NBER WORKING PAPER SERIES

VACCINE SUPPLY: EFFECTS OF REGULATION AND COMPETITION

Patricia M. Danzon
Nuno S. Pereira

Working Paper 17205
http://www.nber.org/papers/w17205

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
July 2011

Vaccine Supply: Effects Of Regulation And Competition
Patricia M. Danzon and Nuno S. Pereira
NBER Working Paper No. 17205
July 2011
JEL No. D4,I11,I18,L11

ABSTRACT

In US vaccine markets, competing producers with high fixed, sunk costs face relatively concentrated demand. The resulting price and quality competition leads to the exit of all but one or very few producers per vaccine. Our empirical analysis of exits from US vaccine markets supports the hypothesis that high fixed costs and both price and quality competition contribute to vaccine exits.

We find no evidence that government purchasing has significant effects, possibly because government purchase tends to increase volume but lower price, with offsetting effects. Evidence from the flu vaccine market confirms that government purchasing is not a necessary condition for exits and the existence of few suppliers per vaccine in the US.

Patricia M. Danzon
Health Care Management Department
The Wharton School
University of Pennsylvania
3641 Locust Walk
Philadelphia, PA 19104
and NBER
danzon@wharton.upenn.edu

Nuno S. Pereira
Dean, Business School
University of Porto
Rua de Salazares
4200-464 Porto, Portugal
and CEF.UP
nsp@egp-upbs.up.pt

I. Introduction

Vaccines can provide an extremely cost-effective technology for dealing with infectious diseases, saving lives and averting millions of dollars of potential health expenditures.[1] But the supply of pediatric vaccines in the US appears precarious, with a declining number of producers and products. In 1967 there were 26 licensed manufacturers, but only 12 in 2002. Five firms produce almost all routine childhood vaccines, with a sole supplier for five of the eight recommended pediatric vaccines.[2] When key suppliers experience manufacturing problems, supply interruptions and vaccine shortages interrupt immunization schedules, sometimes leading to children not being immunized. For flu vaccine, supply shortages during the narrow annual window for effective administration have posed risks to vulnerable populations.

Not all is gloom and doom in the vaccine business, however. Historically, entry of firms and products has been rapid when scientific advance creates new opportunities. Global vaccine sales doubled during the 1990s, from $2.9b. in 1992 to over $6b. in 2000, [3] although global sales of basic vaccines dropped 40% over the same period.[4] Global vaccine sales increased 16 percent from 2008-2009, reaching $22.1b.[5] This growth reflects new pediatric products, including varicella, rotovirus and childhood pneumococcal vaccines, in addition to travel and adult vaccines, including a cervical cancer vaccine and new vaccine combinations. Vaccine manufacturers spend about 16 percent of sales on R&D, a comparable ratio to the pharmaceutical industry. Some large pharmaceutical companies have recently entered the vaccine industry through acquisition (for example, Pfizer's $68b. purchase of Wyeth was partly for its vaccine business; Novartis acquired Chiron, Abbott purchased Solvay), and several biotech firms have entered in the US and other countries. Thus precarious supply of existing vaccines co-exists with healthy entry to produce new vaccines.

The industrial organization literature has proposed general models of entry and exit to an industry (Caves, 1998). Entry has been modeled to reflect such factors as entry barriers, whether set-up costs are retrievable or "sunk", potential entry and exit of competitors, the extent of product substitutability etc. Theories of withdrawal from markets include some of the same but also some different explanations, such as intrafirm cannibalization or interfirm competition in multiproduct competition settings (Ruebeck, 2005), declining demand (Ghemawat and Nalebuff 1985, 1990), age of the firm, firm size, and industry-specific characteristics, such as the extent of scale economies, the dynamics of the demand and knowledge conditions. Entry and exit have also been modeled as interrelated phenomena, with authors finding a high correlation between average entry and exit rates, across time and within industries, supporting the incorporation of entry as a determinant of exit and vice-versa (Carree and Thurik, 1996;

Disney et al., 2003; Dunne et al., 1988). The dynamic processes governing an industry's structure include learning effects, both by producers (Jovanovic, 1982) and consumers, replacement and displacement effects (Carree and Thurik, 1996), and the emergence of a dominant design. Studies also examine levels of market concentration and its consequences for welfare. For example, industries with a low flow of entry and exit may have limited innovativeness and some form of formal or tacit collusion (Geroski and Jacquemin, 1985); on the other hand, a continuous change of competitors may be socially inefficient, particularly in activities with significant investment of capital, time and knowledge.

This paper focuses on exit from (and to a lesser extent entry to) the vaccine industry from 1903 to 2005. We draw on some of the factors considered in the general industrial organization literature but also factors specific to vaccines. Compared to most industries (but similar to other pharmaceuticals), the vaccine industry is highly R&D intensive and heavily regulated, in the US by the Food and Drug Administration (FDA) and by similar authorities in other countries, with high regulatory costs of entry and continued operations. However, unlike most other pharmaceuticals in the US, vaccines also face government as a significant customer, at least for the pediatric vaccines that are recommended by the US Centers for Disease Control and Prevention (CDC). Previous economic analyses of the vaccine industry have focused on the role of government procurement in general -- and government price setting in particular -- in making vaccine markets less attractive than markets for other pharmaceuticals. Liability risks have also allegedly made vaccines unattractive.

We posit that exogenous advances in basic science create the potential to produce new and/or improved vaccines against specific diseases such as hepatitis B, rotovirus etc. Following such a knowledge shock, several firms may engage in R&D to apply this knowledge to produce a vaccine product. This R&D race may result in several, slightly differentiated products that meet regulatory requirements for safety and efficacy entering the market at different times. Even if one product has been approved, other firms may rationally continue with their clinical trials, given the ex ante risks associated with regulatory approval and market acceptance and the fact that significant research costs may already be sunk. We document but do not model this entry process.

Our model of vaccine exits posits that, for a given technology, the vaccine production process is subject to non-increasing costs over a range that may suffice to serve the entire US market. For public and private purchasers, the cross-price elasticity of demand between substitutable products is high and purchasing is structured such that firms adopt non-cooperative, Bertrand pricing strategies. If multiple firms enter the market with close substitutable products and each faces low and non-increasing marginal

cost up to the scale of the market, non-cooperative pricing implies that prices could potentially fall to marginal cost. This creates pressures for all but one product to eventually exit. Products that have higher marginal costs, shocks to fixed costs (such as the need to build new plants) or less desirable safety, efficacy or convenience attributes for consumers are more likely to exit. Prices for the surviving product(s) may nevertheless be constrained by contestability from foreign or previous entrants and/or monopsony power of purchasers, with the relative importance of these factors differing across vaccine types.

In this model, new product entry to a vaccine type usually occurs in waves, following technological or market changes. Exits are triggered by quality and potential price competition, including dynamic entry of superior products, and by regulatory or other shocks that raise costs of incumbent firms or reduce demand. In this model, government procurement as practiced by the CDC reduces prices primarily by exacerbating competition by design of the bidding process, not because the government imposes price regulation. On the other hand, government involvement through vaccine recommendations and mandates increases quantity demanded, and hence may increase the expected number of products/firms in a market, cet. par. Given these offsetting effects of government on price and volume, the net effect of government involvement on number of suppliers or vaccine exit is theoretically ambiguous and must be determined empirically.

Our empirical analysis tests these hypotheses related to vaccine exit using data on vaccine license terminations between 1901 and 2003. The results confirm that the hazard of exit increases with number of competitors and is more likely following the entry of new competitors, whereas sole suppliers are less likely to exit. We find that over time, the vaccine industry has become much more demanding and exit propensities increased after the mid 1960s, which may reflect several factors: higher FDA safety, efficacy and manufacturing quality requirements following the 1962 Amendments to the FDA Act; increased risk of strict tort liability after the 1966 Second Restatement of Torts; and possibly increasing government purchase of some vaccines after the mid 1960s. Correlation between these three trends precludes indentifying their separate effects. However, we do not find support for the common assertion that price regulation by the CDC or its share of volume purchased has contributed to vaccine exit, plausibly because these effects are offsetting. This finding, that government purchase on balance has no negative effect on firms' willingness to remain in the market, is consistent with the theoretical prediction, that competitive markets would likely lead to one or very few suppliers in the long run, given the cost structure of vaccine supply, the relatively small market compared to many pharmaceuticals and limited

storability of most vaccines. This finding is also consistent with casual evidence that vaccine producers in fact seek out government recommendation and purchase of their vaccines.[6]

Section II of the paper describes previous related literature. Section III outlines our model of vaccine supply and market equilibrium. Section IV describes the data and methods. Section V provides descriptive evidence on vaccine entry and exits. Section V reports hazard model estimates of exit for individual vaccine products (licenses) and for vaccine producers. Section VI presents evidence on vaccine availability in Canada, France, Portugal and the UK, compared to the US, and Section VII provides a case study of the flu vaccine market in the US that illustrates the importance of high fixed costs and demand uncertainty.

II. Previous Literature

An extensive previous economic literature describes the institutional structure of vaccine supply and purchase, the economic case of mandatory vaccination, and appropriate subsidies for vaccine demand through reimbursement (see DeBrock, 1985; IOM, 2004). A more limited number of papers examine the effects of CDC procurement on prices and on vaccine shortages (e.g. Salkever and Frank, 1996). Kauf (1999) uses data from 1997-1992 on private catalog and federal contract prices for 3 vaccines (DTP, OPV and MMR) and 1988- 1992 for Hib and Hep B to test empirically whether the public discount percentage is more consistent with models of price discrimination or bargaining power. She concludes that, while it is not possible to eliminate other factors, results favor the bargaining power hypothesis. This conclusion is based primarily on finding a positive association between the public discount percent and the public share of volume. She does not explicitly consider the role of competition and treats number of suppliers as exogenous. She finds that the public discount off private catalog price is also positively related to number of licenses, which she interprets as consistent with the bargaining hypothesis but also with price discrimination. Both these studies use data that ignores private sector discounts and predates CDC's shift away from winner-take-all procurement.

Scherer (2007) takes a more general approach to vaccine shortages. He considers high regulatory costs, inadequate profitability and mergers as possible causes of vaccine shortages, and argues that economies of scale and scope limit the number of vaccine producers. Focusing on the influenza vaccine and assuming that shortages entail foregone vaccination, he provides rough estimates of the costs of vaccine shortages and concludes that maintaining additional production sources with surge capacity would be cost-justified. Scherer's view of vaccine markets as natural monopolies in some ways

resembles our hypothesis; however, he does not consider the dynamic competition process whereby multiple firms enter and then most exit, and his empirical analysis focuses on simulating welfare costs of shortages for influenza, not the determinants of product and firm exit which are the focus of our analysis.

III. Vaccine Market Characteristics

1. Demand

Although vaccines are highly effective at disease prevention, their success is a winner's curse for producers: the longer the treatment efficacy, the smaller is the annual volume demanded. For pediatric vaccines that have lifetime efficacy, potential annual sales volume is limited by the size of the birth cohort. Moreover, idiosyncratic government vaccination policies result in different pediatric vaccine requirements across countries. The potential annual demand is therefore lower for most vaccine formulations than for many therapeutic drugs, especially drugs to treat chronic diseases. For adult vaccines and travelers vaccines, efficacy lasts for several years, hence booster doses are necessary to maintain protection, but usage is generally limited to at-risk subpopulations.

Governments in all industrialized countries require and often subsidize vaccination against major contagious diseases. The rationale is that the social benefits of vaccination exceed private benefits, because a person who gets vaccinated reduces the probability that they themselves get the disease and that they transmit it to others. As more individuals in a group receive vaccination, the risk of contagion for those who remain unvaccinated declines to negligible levels – so-called herd immunity – which in turn creates an incentive for each individual to free ride on vaccination of others, unless vaccination is mandatory. In the US, the Advisory Committee on Immunization Practices (ACIP) is an advisory body comprised of medical experts who recommend vaccination schedules for specific subpopulations. For some pediatric vaccines, compliance with these recommendations may be required for school attendance, which makes the recommendations essentially a mandate. Government recommendations and mandates presumably increase total volume sold for recommended vaccines, compared to unconstrained voluntary market demand. But government recommendation or procurement may also concentrate demand on preferred products and, conversely, reduce demand for competing, non-recommended products.

The effect of government's role on vaccine prices depends on whether and how the government actually procures vaccines, and its market share. In the US, the CDC began purchasing vaccines for low income children in 1966. During the 1980s, CDC's share increased, varying across years and across vaccines from around 30-40 percent for diphtheria, tetanus and pertussus (DTP) and polio, to 40-50

percent and higher for measles, mumps and rubella (MMR). In 1989-1991 a measles epidemic resulted in thousands of cases of measles and hundreds of deaths. Following an investigation which showed that over half of children with measles had not been vaccinated, in 1993 Congress established the Vaccines for Children (VFC) program as an entitlement for children age 18 and below who may not otherwise have access to vaccines.[7] Consequently the public share of childhood vaccines increased to over 50 percent. Procurement strategies have varied over time, as purchasers learned about the effects of their strategies on long term supply. Prior to 1993, the CDC applied a winner-take-all strategy, awarding all sales to the lowest bidder. This resulted in low prices and great volume uncertainty for suppliers. Since 1998, the CDC solicits bid prices annually, which suppliers can adjust monthly but only downward. The CDC posts bid prices of potential suppliers, negotiates broad supply contracts, usually with a near-zero minimum and a negotiated maximum quantity. State and local recipients of federal funds for vaccines purchased under the VFC program choose which approved supplier to use. States that participate in the Universal Purchase program may use their own funds to purchase vaccines for non-VFC-eligible patients at CDC prices.

In the private sector, vaccines are purchased by individual physicians and by hospitals and other institutions that often using group purchasing organization to negotiate prices with vaccine suppliers. These private purchasers are highly price sensitive because they usually face a fixed reimbursement per vaccine type from third party payers. Since they capture any margin, positive or negative, between the reimbursement and their acquisition cost for the vaccine, their cross-price demand elasticity between competing products is likely to be high. In such contexts, suppliers generally compete for market share by offering discounts below the reimbursement price.

The global vaccine market similarly consists of large concentrated purchasers, each with somewhat specific requirements. In most industrialized countries, national governments play a dominant role in defining vaccination schedules, vaccine procurement and price setting. Vaccine purchase for Latin America is largely managed by the Pan American Health Organization (PAHO), but each individual country decides which vaccines to purchase. Procurement and price negotiations are coordinated through PAHO, using competitive bidding. For developing countries, including purchases financed through GAVI, UNICEF serves as the procurement agency. For basic pediatric vaccines, UNICEF accounts for 40% of global volume but only 5% of market value. Between 1992 and 2002, the number of manufacturers offering UNICEF its key DTP, BCG (tuberculosis), TT (tetanus) and measles vaccines dwindled to 3 or 4 for each vaccine.[8] UNICEF has switched from winner-take-all procurement to

spreading its demand across several suppliers, in order to keep them in the market and protect against supply interruptions. Most of the supply to UNICEF is now from Indian and other emerging market suppliers, with only small shares from the large multinational companies that supply the industrialized countries. This partly reflects differentiation of products, as the industrialized countries, especially the US, have moved towards newer, more costly combinations of basic vaccines, acellular pertussis, IPV, and thimerosal-free products, whereas UNICEF purchases older, cheaper formulations.[9]

2. Supply

Cost Structure Bringing a new vaccine to market entails high fixed investments in R&D (research, compound formulation and clinical development) and manufacturing capacity, each component of which is subject to regulatory requirements for safety and quality assurance. The batch process required for vaccines also entails semi-fixed costs per batch. A batch may take 6-18 months to produce, depending on the type of vaccine and production methods. Thus production is characterized by very high fixed and semi-fixed sunk costs and low marginal cost per unit within each batch up to the capacity limit defined by the maximum number of batches for the manufacturing plant.[10] Changing production technology to meet changed regulatory standards or expand scale takes years and millions of dollars, and requires FDA approval for the new plant. Such costs may be worth incurring only if they can be recouped over several years of sales.

Costs related to regulatory compliance have increased over time to meet rising quality standards. In addition, several explicit shocks have necessitated major new investments. In particular, the 1972 requirement that all vaccines demonstrate efficacy imposed new costs on pre-1962 vaccines that had been grandfathered under the 1962 FDA Amendments. The 1999 CDC request that manufacturers remove thimerosal required product and plant redesign and reapproval of manufacturing processes and facilities. The removal of thimerosal, which is a preservative, may have exacerbated the short shelf life problem of vaccines, at least until new technologies could be developed and built into new plants.

Patents and generic entry Patent barriers to entry of competitors are weak for most vaccines, which often rely on propriety strains of the virus and sometimes process patents. These do not preclude other firms from using different strains to supply competing products during the life of any patents. However, because vaccines are biologics, generics have not been able to use the abbreviated new drug application (ANDA) process which enables generic equivalents of chemical drugs to get approval by showing bioequivalence to the originator product. Thus follow-on versions of existing vaccines are

treated as originators and must undertake *de novo* clinical trials to demonstrate safety and efficacy. They would not necessarily be viewed by physicians/patients as perfect substitutes due to differences in vaccine strain.

Dynamic Competition Although originator vaccines do not face generic competitors, their economic value is continually open to challenge by new, improved products. For example, acellular pertussis replaced whole cell pertussis; inactivated polio replaced oral polio; and combination products have replaced single product forms for most pediatric vaccines.[11] Anticipation of improved technologies undermines incentives to invest in new variants of older technologies or plants, particularly given the long lead times required by such investments. The tendency for dynamic entry of new, improved technologies to displace old technologies may be exacerbated by government recommendation of the new over the older product, and concentrated public and private purchasing.

Liability risks Tort liability has sometimes been a more severe risk for vaccines than for most therapeutic drugs, because vaccines treat large numbers of healthy individuals, usually children, and risks may be correlated.[12] Allegations and litigation related to the pertussis vaccine in the 1980s were followed by the exit of three of the four manufacturers of pertussis vaccine (Offit, 2005). In 1986 Congress established the Vaccine Injury Compensation Program (VCIP) to provide no-fault compensation to children injured as a result of pediatric vaccines. Influenza vaccine is also covered by the VCIP, and other vaccines may apply. Vaccine manufacturers may still occasionally face tort claims – for example, recent claims related to thimerosal argued that this was a preservative, not intrinsic to the vaccine. Although these claims have generally not succeeded, the legal costs of defending against claims and the risk that some may eventually succeed may act as a disincentive for vaccine entry. However, this risk is now probably modest, at least for pediatric vaccines that are covered by the VCIP.

3. Market Equilibrium

High fixed costs of regulation and production are not a barrier to entry if these costs can, with reasonable certainty, be recouped over large volume and/or high margins. But the interaction of high fixed costs with relatively low, concentrated and unpredictable demand and perishable supply is likely to result in a market equilibrium that supports only one or few suppliers in most vaccine markets at any point in time. If multiple firms initially enter and each faces non-increasing cost per unit, the equilibrium non-cooperative price is equal to marginal cost assuming Bertrand strategies.[13] The intuition is simple: once regulatory, capacity and batch costs are sunk, with few alternative customers in the current period

and limited storage potential for future use, any excess of price above marginal cost contributes to covering the sunk costs, whereas if a firm loses a contract to a competitor, the product is likely to go to waste. Moreover, because capacity and batch production entail fixed and semi-fixed costs, respectively, that need to be planned a long time in advance, producers tend to target for high volumes of production as they cannot adjust later if demand is higher than anticipated. If such pricing is anticipated, all but one firm will eventually exit and new entry is unlikely, unless the new product has superior quality or lower cost than the incumbent. The likelihood of a sole supplier equilibrium is greater, the smaller the market relative to minimum efficient scale of production; the shorter the shelf-life of the product; and the more uniform are consumer preferences over product quality. Market dominance and survival in vaccines thus tends to be related to product superiority for the majority of patients, not to first mover advantage in a class.

Multiple products may coexist if they differ in efficacy or safety for different patient groups – for example, if some patients cannot tolerate one component of a combination, a variant that excludes that component may survive, as in the case of DTP and DT.[14] Even then, a single firm is likely to dominate in supplying these differentiated products if it has economies of scope from producing both the combination and the component products. By contrast, in many on-patent pharmaceutical classes multiple products coexist because each product works best for some patients; markets are generally larger; customers are mostly atomistic purchasers, are price-insensitive due to insurance, and are not driven by government recommendation; and the greater potential for storage enables manufacturers to inventory excess output for future sale.

With a sole supplier of a mandated childhood vaccine, the government share of the market becomes a bilateral monopoly: the government has significant monopsony power because the manufacturer has incurred significant sunk costs and has no other purchasers of comparable size, but the government also has no alternative suppliers. Given the declining number of producers, it is unsurprising that the CDC discounts decreased over time, from an average of 75 percent off the supplier's catalog price in 1987 to 50 percent in 1997, and that discounts are less on the newest, single manufacturer vaccines, such as varicella (9%) and pneumococcal conjugate (22%).[15]

In summary, the role of government purchasing in US vaccine markets has been to define procurement rules for required vaccines that are eligible for government subsidy. Prior to 1998, this involved competitive tendering and centralized purchasing. Since 1998, the CDC simply solicits bids from willing suppliers and purchasing is devolved to the states. The only direct price regulation is a

ceiling on price increases, set at the growth in the consumer price index (CPI), for vaccines that had federal contracts in 1993. This regulation created incentives for suppliers to develop new formulations of the price-constrained products – such as combinations – which are not subject to the CPI price cap. Of the 48 vaccine licenses in existence in the US in 2004, 17 were issued after 1993 (see Danzon et al. 2005, Exhibit 1). Moreover, the fact that supplier exit and supply disruptions have occurred for flu vaccine, for which the government is a minor purchaser and does not set price, suggests that government purchase is not a necessary condition of firm exits (see below).

The conventional wisdom, that government purchase and "price controls" are the major contributors to lack of vaccine profitability, predicts that vaccine exit would be positively related to the quantity purchased by the government and inversely related to the government price.[16] By contrast, our model predicts that exit is triggered by static and dynamic competition, due to the high fixed costs and concentrated market demand. This model predicts that vaccine exit is positively related to the number of competitors and is more likely following entry of competitor vaccines that have some clear technological superiority, particularly if this superiority is reinforced by government recommendations. Similarly, entry of combination products is likely to displace the single components or smaller combinations.

In addition to withdrawal of vaccine products, the number of vaccine manufacturers has also been reduced through exit and mergers, including the acquisition of Connaught Laboratories by the Mérieux Institute in 1989 and Chiron's purchase of Sclavo in 1998 and Powderject in 2003. Merger of firms need not necessarily lead to exit of products; for example, if the merger is motivated by economies of scope across vaccine types, the range of combination products offered following a merger might increase. But if being acquired by another vaccine manufacturer is the least costly way of absorbing the excess production capacity for a product that has become obsolete, then an acquired product would be more likely to exit. In that case the merger would be a symptom rather than the underlying cause of the exit of the obsolete product.

IV. Data and Methods

1. Data

We collected data on the dates of grant and withdrawal of all vaccine licenses authorized by the FDA for the period 1901 to 2003. For most of our analysis, the unit of observation is a vaccine product license, which authorizes a specific product and plant to manufacture that product. For vaccines that are used both alone and in various combinations, each component vaccine and each combination has a

separate license and counts as a separate observation. For example, diphtheria vaccine exists alone and has been used in seven combinations, tetanus exists alone and has been used in eight combinations. During our time period, 241 licenses were granted, of which 179 were withdrawn and 62 survived as of 2003.

We also report analysis of exit of vaccine suppliers at the firm level, using the FDA data on the firm holding the license. Thirty nine firms held at least one license during our time period; of these, 10 firms were acquired and 12 exited the vaccine business (measured by having no subsequent vaccine licenses).

We obtained quantities purchased and prices paid by CDC, by vaccine, for all years for which data were available. Where data were missing for a few years, we imputed missing values by extrapolating between adjacent values.

2. *Methods, Variable Definitions and Hypotheses*

Because we have interval censored data, we estimate a hazard model of vaccine exit, using a complementary log log function with time varying values of co-variates:

$$H_{jt} = h\{C_{j,t-1}, R_{j,t-1}, Z_{t-1}, X_{t-1}\} \quad (1)$$

In equation (1), H_{jt} is the hazard of exit of product j in period t, conditional on being licensed in period t-1. Explanatory variables include various measures of competition, C; measures of CDC purchase and other regulatory influence, R; other product-specific or firm-specific characteristics, Z; and other factors, X. These variables and related hypotheses are defined below.

Competition Since many vaccines exist both as single products and in combination with other products (e.g. diphtheria + tetanus + pertussis (DTaP); measles, mumps, rubella (MMR)), there is no unique measure of number of competitors for each vaccine. We considered three alternative measures of number of competitor products: Direct Competitors is the number of variants of a specific vaccine (e.g. diphtheria alone) produced by competitor firms (excluding the firm in question), and Indirect Competitors includes all combinations that include the specific vaccine (e.g. all combinations that include diphtheria); and All Competitors is the sum of Direct and Indirect Competitors. Exit is expected to be positively related to both direct and indirect competition. Greater effects are predicted for Direct Competitors (same vaccine) if substitutability is the only issue; however, if patients prefer combination products over single vaccines (due to the greater convenience, lower time costs and perhaps lower out-of-pocket cost), then Indirect Competitors is expected to have a larger effect on exit hazards than Direct

Competitors. We also include an indicator variable, Single, for products that are the sole source of a particular vaccine. Single products are less likely to exit, assuming that sole suppliers face higher mean and lower variance of expected revenue than producers that face competitors.

To test for effects of dynamic quality competition, we include the number of New Products of exactly the same vaccine type between years t and t+1. New product entry is expected to increase the likelihood of exit of established products, if newer entrants on average have superior attributes compared to existing products. We also tested measures of entry defined over t-2 to t+2. The measure reported here, based on entrants in t to t+1, was consistently the most significant, suggesting that exit responds to anticipated as well as actual entry. This variable includes new vaccines introduced by each vaccine's parent firm, so it reflects a firm's own strategy as well as response to competitors. We also include a binary variable, Input, that takes the value 1 if a product is also an input for combinations produced by the same firm in period t.

Government Procurement and Liability Variables Universal Recommendation is a binary indicator of whether the vaccine was recommended for universal purchase by the ACIP; it is expected to be negatively related to the product exit hazard, if ACIP recommendation increases demand for a vaccine.[17]

Government procurement is predicted to have a negative effect on price but possibly a positive effect on volume, with uncertain net effect on exit hazards. To test these hypotheses, we tried three possible measures of the quantity of CDC purchase: total doses of each vaccine type that were purchased by CDC in t-1 (CDC Quantity); the expected number of doses purchased by CDC per licensee (CDCQ/licensee) assuming that the total government purchase were allocated equally among suppliers; and CDC share of doses (Share CDCq). These proxies for expected volume are expected to be negatively related to exit hazard, if CDC procurement increases expected demand for a vaccine. The price per dose paid by CDC for each vaccine type in t-1 (CDCPrice) is expected to be inversely related to the exit hazard.[18] All prices were inflation-adjusted using the CPI price index. A binary variable indicates the years before 1966, the first year of any CDC procurement (Pre CDC) and another binary variable indicates if a vaccine type was not purchased by CDC in t-1 (No CDC).[19] If the net effect of government procurement is to increase the likelihood of vaccine exit, the coefficient of No CDC should be negative. A similar prediction applies tentatively to Pre-CDC; however, since other factors also changed between the pre-1966 and post-1966 environment, including many more potential competitors in the market, the interpretation of this variable is ambiguous and it is included mainly as a control.

A binary variable, Strict Liability (SL) was created to indicate years after 1966, when the Second Restatement of Torts adopted strict product liability. The coefficient is expected to be positive if this increased the liability exposure of vaccine manufacturers in ways that could not be costlessly covered by insurance.[20] However, because SL is perfectly collinear with the Pre CDC indicator, both cannot be included in regression analysis. A binary variable, Vaccine Injury Compensation Program $_{it-1}$, indicates that the vaccine was covered by the VICP in year t-1; the coefficient is expected to be negative if, by reducing expected liability costs, the VICP significantly increased manufacturers' incentives to remain in the market. We also include an indicator Thimerosal, which indicates vaccines that contained thimerosal in years after 1998; it is expected to be positive, if the requirement to remove thimerosal imposed in early 1999 contributed to vaccine exit. OBRA is an indicator for vaccines that were subject to the CPI cap on price increases; it is expected to be positive if this constraint was binding.

Product and Firm-Specific Factors Age is the number of years since the product license was first granted; it is expected to be positive if new products offer superior quality and hence tend to displace older products. Year of Entry measures the vaccine's year of launch. Acquired is a binary indicator for vaccines that have been acquired from the original licensee; the coefficient is expected to be positive if acquisition is a means to exit the market and transfer production capacity to other uses. Foreign is a binary indicator for non-US firms. To test whether vaccines are less likely to be withdrawn if the manufacturer has a large or diversified vaccine portfolio across which to spread firm-specific fixed costs, we include a Herfindahl index of concentration of each manufacturer's products over vaccine types.[21] If economies of scope across vaccine types are significant, due to spreading fixed costs of human or physical capital, risk diversification or potential for product combination, then exit is less likely for diversified firms. Table 1 lists variable definitions with means and standard deviations.

IV. Descriptive Evidence

There were 241 vaccine product licenses granted between 1901 and 2003, of which 179 were withdrawn and 62 survived as of 2003. These products were supplied by a total of 45 firms, including several government and academic suppliers. Of these 45, 18 firms remained as of 2003.

Figure 1 shows the number of entries, exits and total number of licenses by year, for the period 1901-2003. There are few vaccines in the first three decades, with products for polio (1901), smallpox (1903), rabies (1915) and typhoid (1916). Entry occurs steadily from the mid-1930s onward, with spikes around 1952, 1963 and 1970 reflecting entry of 13, 11 and 39 new licenses, respectively.

License exits are rare initially, with only 3 prior to 1970. In 1970, 12 exits occur, of which 11 are due to the exit of a single manufacturer (Miles Inc.). Another large spurt of exits occurs in 1977 through 1981, possibly related to the mid-70s liability "crisis" which raised the price and reduced availability of product liability insurance. This large exit flow again reflects multiple products of a few manufacturers, in particular: Eli Lilly withdrew 14 products; Dow Chemical withdrew 11 products and exited totally in 1978; the Texas Department of Health Resources withdrew 7 products and exited totally in 1979; Pfizer withdrew 4 oral polio products and exited totally in 1979; and Parke Davis withdrew 16 products and exited totally in 1981. These products that were withdrawn between 1970 and 1981 represent several different vaccine types, but many were variants of diphtheria and tetanus, which had become very crowded markets, and three of the four pertussis producers exited. Partly in response to this exodus of manufacturers from the vaccine market, the Vaccine Injury Compensation Program was established in 1986. Whether for this or other reasons, no more manufacturer exits occurred until 1988, when Eli Lilly withdrew its last product and exited, followed by Wellcome in 1994 and Parkedale in 2001. The spike of product exits in 2000-2003 includes 5 by Bioport, 4 by Aventis Pasteur and 14 by Wyeth.

To illustrate the life-cycle of competitive entry, Figure 2 plots the mean number of products of given vaccine type, by year from the date of first launch of that type. The predicting equation is a simple regression of number of competitors on an intercept and a quadratic in years since launch, all of which are significant at the 1% level. Separate estimates are made for Direct Competitors (same product) and for Indirect Competitors (combinations that include this product).[22] Interestingly, entry occurs mainly in Indirect Competitors. The predicted number of Direct Competitors increases slowly from launch to reach a maximum of about 4 and then declines slowly. By contrast, the predicted number of Indirect Competitors increases more sharply and peaks at roughly fourteen.[23] Note that within the average pattern of life-cycle entry shown in Figure 2, the experience varies across different vaccine types. In particular, some of the mandated pediatric vaccines, especially diphtheria, tetanus and pertussis, were in numerous combinations in the 1970s and then were combined with Hib, Hepatitis B and inactivated polio more recently. At the other extreme, vaccines such as smallpox, rabies, cholera, lyme disease, have had only one or two suppliers throughout their life-cycles and have never been combined with other vaccines. We report the multivariate analysis of product exit based on the full sample; however, results were essentially the same and significance increased slightly when we excluded those vaccines that had only a single producer over the entire period.

V. Hazard Function Analysis of Vaccine Exit

Table 2 reports hazard ratios from the hazard function analysis of vaccine exit, including measures of competition, regulation, product and firm characteristics. Table 3 reports alternative specifications to estimate the effects of CDC purchase, controlling only for product age and year of entry. The coefficients are hazard ratios, hence values less (greater) than 1 imply reduced (increased) probability of exit.

In Table 2, the first equation includes only basic product characteristics and a control for the pre-CDC time period which is also the period before formal adoption of strict liability. Unfortunately, because both the procurement and the legal regime changed in 1966 these two variables are highly correlated and cannot be included together. Successive specifications then add various measures of competition, firm characteristics and regulation. The hazard rate of exit increases between 5 and 9 percent for each year the vaccine is on the market. However, this rate also increases around 3 to 6 percent with year of entry, implying that newer vintage vaccines are at higher risk of exit. These estimates are robust to the addition of measures of competition, regulation and other characteristics. The pre-CDC indicator is strongly negative, implying that vaccine exit risk was much lower in the pre-CDC/pre-Strict liability era. The estimated effect of the pre-CDC indicator declines but remains significantly negative in specifications that control for measures of competition, and CDC prices and quantities.

Controlling for these basic product and time period characteristics, each additional Direct Competitor increases the exit hazard rate by roughly 3 percent, and each additional Indirect Competitor increases exit hazard rate by 2 percent. Controlling for number of competitors in year t, the entry of new competitors in year t to t+1 increases the exit hazard of established products by 2-3 percent, consistent with the dynamic competition hypothesis, that new entrants are typically superior products and therefore tend to accelerate the exit of established products. Vaccines that are monopoly suppliers (Single) have an exit hazard over 50 percent lower than vaccines that have competitors. This supports the hypothesis that competition contributes to low prices and hence that sole supplier products are more able to achieve prices necessary to cover long run costs. Vaccines that are inputs to combinations have a 70 percent lower exit hazard than other vaccines, as expected if these core input vaccines tend to complement rather than substitute for the combination vaccines to which they contribute.

The effects of policy variables are mixed. Vaccines that are recommended for Universal Purchase have a 60 percent lower exit rate. Controlling for Universal Purchase, we find no significant effect of whether or not the CDC is a purchaser of the vaccine, the volume of units purchased by the CDC or the CDC price. Similarly, we find no significant effect of eligibility for the Vaccine Injury Compensation

Program or the indicator that a vaccine was subject to the OBRA price control. Following the adverse publicity over thimerosal in 1998 and requirement to eliminate it in early 1999, products that contained thimerosal have an exit hazard that is 44 percent higher. Although this coefficient is not significant at conventional levels, this may reflect the very small number of products involved.

Vaccines that have been acquired are less likely to exit than vaccines that are still owned by their originator firm, but this result is not significant. This evidence suggests that merger of firms has not been a major contributor to exit of vaccine products, although it has reduced the number of vaccine suppliers. Rather, the evidence here tentatively supports the theory of merger as a market for corporate control, in which vaccines are acquired in order to enhance their market potential, not as a means to eliminate excess capacity. The Herfindahl measure of a firm's vaccine portfolio is not significant. However, vaccines produced by foreign firms are less likely to exit, exhibiting a hazard rate that is close to 70 percent lower than US firms. This could suggest that foreign firms face higher regulatory and other costs of entry, such that foreign firms only launch in the US the subset of their products that have atypically high potential value and survival potential.

Table 3 reports more detailed attempts to estimate the effects of CDC purchasing. Controlling for a vaccine's age and cohort, the indicator for the pre-CDC time period is strongly negative, implying increased exit risk in the post-CDC time period. Given the highly correlated timing of increased government purchasing by CDC, increased tort liability risk following the 1966 Second Restatement of Torts and increased FDA-related costs after the 1962 FDA Amendments, their marginal contributions cannot be identified and the Pre-CDC variable must be interpreted as reflecting their combined effects. Controlling for these factors, the coefficient on the indicator for no CDC purchase is positive but not significant. The measures of CDC quantity are not significant. The CDC price is negative, consistent with the expectation that a lower price should increase the exit hazard, but the coefficient is not significant at conventional levels. Our CDC price and quantity variables may be measured with error, which may create bias towards finding no significant effects. We lack data on private sector prices and hence are unable to normalize the CDC price by the private sector price. Even if list prices to private purchasers were available, these would not measure transactions prices which are often significantly discounted. Overall, these results based on the universe of vaccines for the entire industry lifetime suggest that having a Universal Purchase recommendation significantly reduces the probability of exit, consistent with the prediction that universal purchase increases demand for a vaccine. However, the volume and price of CDC purchase do not appear to have significant effects, possibly because the negative effect of

government purchase on price is offset by the positive effect on volume, leading to no significant net effect. The probability of exit was lower before 1966, but whether this reflects absence of CDC purchasing, lower liability threat or other factors cannot be distinguished given the correlation between these factors.

We also examined the exit of firms (as opposed to individual products) from the vaccine business. Explanatory power is lower, implying that there are unmeasured firm-specific factors underling each firm's decision to exit the vaccines market, although some common features may underlie these decisions. Table 4 presents the hazard rates for exit of firms from the vaccine market for any reason. [24] Firm exit probability increases around 10 percent for each year the firm has been in the market, which is consistent with the hypothesis that increasing costs of regulatory compliance as technologies become obsolete may contribute to the probability of exit of firms. At the same time, firms that entered the market later are less likely to stay in the market and are more likely to be acquired, possibly because these are small firms formed to develop newer technologies that become desirable to established firms. Although having recently obtained a new license does not affect the likelihood of firm exit, it decreases the likelihood of a firm being acquired.

VI. Evidence from Other Industrialized Countries

High fixed costs would be most widely spread if each vaccine were distributed globally. In fact, the diffusion of vaccines appears to be more limited than for many drugs, even across industrialized countries. Table 5 lists the licensed producers of each of the major pediatric vaccines and several adult vaccines in Canada, France, Portugal, the UK, and the US.

These data are broadly consistent with hypotheses outlined here, that vaccine production entails high country-specific fixed costs and concentrated demand, such that each market supports at most a few producers. As predicted, each country has few producers of each vaccine. However, for several vaccine types, the US has fewer producers than these other countries which all have smaller potential volumes and more dominant government purchase.[25] The fact that several firms have products available in these countries that are not available in the US suggests that entry into the US is not attractive, given the fixed costs of entry combined with price and volume uncertainty of competing with established products.

The number of licenses per manufacturer and vaccine is also often higher in Canada and Europe than in the US. This suggests that the cost of compliance with more stringent regulatory requirements may contribute to fewer licensed products being maintained in the US. Note that in Table 5 the US

licenses include some that are inactive and some for further manufacturing only, hence this count of licenses overstates the number of active producers in the US. These data also indicate that, although national immunization plans are similar across developed countries, the specific vaccines recommended within each category still vary, for example, in the use of combination vaccines. Country-specific requirements limit the potential for manufacturing economies of scale and may require the development of country-specific products.

VII. Flu Vaccine – A Case Study

A brief history of the supply of flu vaccine in the US illustrates how fixed costs, dynamic competition and preemptive effects of superior products can lead to few suppliers, despite a limited role for government purchase. Influenza is an extreme case of limited storability. The influenza virus has two strains: Type A, which has several subtypes, and Type B. Because these types undergo antigenic "drift", the influenza vaccine must be reformulated each year to match the circulating strains. Since 1998, the World Health Organization has issued separate recommendations in February and September for the Northern and Southern Hemispheres, respectively.[26] In the US, the vaccine composition for the upcoming flu season is determined between February and March. Since the peak flu season is November-March, manufacturers must supply the vaccine by October to early November.

The injectable vaccine is traditionally cultured on embryonic eggs and then sterilized. Monovalent concentrates are produced and combined into the multivalent form, with comprehensive quality control at each step in the process. This time consuming process requires that supply be estimated almost a year in advance, and quick ramp up of production is impossible. A newer method of culturing the viruses using mammalian cells is not yet approved in the US.

There has been a significant increase in flu vaccine production above the approximately 20 million doses distributed annually in the mid-1980's.[27] In 1993, flu vaccine was covered under Medicaid and Medicare Part B. Prior to 2000, the ACIP recommended vaccination primarily of seniors and other high risk individuals. In 2000, the ACIP recommendation was extended to people aged 50 to 65 and to infants aged 6-23 months in 2002. In 2003, pediatric vaccination was approved for use of VFC funds. By 2009, the number of doses per year had increased to 113 million (Table 6). Actual uptake has increased but remains unpredictable at less than 50% of the recommended population. In 2001, only 87.7M of the recommended 152M people were vaccinated.[28] In 2003, although recommended recipients increased to 182M, manufacturers distributed only 83M doses.[29]

In 1999, there were four manufacturers in the US producing a total of 77.9M doses: Aventis Pasteur, Wyeth, Parkedale (owned by King Pharmaceuticals), and Powderject (acquired by Chiron, now part of Novartis). In October 1999, Parkedale was cited by the FDA for violations of manufacturing standards. Six months later, Parkedale was ordered to halt production and distribution because it remained out of compliance. On September 27, 2000 the FDA again ordered operations halted, giving the company 30 days to implement changes. But given the short window for effective vaccination, it was unlikely that the necessary changes could be completed for that year's season. Instead, Parkedale announced its withdrawal from flu vaccine production, writing off some $45M rather than incurring the costs of upgrading. Wyeth had produced influenza vaccine for the US market for over two decades. In October of 2000, Wyeth was fined $30M for the violations and an additional $15,000 per day out of compliance (capped at $5M).[30] In November 2002, Wyeth announced that it would exit, which left only 2 manufacturers of injectible influenza vaccine.[31]

In December 2002, shortly after Wyeth's exit, Aventis pledged $80 million investment to increase filling and formulation capacity, in addition to significant capital investments in 2001 to increase its capacity by 20%.[32] In early 2003, Chiron acquired its Liverpool plant from Powderject and began aggressive expansion to serve the expected growth in US demand. Chiron produced 25.6M doses in 2002, and 35.6M in 2003. Before being shut down by the UK regulatory authorities just weeks before the 2004 influenza season, Chiron estimated it would produce 46-48M doses for the US. It has been suggested this rapid expansion at an aging factory contributed to the contamination problems that occurred.[33] About $75 million has been spent to upgrade the factory in the last five years. In addition, Chiron committed to spending another $100 million to replace part of the plant.[34]

In July 2003, FluMist, an intranasally administered, live attenuated influenza vaccine (LAIV), produced by MedImmune was approved. But because of its restricted indications (initially, for use in healthy people aged 5 – 50) and its relatively high price, FluMist captured only a small share of the expanding market. More generally, LAIV products are unlikely to alleviate vaccine shortages because they are restricted to low risk individuals and they rely on the same embryonic egg based process. For 2004-2005, MedImmune planned to make only 2M doses, despite a capacity to make 20M doses.[35]

This shrinkage of the number of flu vaccine suppliers cannot be blamed on government purchase and price controls. Less than 20% of flue vaccine is publicly purchased.[36] Medicare reimburses for flu vaccine at 95 percent of Average Wholesale Price (AWP), which is a list price set by pricing guides such as the Red Book, based on the manufacturers' list price to wholesalers.[37] Although provider

reimbursement is at 95% of AWP, manufacturer prices are determined by competitive bids for sales to physicians, hospitals and others who dispense flu vaccine. Thus manufacturer prices for flu vaccines reflect competition rather than regulation. Given the high fixed costs and low marginal costs and total absence of storability of flu vaccine, it is not surprising that competition leads to low prices. Faced with low prices and volatile demand, manufacturers have chosen to exit rather than incur the significant costs of bringing manufacturing capacity up to the high standards required. Unpredictability resulting from the production technology and the very short demand window are also critical. Despite the reality of repeated shortages, millions of doses are wasted each year, because of overall demand uncertainty and mismatch of supply to meet the narrow demand window (see Table 6).

But the US flu market also illustrates the importance of threat of dynamic competition from superior products in vaccine investment decisions. While manufacturers are reluctant to invest additional capacity based on current embryonic egg based methods, several companies are developing mammalian cell-based vaccines. Mammalian cell-derived vaccines are expected to provide equivalent or better efficacy, with lower contamination risk, less wastage and shorter production time (see Table 7).[38]

In 2003, Solvay's Influvac TC (cell culture) product was approved in the Netherlands, and since then has been approved in over 60 countries. [39] No cell culture influenza vaccine is yet approved in the US but several are in clinical trials.[40] Given the potential superiority of cell-based products, egg-based products are likely to become obsolete, hence further investment in egg-based capacity is not worthwhile without government subsidy. In November 2009, Novartis inaugurated the US's first large scale flu cell culture vaccine manufacturing facility, which is planned to be running at full scale commercial production in 2013. [41] At the same time, an FDA advisory panel rejected approval of the US's first cell-based influenza vaccine developed by Protein Sciences Corporation.[42]

The global supply of flu vaccines (Table 8) shows a lack of global diffusion similar to other vaccines in Table 5. There are over 30 manufacturers of flu vaccine worldwide but many operate in a limited number of countries.[43] Solvay (now part of Abbott Laboratories), one of the EU's largest suppliers and the leader in the new cell-based methods, does not have a product approved in the US as of December 2010. Despite potential for growth in the US market and lack of government price controls, there was little incentive for other companies to enter or expand using the old technology, although entry was anticipated and is now occurring with newer technologies that will likely eventually render the old technology obsolete. The 2004-2005 influenza vaccine shortage, together with concern over a potential pandemic outbreak, including the avian flu in 2005 and the H1N1 swine flu in 2009, led the US

government to award grants to help companies expand their influenza vaccine capacity and develop faster and more reliable manufacturing processes than the traditional egg culture vaccines. Furthermore, the recommendation for the annual influenza vaccination by the CDC's Advisory Committee on Immunization Practices has been enlarged to cover around 300 million people compared to 200 million in 2004.[44] These changes stimulated an increase in the number of producers from three in 2004 to five in 2010.

Nevertheless, and even though the market for seasonal influenza vaccines across the seven major markets (United States, Japan, France, Germany, Italy, Spain and UK), has had a strong compound annual growth rate of 12.6% since 2005, in fact the US market is still dominated by a small number of firms, with Sanofi-Pasteur, GSK and Novartis (formerly Chiron) producing more than 90% of the vaccines. [45] Since this demand growth will likely flatten off, further consolidation of this market may be likely.

Conclusions

This analysis suggests that US vaccine markets are likely to reach equilibrium with only one or at most a few suppliers of each vaccine type. This reflects the interaction of high fixed costs with concentrated, price-sensitive demand and dynamic quality competition in which product superiority is reinforced by government recommendation. In such conditions, there is no incentive to introduce "me-too" vaccines, which could not plausibly compete with established firms unless they offer some clear quality or cost advantage. Consequently, new vaccine R&D targets improved technologies for existing vaccines or new vaccine categories. Entry of superior products in turn leads to exit of the now obsolete inferior products. Many vaccines that are approved in other industrialized markets have not applied to enter the US, presumably due in part to high costs of regulatory approval and manufacturing compliance, combined with limited and risky demand, with both price and volume uncertainty if multiple firms are competing for the business. The flu vaccine illustrates the contribution to supply problems of high regulatory hurdles, fixed costs, demand uncertainty and the threat of dynamic competition. Pediatric vaccines face similar regulatory, cost and dynamic competitive conditions; pricing may be more controlled, due to the large market share purchased by the CDC, but volume is more predictable, provided that there are only one or two suppliers in the market.

These economic realities pose difficult policy challenges. Harmonization of country-specific regulatory requirements might increase the diffusion of products across the industrialized markets,

particularly between the EU, Canada and the US. However, given the importance of vaccine policy to public health, national health authorities are unlikely to delegate autonomy on vaccine recommendations and schedules. Perhaps the best hope comes from scientific advances that may improve the storability of vaccines or reduce the lead time required for production. Such improvements would mitigate temporary supply disruptions. Although stockpiles would not protect against withdrawal of a sole supplier, both theory and our empirical evidence show that a sole supplier is much less likely to exit, unless a superior product enters the market. But while new technologies are our best hope in the long run, in the short run new technologies may exacerbate supply shortages, by undermining incentives to invest in older plants that are destined to become obsolete.

References

Arnould, Richard.. and Larry De Brock. 1996. "The Application of Economic Theory to the Vaccine Market." In *Supplying Vaccines: An Economic Analysis of Critical Issues*. Edited by Mark Pauly, Chester Robinson, Stephen Sepe, Merrile Sing and Mary Kay Williams, Amsterdam: IOS Press.

Aventis Pasteur. 2002. "Aventis Pasteur Announces Plans to Meet U.S. Demand for Influenza Vaccine." *Press Release, 2 December 2002*, www.us.aventispasteur.com.

Bridges, Carolyn B. 2004. "General Influenza." *Current Issues in Immunization, Net Conference, 8 July 2004*, http://www.cdc.gov/nip/ed/ciinc/nc_July_08.htm (15 November 2004).

Brown, David. 2004. "How U.S. Got Down to Two Makers Of Flu Vaccine." *Washington Post*, 17 October 2004: A01.

Carree, Martin and A. Roy Thurik. 1996. "Entry and exit in retailing: incentives, barriers, displacement and replacement". Review of Industrial 11: 155-172.

Caves, Richard E.. 1998. "Industrial organization and new finding s on turnover and mobility of firms". Journal of Economic Literature 36(4): 1947-1982.

Danzon, Patricia M., Nuno Sousa Pereira and Sapna Tejwani. 2005."Vaccine Supply: A Cross-National Perspective" *Health Affairs* 24(3): 706-717.

DeBrock, Larry M. and Henry Grabowski. 1985. "Economic Aspects of Vaccine Innovation and Manufacturing." In *Vaccine Supply and Innovation*, Institute of Medicine. Washington D.D.: National Academy Press.

Disney, Richard, Jonathan Haskel and Ylda Heden. 2003. "Entry, exit and establishment survival in UK manufacturing". The Journal of Industrial Economics 51(1): 91-112.

Timothy Dunne, Mark J. Roberts, and. Larry Samuelson. 1988. "Patterns of Firm Entry and Exit in US Manufacturing Industries". RAND Journal of Economics 19(4): 495-515.

Foulkes, Arthur E. 2004. "Weakened Immunity: How the Food and Drug Administration Caused Recent Vaccine-Supply Problems." *The Lighthouse* 9, no. 1 (Summer 2004).

Frankel Glenn. and Glenda Cooper. 2004. "Britain: U.S. Told Of Vaccine Shortage: Flu Shot Records Contradict FDA." *Washington Post Foreign Service*, 9 October 2004, A01.

Geroski, Paul A., Jacquemin, Alexis, Vickers, John, and Venables, Anthony. 1985. " Industrial Change, Barriers to Mobility, and European Industrial Policy". Economic Policy 1 (1): 169-218.

Ghemawat, Pankaj and Barry Nalebuff. 1985. "Exit". RAND Journal of Economics 16(2): 184-194.

Ghemawat, Pankaj and Barry Nalebuff. 1990. "The Devolution of Declining Industries". Quarterly Journal of Economics 105(1): 167-186.

Grabowski, Henry. 2005. "Encouraging The Development Of New Vaccines". *Health Affairs* 24(3): 697-700

Hosbach, Philip. 2004. "Aventis Pasteur Perspective." *National Influenza Summit* (20-22 May 2003), http://www.ama-assn.org (15 November 2004).

Institute of Medicine. 2003. "Financing Vaccines in the 21st Century: Assuring Access and Availability." Washington, DC: IOM.

Jarrett, Steve. 2002. "Procurement Strategies for Drugs and Vaccines." *Wharton Impact Conference on Pharmaceutical Innovation in a Global Economy*. Philadelphia: 4-5 October 2002.

Jovanovic, Boyan, 1992. "Selection and the Evolution of Industry". Econometrica, Econometric Society, vol. 50(3): 649-670

Kauf, Teresa L. 1999. "Price Discrimination and Bargaining Power in the U.S. Vaccine Market: Implications for Childhood Immunization Policy." *Quarterly Review of Economics and Finance* 39:249-265.

Klepper, Steven. 1996. "Entry, exit, growth, and innovation over the product life cycle". American Economic Review 86(3): 562-583.

Klepper, Steven and John H. Miller. 1995. "Entry, exit, and shakeouts in the United States in new manufactures products". International Journal of Industrial Organization 12: 567-591.

Lavanchy, Daniel. 2001. *WHO Influenza Surveillance.* Geneva, Switzerland (5 January 2001).

Manning, Richard L. 1994. "Changing Rules in Tort Law and the Market for Childhood Vaccines." Journal of Law and Economics 37(1): 247-75.

Mercer Management Consulting. 2002. "Lessons Learned: New Procurement Strategies for Vaccines." *Final Report to the GAVI Board.* http://www.vaccinealliance.org/Support_to_Country/vpp/index.php.

Nidus Information Services Inc. 2004. "What are the Vaccines for Diphtheria, Tetanus, and Pertussis?" http://www.nym.org/healthinfo/docs/090/doc90diphtheria.html (15 November 2004).

Orenstein Walter A. 2002. "Background/Overview/Meeting Objectives" (Conference Presentation). *National Influenza Summit*, 22-23 May 2002, http://www.ama-assn.org (15 November 2004).

Offit, Paul A. 2005. The Cutter Incident. New Haven: Yale University Press.

Ruebeck, Christopher S. 2005. "Model exit in a vertically differentiated market: interfirm competition versus intrafirm cannibalization in the computer hard disk drive industry". Review of Industrial Organization 26: 27-59.

Salkever, David S. and Richard G. Frank. 1996. "Economic Issues in Vaccine Purchase Arrangements." In *Supplying Vaccines: An Economic Analysis of Critical Issues*. Edited by Mark Pauly, Chester Robinson, Stephen Sepe, Merrile Sing and Mary Kay Williams, Amsterdam: IOS Press.

Scherer, Frederic M. 2007. "An Industrial Organization Perspective on the Influenza Vaccine Shortage." *Managerial and Decision Economics*. 28:393-405.

Thurik, A. Roy and David B. Audretsch. 1996. "The Dynamics of Industrial Organization". Review of Industrial Organization 11: 149-153.

Tree, Julia A., Catherine Richardson Anthony R. Fook, J. Christopher Clegga and Denis Loobya. 2001. "Comparison of large-scale mammalian cell culture systems with egg culture for the production of influenza virus A vaccine strains." *Vaccines* 19, no. 25-26 (14 May 2001): 3444-3450.

U.S. Centers for Disease Control and Prevention. 2003. "Using Live, Attenuated Influenza Vaccine for Prevention and Control of Influenza: Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP)." 52(RR13) (26 September 2003): 1-8, http://www.cdc.gov/mmwr/preview/mmwrhtml/Table%201

U.S. Food and Drug Administration, Center for Biologics Evaluation and Research. 2004. "Availability of Influenza Virus Vaccine 1999," http://www.fda.gov/cber/infosheets/flu092999.htm (15 November 2004).

U.S. Government Accounting Office. 2002. "Childhood Vaccines: Ensuring and Adequate Supply Poses Continuing Challenges." Washington: GAO.

World Health Organization. 2004. "Influenza Vaccine Manufacturers," http://www.who.int/csr/disease/influenza/manulist/en/ (15 November 2004).

Table 1 – Variables

Variables	Definition	N	Mean	SD
Age	Number of years since license was established.	6883	20.74	16.2
Year of entry (YE)	Year the vaccine was licensed.	6883	1950.21	23.51
Strict Liability (SL)	Binary variable equal to one from 1966 onwards, i.e., the year the second Restatement of Torts adopted strict liability.	6883	0.43	0.49
Pre CDC	Binary variable equal to one if year t is before 1966 (first year CDC procured vaccines); zero otherwise.	6883	0.37	0.48
Input	Binary variable that measures if the vaccine may be used as an input for a more complete combination by the firm that owns it in year t	6883	0.3	0.46
Single	Binary variable equal to one if the vaccine is the only one of its type in the market in year t; zero otherwise.	6883	0.12	0.32
Direct competitors (DC)	Number of competing products of exactly the same type in year t from all other producers.	6883	4.85	4.68
Indirect Competitors (IC)	Number of competing products from all other producers that provide the same kind of protection but are not of exactly the same type in year t.	6883	9.4	14.86
New products (NP)	Number of new licenses of the same type that were launched between year t and year t+1.	6883	1.14	4.19
Universal Recommendation (UR)	Binary variable equal to one if type of vaccine was recommended by the Advisory Committee on Immunization Practices in year t; zero otherwise.	6883	0.13	0.34
Foreign	Binary variable equal to one if the firm that owns the license in not headquartered in the USA; zero otherwise.	6883	0.12	0.32
HHI	Herfindahl-Hirschman Index for type of licenses owned by the firm in year t.	6883	0.22	0.25
Acquired	Binary variable equal to one if license	6883	0.14	0.35

	no longer belongs to original manufacturer; zero otherwise.			
Vaccine Compensation Fund (VCF)	Binary variable if vaccine is covered by the National Vaccine Injury Compensation Program; zero otherwise.	6883	0.14	0.34
Obra	Binary variable if vaccine is covered by the Obra cap; zero otherwise.	6883	0.02	0.13
Thimerosal	Binary variable equal to one if the vaccine contains thimerosal and it is after 1998 (the decision to require the removal of thimerosal from all vaccines was taken in early 1999); zero otherwise.	6883	0.02	0.15
No CDC	Binary variable equal to one if type of vaccine is not procured by CDC in year t-1; zero otherwise.	6883	0.87	0.34
CDCQ	Number of doses of that type of vaccine purchased by the CDC in year t-1 (in 10s of thousands).	6821	44.67	172.01
CDCP	Price paid by the CDC for that type of vaccine in year t-1.	6821	0.13	0.53
CDCQs	Number of doses of that type of vaccine purchased by the CDC in year t-1 divided by the number of licenses of that type.	6821	13.86	63.6

Table 2 – Impact of Competition (hazard ratios)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Age	1.053[a]	1.063[a]	1.067[a]	1.068[a]	1.072[a]	1.085[a]	1.076[a]	1.089[a]
	(7.21)	(6.60)	(6.28)	(6.29)	(6.03)	(7.05)	(7.11)	(6.88)
YE	1.031[a]	1.041[a]	1.040[a]	1.041[a]	1.047[a]	1.063[a]	1.054[a]	1.067[a]
	(4.71)	(5.00)	(4.74)	(4.81)	(5.01)	(6.09)	(5.71)	(5.94)
SLDV	14.341[a]	11.332[a]	9.790[a]	9.477[a]	9.483[a]	7.903[a]	9.565[a]	7.319[a]
	(8.48)	(4.97)	(4.63)	(4.56)	(4.41)	(3.86)	(4.12)	(3.74)
Input	0.399[a]	0.322[a]	0.323[a]	0.321[a]	0.251[a]	0.227[a]	0.216[a]	0.223[a]
	(-3.39)	(-3.48)	(-3.31)	(-3.36)	(-3.91)	(-3.62)	(-3.53)	(-3.67)
Single	0.434[a]	0.517[b]	0.539[c]	0.522[c]	0.457[b]	0.446[a]	0.473[b]	0.472[b]
	(-2.71)	(-2.03)	(-1.89)	(-1.93)	(-2.43)	(-2.56)	(-2.34)	(-2.38)
DC		1.055[a]	1.030[b]	1.028[b]	1.024	1.035[c]	1.032[c]	1.036[b]
		(3.37)	(2.007)	(1.98)	(1.34)	(1.95)	(1.85)	(2.09)
IC			1.015[b]	1.013[c]	1.022[a]	1.020[a]	1.019[a]	1.021[a]
			(2.30)	(1.95)	(2.83)	(2.78)	(2.75)	(2.76)
NP				1.028[a]	1.026[a]	1.028[a]	1.028[a]	1.028[a]
				(3.84)	(4.04)	(4.16)	(4.08)	(4.24)
UR					0.388[a]	0.354[a]	0.337[a]	0.343[a]
					(-3.52)	(-3.58)	(-3.42)	(-2.95)
Foreign						0.308[a]	0.310[a]	0.302[a]
						(-4.43)	(-4.37)	(-4.50)
HHI						0.768	0.772	0.803
						(-0.52)	(-0.51)	(-0.44)
Acquired						0.869	0.839	0.893
						(-0.55)	(-0.68)	(-0.46)
VCF							1.225	
							(0.65)	
Obra							0.947	
							(-0.13)	
Thimerosal							1.444	
							(1.25)	
No CDC								1.053
								(0.13)
CDCPrice								0.864
								(-0.85)
CDCQ/license								1.001
								(0.69)
Log-Likelihood	-716.6	-712.8	-709.0	-707.1	-697.7	-683.5	-682.3	-678.9
Wald chi2	115.64	106.69	102.27	118.58	111.98	195.30	371.45	258.03

D.o.f.	5	6	7	8	9	12	15	15
Licenses				241				
Events				179				
Spells	6883	6883	6883	6883	6883	6883	6883	6821

Note: Figures in parentheses are z-statistics. Superscripts a, b and c indicate that the estimated coefficients are significant at the 1%, 5% and 10% significance levels, respectively.

Table 3 – Market trend and CDC's role (hazard ratios)

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Age	1.107[a]	1.103[a]	1.110[a]	1.111[a]	1.111[a]	1.110[a]	1.111[a]
	(14.05)	(10.22)	(10.81)	(10.91)	(10.80)	(10.93)	(10.91)
YE	1.082[a]	1.079[a]	1.086[a]	1.087[a]	1.087[a]	1.086[a]	1.087[a]
	(10.87)	(7.94)	(8.58)	(8.70)	(8.63)	(8.69)	(8.71)
SLDV	4.014[a]	3.703[a]	3.813[a]	3.779[a]	3.774[a]	3.773[a]	3.757[a]
	(8.48)	(5.59)	(5.99)	(6.02)	(6.03)	(6.05)	(6.08)
Pre CDC		0.729	0.860	0.869	0.867	0.856	0.864
		(-0.46)	(-0.22)	(-0.21)	(-0.21)	(-0.23)	(-0.22)
No CDC		1.202	1.222	1.058	1.044	1.136	1.025
		(0.88)	(0.70)	(0.20)	(0.12)	(0.52)	(0.08)
CDCQ			1.000		1.000		
			(-0.13)		(-0.12)		
CDCPrice				0.821	0.822		0.842
				(-1.29)	(-1.30)		(-1.19)
CDCQ/license						0.999	0.999
						(-0.65)	(-0.37)
Log-Likelihood	-726.02	-725.54	-720.22	-719.68	-719.68	-719.99	-719.61
Wald chi2	251.91	265.27	274.35	271.26	276.66	271.05	271.49
D.o.f.	3	5	6	6	7	6	7
Licenses				241			
Events				179			
Spells	6883	6883	6821	6821	6821	6821	6821

Note: Figures in parentheses are z-statistics. Superscripts a, b and c indicate that the estimated coefficients are significant at the 1%, 5% and 10% significance levels, respectively.

Table 4 – Exit of firms (hazard ratios)

	Events treated jointly	Exit	Acquired
Age	1.099[a]	1.074[a]	1.152[a]
	(6.17)	(4.70)	(4.26)
YE	1.085[a]	1.068[a]	1.120[a]
	(5.72)	(4.04)	(3.42)
Single	0.119[b]	0.230	0.048[b]
	(-2.31)	(-1.19)	(-2.24)
Foreign	0.368[c]	0.311	0.744
	(-1.79)	(-1.46)	(-0.35)
HHI	2.627	10.219	0.789
	(1.09)	(1.63)	(-0.18)
Time since last launch	0.966	1.006	0.881[a]
	(-1.15)	(0.16)	(-2.90)
Log-Likelihood	-86.44	-52.66	-42.40
Wald chi2	66.57	64.18	30.63
D.o.f.		6	
Firms		39	
Events	22	12	10
Spells		1269	

Note: Figures in parentheses are z-statistics. Superscripts a, b and c indicate that the estimated coefficients are significant at the 1%, 5% and 10% significance levels, respectively.

Table 5 - Valid License Holders and Year of License by Country in 2004

Type	USA	Canada	UK	France	Portugal
DTP & HBV & IPV & Hib				AVT(2000[1,6]) GSK(2000[1])	AVT(2000[6]) GSK(2000)
DTP & HBV & IPV	GSK(2002[1])				AVT(1998[6]) GSK(2000)
DTP & IPV & Hib		AVT(1997[1])	AVT(1998[1], 2002[1])	AVT(1993, 1993[6], 1998[1], 1998[1,6]) GSK(1997[1])	AVT(1998[6], 2000[6]) GSK(1999)
DTP & HBV					GSK(1996, 1997)
DTP & Hib	AVT(1996[1]) WYE(1993)		AVT(1995) GSK(2002[1])	AVT(1993, 1998[1])	AVT(2000[6]) GSK(2000)
DTP & IPV		AVT(1997[1])	AVT(1998[1], 2001[1]) GSK(2004[1])	AVT(1975[6], 1985, 1998[1,6], 2002[1,6]) GSK(1996[1])	AVT(1998[6], 2001[6], 2002[6])
DTP	AVT(1992[1], 2002[1]) BXT(1998[1]) GSK(1997[1])	AVT(1996[1], 1999[1])	AVT(1993) CHR(1997) GSK(1999[1], 2001[1]**)**	AVT(1997)	AVT(1991[6]) GSK(1996, 1997, 2000) RVL(1980)
DT & IPV		AVT(1984, 1995)	AVT(2003)	AVT(1977[6], 2000[6])	AVT(1999[6])
DT	AVT(1955[2], 1984, 1997) CHR(1997) MBL(1970[2])	AVT(1980[2]) IDB(1991)	AVT(1993, 1993[2]) CHR(1998[2])	AVT(1984, 1996, 1996[2])	AVT(2003) GSK(1996[2]) RVL(1980, 1980[2])
D	SSI(1998)				RVL(1969)
T	AVT(1934, 1970) MBL(1970) SSI(1998)	AVT(1980) IDB(1991)	AVT(1993) CHR(1998, 2001)	AVT(1973, 1978[6]) AVT(1975[4,6]) AVT(1987[5])	AVT(1991[6]) GSK(1996)
P	RFM(1992[1]) TKD(1991[1])				
MeaMR	MRK(1971)	GSK(1998)	AVT(1996)	AVT(1985, 1993[6],	AVT(1999[6])

		MRK(1979)	GSK(1997)	1994[6]) GSK(1999)	GSK(1998) RVL(1989)
MeaM	MRK(1973)				
MeaR		SSB(1996)	AVT(1994)	AVT(1981)	
Mea	MRK(1963)		AVT(1989)	AVT(1986)	GSK(1984)
M	MRK(1967)		AVT(1996)	AVT(1983, 2001[6])	
R	MRK(1969)		AVT(1989, 1992, 1995, 1995)	AVT(1988)	AVT(1985[6])
PNC_c	WYE(2000)	WYE(2001)		WYE(2001)	WYE(2001)
PNC_p	MRK(1977)	AVT(1997) MRK(1978)	AVT(2000, 2000)	AVT(1996, 2001[6], 2001[6]) SLV(1985)	AVT(1998[6], 2001[6])
Polio	AVT(1987[3], 1990[3]) WYE(1963)	AVT(1987[3], 1997[3])	AVT(2004[3]) GSK(1994, 1994)	AVT(1982[3])	AVT(2000[6]) GSK(1984)
Var	MRK(1995)	GSK(1999) MRK(2002)	GSK(2002) AVT(2003)	AVT(2003[6]) GSK(2003)	AVT(2003[6]) GSK(2003)
HBV	GSK(1989) MRK(1986)	GSK(1991) MRK(1987)	AVT(2001) GSK(2001)	AVT(1987[6], 2001[6]) GSK(1994)	AVT(2001[6]) GSK(1987)
HAV&HBV	GSK(2001)	GSK(1997)		GSK(1996)	GSK(1996, 2002)
HAV	GSK(1995) MRK(1996)	AVT(1998) BBT(1999) GSK(1995) MRK(1996)	AVT(1996, 1996) GSK(1994) ISB(1999)	AVT(1996, 1996[6], 1997[6]) GSK(1994) ISB(2003)	AVT(1997[6], 1997[6]) GSK(1997) ISB(2000)
HAV&Typ			AVT(2001, 2001) GSK(1999)	AVT(2003[6], 2003)	AVT(2002[6])
Hib&HBV&Men					AVT(1999[6])
Hib&HBV	MRK(1996)		GSK(1996)		
Hib	AVT(1993[7]) MRK(1989) WYE(1988)	AVT(1992) MRK(1997)	AVT(1992) GSK(1999) WYE(1992)	AVT(1992, 1992[6]) GSK(1997)	AVT(1996[6,8], 1999[6]) GSK(1998) WYE(1994)

Men ACWY	AVT(1981)	AVT(1983)	AVT(1997) GSK(1993)	AVT(2002[6])	
Men A&C	AVT(1976)	AVT(1993) GSK(1992)	AVT(1994)	AVT(1996)	AVT(2000[6])
Men C	AVT(1975)	CHR(2001) IDB(2001) WYE(2003)	WYE(1999) BXT(2000) CHR(2000, 2001)	AVT(2002[6]) BXT(2003) CHR(2002) WYE(2002)	AVT(2001[6]) BXT(2001) CHR(2001) WYE(2000)
Men A	AVT(1975)				
Flu	AVT(1947) CHR(1988) MIN(2003)	AVT(1981,1996) IDB(1991)	AVT(1998, 1999) CHR(1998, 1999, 2001) GSK(1998) ISB(2002) SLV(1998, 2000, 2004)	AVT(1998, 1998, 2001[6]) EVN(1998) CHR(1998, 1999, 2001) GSK(1998) PFM(1991) SLV(1998, 2000)	AVT(1998[6], 1998[6], 2000[6]) CHR(1999, 2000) EVN(1996) ISB(2001) GSK(1998) SLV(1998, 2001, 2004)
BCG	AVT(1998) ORG(1987)	AVT(1961, 1990) IDB(1991, 1994) ORG(1995)	SSI(2002)	AVT(1976, 1978[6], 1987) SSI(2004)	JMF(2003) LIB(1992)

1 – Acellular Pertussis
2 – For adults
3 – IPV
4 – Combined with IPV
5 – Combined with Influenza
6 - In 1994, Merck Vaccine Division and Pasteur Mérieux Connaught (now Aventis Pasteur) formed a joint venture to market human vaccines in Europe and to collaborate in the development of combination vaccines for distribution. The equal shares joint venture is known as Aventis Pasteur MSD, S.N.C.
7 – Combined with Tetanus Toxoid
8- Combined with Men C

AVT – Aventis Pasteur
BIK - BIKEN - The Research Foundation for Microbial Diseases, Osaka University
BBT – Berna Biotech Ltd.
BPT – BioPort Corporation
BXT – Baxter Healthcare
CHR – Chiron S.R.L.
EVN – Evans Vaccines
GOV – United Kingdom Department of Health
GSK – GlaxoSmithkline Inc.
IDB - ID Biomedical Corporation
ISB - Istituto Sieroterapico Berna, S.r. l.
JMF - J. M. Farmacêutica, Lda.
LIB – Laboratorios Inibsa, S.A.
MBL - Massachusetts Biologic Laboratories
MIN - MedImmune Vaccines, Inc
MRK - Merck&Co, Inc
ORG – Organon Teknika Corporation
PFM – Pierre Fabre Medicament
RVL - Raúl Vieira, Lda.
SBL – SBL Vaccine AB
SLV – Solvay Pharma
SSB - Swiss Serum and Vaccine Institute Berne
SSI - Staten Serum Institute
TKD - Takeda Chemical Industries, Ltd.
WYE - Wyeth Lederle Vaccines SA

Table 6 – Total Doses of Flu Vaccine Produced and Distributed, by Manufacturer:
US 2000-2009

Flu Season	**Total # Doses Produced**	**Total # Doses Distributed**	**Supplier**	**Product**	**Doses Produced**	**% of Total US Doses Distributed**
2000-2001	77.9M	70.4M	Aventis Pasteur	Fluzone	35M[A]	45%
			Wyeth	Flusheild Pnu-Immune	24M	31%
			Medeva[B]	Fluvirin	20M	26%
			Parkedale	Fluogen	0M[C]	0%
2001-2002	87.7M	77.7M	Aventis Pasteur	Fluzone	50M	57%
			Wyeth	Flushield Pnu-Immune	21M	24%
			Powderject	Fluvirin	17M	19%
2002-2003	95.0M	83.0M	Aventis Pasteur	Fluzone	43M[E]	45%
			Wyeth	Flushield Pnu-Immune	21M	22%
			Powderject[D]	Fluvirin	26M	27%
2003-2004	86.9M	83.1M	Aventis Pasteur	Fluzone	43M	49%
			Chiron	Fluvirin	39M	45%
			MedImmune/ Wyeth	FluMist	5M[F]	6%
2004-2005	61M[G]	57.0 M	Aventis Pasteur	Fluzone	58M[H]	95%
			Chiron	Fluvirin	0M[I]	0%

			MedImmune	FluMist	3M	5%
2005-2006	88.5M	81.5M	Chiron	Fluvirin	15M	17%
			GlaxoSmith Kline	Fluarix	7M	8%
			MedImmune	FluMist	3M	3%
			Sanofi-Pasteur[J]	Fluzone	63M	71%
2006-2007	120.9M	102.5M	GlaxoSmith Kline[K]	Fluarix FluLaval	41M	34%
			MedImmune	FluMist	3M	3%
			Novartis Vaccines	Fluvirin	25.6M	21%
			Sanofi-Pasteur[J]	Fluzone	51.3M	42%
2007-2008	140.6M	112.8 M	CSL	Afluria	2M	1%
			GlaxoSmith Kline[K]	Fluarix FluLaval	35M	25%
			MedImmune	FluMist	7M	5%
			Novartis Vaccines	Fluvirin	46M	33%
			Sanofi-Pasteur[J]	Fluzone	50M	36%
2008-2009	135.9M	113 M	CSL	Afluria	8.1M	6%
			GlaxoSmith Kline[K]	Fluarix FluLaval	43.5M	32%
			MedImmune	FluMist	6.8M	5%
			Novartis Vaccines	Fluvirin	27.2M	20%
			Sanofi-Pasteur[J]	Fluzone	50.3M	37%

A: Includes 9M contracted later in the season by the CDC, of which only 2M were ever administered

B: Medeva was purchased by Celltech in January 2000 and in turn sold to Powderject shortly after

C: Faced cGMP violations and production was suspended. Parkedale had planned to distribute 12M doses

D: Powderject was purchased by Chiron in July 2003

E: 43M doses were already distributed as of October 31, 2002. There is no data available for entire season.

F: Only 450,000 doses of the 5M were ever administered

G: 100M doses were originally planned before Chiron's production was suspended

H: Only 50M planned, but Aventis pledged 8M additional doses to help alleviate shortage caused by Chiron's manufacturing problems

I: Production suspended by UK regulatory authorities. Chiron had planned to distribute 46M to 48M doses

J: Previously Aventis Pasteur

K: The license belongs to ID Biomedical Corp of Quebec, which is a wholly-owned subsidiary of GlaxoSmithKline.

* Individual manufacturer production values may not add up to total production values due to rounding

Table 7 - Production Time for Egg-based vs. Cell-based Influenza Vaccine

Process	Egg-based	Cell culture based
Seed prep	2-8months	1-2months
Substrate availability	0-3months	0-0.5months
Facilities	Open system	Closed system
Timely availability pandemic vaccine	(-)	(+)

Source: National Influenza Summit: May 2003 "Vaccine Production Using Cell Culture" Solvay Pharmaceuticals

Table 8 - Major WHO Approved Global Manufacturers of Inactivated Influenza Vaccine

Producer	Country	Brand name
Medimmune-Avirion	USA	FluMist
Baxter-- Immuno AG	Austria Czech Republic	
CSL	Australia	Fluvax
GSK	Belgium	FluarixNH Fluarix SH
Butantan (Filler)	Brazil	Gripe Vaccine
Sanofi Pasteur	France	Mutagrip Vaxigrip Tetagrip
	USA	Fluozone
Novartis	Germany	Fluad
	Italy	Antigripal S1
	UK	Fluvirin Evagrip
Denka Seiken Co, Ltd	Japan	Influenza Seiken HA
Chemo-Sero-Therapeutic Research Institute	Japan	Influenza Kaketsuken HA
Kitasato Institute	Japan	Influenza HA
Biken	Japan	Influenza Biken
Dong Shin Pharmaceuticals (Filler)	Korea	Dong Shin Influenza HA
Korea Vaccine Co. Ltd (Filler)	Korea	Influ-kovax
Korea Green Cross (Filler)	Korea	Inflexal V
Solvay Healthcare	Netherlands	Influvac
Cantacuzino Institute	Romania	VACCIN GRIPAL TRIVALENT, PURIFICAT [a]I INACTIVAT
Immunopreparat Research productive association, Ufa	Russia	Influenza Vaccine
Products Immunologicals and Drugs. Irkustk		Influenza Vaccine
RIVS, Saint Petersburg		Influenza Vaccine
Berna -Crucell	Switzerland	Inflexal V, Vitagrip, Fluviral
ID Biomedical	Canada	FluInsure

Wyeth Lederle	USA	Flushield
Torlak Institute	Serbia&Montenegro	Vaccinum Influenzae
Zhejiang Tianyuan - BioPharmaceutical Co. Ltd	China	Influenza
Sinovac Kexing Biological Product Co., Ltd		AnFlu TM
Beijing Institute of Biological Products (BIBP)		Influenza
Shanghai Institute of Biological Products (SIBP)		Influenza
Changchun Institute of Biological Products (CCIBP)		Influenza
Changchun Changsheng Life Sciences Ltd		Influenza
Lanzhou Institute of Biological Products (LIBP)		Influenza
Shenzhen-Sanofi Pasteur (Filler)		Influenza
Changzhou Yanshen Biotechnology Co., Ltd		Influenza
Liaoning Tiancheng Bio-pharmacy Insitute Co. Ltd		Influenza
Omninvest Ltd.	Hungary	Influenza

SOURCES: World Health Organization: "Influenza Vaccine Manufacturers", http://www.who.int/csr/disease/influenza/Influenza_vaccine_manufacturers2009_05.pdf;

Figure 1 – Entry and Exit of Vaccine Products (FDA-approved Licenses) 1901-2001

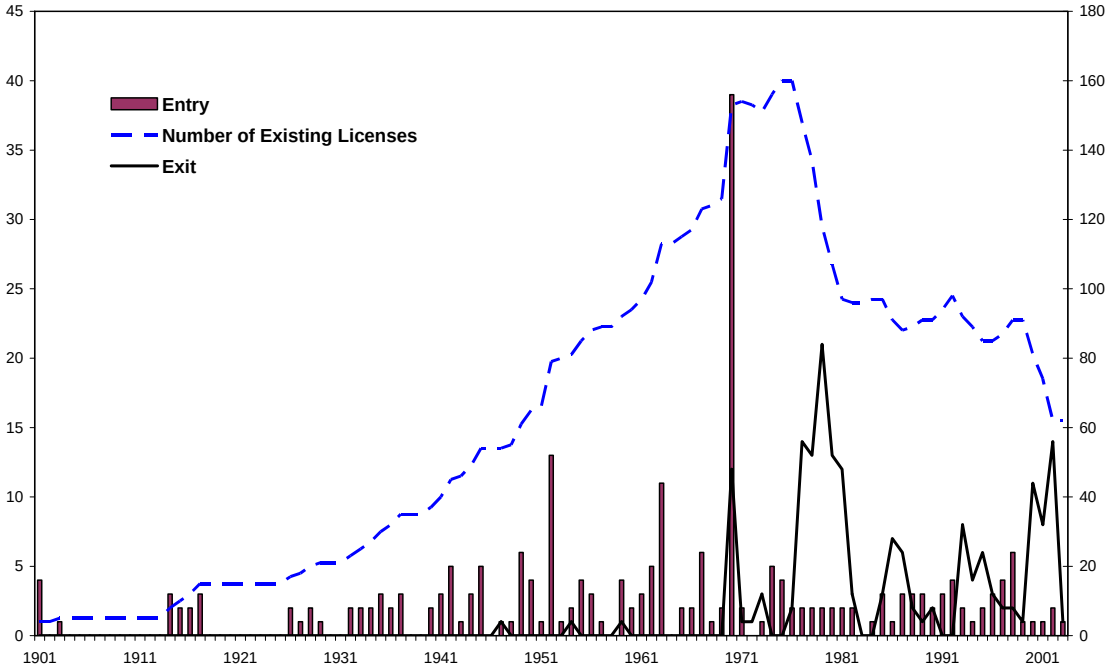
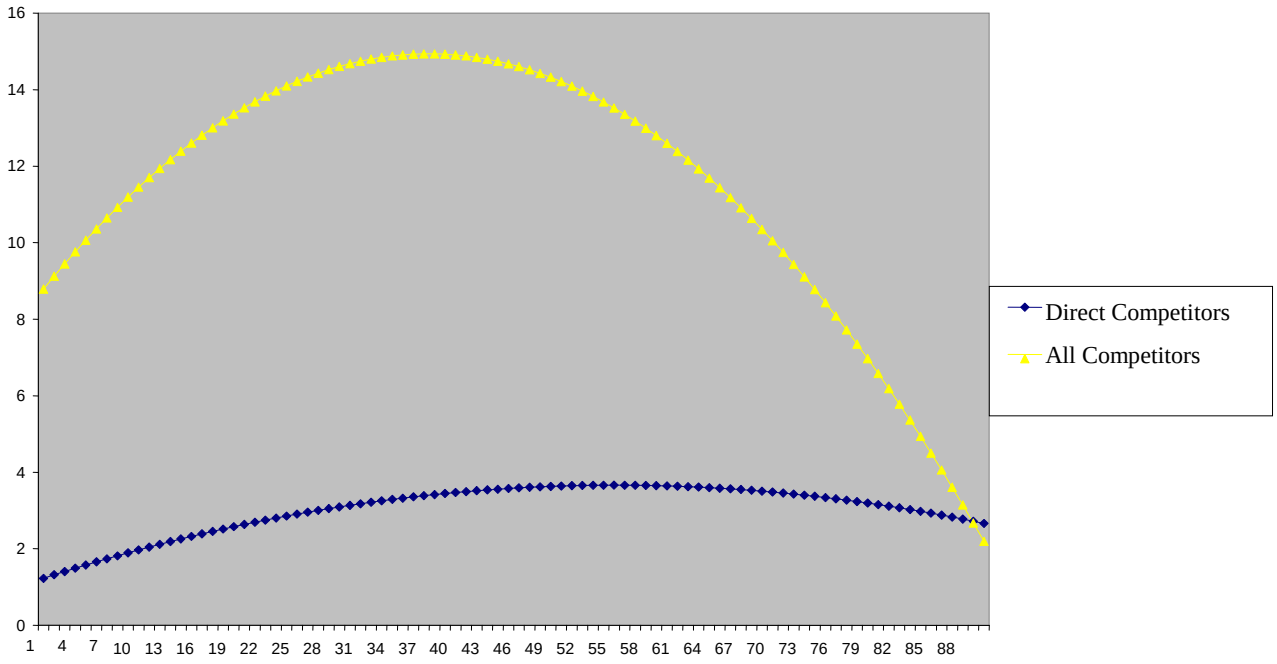


Figure 2 - Predicted Number of Competitors as a Function of Years of Market Existence



Note: Direct Competitors is the number of licensed vaccines of exactly the same type in year t that are owned by other producers. All Competitors is the sum of Direct Competitors plus other licensed vaccines that include the vaccine in question in year t, including combination vaccines.

[1] This is true particularly for traditional pediatric vaccines against highly infectious diseases, such as polio, measles, etc. In general, the cost-effectiveness of any specific vaccine depends on the price, the target population and the measure of effectiveness. This analysis does not distinguish between pediatric and adult vaccines, because the analysis applies to all types.
[2] Institute of Medicine (2004); GAO (2002).
[3] S. Jarrett, "Procurement Strategies for Drugs and Vaccines," Wharton Impact Conference on Pharmaceutical Innovation in a Global Economy (4-5 October 2002).
[4] Mercer Management Consulting (2002), http://www.vaccinealliance.org/Support_to_Country/vpp/index.php. Basic pediatric vaccines include measles, mumps, rubella, diptheria, TB, pertussis, polio, tetanus, typhoid etc. These older vaccines are part of pediatric vaccination schedules in most countries, with financing for the poorest countries through the Global Alliance for Vaccines and Immunization (GAVI).
[5] USAToday 8/13/2010. http://www.usatoday.com/money/industries/health/2010-08-13-vaccines_N.htm (last accessed 9/13/2010).
[6] Government recommendation may increase coverage by private insurance as well as public programs.
[7] States handle enrolment of eligible patients and eligible doctors, who receive free vaccine for these patients. http://www.cdc.gov/vaccines/programs/vfc/parents/default.htm#history. Last accessed 12/16/2010.
[8] Jarrett, "Procurement Strategies for Drugs and Vaccines."
[9] Thimerosal is a mercury-containing preservative that was used in multi-dose vaccine vials that has been alleged to be associated with autism.
[10] R&D cost for vaccines is estimated to be comparable to other drugs (Grabowski, 2005). Vaccine production requires unusually high investments in quality assurance, as a condition of getting and maintaining the plant license. Fixed costs have been estimated at 60 percent of total production costs and semi-fixed batch costs at an additional 25percent (Mercer, 2002).
[11] Combinations are usually produced by the producer(s) of the component parts.
[12] If a vaccine produces adverse effects, many patients are likely to be affected. The risks associated with individual vaccine doses are therefore correlated, not independent, as required for diversification and insurability.
[13] The assumption that each firm sets its price and customers choose quantities characterizes the CDC procurement process. It is also a plausible model of private purchasing in which buyers negotiate price discounts from competing suppliers.
[14] The pertussis component is usually not given to adults because whooping cough is less severe in older people while the vaccine side effects may be more severe. Patients also receive diphtheria and tetanus boosters every ten years. Nidus Information Services Inc., "What are the Vaccines for Diphtheria, Tetanus, and Pertussis?" http://www.nym.org/healthinfo/docs/090/doc90diphtheria.html (15 November 2004).
[15] Institute of Medicine (2004). In fact, the catalog price may overstate transactions prices paid by private customers due to confidential discounting.
[16] This argument implicitly assumes that producers underestimate the extent of government regulation prior to entry.
[17] We also tested for effects of partial recommendation, but it was not significant.
[18] Our absolute price is an imperfect proxy for the theoretically preferred mark-up of price over marginal cost, which is not feasible because data on marginal cost are unavailable. Absolute price should be correlated with the price-marginal cost mark-up if marginal cost is similar across vaccines in a given year, which is plausible for most of the vaccines, However, given the potential measurement error in our price variable, conclusions on effects of CDC price are tentative.
[19] The correlation between Pre CDC and No CDC is only 0.3, because many vaccines were not purchased by CDC, even after 1966.
[20] Manning (1994) reports large price increases related to liability, especially for the pertussis vaccine. Offit (2005) shows that the liability of vaccine manufacturers was established in the 1955 Cutter incident, in which patients were infected with live polio vaccine, leading 70,000 to become ill, 200 became permanently paralyzed and 10 died. We nevertheless use 1966 as the start date for strict liability because this formalized the law.
[21] We also considered a measure of the number of vaccines licenses held by that manufacturer in t-1. This was highly correlated with the Herfindahl, and was therefore dropped.

[22] For example, if there were two single diphtheria vaccines and one combination vaccine, DPT, which includes diphtheria, each single diphtheria has one Direct Competitor and one Indirect Competitor.
[23] The predicted median survival of these products is thirty years, with 25th and 75th percentiles at 17 and 49 years, respectively, and a mean of 33.8 years. These predicted values are from a Kaplan-Meier survival estimator applied to the censored observations.
[24] We also ran separate regressions for exits due to closing vs. acquisition of the firm.
[25] Although we were unable to obtain reliable price data, the limited data available to us indicate that foreign prices are no higher and usually lower than in the US.
[26] D. Lavanchy, WHO Influenza Surveillance, Geneva, Switzerland (5 January 2001).
[27] U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, "Availability of Influenza Virus Vaccine 1999," http://www.fda.gov/cber/infosheets/flu092999.htm (15 November 2004).
[28] Dr. Bridges, "General Influenza," Current Issues in Immunization, Net Conference, 8 July 2004, http://www.cdc.gov/nip/ed/ciinc/nc_July_08.htm (15 November 2004).
[29] W.A. Orenstein, "Background/Overview/Meeting Objectives" (Conference Presentation) National Influenza Summit, 22-23 May 2002, http://www.ama-assn.org (15 November 2004).
[30] Foulkes (2004).
[31] D. Brown, "How U.S. Got Down to Two Makers Of Flu Vaccine," *Washington Post*, 17 October 2004: A01.
[32] Aventis Pasteur, "Aventis Pasteur Announces Plans to Meet U.S. Demand for Influenza Vaccine" Press Release, 2 December 2002, www.us.aventispasteur.com (15 November 2004).
[33] "The problem was they really stressed the system this year to get to that 50, 52 million doses," said Geoffrey C. Porges, an analyst at Sanford C. Bernstein & Company who formerly worked in the vaccines business at Merck.
[34] G. Frankel and G. Cooper, "Britain: U.S. Told Of Vaccine Shortage: Flu Shot Records Contradict FDA" *Washington Post Foreign Service*, 9 October 2004, A01.
[35] U.S. Centers for Disease Control and Prevention, "Using Live, Attenuated Influenza Vaccine for Prevention and Control of Influenza: Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP)," 52(RR13) (26 September 2003): 1-8, http://www.cdc.gov/mmwr/preview/mmwrhtml/Table%201 (15 November 2004).
[36] P. Hosbach, "Aventis Pasteur Perspective," National Influenza Summit (20-22 May 2003), http://www.ama-assn.org (15 November 2004).
[37] Although Medicare reimbursement for other Part B drugs changed in 2004 to average selling price (ASP) plus 6 percent, reimbursement for flu, pneumococcal and Hepatitis B vaccines remains at 95% of AWP.
[38]Tree et al. (2001).
[39] Solvay Pharmaceuticals was acquired by Abbott in September 2009 http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0781.htm
[40] These include small new entrants to the flu vaccine business, such as Protein Sciences, BioDiem, and Vaxin Technology, some with funding from NIH, as well as Sanofi-Aventis and GlaxoSmithKline. Chiron's influenza cell-culture research program has completed Phase II clinical trials in Europe.
[41] http://www.novartis.com/newsroom/media-releases/en/2009/1356789.shtml
[42] http://www.medpagetoday.com/InfectiousDisease/URItheFlu/17128
[43] World Health Organization, "Influenza Vaccine Manufacturers," http://www.who.int/csr/disease/influenza/manulist/en/ (15 November 2004).
[44] http://www.cdc.gov/flu/professionals/vaccination/pdf/influenza_vaccine_target_populations.pdf
[45] http://www.tradingmarkets.com/news/stock-alert/abt_abbott-calls-off-sale-of-flu-vaccine-business-in-europe-1149378.html