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Health Policy and Technological Change: Evidence from the vaccine industry

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The development of new drugs has been a major source of the dramatic health improvements of the 20th century, yet we know little about the determinants of investment in these new technologies. This paper provides empirical evidence of the unintended role that health care policies, designed to increase access to existing medical technology, can play in affecting the rate of extension of the health care production possibility frontier. I examine the effect of discrete policy changes that, while designed to increase vaccination against particular diseases, also increased the return to investing in developing new versions of vaccines against these diseases. The results indicate that these demand-side incentives were associated with a substantial increase in investment in inventive activity. The central estimates suggest a 2.5-fold increase in the number of new clinical trials started each year for vaccines against diseases affected by the policies. In addition, there is suggestive evidence that companies devote more resources to the success of these clinical trials when demand-side incentives increase. However, the investment response is limited to relatively late stages in the R&D pipeline. In particular, there is no evidence of an effect of these policies on earlier stages of the R&D pipeline that represent more basic research, as measured by the decision to start new pre-clinical trials or the filing of a successful patent application. Under conservative assumptions, the health benefits from the induced investment in vaccine development are equivalent to the health benefits from the increased utilization of the existing vaccine technology induced by the policies.

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Ever since Schmookler, economists have debated the relative roles of demand factors and of the state of technological knowledge in determining the rate and direction of technological progress.[1] Modern growth theory emphasizes not only that technological change is the driving force behind economic growth, but also the endogeneity of this technological progress to economic incentives. In the health sector, technological progress has been the driving force behind both the dramatic health improvements of the 20th century and the spiraling costs of health care. The potential role of demand-side factors, and in particular, health policy, 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 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, and none that I know of in the health care sector, on the role of demand in affecting the rate of technological progress.[2] This paper presents the first such evidence.

I focus on a particular type of demand-side incentives for technological change, specifically those embodied in health policies whose stated purpose is to increase utilization of existing medical technology. Whether -- and how much –such demand-side incentives matter for technological change in the health care sector is an open empirical question. In particular, three factors suggest that the responsiveness of the rate of technological change to demand-side incentives embodied in health policy may be limited. First, the state of technology and the cost of

[1] This literature dates back to Hick's (1932) "induced innovation hypothesis"; for a modern version of this theory, see e.g. Acemoglu (2001). Schmookler (1966) laid the foundation for the modern debate by staking out the extreme position that technological change was essentially determined entirely by demand factors, with relatively little role for the state of scientific knowledge.

[2] Most of the empirical work testing the induced-innovation hypothesis has been in the environmental literature (see e.g. Newell, Jaffe and Stavins (1999) on the role of demand-side factors in affecting the rate and direction of innovation in energy-consuming products).

different innovations – or what Kennedy (1964) terms the "innovation possibilities frontier" – may provide a binding constraint on the ability to respond to demand-side incentives, particularly in the short run. Second, the long lags in the 15+ year R&D pipeline combined with uncertainty about the future health care policy climate may severely dampen the response of *current* investment to *current* policy. Third, and relatedly, the endogeneity of health policy to technological change may also weaken the incentive for developers to heed the current policy climate in making investment decisions. This can cut both ways: political pressure may increase the profitability of breakthrough technologies by providing the impetus for public health insurance programs to cover the new technology, or they may decrease the profitability by increasing the incentives for hold-up once the sunk investment costs have been made.[3]

I focus on R&D in a specific sector of the pharmaceutical industry, the vaccine industry. Vaccines share the key development features of the rest of the pharmaceutical industry. Specifically, vaccine development, like pharmaceutical development more generally, involves for-profit companies investing large sunk costs in long-term projects with uncertain outcomes, whose ultimate fate is determined by the FDA, and for which a successful product, once developed, can be produced at very low marginal cost. As such, 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 vaccine industry is also a particularly compelling setting for studying the effects of health policy on technological change. Vaccine development continues to hold the potential to produce dramatic health benefits. This is particularly true in developing countries, where vaccines against many widespread diseases such as AIDS and malaria currently do not exist. It also applies

[3] An example of the former is Medicare's 1986 decision to begin covering immunosuppressive drugs following a Medicare-covered kidney transplant; this decision followed quickly on the heels of the 1984 (?) FDA approval of the first successful immunosuppressive drug to prevent organ rejection. A recent example of the latter is the government threats to override Bayer's patent of the antibiotic Cipro – and Bayer's ultimate agreement to supply the drug to the government at a lower cost – when anthrax-laced letters raised fears of a widespread anthrax infection.

in developed countries, where improved versions of vaccines against diseases such as anthrax and small pox may offer substantially increased protection against the rising threat of bio-terrorism. Existing theoretical and empirical work suggests limits to the ability of direct government spending to stimulate private investment in the development of specific vaccines.[4] However, the government plays a central role in affecting the demand for vaccines; it is a major purchaser of many vaccines, purchasing 60% of all childhood vaccine doses in the United States in 1997,[5] and extremely influential in determining which vaccines are routinely administered to children (see e.g. Schwartz and Orenstein 2001). Understanding the role that the demand-side incentives embodied in public policy can play in affecting investment in vaccine development in therefore of great interest.

The empirical approach is to examine three discrete policy changes that increase the demand-side incentives to develop new versions of vaccines against six particular diseases. Because they occur at a discrete point in time, I can try to distinguish the effects of these policies from any general secular trends that have contributed toward increasing R&D in the vaccine industry. Because they affect only particular vaccines, 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 supply-side changes that may also affect R&D incentives.

The empirical results shed light on three issues. First, I investigate the open empirical question of *whether* investment in inventive activity in the vaccine industry responds to the demand-side incentives embodied in health policy.[6] The empirical evidence suggests that it does.

Second, I consider the magnitude of the investment response. The policies, whose primary and stated purpose was to increase utilization of existing vaccine technology rather than to spur

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[4] See Kremer (2001) for the conceptual issues. For empirical evidence of the limited effect of direct government spending on stimulating private R&D, see e.g. Cohen and Noll (1991), Hall (1996), or Wallsten (2000).

[5] Estimates of the public share of childhood vaccine purchases are based on CDC data provided by Bob Snyder of the CDC.

[6] 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).

innovation, in fact had substantial effects on the rate of investment in vaccine development. The central estimates suggest that the policies are associated, on average, with an increase of about 1.2 new vaccine clinical trials per year for each affected disease. This represents a 2.5-fold increase in the number of new vaccine clinical trials for these diseases and implies, given the 39% success rate of vaccine clinical trials (Struck 1996), the licensure of additional new vaccine for each affected disease every two years. Additional evidence is suggestive of companies also devoting more resources toward the ultimate success of these clinical trials when demand-side incentives increase.

A large empirical literature has examined the effects of a wide range of health policies on improving health outcomes by increasing access to and utilization of the health care system. The results in this paper suggest that the almost total focus on these "static" effects of health policy is misguided. Specifically, it overlooks the potential impact of health policy on health outcomes via its "dynamic" impact on the extension of the technological possibilities frontier. When I make an extremely conservative comparison of the dynamic health benefits associated with the induced innovation relative to the static health benefits associated with the policies' increase in utilization of the existing vaccine technology, I find that the dynamic benefits are roughly the same as the static benefits.

Finally, I attempt to gauge the nature of the investment response to the demand-side incentives by investigating which margins of the innovation process are responsive to demand-side incentives. Here, the results point to potential limits to the ability of demand-side incentives in affecting technological change. In particular, when I investigate which margins along the 15+ year pipeline respond to the economic incentives in the new policies, I find that the investment response is confined to the last stage of the R&D pipeline, the clinical trials. I find no evidence of an effect of the demand-side incentives on decisions to invest in earlier stages of vaccine development, as measured by the decision to start new pre-clinical trials, or the filing of ultimately successful patent applications. This suggests that the investment response, at least to

the policies studied, is limited to commercializing existing technologies rather than creating fundamentally new technological opportunities.[7]

The rest of the paper proceeds as follows. Section two provides background on vaccine development. Section three describes the three policy changes in detail. Section four describes the data. Section five presents the main empirical results of the effect of demand-side incentives on investment in clinical trials. Section six presents additional empirical results on which margins of the innovation process are responsive to demand-side incentives. Section seven performs a back-of-the-envelope comparison of the health benefits from the policies' effect on utilization of the existing vaccine technology relative to the health benefits from their effect on inducing investment in developing improved vaccines. Section eight concludes.

2. Background on vaccine development

The vaccine R&D pipeline is the same as for any pharmaceutical product.[8] It can be roughly divided into three sequential categories: basic research (which may produce new patentable technologies), pre-clinical trials (testing in animals), and clinical trials (testing in humans). Successful clinical trials will result in FDA approval for the launch of a new product. As a compound moves up 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. Clinical trials are widely viewed as the most time consuming, and costly component of the R&D process. In 2001, companies spent about $1.1 billion – or about 4% of total company-financed R&D – on biologicals, of which vaccines are the primary component (PhRMA 2001).[9]

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[7] Additional work will also examine what type of companies responded to the increased investment incentives.

[8] The information in this paragraph is based on Gelijns (1990), Mathieu (1997), and National Vaccine Advisory Committee (1997).

[9] By contrast, revenue from vaccine sales represent only about 1% of pharmaceutical revenues (Grabowski and Vernon 1997).

Within the pharmaceutical industry, vaccines are viewed as a steady and reliable source of modest profits. Development times are comparable to those for other pharmaceutical products; the average time from initiation of a successful vaccine clinical trial to licensure is 7.6 years (Struck 1996) compared to estimates of 6 to 8 years for pharmaceutical products generally ((DiMasi 1991, OTA 1993). Success rates, however, appear somewhat higher for vaccines. Struck (1996) estimates a 39% approval rate for vaccines in clinical trials between 1983 and 1994, compared to the 23% success rate for the entire industry for clinical trials started between 1970 and 1982 (DiMasi et al. 1991). The major role that the government plays in recommending and purchase vaccines, reduces uncertainty about the ultimate market size of a successful product. It also reduces marketing costs (Sanyour interview). On the flip side, however, large public purchases hold down prices. In addition, vaccines require substantially greater up-front investments than the typical pharmaceutical product because of the FDA requirement – unique to vaccines – that the company file an establishment license agreement (ELA) and start building the physical manufacturing capacity prior to approval of the product (Grabowski and Vernon 1997).[10]

Attempts to develop or improve vaccines against different diseases share several common technological features. First, many vaccines involve an adjuvant; a substance that enhances the immune-stimulating properties of the vaccine (NIH, 1998); the development of a new adjuvant can benefit vaccine development for many diseases. In addition, vaccine development in the 1980s and 1990s benefited generally from a series of common technological advances (see e.g. Ellis 1999). Chief among these was the use of molecular biology and recombinant DNA technology that resulted in a whole new category of vaccines: DNA-based vaccines.

Not surprisingly, given these technological advances, vaccines have shared in the rapid – 10 percent per year in real dollars – growth in industry investment in pharmaceutical R&D (OTA

[10] This ELA requirement is often cited as a key contributor to the extremely high concentration of the market for vaccine manufacturing. The market for vaccine development, however, is substantially less concentrated; new entrants often begin development of new products and then either merge with or are acquired by a more established company prior to licensure (Pauly and Cleff 1996).

1993, Grabowski and Vernon 1997). It will be the key challenge of the empirical work in this paper to distinguish the effect of increases in demand-side incentives on investment in new vaccines from the increases that would have arisen simply because of the technological advances of the last two to three decades. The common technological components of vaccine development provide the opportunity to use vaccines against diseases that were not affected by the policies to try to control for changes in vaccine R&D investment that are driven by exogenous changes in the innovation possibilities frontier.

Much of the inventive effort directed at vaccines – and all of the effort for the diseases affected by the policies –involves attempts to develop improved versions of vaccines against diseases for which some vaccine already exists. Such improvements may take the form of increased efficacy in disease prevention or reduced risk of negative side-effects. These not only convey direct health benefits but also may indirectly improve health by increasing utilization (Institute of Medicine, 1985a). For example, the high rate of adverse consequences from the existing small pox vaccine has been a serious deterrent to national defense plans to vaccinate more Americans against this potential bio-terrorist threat.[11] In addition, vaccine development often involves attempts to develop a combination vaccine that combines existing vaccines against different diseases into a single vaccine, thus reducing the number of different shots and visits to a health care provider needed to complete the immunization schedule; such reduction can also have important effects for utilization rates, particularly for children's vaccines (see e.g. Decker and Edwards (1999) or American Academy of Family Physicians (2000)).

3. The case studies: three policies that increased the return to investing in specific vaccines

The empirical approach of this paper is to identify discrete policy changes that increase the demand-side incentives for developing improved versions of vaccines against particular diseases. I limited myself to policy changes that met five essential criteria. First, they had to occur at an identifiable point in time; the effect of slow-moving secular trends – such as the growth in

[11] *New York Times*, "Smallpox proposal raises ethical issues" June 22, 2002.

managed care or the aging of the population – on innovation incentives 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 so that investment in developing vaccines against other infectious diseases could potentially be used to try to control for technological or other supply-side trends that may also affect the incentives to invest in vaccine development. Third, the policies could not prompted by technological developments, otherwise 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 eliminated many candidate policies. Fourth, they had to be expected to have a non-negligible effect on the demand-side incentives for developing a new vaccine against the particular disease. This requirement caused me, among other things, to limit my focus to U.S. policies, since the U.S. is the single largest market for pharmaceuticals, accounting for over two-fifth of world-wide spending on pharmaceuticals in 1998 (IMS Health 2000, cited in PhrMA 2000). Finally, the policies had to occur between 1983 and 1999, the time frame for which I have data on key measures of R&D activity.

I identified three very different policy changes – affecting vaccines against six different infectious diseases – that met all five 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 to 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). The final 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 the childhood vaccines for polio, diphtheria and tetanus (DT), measles, mumps, or

rubella (MMR), or pertussis.[12] In return for an excise tax, the government introduced a no-fault compensation system in which individuals claiming injury from a covered vaccine could file a petition with the government for compensation. Individuals could file a lawsuit against the physician or the manufacturer only after the claim was adjudicated by the VICP.

Appendix A provides detailed evidence on the rationale for these policies, the determination of the timing of the policy, and the expected impact of the policy on demand-side incentives to develop vaccines against the affected diseases. There exists little quantitative evidence that can be brought to bear on these features. Nevertheless, documentary evidence and extensive conversations with vaccine developers, vaccine marketers, policy-makers, and physicians combine to paint a compelling picture on three key points. First, the explicit objective of each of these policies was to increase vaccination rates, either through recommending (or requiring) that children be vaccinated (the ACIP 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.

Second, these policies were not a response to a technological change in vaccines against the affected diseases, nor did they follow closely on the heels of the development of a new vaccine against the affected diseases. The recommendation for universal hepatitis B vaccination of the birth cohort in 1991 followed a prolonged political battle that pitched enthusiasts of the advantages of being able to reach the entire birth cohort against those who feared that adding a non-childhood disease to the childhood immunization schedule would only enhance the difficulty

[12] As will be described in more detail below, vaccines often consist of combined immunization for several different diseases. Certain diseases are always produced in combination – such as measles, mumps and rubella, or diphtheria and tetanus. Therefore I count the combined product as one type of vaccine rather than three (or two) separate vaccines.

of achieving compliance with the existing vaccination schedule for childhood diseases. Medicare coverage of the influenza vaccine in 1993 followed over five years of demonstration projects designed to assess the cost-effectiveness of providing flu vaccines to Medicare beneficiaries. And the VICF was designed in response to a surge in product-liability lawsuits in the early 1980s that had prompted the withdrawal of companies from the manufacture of childhood vaccines and raised concerns about the continued availability of these childhood vaccines.

Third, all of these policies were expected at the time – from the perspective of people in the industry – to provide substantially increased demand-side incentives to develop new vaccines against the affected diseases. The increase in the return to investing in developing new vaccines against the affected diseases took a different form in the different policies; the empirical evidence therefore speaks to whether a variety of different types of demand-side incentives appear, on average, to affect investment decisions. The Hepatitis B recommendation provided increased demand-side incentives through the expectation of an increase in market size. Medicare coverage of the influenza vaccine combined with the information campaign was also expected to increase market size; additional demand-side incentives could stem from the potential for insurance coverage to weaken price sensitivity and thus result in higher prices. The VICF, on the other hand, reduced individual developer's exposure to risk through the creation of a common pool of funds to pay for lawsuits; in an option-value model of investment, this should result in increased investment (see e.g. Dixit and Pyndick 1994). In addition, the VICF also increased investment incentives by reducing expected liability costs, since the program included several measures to limit payouts for successful claims, including a cap on the payment for deaths (GAO 1999; HRSA 2002).

4. The data

Financial data on R&D expenditures of pharmaceutical companies for vaccines against particular diseases are unavailable. Indeed, at early stages in the R&D pipeline they may not even exist, as researchers may not yet know the therapeutic attributes of the compound under study.

Instead, I measure four outcomes of the underlying expenditure decisions. Three outcomes are designed to capture the decision to start a project at increasingly early stages of the R&D pipeline. They are, respectively: the start of a new clinical trial, the start of a new pre-clinical trial, and the filing of an (ultimately successful) patent application. The fourth measure is designed to capture the amount of resources devoted to a project once started; it is measured by whether a clinical project is stopped after only a year of clinical trials, or allowed to continue for more than one year. The following subsections describe the two primary data sources in more detail.

4.1 Data on new clinical trials, new pre-clinical trials, and continuation decisions

Data on new clinical or pre-clinical trials and on continuation decisions for a clinical trial, once started, come from an annual business publication, The NDA Pipeline, which has been published since 1982.[13] It is published by the F-D-C Reports, a well-regarded, long-established, research firm that serves the pharmaceutical industry.[14] The publication contains a listing for each company of all of its pharmaceutical products in development at the end of the calendar year, what stage in the pipeline each product is at, and a one-sentence description of the characteristics of each product.

The publication is U.S. centric: it aims to cover all companies with a presence in the United States. Data are collected from four primary sources.[15] These include any information publicly released by the company (for example to potential investors 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.

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[13] 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.
[14] Additional information about the company and its publication can be found at http://www.fdcreports.com.
[15] Based on conversations and e-mail correspondence with the F-D-C reports.

The general sense from people who work in the industry or use the reports is that these are reliable data.[16] While probably not completely comprehensive, the collection method is believed to ensure that it will get the vast majority of compounds in the development pipeline. It is, however, judged considerably more reliable for measuring clinical activity than pre-clinical activity, since firms may be less eager to advertise the former, given their much higher failure rate. I was able to check the general quality of the data both by ascertaining that any product I knew about was indeed in the data, and by observing the general continuity from year to year: products only rarely appear in the pipeline for a year, leave for several years, and then reappear.

The primary advantage of these data – besides their high quality – is that they are the only source that can be used to construct a compound's date of entrance into the pipeline and follow its subsequent progress through the pipeline, rather than merely providing information on its current status.[17] The primary disadvantage of these data is that they rely heavily on information that the company chooses to report. Companies are in general eager to report on substantive projects, for it attracts positive publicity and potential investor support and does not contain enough information to hurt them against their competitors. However, as noted above, this company eagerness to report is believed to apply more to clinical trials than to pre-clinical trials. Moreover, reports of stopping a project are virtually non-existent in the data; they must be inferred from a compound's disappearance from a company's portfolio from one year to the next.

I used 18 volumes of the publication, from 1982 through 1999, to compile a 17-year panel, starting in 1983, for each new compound's development history, from the start of a pre-clinical or a clinical trial, to its ultimate fate (when development is stopped or when the product is approved

[16] This was corroborated by the opinion of Dr. Joseph DiMasi of the Tufts Center for Drug Development which has proprietary access to more detailed R&D spending data (email correspondences February 2001).
[17] The data describe what phase of clinical trial the vaccine is in if it is in clinical trial. However, I do not have enough power to perform a separate analysis on the effect of the policies on transitions between phases. In addition, the lack of clear demarcating boundaries between phases of clinical trials (DiMasi et al. 1991) makes any attempt to analyze transition probabilities between phases problematic.

by the FDA).[18] I include in the sample all prophylactic vaccines for humans against infectious diseases, except for HIV/ AIDS.[19] I exclude vaccines designed to treat rather than prevent a disease and vaccines against cancer. Figure 1 shows the number of new clinical trials per year for the entire sample; it reflects the general increase in R&D activity.

4.1 Data on new patents

The U.S. Patent and Trademark Office has a searchable, on-line database with all approved patents dating back to 1976. I use this to create a database of the filing date of an (ultimately) successful patent application for patents approved through the end of 2001. 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 use a consistent 17-year time series from 1980 through 1996.[20]

5. The investment response to demand-side incentives: evidence from new clinical trials

5.1 Overview

Before presenting the formal econometric methodology and results, I begin by presenting some descriptive statistics that convey the substance of the empirical results. Table 1 contains the essence of the findings of the effect of increased demand-side incentives on the number of new clinical trials. The upper left panel shows the number of new clinical trials per year for vaccines

[18] The data are available as a repeated cross-section: each year's volume contains a listing of the vaccines in the pipeline in that year and their position in the pipeline. I turn this into a panel on each new compound's history by using the information on the company producing the product and the short description of each product to follow it from year to year. Many products also contain several additional paragraphs of detailed description which can be helpful in linking products from year to year.

[19] I exclude R&D on the AIDS vaccine because the changing public policies toward AIDS – both in terms of public health insurance coverage and in terms of supply-side R&D incentives – make it useful neither as a treatment or control vaccine.

[20] Inclusion of earlier years of data does not affect results. I chose 17 years of data to match the NDA Pipeline Data.

against each of the diseases affected by a change in policy.[21] I measure the beginning of a policy – denoted by the change from unbolded to bolded entries – as the first full year the policy was in effect.[22] The data reveal a basic pattern of an increase in the average number of new clinical trials per year after the introduction of a policy for vaccines against four of the six affected diseases: pertussis and DT (both affected by the VICF), hepatitis B and the flu vaccine. For these four diseases, there is, on average, an increase of about two new vaccine clinical trials per year per disease. This increase in new clinical trials tends to occur after about a one-year lag following the introduction of the policy, and to persist into later years.[23] There is no evidence, however, of an increase in new clinical trials for vaccines against two of the diseases –MMR or polio– associated with the policies.

A central concern with the time series analysis is that, as discussed above, the entire time period is one of increasing R&D and of technological advances that benefited vaccine development. 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 exogenous supply-side changes that may also have affected investment decisions. The primary candidate for confounding the effect of demand-side incentives is the effect of the technological advances described above.

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[21] New clinical trials for a flu vaccine refer not to the annual version of the vaccine against that year's influenza strain, but rather the underlying inoculation mechanism that is then adapted each year.
[22] 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" in the sense of being known to be happening.
[23] The one-year lag in response is consistent with the opinion of industry members that it could take a year or two for a decision to engage in more clinical trials to translate into a new clinical trial (e.g. Sanyour interview).

The choice of appropriate control diseases is an important and difficult one. The common technological basis for vaccines suggests the selection of a control group from among vaccines against other infectious diseases not affected by the policies. The most inclusive control group could include any other infectious disease in humans. However, this would include a large number of diseases for which there were no clinical trials at any point in the data, such as dengue fever, anthrax, small-pox, leprosy, and multiple sclerosis. Since such diseases by definition experience *no* increase in the number of new clinical trials over the time period, inclusion of such diseases in the control group could bias me toward finding an effect of the policies.

I therefore choose as a starting point a control group that consists of all 26 diseases for which there was at least one new clinical trial during my 17 years of data ("any clinicals"). This includes a large number of diseases for which there were no clinical trials in the first half of the data. Attempts to develop vaccines against some of these diseases – such as lyme disease – were made possible only with technological advances (Ellis 1999). By including such vaccines in the control group, I allow for a maximal possible role for technological change, a role that exceeds at least in percentage terms the effect on my affected diseases.

However, the "any clinicals" control group suffers from three potential limitations. First, the definition of the control diseases involves selection on the dependent variable: to be a control disease, there must be at least one new clinical trial. Second, the diseases in the treatment and control group differ on some important characteristics. In particular, in the period before any policy is in effect (1983-1986), the average rate of new vaccine clinical trials per year per disease is much lower for the control group than for the treated group (0.09 vs. 0.46). This follows directly from my decision to include in the control group diseases for which technological advances during the 1980s made possible the first attempts to develop a vaccine. In addition, at the start of the time period, there exists a vaccine against each of the affected diseases, but only 7 (27%) of the control diseases. In the empirical work, I can control for any fixed differences across the treatment and control diseases in the rate of new vaccine clinical trials. However, the

difference-in-differences analysis will be contaminated if diseases that differ on characteristics such as the amount of investment activity in the early years or whether a vaccine already exists are on different trends in the number of new vaccine clinical trials per year. A third concern is that a key characteristic of an appropriate control disease is that it is at a similar place on the innovation possibilities frontier as the treated diseases. In other words, the control diseases should control for the innate, unobserved, "technological potential" of the treated diseases.

To try to address these three issues, I define three alternative control groups that are strict subsets of the "any clinicals" control group. These control groups are designed to match on particular desirable features of the control diseases, specifically: similar activity in the pre-period, approved vaccines already existing, and technological potential. Table 2 provides summary statistics on the diseases included in each control group and in the treated group. It indicates, among other things, that diseases that match on one feature to do not necessarily match on another. Appendix B provides more detailed information on each disease separately.

The second control group, the "early clinicals", consists of the 10 diseases that had at least one new vaccine clinical trial in the first half of the data (i.e. before 1992); the average number of new clinical trials between 1983 and 1986 is substantially higher for this "early clinicals" group (0.23) and closer to the treated group (0.46) than the "all clinicals" control group (0.09).[24] The third control group, "existing approvals" consists of the 7 diseases that are included in "any clinicals" and had a vaccine in existence prior to the start of the data, in 1983. The fourth and final control group, "technology" is designed to select the sub-set of "any clinicals" that has the greatest innate technological potential. To do so, I draw upon the Institute of Medicine's 1985 report that lists 14 diseases for which new or improved vaccines would have substantial health

[24] An alternative approach would be to define the "early clinicals" control group as the set of 7 diseases that had at least one new clinical trial in the period 1983-1986 that predates all of the policies; the average rate of new vaccine clinical trials per year per disease for this control group is even higher, at 0.32. However, an unattractive feature of this approach is that one of the treated vaccines – the flu – had no new clinical trials before 1990. The estimated effect of the policy is essentially the same – and indeed very slightly larger – when this alternative definition of the "early clinicals" control group is used.

benefits in the United States and whose development was considered technologically feasible within the decade (Institute of Medicine 1985a). I define the "technology" control group as the 9 diseases from this list that are not affected by the policy (3 of the diseases were) and had at least one new clinical trials during the period studied (this excludes another 2). This approach has the extremely attractive feature that it selects the control diseases based on their otherwise-unobservable technological potential. It may, however, 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 are not included because the technological difficulties were considered too great or whether their development was not expected to convey substantial health benefits is unclear.

The bottom four rows of Table 1 show the trend in the number of new clinical trials per year for each of these four control groups. Consistent with the stylized fact of increasing R&D over this time period, all show a slight upward trend in the mean number of new vaccine clinical trials per year over the 1983-1999 time period.

The right-hand side of Table 1 shows the change in the average number of new clinical trials after the introduction of the policy for each affected disease. The first column shows the simple "before and after" change in means; the other four columns show the difference-in-differences estimate of the change in the average number of new clinical trials 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 slightly smaller than the simple (single) time differences. The estimates are not sensitive to the choice of control group.

The effect of the policies is statistically significant for vaccines against four of the six affected diseases. The rest of this section is devoted to verifying in a more formal manner the statistical importance and robustness of the descriptive results presented in Table 1.

5.2 Empirical framework

The unit of observation is a given disease in a given year. I focus on two dependent variables: the number of new vaccine clinical trials for that disease in that year and a binary measure of whether there were *any* new vaccine clinical trials for that disease in that year.

New clinical trials may be either for vaccines against individual diseases or for combination vaccines that provide immunization against multiple diseases. Since a combination vaccine for hepatitis B and HIB has immunization value against both diseases, it is counted twice in the data: once as a new clinical trial for Hepatitis B, and once as a new clinical trial for HIB. This introduces a potential difficulty in the difference-in-differences specification: if, for technological reasons, the treated diseases are most easily combined with control (simultaneously-treated) diseases, and the impact of the increase in the return on investment is to induce 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 for upward bias is small. It applies only to the estimated effect of the VICF that affected multiple diseases simultaneously. I partially address the issue by grouping five of these affected diseases – measles, mumps and rubella, and diphtheria and tetanus – 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 diseases ultimately affected by the VICF, 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 the next section I look separately at the effect of the policies on new clinical trials for solo versions of vaccines and continue to find evidence of an effect there.

As discussed above, I pursue two types of empirical strategies: deviations from disease-specific trends, and difference-in-differences. In the former approach, I limit the sample to the affected diseases and estimate the following equation:

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

The dependent variable – Newtrials_{it} – measures either the number of new clinical trials in year t for disease i, or whether there were any new clinical trials in year t for disease i. α_i is a disease-specific fixed effect; it controls for the different mean level of new clinical trials across different affected diseases. γ_t is a year fixed effect; it allows for the most flexible control 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 controls 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 a given year for a given disease.[25] With the controls in place, λ, the coefficient on ADOPT, measures changes in the number of new clinical trials associated with the policies, after controlling for fixed differences across diseases in the average number of new clinical trials per year, common year-to-year changes in the number of new clinical trials, and a disease-specific linear trend. The primary drawback to this approach is that it requires imposing a functional form assumption on 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:

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

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 fully-flexibly for common secular changes and disease-specific fixed effects. The identifying assumption is that, absent the policies, the

[25] I measure the beginning of the policy as the first full year the policy was in effect (or in the case of the VICF, known).

affected and control diseases would have had similar trends in the number of new vaccine clinical trials. Below, I conduct a partial test of this 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.

A potential concern with the difference-in-differences strategy is the possibility that new vaccine investment in the affected diseases induced by the policies may occur at the expense of vaccine investment that would otherwise have occurred in the unaffected diseases. Such crowd-out not only undermines the validity of the use of control diseases, 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 demand primarily 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 only about 4% (PhRMA 2001). Third, I find no evidence of substantively or statistically significant structural breaks in a linear or quadratic trend in the number of new clinical trials for diseases in the control groups associated with the introduction of the first policy, the VICF, which affected four of the six diseases.

The estimation approach is determined by the panel nature of the data and the distribution of the dependent variable. When the dependent variable is the number of new clinical trials in each

year for each disease, it ranges from 0-7.[26] I therefore estimate equations (1) and (2) using both a linear and a non-linear fixed effects model. The linear model's primary attractions are its ease of interpretation and its small sample properties. The count nature of the dependent variable suggest 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 size and shape of the size are sufficient for asymptotic inference. When the dependent variable is a binary measure of whether there are any clinical trials in a given year for a given disease, I again estimate the model using two different estimation techniques: a linear panel model and a conditional fixed effects logit model.

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 take the sample of control diseases, randomly assign treatment status to four of them in one year, and two others in two different years between 1985 and 1997, and re-estimate λ.[27] 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.[28] In general, the adjusted and unadjusted p-values are very similar.

5.3 Basic results

Table 3 reports the results from estimating equations (1) and (2) on the number of new clinical trials. I report results from the deviations-from-trends framework estimated with the linear fixed effects model, and from the difference-in-differences framework estimated for each

[26] Appendix Table D1 provides more detail on the distribution of the dependent variable.
[27] For equation (1) which is estimated on the treated only sample, I use the full sample of control vaccines ("any clinicals"); the results are not sensitive to this choice.
[28] Because I only perform 200 independent draws, I cannot estimate the exact value of the p value if it is below .01. Therefore for both the unadjusted and adjusted p-values I simply report that it is less than .01 if it is rather than an exact number. For others, I round the p-value up to the nearest 0.01.

of the four possible control groups, with both the linear fixed effects model and the conditional fixed effects negative binomial model.[29] The results show a striking uniformity in both significance and magnitude across these varied specifications. The effect of the policies is positive and statistically significant at at least the 5 percent level in eight of the nine specifications. The linear estimates suggest that the policies are associated, on average, with an increase of 1.2 to 1.3 new vaccine clinical trials per year for an affected disease. Between 1983 and 1986, each affected disease has 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. Given a 39% success rate for new vaccine clinical trials (Struck 1996), this implies that, after the initial 6 to 8 years it would take the new clinical trials to begin to reach approval, there would be an additional new vaccine against each disease almost every two years, relative to what would have been developed absent these new incentives. The negative binomial estimates are only slightly more sensitive to the specification. The three significant estimates suggest that the policies are associated with 2.2 to 2.8 times more new vaccine clinical trials per year per affected disease; it is reassuring that the estimated magnitude of the effect is similar in the linear and negative binomial specifications. The one insignificant estimate – when "any clinicals" is the control group – suggests an effect of comparable magnitude.[30]

I explored the sensitivity of these findings to enriching the deviations-from-trends estimation to allow each disease to have its own quadratic trend, and to enriching the difference-in-differences estimation to allowing for disease-specific linear trends or disease-specific quadratic trends. In the linear model – for which the full set of results are given in Appendix C – all of the

[29] The size and shape of the data do not permit estimation of the deviation-from-trends model (equation (1)) with the conditional fixed effects negative binomial model.

[30] These results speak to the average investment response. I examined whether the investment response to the risk-reducing VICF was different than the response to the market-enlarging effects of the hepatitis B and influenza policies. Both types of policies were separately associated with a significant increase in the number of new clinical trials started each year for their affected diseases. However, the investment response for diseases affected by the VICF was roughly half of that for the market-enlarging policies.

results remain significant at at least the 5% level.[31] The estimated magnitude of the effect of the policies declines somewhat in the difference-in-differences specification from 1.2-1.3 to 0.81-1.0.

I also examine whether the policies are associated with a change in whether there are *any* new clinical trials in a given year for a given disease. Table 4 reports the results, which are suggestive of an effect on this extensive margin. There is strong evidence of an effect on this margin in the linear fixed effects specification but only weak evidence of an effect in the conditional fixed effects logit model. In the sensitivity analysis incorporating disease-specific quadratic trends in the deviations-from-trend estimation, and disease-specific linear or quadratic trends in the difference-in-differences estimation, the linear results are essentially unchanged while the conditional fixed-effects logit results appear substantially stronger (results not shown). The linear estimates suggest that the policies are associated with a 0.2 to 0.3 percentage point increase – or a 50 to 75 percent increase – in the probability of starting a new vaccine clinical trials for a given disease in a given year.[32]

Finally, I enrich the difference-in-differences estimation of the effect of the policies on the number of new clinical trials to allow for dynamics both in the periods prior to the policies and in the timing of the response to the policies. Specifically, I replace the single ADOPT indicator variable with a series of mutually exclusive and exhaustive indicator variables for different periods relative to the implementation of the policies: 7 or more years prior to the policy, 4-6 years prior to the policy, 1-3 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.[33]

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[31] Once again, the size and shape of the data do not permit estimation of the negative binomial model with these disease-specific trends.

[32] Between 1983 and 1986, the average probability of starting a new vaccine clinical trial for an affected disease in a given year was 0.4

[33] Depending on the policy, there are between 4 and 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 age groupings to preserve the power of the statistical tests.

Figure 2 shows the results of estimating this dynamic version of equation (2) using a linear panel model and the "any clinicals" control group.[34] The figure graphs the coefficients on each of the different indicator variables representing different periods relative to the implementation of the policy; the dotted lines represent the 95 percent confidence intervals for these coefficients, based on the unadjusted standard errors; the adjusted standard errors (not shown) are comparable. The omitted category is 1-3 years prior to the policy for which I set the number of new clinical trials to its average for the affected diseases in this period.

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 control diseases would have had similar trends in the number of new clinical trials per year.

Second, the results indicate that the effect of the policies persists throughout the time period that I can observe. This suggests that the induced-increase in clinical trials did not represent merely a speeding up of the rate of planned investment. Rather, it suggests that the increased investment activity is in technologies that would not otherwise have been economically feasible and that the policies thus 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 and has been the subject of much policy discussion (see e.g. Institute of Medicine 1985a and 1985b). What has not been known, and what the results in this paper

[34] To conserve space, I do not report the results from the other three control groups; 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 3, the results are no longer significant.

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.

5.4 Resources devoted to the new clinical trials

The previous results speak to an increased willingness to start new projects associated with increased demand-side incentives. I now examine the effect of these incentives on the amount of resources devoted to the success of these new projects. A priori, the sign of the effect is ambiguous. On the one hand, the increased return to investment should increase willingness to invest in each project. On the other hand, the marginal projects whose undertaking is induced by the increased return to investment may be ones with lower ex-ante success rates; this should make companies less willing to devote resources to their success.

I proxy for increased resource devotions by an increase in the "success" rate of a project. Success is a binary indicator that takes the value 1 if the project is either approved by the FDA or in clinical trial for more than 1 year, and coded 0 if the project is stopped after 1 year. The high mean of the dependent variable – 86 to 89 percent of projects experience "success" by this measure – makes this a difficult margin on which to capture an effect. The results should therefore be viewed as suggestive in nature.[35]

The data for this component of the analysis are at the project-level: there are 163 new clinical projects started between 1983 and 1998.[36] I estimate the following equation:

$$\text{Success} = \sum_t \text{Startedyear(t)} + \sum_i \text{disease(i)} + \lambda \text{ADOPT} + \varepsilon \qquad (3)$$

Success is allowed to depend on a set of mutually exclusive indicator variables for the year the project entered clinical trials (Startedyear), a set of indicator variables for whether or not the

[35] Looking at a longer window creates greater censoring issues and, more critically, the loss of completed observations on the fate of ultimately-affected diseases that are fully in the pre-period.

[36] I exclude the 28 new clinical trials started in 1999 from the analysis since I do not observe them for long enough to know whether or not they continue for more than a year. I also exclude any clinical trial involving a vaccine against an affected disease in the year before the policy went into effect, since I do not observe them for the full window of time under the "pre-policy" regime; in practice, this involves excluding only 3 new clinical trials.

project would provide vaccination against each disease in the data, and the key variable of interest ADOPT, which is an indicator variable for whether the project involves one of the affected diseases *and* was started after the policy affecting that disease was in effect.

Once again, I employ a difference-in-differences approach, with the four different definitions of the control group. I report results in Table 5, based on estimating equation (3) with a linear probability model, a logit model, and a probit model. The results are consistent with the increased return on investment being associated with an increased devotion of resources to the success of new projects.

6. The nature of the investment response

The results in the previous section established the principle finding that investment in vaccine development responds to policies that increase the return on such investment. This section delves deeper into the *nature* of this investment response. Specifically, I conduct two separate investigations designed to gauge the extent to which there is induced investment in developing fundamentally new technologies, rather than just commercializing related technologies.

6.1 Combination vs. solo versions of vaccines

I exploit the distinction between two types of vaccines: combination vaccines, which provide immunization against multiple diseases, and solo vaccines. Clinical trials for solo vaccines represent more of an attempt to commercialize a fundamentally new technology, than combination vaccines, which are developed by combining existing technologies for immunizing against individual diseases into a single administration. Combination vaccines, often referred to within the industry as "mix and match", are considered to be cheaper and lower risk to develop (see e.g. Greenberg interview, Wolters interview), which might lead us to expect more of a response on this margin. However, if there is more of a reservoir of technically-feasible but not-quite-economically-attractive products for solo vaccines, this would suggest more of an investment response on the solo-vaccine margin.

I re-estimate equations (1) and (2) on two separate dependent variables: the number of new solo vaccine clinical trials in a given year for a given disease, and the number of new combination vaccine clinical trials in a given year for a given disease.[37] Table 6 reports the results. The results from the linear fixed effects model suggests effects on both margins. However, in results not shown here, I find that all of the linear estimates for solo vaccines are robust to the sensitivity tests of incorporating disease-specific quadratic trends in the deviations-from-trend estimation, and disease-specific linear or quadratic trends in the difference-in-differences estimation; none of the results for the combination versions of vaccines is robust to these sensitivity tests. Table 6 also contains the puzzling finding that none of the results from the basic specifications are still significant for either dependent variable in most of the negative binomial specifications. On balance, the evidence is more suggestive of an effect for solo versions of vaccines than for combination versions of the vaccines. There is thus reason to believe that the investment response represents attempts to develop substantively new vaccine technologies.

6.2 The investment response at earlier stages in the R&D pipeline

I also investigate whether there is an investment response to demand-side incentives at two early stages of the R&D pipeline than clinical trials: the decision to start new pre-clinical trials and the completion of research that results in the filing of ultimately successful patent applications. Investments in such earlier stages represent more fundamental contributions to the state of technology than investments in new clinical trials, which involve attempts to commercialize existing technologies. As with new clinical trials, there is a general increase in these R&D activities over the time period.

A priori, there are two reasons to expect less of an investment response on these earlier margins: these early stages involve greater risk of failure and they are further away in time from

[37] Appendix Table D1 shows the distribution of these dependent variables.

when profits might be earned, making the uncertainty about future policy more of a deterrent.[38] Two additional factors suggest there might be even less of an investment response on the patents margins. Patents tend to involve a greater proportion of actors who are not in the for-profit sector, and a greater proportion of the investment inputs into patent creation are the human capital of scientists (rather than say, animals and humans needed for the clinical trials); the supply response on this margin may be quite inelastic, particularly in the short run (see e.g. Goolsbee (1998) or Romer (2001)). Again, however, there is no a priori reason why there might not be a greater stock of technologically-feasible but not economically-attractive ideas that could produce new patents or new pre-clinical trials than there is for clinical trials. This could produce a greater responsiveness on these earlier margins.

Both the measure of new pre-clinical trials and the measure of new patent filings have their limitations. As discussed, the data on new pre-clinical trials from The NDA Pipeline is probably less comprehensive than the data on new clinical trials. The patent data – while extremely accurate – suffers from two other potential limitations. First, a lower proportion of new technologies are patented in vaccines than in other pharmaceuticals. Most of the technology is naturally occurring and based on components of living organisms; vaccine patents tend therefore to be limited to process rather than product patents. Second, the filing date of an ultimately successful patent will capture with a lag any increase in investment in patentable processes.[39]

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

[38] Compare, for example, the estimated 23% approval rate for new compounds entering clinical trials (DiMasi et al. 1991) with the estimate that only about 1% of compounds entering pre-clinical trials will even make it to clinical trials (Gelijns 2000).

[39] To try to address this issue, I also examine the sensitivity of the results on new patent filings to allowing for a 3 year lag in the response (i.e. looking for an effect 4+ years out). The results are not sensitive to this alternative specification. Of course, to the extent that lags are even longer, I may not be capturing them.

consistency, the same groups of control diseases used for the analysis of new clinical trials.[40] The distributions of the dependent variables are given in Appendix Table D2.

Table 7 reports the results. The evidence does not suggest a substantive or statistically significant change in either of these investment activities associated with the policies.[41] The lack of a decline in investment activity suggests that the increased investment in new clinical trials was not financed by a substitution of effort away from investment in earlier stages of the R&D pipeline. There is not, however, any evidence, of increased investment in these earlier stages in the R&D pipeline in response to the policy incentives. An unanswered question is whether larger economic incentives could generate a positive response on these margins and whether technological constraints are ultimately binding on these more basic stages of R&D. The latter would suggest a limit to the ability to sustain a long-run increase in new clinical trials in response to demand-side incentives, since the stock of existing technologies to be commercialized would ultimately be depleted.

7. Implications: 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 ("static" consequences) and to the health benefits from improved versions of the existing vaccines ("dynamic" consequences). It is assumed that the induced inventive activity is socially beneficial. While, in theory, the level of private R&D may be either too much or too little from a social perspective (see e.g. Tirole 1990), in practice, the preponderance of empirical evidence suggests that the social returns to R&D far exceed the private returns (see e.g. Griliches (1992) or Jones and Williams (1998)). This seems particularly

[40] The results, however, are not sensitive to defining the control diseases as those that had any new pre-clinical trials during the data, or any new pre-clinical trials before 1992.

[41] When the number of new patents is the dependent variable, two of the negative binomial specifications suggest a significant decrease in the number of new patents filed. However, this finding is only significant with the unadjusted standard errors.

compelling for vaccine development, where there are substantial positive public health externalities. Indeed, Kremer (2001) performs a back-of-the-envelope calculation that suggests that the social returns to developing a malaria vaccine may be 10 to 20 times greater than the private returns.[42]

The calculation requires several additional assumptions. In all instances, as I describe in more detail below, I have erred on the side of being conservative in estimating the potential health benefits from the induced inventive activity, and liberal in estimating the health benefits from the increased use of existing technology. The results should therefore be viewed as a lower bound on the magnitude of the dynamic health benefits relative to the static health benefits. Nevertheless, even this lower bound suggests that the dynamic benefits are of the same order of magnitude as the static benefits.

I limit the analysis to two of the three policies, the recommendation for universal hepatitis B vaccination of the birth cohort and Medicare coverage of the flu vaccine, for which it is possible to estimate the increase in vaccination (the key static benefit). The vaccine injury compensation fund 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.

7.1 Calculation of static health benefits

The static health benefits depend on the increase in vaccination rates associated with the policies, the health benefits from successful vaccination, and the success rate, or "efficacy" of the vaccine at disease prevention. The following equation summarizes this relationship; the year in which the policy goes into effect is denoted t=1:

$$\text{Static benefits} = \sum_{t=1}^{\infty} \frac{(V_t - V_0) * E_0 * \text{VPIV}}{(1+r)^t} \qquad (4)$$

[42] Of course, the fact that on average, the social return to vaccine development exceeds the private return does not mean that the *marginal* increase in inventive activity induced by the demand-side incentives is socially beneficial. It is in principle, possible, that the induced investment represents almost entirely business-stealing activity with little social value. Unfortunately, I have not found a way to test this possibility with the existing data.

V_t denotes the vaccination rate in year t. I make liberal assumptions about the increase in vaccination rates associated with the two policies, assuming that all of the time series increase in vaccination rates following the policy is attributable to the policy.[43] This approach suggests that the policies could have been associated with as large as a 16 percentage point increase in influenza vaccination rates among Medicare beneficiaries (from 51% in 1993 to 67% in 1999), and as large as a 90 percentage point increase in vaccination rates for hepatitis B among the birth cohort (from less than 1 percent vaccination rates in 1989 to 90 percent vaccination in 2000). Appendix A provides more information on the data behind these calculations and on the distribution of the increase in vaccination rates over the time period following the policies, which affects the calculation of the static health benefits. I assume that the vaccination rates in 1999 (or 2000) induced by the policies will persist in the long-run and therefore extrapolate these rates forward for future periods.

E_0 denotes the vaccine's efficacy prior to the policy going into effect. I assume a 70% efficacy for the flu vaccine for the elderly; this is the upper end of the 40-70% range of estimates reviewed by Kilbroune and Arden (1999). I assume a 95% efficacy for the hepatitis B vaccine in infants (Mahoney and Kane (1999)), although efficacy of the existing Hepatitis B vaccine may have been lower in 1992 when the Hepatitis B recommendation was implemented.

VPIV stands for "vaccine preventable illness value." It measures the health benefits from 100% vaccination of the target population by a vaccine that is 100% effective. I use the VPIV estimates developed by the Institute of Medicine (Institute of Medicine 1985a). The VPIV is expressed as the undesirability of the population-wide morbidity and mortality associated with the disease relative to the undesirability of the death of an infant. Such an exercise is obviously fraught with subjective assumptions. One of the advantages to using the Institute of Medicine's

[43] This ignores the existence of a pre-existing upward trend in influenza vaccination rates for Medicare beneficiaries, as well as the possibility that some of the increases in the hepatitis B vaccination rate in later years may have been due to the approval of new hepatitis B vaccines, rather than the direct result of the policy.

estimates is that I can use it for all of the "disease burden" estimates in the calculations, so that the comparisons are at least internally consistent.[44]

I experiment with two different discount rates (r): a 3% and a 5% real discount rate. The latter is what the Institute of Medicine uses in discounting potential benefits from future vaccine development. (Institute of Medicine 1985a). The results of calculating equation (4) based on these parameters are reported in Table 8.

7.2 Calculation of dynamic health benefits.

There are at least five different mechanisms by which increased investment in new clinical trials for the Hepatitis B and influenza vaccines might produce future health benefits. These include: the 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 vaccines with higher efficacy, increased vaccination rates for these two diseases in response to the decrease in side effects and increase in efficacy, and increased vaccination rates for other diseases to the extent that the improved vaccines reduce the general fear of vaccines or result in combination vaccines that reduce the number of shots needed to comply with the overall immunization schedule (see e.g. Institute of Medicine (1985a).

Of these five potential dynamic benefits, I can find reasonable estimates for only two: increases in efficacy and increases in utilization for the affected diseases. I therefore ignore the potential dynamic benefits accruing from the other three mechanisms.[45] I use the Institute of Medicine's (1985a) estimate that an improved version of the flu vaccine is expected to have an efficacy of 85% (an increase of 15% over the 70% current efficacy). For the hepatitis B vaccine, since current efficacy is 95%, I assume that there is no potential for further increases in efficacy. I assume an upper bound on the vaccination rate of 95%. This seems to be the rate that health

[44] In addition, the choice of VPIV will not affect the *ratio* of the dynamic to static health benefits.
[45] The possibility of spillovers could, in an extreme sense, inflate the expected dynamic benefits infinitely: there is an infinitesimal chance that the induced inventive activity could prompt the discovery of a compound with infinite benefits.

experts accept as a possible upper bound (see e.g. Institute of Medicine (1985a)); given the self-limiting nature of demand for vaccines described by Geoffard and Philipson (1997), vaccination rates at 100% may be unrealistic.

Since the static impact of the hepatitis B policy was estimated to bring the vaccination rate up to 90%, to be conservative I assume no possible increase in utilization of hepatitis B. Because of these assumptions – and the ignoring of the other potential dynamic benefits – the conservative benchmark assumes *no* dynamic health gains from the hepatitis B vaccine. My conservative estimate of the dynamic health benefits from the induced innovation are therefore a function only of predicted increases in efficacy and in vaccination rates for the flu vaccine. This biases downward considerably the relative estimates of dynamic compared to static health benefits.

The following equation represents the dynamic benefits for the flu policy, from the perspective of 1994:

$$\text{Dynamic benefits} = \sum_{t=1}^{\infty} \frac{[(V_t * E_t) - (V_S * E_0)] * VPIV}{(1+r)^{t+8}} \qquad (5)$$

The notation is the same as in equation (4); V_S denotes the vaccination rate achieved by the static effects of the policy (i.e. 70% in the case of the flu vaccine). I assume that the dynamic health benefits only begin to accrue after 9 years. This allows a one year lag in the response of new clinical trials to the policy (based on the evidence in Table 1), and 8 years from the start of the new clinical trial to approval (Struck 1996). The empirical estimates suggest that, beyond this point, the policy should be associated with on average a new approved product every 2 years. The Institute of Medicine (1985a) assumes that the benefits of new vaccines for hepatitis B and flu could be achieved within 10 years from the start of development. To be conservative, I assume that the full benefits are achieved after three new product approvals, thus taking 13 years in total for the full dynamic benefits to be achieved, and that each new product conveys 1/3 of the total benefits.

The results of calculating equation (5) based on these parameters are reported in Table 8.

7.3 Comparison of static vs. dynamic health benefits

Since, by assumption, there are no dynamic health benefits for the hepatitis B policy, the ratio of dynamic to static health benefits for hepatitis B is zero. However, the results in Table 8 indicate that, for the flu policy, the discounted value of the dynamic health benefits is about double the static benefits, even with ignoring many of the possible dynamic 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 comparable to the static benefits.

The results therefore suggest that in considering the health consequences of health policies it is critical to consider not just their static benefits via increasing utilization of existing technology, but also their dynamic benefits via improving the technological opportunity set. For example, in evaluating alternative proposals for extending health insurance to the poor, economic analysis has focused on the marginal increase in insurance coverage per dollar spent of alternative policies. The results of this paper suggest that this type of analysis is incomplete. For example, two of the possibilities that are often discussed – namely, tax subsidies to private health insurance purchased by the poor and extension of public health insurance coverage – are likely to have diametrically *opposed* dynamic consequences, with public health insurance potentially reducing demand-side incentives through low reimbursement rates and tax subsidies to private health insurance potentially increasing demand-side incentives through reduced price sensitivity of the consumer.

8. Conclusion

This paper provides empirical evidence of the dynamic consequences that health policies, designed to increase access to existing medical technology, can have on the development of new medical technologies. I examine the investment response to three policies that increased the return on investment 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 an average increase of 1.2 to 1.3 new vaccine clinical trials per year for each affected disease; this represents a 2.5-fold increase in the number of new vaccine clinical trials for these diseases. Additional evidence is consistent with pharmaceutical companies also devoting increased resources toward the success of each new clinical trial when the return to successful development increases. However, the effects of the increased demand-side investment incentives appear to be limited to the latest stage of the R&D pipeline: clinical trials. I find no evidence that these incentives affect decisions to engage in more basic inventive activities, such as pre-clinical trials or basic research that can lead to new patents. An unanswered question is whether larger demand-side incentives would have an effect on these more fundamental aspects of R&D, or to what extent there is a limit on the ability to "dial-up" the investment response to demand-side incentives. I regard this as a fruitful area for further work.

Under conservative assumptions, the health benefits from the induced investment in vaccine development are equivalent to those from the increased utilization of existing vaccine technology induced by the policies. The results in this paper therefore underscore the inadequacy of considering only static health consequences when evaluating the effects of health policies on health outcomes.

An important issue for interpreting the empirical results is whether the new clinical trials induced by the demand-side incentives embodied in the policies represent a *net* increase in investment activity or merely a substitution of activity. While the available data do not permit a definitive test of these alternatives, two pieces of evidence suggest that the induced activity is not merely substitution. First, the new activity does not appear to represent merely a substitution in the timing of planned activity toward an earlier point in time; the estimated increase in the number of new clinical trials for affected diseases persists in the long-run, as measurable in the data. Second, there is no evidence that companies respond to the increased

incentives by substituting investment from earlier stages of the R&D pipeline, such as pre-clinical trials, to later stages.

The empirical evidence in the paper bears most directly on how demand-side incentives affect decisions to develop improved versions of existing vaccines. This is currently of considerable interest for existing, but old, versions of vaccines against diseases such as small pox and anthrax, due to the increased demand for them in the face of increased fear about bio-terrorist attacks. Most interest in new vaccines for developing countries, however, involves the creation of first versions of vaccines against diseases such as malaria or HIV. To the extent that a critical determinant of the investment response is that existence of a reserve of technologically but not economically feasible products, there is reason to believe that the investment response to demand-side incentives may be comparable for improved versions of existing vaccines and for new vaccines. For example, in 1985, the Institute of Medicine produced a list of 19 diseases for which improved versions of existing vaccines or first versions of the vaccine would have substantial health benefits in developing countries and that were judged technologically feasible within the decade; 6 of these were diseases for which vaccines already existed while 13 were not (Institute of Medicine, 1985b).

As discussed, vaccine development shares many key features with development of other pharmaceutical products. As such, the results in this paper are suggestive of the effects of demand-side incentives on pharmaceutical products more generally. 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 also exhibit the same responsiveness to financial incentives. To the extent that they are *less* responsive, demand-side incentives may affect not only the rate of technological progress in the health sector, but also the composition of care. I regard this as a natural direction for future work.

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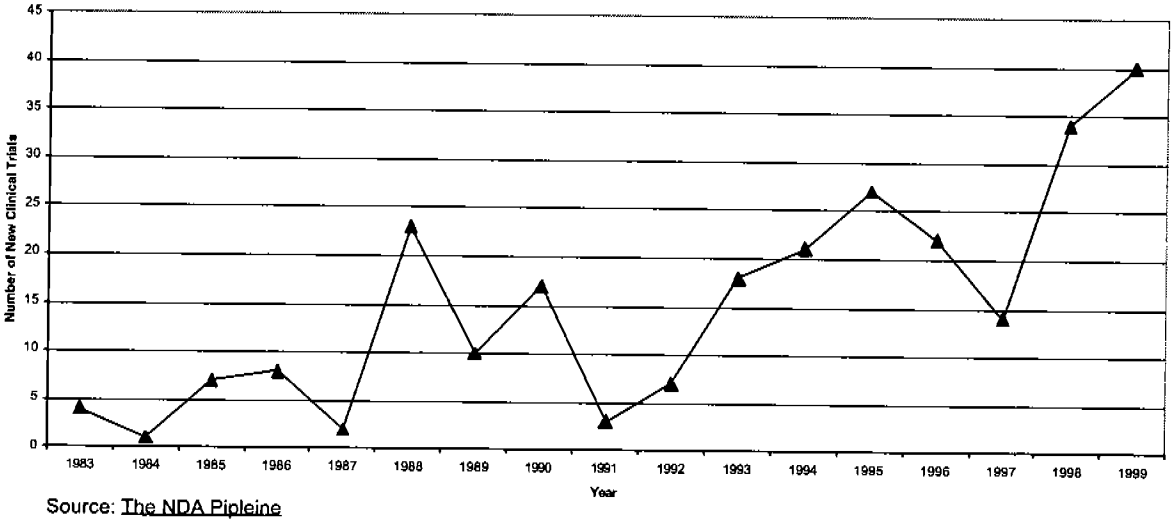
Figure 1: New Vaccine Clinical Trials, 1983-1999



Source: The NDA Pipleine

Table 1: Number of new vaccine clinical trials per year

Disease	Year Clinical Trials Started																
	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99
Pertussis	**1**	1	0	0	**0**	**5**	**4**	**5**	**1**	**1**	**3**	**4**	**5**	**1**	**0**	**2**	**6**
MMR	0	0	1	0	**0**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
DT	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**	**4**
Flu	0	0	0	0	0	0	0	2	1	0	**1**	**2**	**1**	**3**	**2**	**4**	**3**
Control diseases																	
"Any clinicals"	.04	0	.12	.19	.04	.42	.15	.19	.04	.19	.35	.46	.38	.42	.42	.81	.69
"Early clinicals"	.10	0	.30	.50	.10	1.1	.40	.50	.10	.30	.20	.60	1.0	.60	.30	.30	.70
"Prior approvals"	0	0	0	.43	0	.14	0	0	0	.29	.86	.71	.29	.57	.29	.71	.71
"Tech-nology"	.11	0	.22	.11	.11	.56	.11	.44	.11	.33	.22	.44	.89	.56	.44	.56	.67

Change in Avg # of New Clinical Trials Per Year After Poli				
Abs. Change	Relative to "Any Clinicals"	Relative to "Early Clinicals"	Relative to "Prior Approvals"	Relative to "Tec nology"
2.35** (1.09)	2.08*** (0.43)	2.09*** (0.56)	2.10*** (0.54)	2.04*** (0.54)
-0.02 (0.26)	-0.29 (0.38)	-0.27 (0.46)	-0.26 (0.38)	-0.33 (0.42)
1.83 (1.06)	1.56*** (0.43)	1.58*** (0.55)	1.58*** (0.53)	1.52*** (0.53)
0.19 (0.46)	-0.07 (0.39)	-0.06 (0.48)	-0.05 (0.40)	-0.12 (0.44)
1.97** (0.67)	1.64*** (0.34)	1.82*** (0.44)	1.48*** (0.39)	1.66*** (0.41)
2.14*** (0.42)	1.76*** (0.04)	1.88*** (0.42)	1.74*** (0.35)	1.76*** (0.38)

Notes:

- Changes to bold indicates the start of a new policy
- Entries for control groups represent average number of new clinical trials per year
- Standard errors in parentheses
- ***, **, * indicates significance at the 1%, 5%, and 10% level respectively.

Table 2: Summary statistics for treatment and control groups

Group	Included Diseases	Number of Diseases	Percent of diseases with new clinical trials before 1992	Percent of diseases with existing vaccines before 1983	Percent of diseases on Institute of Medicine's (1985a) list	Average number of new clinical trials per year per disease:	
						1983-1986	1996-1999
Treated diseases	DT, Hepatitis B, Influenza, MMR, Pertussis, Polio,	6	100%	100%	50%	0.46	2.04
"Any clinicals"	Chlamydia, Cholera, Cytomagalovirus, E. Coli, Epstein-Barr Virus, Gonorrhea, Haemophilus Influenza B, Helicobacter pylori, Hepatitis A, Hepatitis C, Herpes, Human Papilloma Virus, Japanese Encephalitis, Lyme Disease, Malaria, Meningitis, Otitis Media, Parainfluenza, Pneumonia, Respiratory Syncytial Virus, Rotavirus, Streptococcus, Tuberculosis, Typhoid, Varicella, Yellow Fever	26	38%	27%	35%	0.09	0.59
"Early clinicals"	Cholera, Gonorrhea, Haemophilus Influenza B, Hepatitis A, Herpes, Malaria, Parainfluenza, Rotavirus, Typhoid, Varicella,	10	100%	20%	60%	0.23	0.48
"Prior approvals"	Cholera, Meningitis, Pneumonia, Streptococcus, Typhoid, Tuberculosis, Yellow Fever	7	29%	100%	14%	0.11	0.57
"Technology"	Cytomagalovirus, Gonorrhea, Haemophilus Influenza B,, Hepatitis A, Herpes, Parainfluenza, Respiratory Syncytial Virus, Rotavirus, Streptococcus	9	67%	11%	100%	0.11	0.56

Table 3: Effect of policies on number of new clinical trials

	Linear Fixed Effects Model					Conditional Fixed Effects Negative Binomial Model			
	Treated sample only (deviation-from-trend estimation)	Control Group : "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"	Control Group: "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"
ADOPT	1.275***	1.187***	1.269***	1.206***	1.195***	1.627	2.802***	2.151**	2.194**
	(0.486)	(0.183)	(0.240)	(0.261)	(0.241)	(0.516)	(0.920)	(0.785)	(0.754)
Unadjusted p-value	0.01	<0.01	<0.01	<0.01	<0.01	0.12	<0.01	0.04	0.02
Adjusted p-value	<0.01	<0.01	<0.01	<0.01	<0.01	0.23	<0.01	0.06	0.03
Mean Dep. Var	1.27	0.47	0.74	0.75	0.72	0.47	0.73	0.75	0.72
Number of Diseases	6	32	16	13	15	32	16	13	15
N	102	544	272	221	255	544	272	221	255

Notes: First column reports results from equation (1); all other columns report results from equation (2). All regressions include year and vaccine fixed effects. Coefficients reported for negative binomial model are exp(?). 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 Table 2 for description of control groups.

Table 4: Effect of policies on *any* new clinical trials (zero-one margin)

	Linear Fixed Effects Model					Conditional Fixed Effects Logit Model				
	Treated sample only (deviation-from-trend estimation)	Control Group = "Any Clinicals"	Control Group = "Early Clinicals"	Control Group = "Prior Approvals"	Control Group = "Technology"	Treated sample only (deviation-from-trend estimation)	Control Group = "Any Clinicals"	Control Group = "Early Clinicals"	Control Group = "Prior Approvals"	Control Group = "Technology"
ADOPT	0.320*	0.188**	0.258**	0.187*	0.207**	4.744**	0.464	1.349*	0.833	0.799
	(0.181)	(0.088)	(0.106)	(0.110)	(0.104)	(2.000)	(0.669)	(0.701)	(0.768)	(0.738)
Unadjusted p-value	0.08	0.03	0.02	0.09	0.05	0.02	0.49	0.06	0.28	0.28
Adjusted p-value	0.07	0.04	<0.01	0.25	0.14	0.56	0.61	0.06	0.65	0.66
Mean Dep. Var	0.56	0.27	0.39	0.37	0.37	0.56	0.27	0.39	0.37	0.37
Number of Diseases	6	32	16	13	15	6	32	16	13	15
N	102	544	272	221	255	102	544	272	221	255

Notes: Dependent variable is whether there are *any* new clinical trials for vaccines against a given disease in a given year (zero-one margin). The first column on each half of the table reports results from estimating equation (1); all other columns report results from estimating equation (2). See notes to Table 3 for more details.

Figure 2: Dynamic effect of policies on new clinical trials

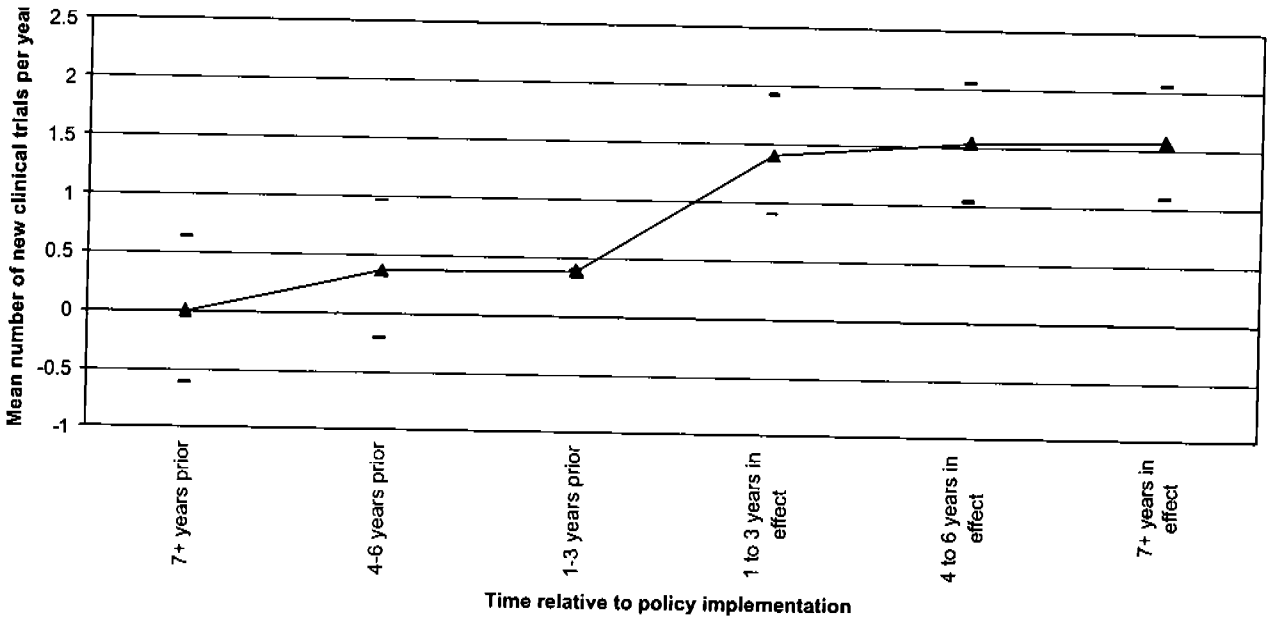


Table 5: Effect of the policies on intensity of investment

	Linear Probability Model				Logit				Probit			
	Control Group = "Any clinicals"	Control Group = "Early clinicals"	Control Group = "Prior approvals"	Control Group = "Technology"	Control Group = "Any clinicals"	Control Group = "Early clinicals"	Control Group = "Prior approvals"	Control Group = "Technology"	Control Group = "Any clinicals"	Control Group = "Early clinicals"	Control Group = "Prior approvals"	Control Group = "Technology"
ADOPT	0.356*** (0.133)	0.302** (0.133)	0.526*** (0.187)	0.360** (0.148)	5.166*** (1.845)	4.555*** (1.917)	**Can't estimate**	4.791** (2.001)	3.053*** (1.024)	2.702** (1.100)	**Can't estimate**	2.848** (1.142)
Unadjust. p-value	<0.01	0.03	<0.01	0.02	<0.01	0.02		0.02	<0.01	0.02		0.02
Mean Dep. Var	0.87	0.89	0.87	0.86	0.87	0.89		0.86	0.87	0.89		0.86
N	163	123	101	109	163	123	101	109	163	123	101	109

Note: Results reported are from estimating equation (3). The dependent variable is an indicator variable for whether the project was either approved or in clinical trials for more than one year; it is zero if the project was stopped after a year. See Table 2 for a description of the control groups.

Table 6: Effect of policies on new clinical trials for solo vs. combination versions of vaccines

	Linear Fixed Effects Model					Conditional Fixed Effects Negative Binomial Model			
	Treated sample only (deviation-from-trend estimation)	Control Group: "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"	Control Group: "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"
SOLO VERSIONS OF VACCINES									
ADOPT	0.864*** (0.308)	0.393*** (0.133)	0.541*** (0.169)	0.473*** (0.178)	0.481*** (0.162)	1.157 (0.431)	2.57** (1.01)	1.590 (0.684)	1.863 (0.767)
Unadjusted p-value	<0.01	<0.01	<0.01	<0.01	<0.01	0.70	0.02	0.28	0.13
Adjusted p-value	0.02	<0.01	<0.01	0.05	<0.01	0.82	0.04	0.36	0.23
Mean Dep. Var	0.55	0.29	0.40	0.38	0.37	0.29	0.40	0.38	0.37
COMBINATION VERSIONS OF VACCINES									
ADOPT	0.411 (0.349)	0.795*** (0.121)	0.728*** (0.172)	0.733*** (0.189)	0.714*** (0.177)	3.096 (2.267)	4.241* (3.217)	4.597* (4.108)	3.388 (2.661)
Unadjusted p-value	0.24	<0.01	<0.01	<0.01	<0.01	0.12	0.06	0.09	0.12
Adjusted p-value	0.01	<0.01	<0.01	<0.01	<0.01	0.15	0.09	0.11	0.12
Mean Dep. Var	0.73	0.19	0.34	0.37	0.35	0.19	0.34	0.37	0.35
Number of Diseases	6	32	16	13	15	32	16	13	15
N	102	544	272	221	255	544	272	221	255

Notes: See Table 3

Table 7: Effect of policies on investment in earlier stages of the R&D pipeline

	Linear Fixed Effects Model					Conditional Negative Binomial Fixed Effects Model			
	Treated sample only (deviation-from-trend estimation)	Control Group: "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"	Control Group: "Any Clinicals"	Control Group: "Early Clinicals"	Control Group: "Prior Approvals"	Control Group: "Technology"
NEW PRECLINICAL TRIALS									
ADOPT	-0.326 (0.423)	0.115 (0.173)	0.310 (0.196)	0.057 (0.236)	0.109 (0.213)	0.623 (0.214)	1.286 (0.456)	0.684 (0.320)	0.808 (0.305)
Unadjusted p-value	0.44	0.51	0.12	0.81	0.61	0.17	0.49	0.42	0.57
Adjusted p-value	0.23	0.56	0.05	0.96	0.78	0.96	0.53	0.81	0.99
Mean Dep. Var	0.78	0.46	0.51	0.54	0.55	0.46	0.51	0.54	0.55
NEW PATENTS									
ADOPT	0.199 (0.581)	-0.031 (0.220)	-0.029 (0.268)	-0.164 (0.290)	-0.039 (0.278)	0.641** (0.145)	0.729 (0.179)	0.510*** (0.138)	0.685 (0.169)
Unadjusted p-value	0.73	0.89	0.92	0.57	0.89	0.05	0.20	0.01	0.13
Adjusted p-value	0.45	0.98	0.92	0.68	0.90	0.43	0.53	0.43	0.60
Mean Dep. Var	1.40	0.70	0.90	0.90	0.94	0.70	0.90	0.90	0.94
Number of Diseases	6	32	16	13	15	32	16	13	15
N	102	544	272	221	255	544	272	221	255

Notes: For the top panel, the dependent variable is the number of new pre-clinical trials; for the bottom panel, the dependent variable is the number of filings for (ultimately successful) patents. See notes to Table 3 and text for more details.

Table 8: Static vs. dynamic health benefits from policies

Disease	Initial Parameters			Static Effects			Dynamic Effects				Ratio: Dynamic Benefits / Static Benefits	
	Vaccine Preventable Illness Value (VPIV)	Initial Vaccination Rate (V_0)	Initial Efficacy Rate (E_0)	Change in Vaccination Rate $(V_S - V_0)$	Static Benefits r = 0.03	r=0.05	Change in Vaccination Rate $(V_D - V_S)$	Change in Efficacy Rate $(E_D - E_0)$	Dynamic Benefits r = 0.03	r=0.05	r = 0.03	r=0.05
Hepatitis B	2,936	0	0.95	0.90	63,544	30,074	0	0	0	0	0	0
Flu	10,644	0.51	0.70	0.67	37,992	22,097	0.25	0.15	91,315	43,275	2.40	1.96
Average											1.20	0.98

Notes: S denotes first time period in which static effects have all been realized; D denotes first time period in which dynamic effects have all been realized. Reported benefits are the discounted present value of health benefits expressed in Infant Mortality Equivalence (i.e. relative to the disutility of an additional infant death). See text for more detail on the calculation and the inputs. The VPIV represents estimates of the infant mortality equivalence associated with the reduced disease burden from 100% vaccination of the target population with a vaccine that is 100% effective; these numbers are taken from Institute of Medicine (1985a).

Appendix A: Detailed description of policy changes.

1. ACIP recommendation of universal Hepatitis B vaccination for infants (July 1991)

- *Rationale:* High risk groups for hepatitis B infections are considered to be homosexuals, intravenous drug users, promiscuous heterosexuals and health care works. (CDC 2002). These are groups that do not have a great deal of contact with the health care system. As a result, prior to this recommendation, attempts to selectively vaccinate people with identifiable risk-factors had not been successful (see e.g. Institute of Medicine 1985a; CDC (2002)). The decision to recommend universal vaccination of the birth cohort followed a long-drawn out political process in which the benefits of being able to ensure vaccination of the at-risk group were weighted against the possibility that this recommendation might decrease parental willingness to comply with the overall childhood immunization schedule (which was otherwise limited to childhood diseases such as measles, mumps, rubella, diphtheria, tetanus, pertussis, and polio). The fact that Hepatitis B is not a childhood disease prompted the concern that its recommendation could increase the general mistrust that many parents feel for the recommended vaccinations. (Snyder interview, Grady interview, Kaye interview)
- *Was the timing the result of technological developments?* The first Hepatitis B vaccine, developed by Merck, was approved in the US in 1981. The policy could clearly not have been implemented without the existence of a vaccine, but there is no indication either in the records of the ACIP committee (ACIP, 1991) or in conversations with policymakers (e.g. Snyder) that recent changes in the nature of the hepatitis B vaccine in any other way influenced the decision. Rather, the decision appears based on a recognition of the lack of success in reaching the at-risk group, and a long drawn out political battle over adding the vaccine to the recommended childhood immunization schedule. Furthermore, since it occurred 10 years after the introduction of the first vaccine and occurred after much wrangling and doubts as to its success, it is hard to argue that the policies ultimate adoption, much less its timing, could have been anticipated.
- *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.[46] Indeed, subsequent evidence indicated a dramatic and rapid expansion of infant hepatitis B vaccination following the national recommendation; for example, the National Health Interview Survey indicated that completion of the immunization schedule for infants 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). By 2000, national coverage rate for hepatitis B vaccine among children aged 19-35 months increased from 16% in 1993 to 90% in 2000 (CDC 2002). I estimate that much of this increase was likely to be caused by the policy. For example, Hepatitis B vaccination rates for children under 6 increased from under 15% in 1992 to over 65% in 1996. By contrast, vaccination rates for other childhood vaccines such as measles, mumps and rubella, remained roughly flat, increasing from only 74 percent to 78 percent over this period.[47]

  In addition to the increased expected market size, the profitability of the hepatitis B vaccine was expected to increase due to the fact that there was not only going to be a large market but that it would not require marketing efforts and expenditures on the part of the pharmaceutical industry. (Sanyour interview, Greenberg interview).

  Several different mechanisms translate an ACIP recommendation into dramatic changes in standard immunization practices:

[46] 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."

[47] Author's calculations based on a annual surveys from the National Health Interview Survey, Immunization supplement from 1992 to 1996. Childhood vaccination records for Hepatitis B were not requested prior to 1992. The reported statistics are regression-adjusted for the child's gender and race and the education of the (responding) parent. The five-year sample size is about 34,000.

- 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 ACIP (Snyder interview; Woodruff et al. 1996).[48]
- Pediatrician's private practice also tends to following the ACIP recommendation both because it provides potential cover for lawsuits following adverse reactions and because it provides 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 the ACIP's recommendation the following year.
- States use the ACIP recommendation to compile their list of required vaccinations for attending day care or public school (Alfona interview)[49] School immunization laws have a large effect on vaccination rates (see e.g. Orenstein and Hinman, 1999).
- Many private schools and employers require proof of compliance with the ACIP recommended schedule.[50]

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 information campaigns about its benefits, 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.
- *Expected impact of the policy.*

  The ACIP's vaccine target population for the flu consists of individuals over age 65 as well as individuals with certain health problems that puts them at risk of vaccine complications (Institute of Medicine 1985a). As a result, 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. As one individual 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." (Sanyour interview, Kaye interview). 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. Using the bi-annual BRFSS data, I calculate that influenza vaccination rates among Medicare beneficiaries rose from 51% in 1993 to 67% in 1999. Even this modest increase may have been in part due to a pre-existing upward trend in flu vaccination rates for the elderly. Using bi-annual NHIS data, I calculate a comparable vaccination rate increase from 33% in 1989 to 52% in 1999.

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[48] Data are from the CDC Vaccines for Children Program. The CDC also promoted immunization for children who were beyond infancy at the time that the recommendation went into place.

[49] Indeed, following the ACIP recommendation, many states introduced school-based "catch-up" vaccination programs for 11 to 12 year olds.

[50] Indeed, I was allowed to enroll in Harvard in 1991 without being vaccinated for Hepatitis B but in 1998 had to get vaccinated in order to be allowed to enroll in MIT.

However, more important than the actual response was the expected response.[51] Three primary mechanisms were behind the industry's belief that Medicare coverage would result in increased profitability of the flu vaccine:

- A belief that vaccination rates among the elderly would be extremely responsive to Medicare coverage
- 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.
- There is believed to be a multiplier effect from Medicare policy to private insurance policies[52], private physician 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 prompted concerns in the government about 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?* No. Pharmaceutical companies had lobbied for something like the VICF since the early 1970s (Kitch et al. 1999). The exact timing seems to have been prompted by a surge in lawsuits against childhood vaccine manufacturers starting in 1984 (Kitch et al. 1999).
- *Expected impact of the policy.* Individuals in the vaccine industry are quick to point to this as a huge boost to the industry that was seen as such at the time. They are 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. In practice, the number of lawsuits against manufacturers fell dramatically after the introduction of the system. The VICP provided two mechanisms for increased investment incentives. First, by creating a common pool of funds to pay for lawsuits, it reduced individual developer's exposure to risk; in an option-value model of investment, this should result in increased investment (see e.g. Dixit and Pyndick 1994). Second, in practice, it reduced not only the variance but also the mean payment, since the program included several measures to limit payouts for successful claims, including a cap on the payment for deaths (GAO 1999; HRSA 2002).

[51] 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).

[52] See e.g. *New York Times,* "A new transplant frontier: intestines" October 31, 2000.

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	v	v	v	1.25	3.25	1981
Influenza	v	v	v	0	3	1945
Polio	v	v		0.5	0.75	1955
Diphtheria, Tetanus (DT)	v	v		0.25	2.75	1949
Measles, Mumps, Rubella (MMR)	v	v		0.25	0.25	1971
Pertussis	v	v	v	0.5	2.25	1914
Control Diseases						
Hepatitis A	v		v	0	0.25	1995
Varicella (Chicken Pox)	v			0.25	0.75	1995
Herpes	v		v	0	0.25	Not yet
Malaria	v			0.25	1	Not yet
Cholera	v	v		0.25	0	1914
Haemophilus Influenza B (HIB)	v		v	0.5	1.25	1985
Rotavirus	v		v	0	0.25	1998
Parainfluenza	v		v	0.25	0.5	Not yet
Gonorrhea	v		v	0.25	0	Not yet
Typhoid	v	v		0.5	0.5	1914
Hepatitis C				0	0.75	Not yet
Lyme Disease				0	0.5	1998
Tuberculosis (BCG)		v		0	0	1950
Meningitis		v		0	2	1974
Yellow Fever		v		0	0.25	1953
Chlamydia				0	0.25	Not yet
Cytomagalovirus			v	0	0	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
Respiratory Syncytial Virus			v	0	1.5	Not yet
Streptococcus		v	v	0	1	1952
Pneumonia		v		0	0.25	1977

Sources: The NDA Pipeline and CBER.[53]

Notes: Control diseases include all 26 control diseases included in the "any clinicals" control group. The first three columns show which 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 1992. "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.

[53] The data on approvals comes from a FOIA of CEBR records conducted by Kendall Hoyt. I am extremely grateful to her for providing me with this information.

Appendix C: Sensitivity analysis of results in Table 3.

	Deviation from Trend (treated sample only)	Difference-in-Differences							
		Control Group: "Any Clinicals"		Control Group: "Early Clinicals"		Control Group: "Prior Approvals"		Control Group: "Technology"	
ADOPT	1.273***	0.883***	0.881***	0.811**	0.809**	1.025***	1.022***	0.883***	0.880***
	(0.486)	(0.274)	(0.274)	(0.341)	(0.341)	(0.356)	(0.355)	(0.336)	(0.336)
Unadjusted p-value	0.01	<0.01	<0.01	0.02	0.02	<0.01	<0.01	<0.01	<0.01
Adjusted p-value	<0.01	<0.01	<0.01	0.01	0.01	<0.01	<0.01	<0.01	<0.01
Mean Dep. Var	1.27	0.47	0.47	0.74	0.74	0.75	0.75	0.72	0.72
Disease-specific trend	Quad.	Linear	Quad.	Linear	Quad.	Linear	Quad.	Linear	Quad.
Number of Diseases	6	32	32	16	16	13	13	15	15
N	102	544	544	272	272	221	221	255	255

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 3 for more detail.

Appendix D: Distribution of dependent variables

Table D1: Cumulative frequency distribution of number of new clinical trials per year per disease

	Entire Sample					Solo Vaccines Only					Combination Vaccines Only				
	Treated Vaccines Only	Treated + "Any Clinicals"	Treated + "Early Clinicals	Treated + "Prior Appr-ovals"	Treated + "Tech-nology"	Treated Vaccines Only	Treated + "Any Clinicals"	Treated + "Early Clinicals	Treated + "Prior Appr-ovals"	Treated + "Tech-nology"	Treated Vaccines Only	Treated + "Any Clinicals"	Treated + "Early Clinicals	Treated +"Prior Appr-ovals"	Treat + "Tecl nolog
0	44.1	73.0	60.1	62.9	62.8	66.7	79.4	72.1	74.2	73.7	63.7	88.8	81.3	80.1	81.6
1	69.6	89.5	63.8	82.4	83.9	85.3	94.1	91.9	91.4	92.2	82.4	96.1	92.3	91.9	91.8
2	81.4	94.9	91.2	90.5	91.4	94.1	98.4	97.1	96.8	97.7	91.2	98.2	96.3	95.9	96.1
3	88.2	97.4	94.9	94.6	94.9	99.0	99.6	99.3	99.6	99.6	95.1	98.9	97.8	97.7	97.7
4	92.2	98.4	96.7	96.4	96.5	100	100	100	100	100	96.1	99.3	98.5	98.2	98.4
5	98.0	99.6	99.3	99.1	99.2						99.0	99.8	99.6	99.6	99.6
6	99.0	99.8	99.6	99.6	99.6						100	100	100	100	100
7	100	100	100	100	100										
N	102	544	272	221	255	102	544	272	221	255	102	544	272	221	255

Table D2: Cumulative frequency distribution of number of new pre-clinical trials and number of patent filings per year per disease

	New Pre-Clinical Trials					New Patent Filings				
	Treated Vaccines Only	Treated + "Any clinicals"	Treated + "Early clinicals"	Treated + "Prior Approvals"	Treated + "Technology"	Treated Vaccines Only	Treated + "Any clinicals"	Treated + "Early clinicals"	Treated + "Prior Approvals"	Treated + "Technology"
0	56.9	63.4	66.2	68.3	63.9	40.2	62.9	55.2	57.9	55.7
1	76.5	90.3	87.9	86.0	87.1	63.7	83.5	77.2	78.7	75.7
2	93.1	97.2	96.7	95.0	96.1	80.4	91.9	89.0	87.8	88.6
3	98.0	98.9	99.3	98.2	98.8	87.3	95.9	93.0	92.8	92.6
4	98.0	99.6	99.3	99.1	99.2	93.1	97.6	97.1	95.5	96.1
5	100	100	100	100	100	98.0	99.1	99.3	98.6	98.8
6						99.0	99.6	99.6	99.1	99.2
7						99.0	99.8	99.6	99.6	99.6
8						99.0	99.8	99.6	99.6	99.6
9						100	100	100	100	100
N	102	544	272	221	255	102	544	272	221	255