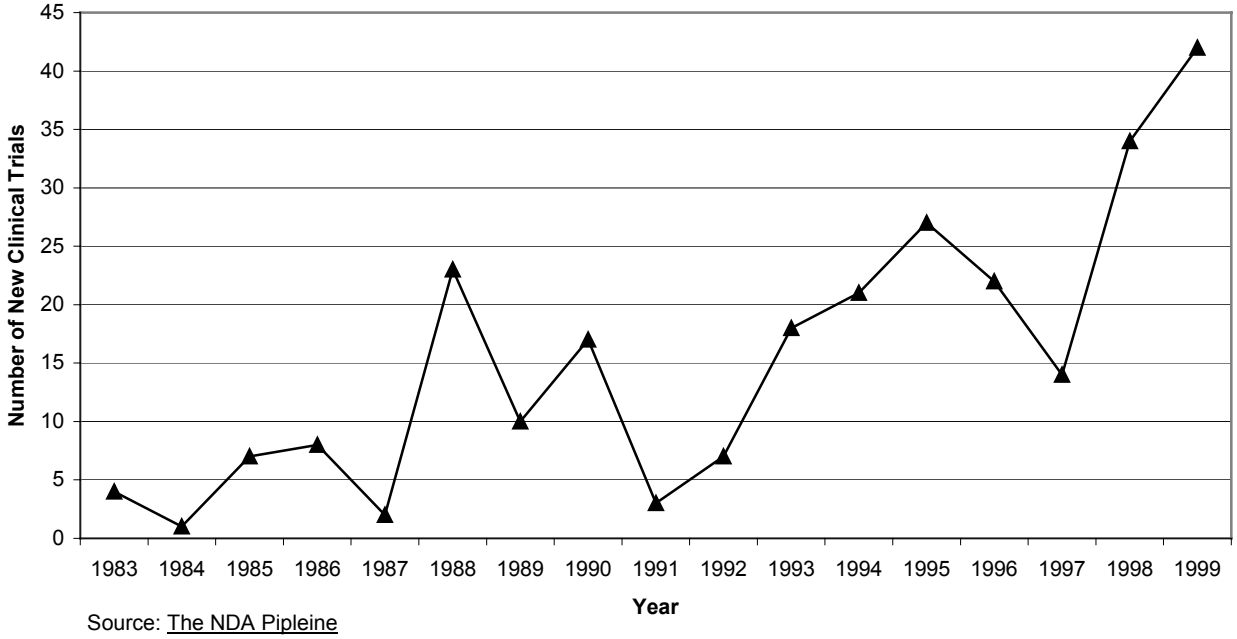
Cited interviews

Doctors
Dr. Jonathan Friedberg. Physician and clinician, MGH. Telephone conversation October 2000.
Dr. George Grady. Physician and vaccine researcher (Massachusetts Public Health Biologics Laboratories). Telephone conversation November 2000.

Individuals in the pharmaceutical industry.
Deborah Alfona, Merck. Telephone conversation, June 2001. Director of health policy for vaccines.
Harry Greenberg, Aviron. Mountain View CA, February 2001.
Bronwen Kaye, American Home Products. Telephone Interview, December 2000.
Alison Keith, Pfizer. Cambridge, MA. August 2000.
Richard Manning, Pfizer. Telephone conversation, September 2000.
Lorri Michael, Merck. Telephone conversation June 2001.
Courtney Piron, American Home Products. Telephone conversation, October 2000.
Jill Pulley, Aviron. Mountain View CA, February 2001.
Mark Sanyour, Merck. Telephone Interviews, May 2001 and July 2002.
Jan Wolters, Merck. Cambridge, MA June 2001.

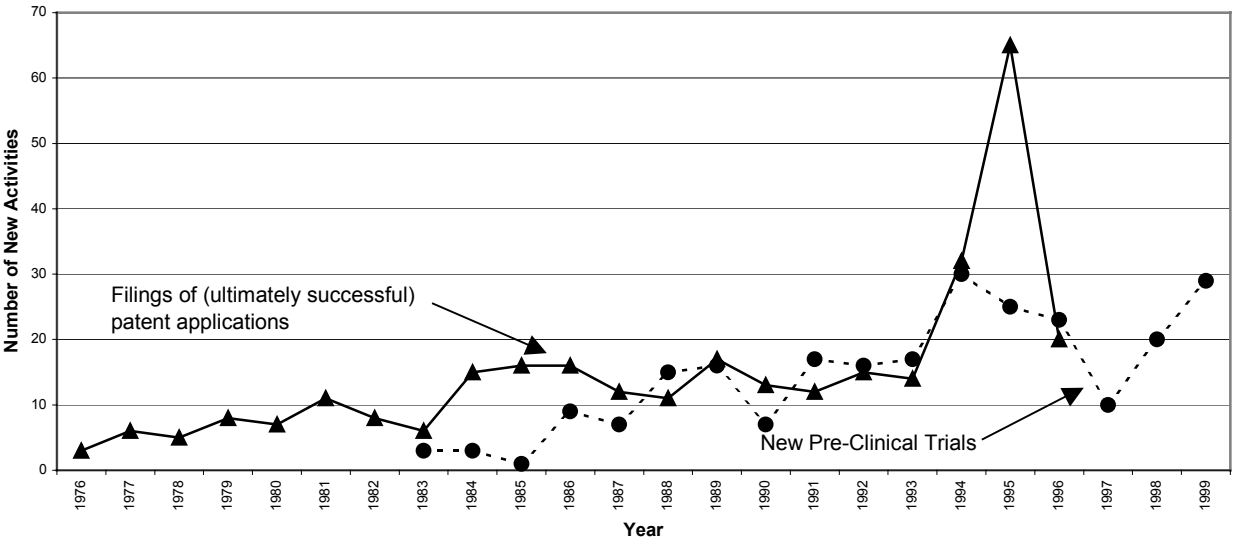
Public Sector
Amie Batson, World Bank. Telephone conversation, April 2001.
Bob Snyder, CDC. – several phone and email correspondences

Figure 1: New Vaccine Clinical Trials, 1983-1999



Source: The NDA Pipleine

Figure 2: Early Stages of Vaccine R&D Activity, 1976-1999



Source: The NDA Pipeline (pre-clinical trials); USPTO (patent filings)

Table 1: 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	0	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

Notes:

- The vertical black line and 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 2: Summary statistics for treatment and control groups

Group	Number of Diseases	Percent of diseases with new clinical trials before 1987	Percent of diseases with existing vaccines before 1983	Percent of diseases for which vaccines judged to have technological potential	Average # of new vaccine clinical trials per year per disease (1983-1986)
Treated diseases	6	83%	100%	50%	0.46
Control Diseases					
"Any clinicals"	26	38%	27%	35%	0.09
"Early clinicals"	7	100%	29%	43%	0.32
"Prior approvals"	7	29%	100%	14%	0.11
"Technology"	9	67%	11%	100%	0.11

Table 3: Mean Change in Number of New Vaccine Clinical Trials Per Year After Introduction of Policy

Disease	Absolute Change	Relative to "Any Clinicals"	Relative to "Early Clinicals"	Relative to "Prior Approvals"	Relative to "Technology"
Pertussis	2.35	2.08	2.10	2.10	2.03
Measles-Mumps-Rubella	-0.02	-0.29	-0.27	-0.26	-0.34
Diphtheria-Tetanus	1.83	1.56	1.58	1.58	1.51
Polio	0.19	-0.08	-0.06	-0.05	-0.12
Hepatitis B	2.10	1.76	1.95	1.61	1.77
Flu	2.14	1.76	1.86	1.74	1.74

Table 4: Effect of policies on number of new clinical trials

	Linear Fixed Effects Model						Conditional Fixed Effects Negative Binomial Model				
	Treated Sample Only (Dev. from Trend)	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Technology	Propensity Score Weighting	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Technology	Propensity Score Weighting
ADOPT	**1.282*** (0.483)**	**1.210*** (0.184)**	**1.307*** (0.273)**	**1.233*** (0.263)**	**1.212*** (0.242)**	**1.192*** (0.248)**	**1.641 (0.519)**	**3.111*** (1.036)**	**2.183** (0.795)**	**2.197** (0.753)**	**1.894*** (0.459)**
Unadjusted p-value	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.12	<0.01	0.04	0.03	<0.01
Adjusted p-value	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.38	0.01	0.06	0.04	0.09
Mean Dep. Variable	1.28	0.48	0.87	0.75	0.73	0.54	0.48	0.87	0.75	0.73	0.54
Number of Diseases	6	32	13	13	15	32	32	13	13	15	32
N	102	544	221	221	255	544	544	221	221	255	544

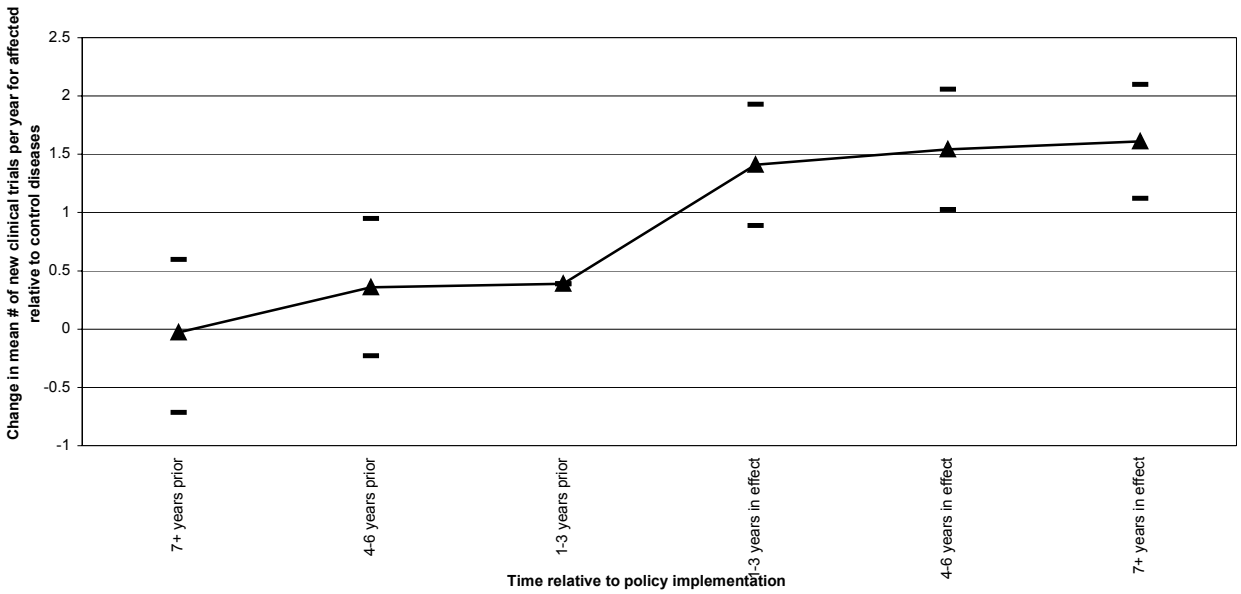
Notes: First column reports results from equation (1); all other columns report results from equation (2). All regressions include year and disease fixed effects. Coefficients reported for negative binomial model are exponentiated coefficients, which can be interpreted as incidence ratios. Unadjusted standard errors are in parentheses. Adjusted p-values are calculated using the randomized inference approach of Bertrand, Duflo and Mullainathan (2002). ***, **, * indicate significance at the 1%, 5% and 10% level respectively, using the unadjusted p-values. See text and Table 2 for description of control groups.

Table 5: Sensitivity analysis of results in Table 4.

	Deviation from Trend (Treated Sample Only)	Difference-in-Differences									
		Control Group: Any Clinicals		Control Group: Early Clinicals		Control Group: Prior Approvals		Control Group: Technology		Propensity Score Weighting	
ADOPT	**1.280*** (0.484)**	**0.870*** (0.274)**	**0.867*** (0.274)**	**0.872** (0.376)**	**0.869** (0.375)**	**1.013*** (0.357)**	**1.010*** (0.336)**	**0.882*** (0.336)**	**0.879*** (0.336)**	**0.824** (0.374)**	**0.821** (0.373)**
Unadjusted p-value	0.01	<0.01	<0.01	0.03	0.02	<0.01	<0.01	<0.01	0.01	0.03	0.03
Adjusted p-value	0.01	<0.01	<0.01	0.02	0.02	<0.01	<0.01	<0.01	<0.01	0.05	0.05
Mean Dep. Var.	1.28	0.48	0.48	0.87	0.87	0.75	0.75	0.73	0.73	0.54	0.54
Disease-specific trend	Quadratic	Linear	Quadratic	Linear	Quadratic	Linear	Quadratic	Linear	Quadratic	Linear	Quadratic
Number of Diseases	6	32	32	13	13	13	13	15	15	32	32
N	102	544	544	272	272	272	272	255	255	544	544

Notes: Reported results are from estimating equations enriched versions of equations (1) and (2) that incorporate, respectively, disease-specific quadratic trends in the deviations from trend specification, and disease-specific linear trends or disease-specific quadratic trends in the difference-in-differences specification.. All results are for the linear fixed effects model. See notes to Table 4 for more detail.

Figure 3: Timing of effect of policies on new clinical trials



Note: Figure graphs the coefficients on the ADOPT variables from estimating equation (4); the regression includes year and disease fixed effects. The coefficients are from a linear regression on a sample consisting of the affected diseases and the "any clinicals" control group. The reference period (1-3 years prior to adoption) is set at the mean of the dependent variable for the affected diseases in this period.

Table 6: Effect of policies on number of new approved vaccines

	Deviation from Trend (Treated Sample Only)	Difference-in-Differences				
		Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Technology	Propensity Score Weighting
$ADOPT_{(1-6)}$ (Policy in place 1-6 years)	**-0.043 (0.202)**	**-0.051 (0.072)**	**-0.081 (0.101)**	**-0.050 (0.092)**	**-0.083 (0.102)**	**-0.057 (0.060)**
Unadjusted p-value	0.83	0.48	0.42	0.59	0.42	0.34
Adjusted p-value	0.63	0.41	0.40	0.38	0.48	0.32
$ADOPT_{(7+)}$ (Policy in place 7+ years)	**0.455 (0.417)**	**0.364*** (0.084)**	**0.346*** (0.127)**	**0.409*** (0.115)**	**0.305** (0.126)**	**0.348** (0.136)**
Unadjusted p-value	0.28	<0.01	<0.01	<0.01	0.02	0.02
Adjusted p-value	0.08	<0.01	0.01	<0.01	0.05	0.02
Mean Dependent Var.	0.18	0.07	0.12	0.10	0.11	0.08
Number of Diseases	6	32	13	13	15	32
N	108	576	234	234	270	576

Notes: Dependent variable is number of approved vaccines against a given disease in a given year. The first column reports results from estimating equation (1); all other columns report results from estimating equation (2). In both equations, 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 ($ADOPT_{(7+)}$). All results are based on linear estimation. See notes to Table 4 for more detail.

Table 7: Effect of policies on number of new pre-clinical trials.

	Linear Fixed Effects Model						Conditional Fixed Effects Negative Binomial Model				
	Treated Sample Only (Dev. from Trend)	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Tech-nology	Prop. Score Weighting	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Tech-nology	Prop. Score Weighting
ADOPT	**-0.326 (0.423)**	**0.115 (0.173)**	**0.298 (0.212)**	**0.057 (0.236)**	**0.109 (0.213)**	**0.184 (0.234)**	**0.623 (0.214)**	**1.275 (0.489)**	**0.684 (0.320)**	**0.808 (0.305)**	**0.744 (0.198)**
Unadjust. p-value	0.44	0.51	0.17	0.81	0.61	0.44	0.17	0.53	0.42	0.57	0.27
Adjusted p-value	0.23	0.56	0.07	0.96	0.78	0.68	0.96	0.10	0.81	0.99	0.35
Mean Dep. Var	0.78	0.46	0.53	0.54	0.55	0.47	0.46	0.53	0.54	0.55	0.47
Number of Diseases	6	32	13	13	15	32	32	13	13	15	32
N	102	544	221	221	255	544	544	221	221	255	544

Notes: The dependent variable is the number of new pre-clinical trials. First column reports results from estimating equation (1); all other columns report results from estimating equation (2). See notes to Table 4 and text for more details.

Table 8: Effect of policies on number of new patent filings.

	Linear Fixed Effects Model						Conditional Fixed Effects Negative Binomial Model				
	Treated Sample Only (Dev. from Trend)	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Tech-nology	Prop. Score Weighting	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Tech-nology	Prop. Score Weighting
FILINGS BY FOR-PROFIT COMPANIES											
ADOPT	**-0.137 (0.434)**	**0.198 (0.126)**	**0.129 (0.182)**	**0.166 (0.179)**	**0.160 (0.169)**	**0.260 (0.205)**	**0.759 (0.240)**	**0.661 (0.263)**	**0.774 (0.281)**	**0.769 (0.273)**	**0.840 (0.214)**
Unadjusted p-value	0.76	0.12	0.48	0.36	0.35	0.21	0.39	0.30	0.49	0.46	0.50
Adjusted p-value	0.44	0.11	0.43	0.27	0.37	0.12	0.44	0.45	0.53	0.53	0.55
Mean Dep. variable	0.63	0.27	0.38	0.38	0.38	0.29	0.27	0.38	0.38	0.38	0.29
FILINGS BY NON-PROFIT ENTITIES											
ADOPT	**0.414* (0.248)**	**0.120 (0.103)**	**0.225** (0.103)**	**0.061 (0.136)**	**0.075 (0.138)**	**0.097 (0.142)**	**0.915 (0.399)**	**1.415 (0.756)**	**0.751 (0.412)**	**1.045 (0.497)**	**0.867 (0.302)**
Unadjusted p-value	0.10	0.25	0.04	0.66	0.60	0.50	0.84	0.52	0.61	0.93	0.69
Adjusted p-value	0.05	0.40	0.05	0.81	0.85	0.41	0.86	0.60	0.75	0.98	0.75
Mean Dep. Variable	0.28	0.19	0.18	0.22	0.24	0.19	0.19	0.18	0.22	0.24	0.19
Number of Diseases	6	32	13	13	15	32	32	13	13	15	32
N	126	672	273	273	315	672	672	273	273	315	672

Notes: The dependent variable is the number of new patent filings. The top panel reports the results for the sample of for-profit companies. The bottom panel reports the results for the sample of non-profit entities. First column reports results from estimating equation (1); all other columns report results from estimating equation (2). See notes to Table 4 and text for more details.

Table 9: Effect of increase in expected market revenue on vaccine investment

	Control Group: Any Clinicals	Control Group: Early Clinicals	Control Group: Prior Approvals	Control Group: Technology	Propensity Score Weighting
ΔExpMktRev	**0.061*** (0.010)**	**0.064*** (0.014)**	**0.054*** (0.012)**	**0.059*** (0.012)**	**0.064*** (0.021)**
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 dep. variable (millions of dollars)	6.06	11.65	8.89	8.92	6.82
Number of Diseases	28	9	9	11	28
N	476	153	153	187	476

Notes: Results are based on linear estimation of equation (5). The dependent variable is the implied present discount value of the spending associated with the number of new clinical trials for a given disease in a given year. $\Delta ExpMktRev_{it}$ denotes the change in expected market revenue associated with the introduction of a policy. The affected vaccines are limited to hepatitis B and the flu; the diseases affected by the Vaccine Injury Compensation Fund are excluded from the analysis. Unadjusted standard errors are in parentheses. Adjusted p-values are calculated using the randomized inference approach of Bertrand, Duflo and Mullainathan (2002). ***, **, * indicate significance at the 1%, 5% and 10% level respectively, using the unadjusted p-values. See text for more details.

Table 10: Static vs. dynamic health benefits from policies

Disease	Inputs					Ratio of Dynamic Benefits / Static Benefits	
	Vaccination Rates			Efficacy Rates			
	V_0	V_S	V_D	E_0	E_D	r =.03	r=.05
Hepatitis B	0	0.90	V_S	0.80-0.95	E_0	0	0
Flu	0.51	0.67	0.82	0.58	0.85	2.77	2.44
Average						1.39	1.22

Notes: Subscript 0 denotes the year right before the policy goes into effect, subscript S denotes the first year in which static effects have all been realized and subscript D denotes a year in which the full dynamic effects have all been realized. Data on V_0 and V_S are taken from Appendix Figure A1. For the flu vaccine, estimates of the initial efficacy rate (E_0) are based on Kilburn and Arden's (1999) review of the studies testing efficacy. Estimates of the potential efficacy of an improved flu vaccine (E_D) and in the increase in vaccination rates associated with this improved vaccine $(V_D - V_S)$ come from Institute of Medicine (1985a). For hepatitis B, estimates of initial efficacy are based on the CDC's estimates at the time of the CDC recommendation for universal hepatitis B vaccination (CDC 1991a).

Appendix A: 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 works. (CDC 2002a, Institute of Medicine 1985a). A long political battle ensued in which advocates of universal vaccination of the birth cohort as a way of reaching the subsequently-at-risk population were pitched against those concerned that adding a non-childhood disease to the childhood immunization schedule might decrease parental willingness to comply with the overall childhood immunization schedule (Snyder interview, Grady interview, Kaye interview). Prior to the Hepatitis B recommendation, there were no vaccines against non-childhood diseases included in the recommended childhood immunization schedule.

Was the timing the result of technological developments? As discussed above, the timing was the result of a decade-long political battle. There is no indication either in the records of the Advisory Committee on Immunization Practices (CDC 1991a) or in conversations with policymakers (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 sub-section of the population to a guaranteed annual cohort of the 4 million live births per year.[57] 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 indicated a dramatic and rapid expansion of infant hepatitis B vaccination following the national recommendation; for example, infant immunization increased from less than 1% of children born in 1989 to 40% of children born in the fourth quarter of 1992 (Woodruff et al. 1996). It seems reasonable to conclude that much of this spurt was due to the recommendation. Moreover, in the subsequent years, vaccination rates for hepatitis B continued to grow, reaching 90% for children aged 19-35 months in 2000 (CDC 2002a). Figure A1 shows the growth rate of hepatitis B vaccination by calendar year.[58] The increase in hepatitis B vaccination rates does not appear to reflect a general increase in childhood vaccination rates; for example, using the annual National Health Interview Survey's Immunization Supplement between 1992 and 1996, I calculate that hepatitis B vaccination rates for children under three rose from 15 percent to 75 percent for hepatitis B, but only from 64% to 68% for MMR. In addition to the increased expected market size, the government recommendation was also expected to increase the profitability of the hepatitis B vaccine by reducing the need for marketing efforts and expenditures on the part of the pharmaceutical industry (Sanyour interview, Greenberg interview).

Four different mechanisms translate a CDC recommendation into dramatic changes in standard immunization practices. First, public programs, supported by the CDC, immunize 50-60% of the newborns annually in the United Sates, and public immunization policy follows the recommendations of the CDC (Snyder interview; Woodruff et al. 1996). Second, pediatricians' private practice also tends to following the CDC recommendation both because it provides potential cover for lawsuits following adverse reactions and because it creates the potential source of a lawsuit if the immunization is not done and the child falls ill. (Grady interview). Indeed, the American Academy of Pediatrics officially endorsed

[57] As one pharmaceutical executive put it memorably: "trying to sell a vaccine for which there isn't an ACIP recommendation for universal or near universal coverage of the birth cohort is like pissing in the wind."
[58] Note that the calendar year effects are expected to occur with a lag since the immunization schedule is not completed until 18 months. Unfortunately, no consistent series on hepatitis B is available prior to the recommendation going into effect.

the CDC's recommendation the following year. Third, states use the CDC recommendation to compile their list of required vaccinations for attending day care or public school (Alfona interview).[59] School immunization laws have a large effect on vaccination rates (see e.g. Orenstein and Hinman, 1999). Fourth, many private schools and employers require proof of compliance with the CDC-recommended schedule.

2. Medicare coverage of influenza vaccine (May 1993).
Rationale: Based on a five-year, congressionally-mandated series of demonstration projects of the consequences of Medicare coverage of the flu vaccine and of information campaigns about the benefits of flu vaccines for the elderly, it was determined that Medicare coverage would have a substantial effect on vaccination rates for the elderly, and that this intervention was cost-effective. Medicare coverage was accompanied by a HCFA-initiated information campaign starting in the fall of 1993 that was designed to promote use of the new benefit (CDC (1994)).

Was the timing the result of technological developments? A flu vaccine was first approved in 1945. There were no recent technological developments in the flu vaccine technology in the decade or more prior to the Medicare decision; the most recent flu vaccine prior to the policy had 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, Kaye interview).[60] The vaccine industry was not alone in forecasting large increases in flu immunization associated with Medicare's coverage for the flu vaccine and its associated publicity efforts; 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, as can be seen in Figure A1. Although influenza vaccination rates among Medicare beneficiaries rose from 51% in 1993 to 67% in 1999 (CDC 2002b), Figure A1 suggests that even this modest increase may have been in part due to a pre-existing upward trend in flu vaccination rates for the elderly.

However, more important than the actual response was the expected response.[61] Three primary mechanisms were behind the industry's belief that Medicare coverage would result in increased profitability of 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

[59] Indeed, following the CDC recommendation, many states introduced school-based "catch-up" vaccination programs for 11 to 12 year olds.
[60] 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."
[61] For example, Pauly and Cleff (1996) note that if there is a link between the profitability of existing vaccines and investment in R&D for new vaccines, "the strongest basis for such a relationship would be manufacturer perception (whether correct or incorrect) in a connection between the profits of old products and the profits of new products" (p.20).

practices, government vaccination practices, and state mandates. (Grady interview; Friedberg MGH; Alfona interview).

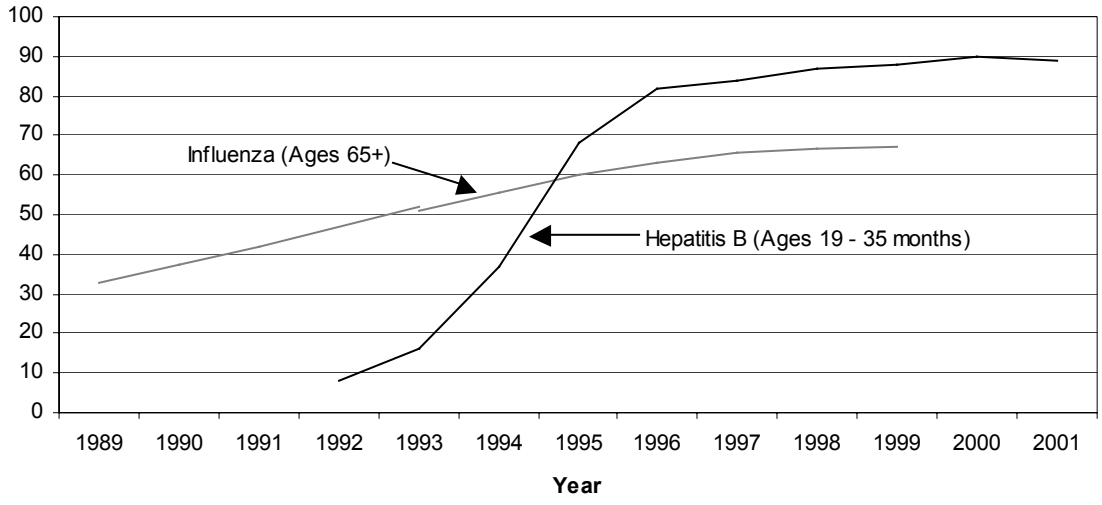
3. Vaccine Injury Compensation Fund (1986)
Rationale: The VICF was prompted by the withdrawal of pharmaceutical companies from vaccine manufacture for the affected childhood vaccines in the wake of increased lawsuits and difficulties obtaining product liability insurance in the early and mid 1980s (Kitch et al. 1999; Institute of Medicine 1985b). This raised the specter of vaccine shortages and resultant epidemics of these childhood diseases (GAO 1999; Institute of Medicine 1985a).

Was the timing the result of technological developments? Pharmaceutical companies had lobbied for something like the VICF since the early 1970s. The exact timing seems to have been prompted by a surge in lawsuits against childhood vaccine manufacturers starting in 1984 (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 as a huge boost to the industry, and one that was viewed as such at the time of enactment. Indeed, it had been actively lobbied for by the industry for over a decade prior to its enactment (Kitch et al. 1999). 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 11th is indicative of this being deemed beneficial to the industry.

The main body of the paper describes the two mechanisms by which the VICF increased investment incentives.

Figure A1: Trends in Vaccination Rates



Notes: Flu: Vaccination rates are for those aged 65+. Data from 1989 – 1993 are based on author's tabulation of the National Health Interview Survey; Data from 1993 – 1999 are from CDC (2002b) estimates from BRFSS data. All data are bi-annual and available in odd-numbered years. Hepatitis B: Vaccination rates are for those aged 19 – 35 months. Annual data are from CDC (2001, 2000, 1997, 1996a, and 1994) and are based on the National Immunization Survey and the National Health Interview Survey.

Appendix B: Detailed description of the data

Disease Name	Included in Restricted Control Groups? "Early clinicals"	"Prior Approvals"	"Technology"	Average number of new clinical trials per year per vaccine 1983-1986	1996-1999	Year Vaccine First Approved
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

Sources: All columns but the last one based on The NDA Pipeline. Hoyt (2002) provided the approval dates.
Notes: Listed control diseases include 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 U.S