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ABSTRACT

AN INDUSTRIAL ORGANIZATION PERSPECTIVE ON THE INFLUENZA VACCINE SHORTAGE

Author: F.M. Scherer, Senior Fellow, American Antitrust Institute; Aetna Professor Emeritus, John F. Kennedy School of Government, Harvard University; and lecturer, Woodrow Wilson School, Princeton University.

This paper analyzes reasons advanced for the recent shortage of influenza vaccine in the United States and numerous other similar shortages in recent years. Explanations have included high regulatory costs, inadequate profitability, and mergers. Building from the information base developed through an Institute of Medicine study and other work, it advances the discussion in several respects. Using Census data, it shows that vaccine producers realize unusually high price-cost margins, but are probably also unusually capital-intensive. Applying theories of scale economies to existing information, it identifies the extent to which, for diverse types of vaccines, economies of scale limit the number of vaccine producers, exposing the nation to stochastic shortage risk. It proposes a hypothetical but plausible cost function for influenza vaccine production. A benefit/cost analysis then explores whether it is economically worthwhile to maintain additional production sources with surge capacity. It is found that under plausible demand, external benefit, and stochastic supply failure conditions, such multiple sourcing yields more benefits than its cost. One implication of the analysis is that better data on vaccine costs and profits are needed -- data the Federal Trade Commission has the power and mission to assemble.

Key words: Vaccines, economies of scale, stochastic supply failure, profitability, external benefits, public regulation.

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Contact: F.M. Scherer, fmscherer@comcast.net

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AN INDUSTRIAL ORGANIZATION PERSPECTIVE ON THE INFLUENZA VACCINE SHORTAGE

American Antitrust Institute Working Paper #04-03

F. M. Scherer*
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In early October 2004, it became known that because of contamination problems requiring cessation of shipments from its Liverpool, England, plant, the U.S.-based Chiron Corporation would be unable to supply to the U.S. market nearly half of the 100 million vaccine doses planned for administration to U.S. citizens in anticipation of the 2004-05 influenza season. Because only two companies -- Chiron and Aventis-Pasteur of France -- were licensed to supply injectable influenza vaccine in the U.S. market¹ and Aventis-Pasteur was unable significantly to increase production at its plant in northeastern Pennsylvania beyond its planned output of 55 million doses, stringent rationing of immunizations to the most vulnerable U.S. citizens had to be implemented.

The influenza vaccine shortages in the fall of 2004 were not unprecedented. Immunization programs in the United States have repeatedly experienced vaccine production failures that have led to shortages, rationing, and black markets. During the 1980s, there were significant shortages of the diphtheria-tetanus-pertussis vaccine administered to children. Between 2000 and 2002, supplies of tetanus-diphtheria and pneumococcal conjugate vaccine were short by 40 percent, of varicella (chickenpox) vaccine by 26 to 29 percent, and of measles-mumps-German measles vaccine by some 15 percent. Institute of Medicine (2004, pp. 132-135). A survey of state immunization programs in early 2002 reported 52 cases in which there were shortages of two or more vaccines and 31 cases in which five or more vaccines whose supply was inadequate. U.S. GAO (2002), p. 11. In nine cases, shortages of one or more vaccines persisted for a year or longer.

*Senior Fellow, American Antitrust Institute; Aetna Professor Emeritus, John F. Kennedy School of Government, Harvard University; and lecturer, Woodrow Wilson School, Princeton University. The author thanks William S. Comanor, Mark Pauly, Dr. Dean Jamison, and Dr. Cecile Viboud for valuable comments and documents.

1. A third authorized supplier, Medimmune Inc., makes only intranasal influenza vaccine sprays, with demand limited to less than two million doses per year.

There are two over-arching reasons for the high incidence of shortages. For one, vaccines are typically derived from living pathogenic organisms. They are more complex in their molecular structures and in the processes used to produce them than the so-called "small molecule" preparations which are the forte of the pharmaceutical industry. Murphy's Law applies with a vengeance: if anything can go wrong, it will, at least with some appreciable statistical probability. And the consequences of a bad batch can be lethal.² Second, more than a dozen vaccine producers exited partially or entirely from the business during the 1970s and 1980s, and the number remaining with authorization to deliver the typical vaccine to U.S. citizens is small.³ Although an Institute of Medicine study listed 16 different companies, half domestic and half foreign-owned, with authorization in 2003 to supply standard vaccines in the United States, product specialization severely limits the number of suppliers for any given vaccine. Thus, four companies together produce nearly all of the standard childhood vaccines. Five vaccines recommended for administration in the United States during 2003 were obtained from only one producer, and most of the others had only two producers (e.g., injectable influenza vaccine) or three sources. Institute of Medicine (2004, p. 124; and Arnould and DeBrock (2003). With a small number of producers for any given vaccine, a significant random disturbance in the production of a single firm can precipitate large product shortfalls and rationing.⁴

This paper examines the problem of vaccine shortages from the perspective of competition policy. Competition policy is construed here more broadly than a focus on antitrust alone, but takes into account also regulatory and government procurement policies.

Why So Few Vaccine Suppliers?

When the supply of important products is tightly concentrated and when substantial exodus from an industry has been observed, a competition policy study must begin by asking why. Several reasons are given in the relevant recent literature.

2. The author became gravely ill, and his bunkmate died, when a bad batch of vaccine was administered to U.S. Army inductees at Fort Chaffee, Arkansas, in 1954.

3. Census Bureau concentration statistics for vaccine production are fragmentary, with reporting discontinued after 1982. From 1967 to 1977, the reported four-firm sales concentration ratio for "vaccines, toxoids, and antigens for human use" rose from 66 to 90, and for 1982 the value was suppressed -- usually an indication of values near 100.

4. "Shortages" can of course be averted if prices rise, perhaps sharply, to choke off demand. But most vaccine prices are fixed or at least benchmarked through bargaining between suppliers and government procurement authorities.

For one, because vaccines can fail with potentially serious consequences, producers have traditionally been exposed to significant tort liability risks. This, plus an increase in the number of liability suits to 225 in the year 1984, was a material inducement to the exit of numerous producers. In response to a supply crisis, the U.S. Congress created in 1986 the National Vaccine Injury Compensation Program, establishing an essentially no-fault approach to compensating individuals injured through childhood vaccinations, which receive substantial federal funding support. Damages payments are financed by an excise tax on childhood vaccines (comprising roughly 70 percent of the vaccine market). Conventional tort liability rules remained for other vaccines, notably, those administered primarily to adults. However, earlier in 2004, Congress passed a bill adding influenza vaccines to the compensation program, and political pressures will presumably induce President Bush to sign it into law.⁵

Second, for all childhood vaccines and also some others, federal government agencies, including the Centers for Disease Control and Prevention as well as the Veterans Administration and Defense Department, play a key role in negotiating Federal Supply Schedule prices with producers. As a monopsonistic buyer, especially for older vaccines without patent protection, the government is able to extract favorable bargains. See Institute of Medicine (2004, pp. 127-131). For some older vaccines, general inflation-adjusted price caps have also been established under the Vaccines for Children laws. Although the prices attainable for innovative patented vaccines are in principle sufficiently flexible to attract appreciable research and development investments,⁶ especially by small biotechnology firms, older vaccines are said by industry representatives to be "low-margin commodities," relatively unattractive as targets for continuing investment in vaccine production facilities. See Institute of Medicine (2002, p. 108).⁷

For influenza vaccines, the federal government role in pricing has been modest. Only about two percent of the influenza vaccine in recent years was purchased under federal contracts, although for the 2004-05 season, federal purchases were larger, since the government stockpiled 4.5 million doses in preparation for expected demand of roughly 100 million doses. Despite modest federal participation, the price negotiated by federal agencies appears to be a reference for the prices paid by large numbers of private purchasers. In 2003, according to Institute of Medicine study group calculations (2004, p. 133) the federal influenza vaccine price was \$5.53 per dose and the weighted average private price (presumably, a list price, from which unannounced discounts may have been

5. "Flu Vaccine Policy Becomes Issue for Bush," New York Times, October 20, 2004, p. A20.

6. On the responsiveness of industry R&D efforts to changes in perceived market demand, see Finkelstein (2003).

7. Conceivably, low margins might also discourage some quality control measures whose absence increases the probability of production line failure.

taken) \$6.50. In the prior year, the comparable prices were \$5.53 (federal) and \$5.00 (private). Private prices may have dropped below the Federal Supply Schedule price -- an unusual occurrence - - because supplies exceeded effective demand in that season.

For many older vaccines, prices much lower than those seen in the United States are quoted on large-volume vaccine sales through UNICEF to third-world nations, mostly by companies operating in Europe. See Institute of Medicine (2004, p. 108), and Rosegrant (1998). Since European costs are probably similar to those in the United States, even the prices set by hard-bargaining U.S. agencies may leave appreciable margins above marginal production costs.

An Institute of Medicine committee studying the financing of U.S. vaccine production found that "verifiable, quantitative information on costs, revenues, and profits is lacking; and this lack of information [was] an important limitation of the [committee's] study."⁸ Institute of Medicine (2004 p. 111). Similarly, in a background paper for the study, Arnould and DeBrock (2003, p. 25) observe that "we have no cost data that would permit a detailed estimation of cost functions." Vaccine production is a small fraction of pharmaceutical companies' activities, and financial information on it is seldom broken out under a separate line of business reporting category. Some insight can be gleaned from U.S. Census reports.⁹ For NAICS industry category 3254144, "Vaccines, toxoids, and antigens, for human use," sales (in Census terminology, value of shipments) in 2002 were \$3.02 billion. The percentage surplus of sales revenue over materials purchases and total payroll expenses, including an estimate of fringe benefit costs, or the so-called price-cost margin (PCM), was 56.3 percent.¹⁰ This price-cost margin is an estimate of the cash flow available after paying variable in-plant production costs to cover fixed plant, R&D, and corporate overhead costs along with a contribution to profits. For industry category 3254147, which embraces other non-diagnostic products for human use including antitoxins and therapeutic immune serums, the price-cost margin was 71.4 percent. A benchmark for assessing these figures is the comparable PCM for the pharmaceutical preparations industry, 62.3 percent. These are extraordinarily high ratios; the average for all manufacturing industries in 2001 was 28 percent.¹¹

It is also said that, compared to the sales realizable on "blockbuster" pharmaceutical products, vaccine markets offer limited sales potential. Vaccines are administered to a patient only once or a few times, while maintenance drugs for cardiovascular, gastric, nervous system, and other disorders may be taken daily for years on end. Sales potential is undoubtedly quite limited for many of the more specialized vaccines such as anthrax, cholera, rabies, and plague (as it is also for non-leading pharmaceutical products). However, for the most important vaccines the market can hardly

8. According to a staff member, the leading vaccine producers were reluctant to provide cost and profit information.

9. Census of Manufactures: 2002, Industry Series report on Biological Product (Except Diagnostic) Manufacturing, available on the Census Bureau's web site.

10. Arnould and DeBrock (2003, p. 30), report a "contribution margin" estimate by Mercer Management Consulting of 44 percent, said to be similar to the 46 percent ratio for pharmaceuticals.

11. The needed aggregates for 2002 have not yet been published.

be said to be small. Thus, at the \$6-8 price prevailing on influenza vaccine dose sales in 2004 and an estimated demand of 100 million units, the resulting U.S. sales of \$700 million compare well to those of all but the most popular demanded traditional drugs. Institute of Medicine (2004, pp. 130-133). Similarly, with four million infants being born annually in the United States, prices in the recently prevailing range of \$10 to \$58 per dose imply annual sales of \$40 million to \$230 million, multiplied several times over when a vaccine must be administered repeatedly to confer full immunity. Tiny the main vaccine markets are not.

What matters in determining the potential for having multiple viable producers in a product category is the size of the market relative to the volumes required to realize most or all economies of scale. And as we shall see in the more detailed analysis that follows, for at least some vaccines, significant economies of scale persist out to quite large annual sales volumes. An adverse relationship between market size and scale economies may explain much of the high concentration in vaccine production.

Finally, the Institute of Medicine study group suggests in its 2004 report (p. 124) that "By the early- to mid-1990s, global mergers, acquisitions, and joint ventures had reshaped the industry as a whole.... The decline in the number of vaccine producers reflects the consolidation that is occurring within the pharmaceutical industry as a whole." It goes on to observe (p. 125) that in the specific case of diphtheria-tetanus-pertussis (DTaP) vaccine for children, in which the number of suppliers fell from five to two:

[T]he corporate history of the five DTaP vaccines licensed in the United States reflects both the astounding number of acquisitions and mergers that have taken place within the industry and the extent to which these activities have concentrated the production of relatively expensive medicines in the hands of very large American or European multinational corporations.

In an earlier analysis, Mowery and Mitchell (1995) identified a "staggering" extent of acquisitions and alliance formations among vaccine manufacturers during the late 1980s and early 1990s as one reason for the declining number of suppliers.

If the matter were as straightforward as the these analyses suggest, a major failure of the U.S. antitrust agencies' merger policy is implied. However, this is less than clearly established. The wave of mergers could leave the distribution of plant-level sources unaltered, or it could have either of two negative effects on the number of vaccine sources: it could cause a company to shut down one or more production lines for a particular vaccine and concentrate production at a single site (with possibly favorable scale economy consequences); or it could trigger a new managerial assessment of vaccine operations' profitability and lead to their shutdown, with no alternative production sites existing within the merged company to add output of the affected product. In the latter case, if the product line was in fact unprofitable, the shutdown could have occurred with or without merger. The evidence available to me was insufficient to evaluate the incidence of merger consequences. In the case of DTaP vaccines, two product disappearances were apparently

attributable to line closures per se. Of the three remaining DTaP vaccines, two were merged and continued to be produced at two different sites by Aventis-Pasteur, so stochastic risk was not increased. Institute of Medicine (2004, p. 125). For influenza vaccines, immediately preceding the 2002 crisis was a shutdown of production by Wyeth, whose structure and participation in vaccine production evolved through numerous mergers. However, disappointing sales in the 2002-03 season compelling the disposal of vaccines that would be obsolete in the next season, rather than merger, were the apparent impetus to the shutdown.¹² Data needed to identify the antecedents and consequences of other vaccine line closures could probably be extracted from product and plant authorization records archived at the Food and Drug Administration. However, the research could not be accomplished within the framework of this report. A follow-up study, e.g, by the Federal Trade Commission, would be desirable.

Such a study might also explore the consequences of a joint venture. In 1992 Merck and a company later absorbed by Aventis entered a joint development and marketing agreement for several combination pediatric vaccines. According to Merck's 10-K report for 2004, no vaccines are currently being promoted under the agreement. However, analysis of the two companies' FDA-approved vaccine lists indicates that the products covered under the agreement tend to be produced by one company or the other, but not by both. A U.S. antitrust agency should investigate whether a product specialization agreement between the two companies has limited the number of competing production sources, and if so, whether it has a compelling efficiencies rationale.

More on Economies of Scale

To advance farther, we need to explore more thoroughly the nature and magnitude of scale economies in vaccine development and production. I do so building upon the fragmentary evidence reported by the Institute of Medicine (2004), other data in the public record, a telephone interview with a vaccine plant manager, and -- not unimportant -- first principles underlying the theory of scale economies. On the relevant theory, see Scherer et al. (1975, Chapters 2 and 7) and Baumol et al. (1982, Chapter 4).

At a theoretical level, it is necessary to recognize that scale economies are likely to be of two main forms: plant-specific and product-specific.

Plant-specific economies are associated with the advantages of spreading such costs as plant administration, quality control, laboratory operation, health and safety, and utilities over a higher volume of output. Plant investments in the range of \$100-150 million are reported by Grabowski and Vernon (1997, p. 29). Grabowski and Vernon state also that vaccine production tends to be more capital-intensive than small-molecule pharmaceutical manufacturing. Weakly confirming

12. See "With Few Suppliers of Flu Shots, Shortage Was Long in the Making," New York Times, October 17, 2004, p. A20; and "Flu Shot Shortage Shows System Flaws," Boston Globe, October 10, 2004, both quoting Wyeth official Peter Paradiso.

evidence comes from 2002 U.S. Census reports. For the broad "biological products" category of which the vaccines subcategory 3254144 is the largest component, the end-of-year gross book value of plant and equipment was 61.9 percent of sales, compared to 29.7 percent for pharmaceuticals in 2002 and 40 percent (in 1997) for all manufacturing.

When the volume for a single product is too small to keep a plant of least-cost size busy, plant-specific economies may blend into economies of scope, that is, the advantages of assigning more than one product variety to a given plant. Product-specific economies come from spreading fixed pre-production, job setup, and quality control costs over a larger volume of output, cost reductions associated with learning-by-doing, and advantages that may come from the ability to use larger process units and greater specialization when production volumes are higher. These may pertain to the volume of a single product's production in total, or for batch production, the size of individual production lots.

To apply these principles, we must recognize at least three broad vaccine cases for purposes of identifying product-specific scale relationships. Scale economies are likely to be most important, at least in assessing long-run costs, for new vaccines that must pass through lengthy and costly stages of pre-clinical research, product development, clinical testing, and regulatory evaluation (RDT&E¹³) (in the United States, by the Food and Drug Administration). For older already-approved vaccines, these RDT&E costs are largely bygone and can be ignored; the first pre-production fixed costs come from qualifying a particular plant to produce an older vaccine it has not previously manufactured. Once those front-end costs are incurred, annual requalification costs are much more modest. Influenza vaccines have still different cost characteristics.¹⁴ Because of genetic mutation, the specific viruses to be combatted change from year to year, and so the product itself is regularly altered. However, because the production techniques change little from year to year, the RDT&E activities that precede production of completely new vaccines can be truncated to a shorter and less costly cycle. National health authorities throughout the world cooperate to identify the influenza viruses that will pose the most severe threat in the coming season. Public laboratories purify the viruses to create high-yield seed viruses, which they provide to designated private-sector producers. The private firms then perfect the production process they will use to manufacture vaccine from the seeds, test their process in full-scale equipment, and conduct a limited number of animal and human tests to ensure that the killed viruses are safe and effective, thereupon receiving regulatory approval to begin commercial production. On average, this cycle takes from six to eight

13. This acronym, signifying "research, development, test, and evaluation" and originating in the Department of Defense, is more descriptive of the drug and vaccine development process than the more traditional "R&D."

14. See Ebbert et al. (1997) and U.S. Department of Health and Human Services, National Vaccine Program Office, "Pandemic Influenza Preparedness and Response Plan," http://www.dhhs.gov/pandemicplan/exec_summ.html, August 2004.

months between identification of the influenza strains to be combatted to initial availability of vaccine for marketing. Again, because the cycle is shorter and the early stages are performed in public sector laboratories, front-end costs for producing firms are much lower than in the case of completely new vaccines.

The research and development costs for a completely new vaccine are said to be on the same order of magnitude as those for more conventional pharmaceuticals -- estimated in the most recent survey, with a probable bias on the high side due to its neglect of orphan and other low-volume drugs, at \$400 million out-of-pocket for a successful new product, averaging in the cost of failed projects. See di Masi et al. (2003). For private-sector producers, pre-clinical costs may be reduced through extensive cooperation with and research grants from government agencies, notably, the U.S. National Institutes of Health, said to have provided roughly one-third of all U.S. vaccine research funding. Institute of Medicine (2004, p. 119). Although the evidence is meager, Grabowski and Vernon (1997, p. 20) speculate that failed project costs may also be lower for vaccines than for conventional pharmaceuticals because clinical testing success probabilities are higher. Many clinical trials must be carried out -- according to one source, as many as 60,000 -- to prove the safety and efficacy of a new vaccine before approval by the Food and Drug Administration is attained. Despite the lack of definitive data, it seems clear that front-end RDT&E costs for a new vaccine may be measured in the hundreds of millions of dollars. These are essentially sunk fixed costs once production actually commences.

For older vaccines and also for influenza vaccines, plants and the production processes they will use must be pre-qualified by the Food and Drug Administration. Pre-qualification includes both inspection of the facilities and testing the safety and efficiency of vaccine samples produced using those facilities (not smaller pilot lines). According to the Institute of Medicine (2004, pp. 126-127), FDA pre-qualification requirements have become increasingly stringent over time -- sufficiently much so that some companies have ceased the production of specific vaccines rather than undergo re-qualification of a new production process. Although no quantitative estimates have been found, it would appear that front-end product-specific pre-qualification costs may run to tens of millions of dollars.

The production of vaccines typically occurs on a batch basis, although the specifics of the processes vary from vaccine to vaccine. Influenza and measles vaccine virus seeds are replicated, for example, in chicken egg embryos; live polio virus is grown in monkey kidneys; tetanus toxoid is cultured in 1000-liter fermenters (about the size of a micro-brewery brewing vat), etc. See Plotkin and Orenstein (1997, various). The replicated vaccine strains are harvested, purified, preliminarily tested; killed, transformed, blended and sterilized as needed; suspended in liquid media with preservatives, and then, for each batch, subjected to laboratory and animal tests. After passing these tests, they are packaged in appropriate vials and again tested.¹⁵ Usually, they must be stored and transported to using clinics under carefully controlled refrigerated conditions.

15. The quality failures at Chiron's Liverpool plant apparently occurred at the packaging stage.

There are both fixed and variable batch costs. The fixed costs include the carrying cost of the physical plant and equipment; setup costs; and especially, batch testing costs. Savings can be achieved by producing in larger batches, although the opportunities for doing so may be limited for technical and quality-control reasons. Variable costs include raw materials, nutrients, some process labor, packaging materials, and, for childhood vaccines, the excise tax from which no-fault liability claims are paid.

According to the Institute of Medicine task force (2004, p. 114), quoting work by Mercer Management Consulting Co., fixed production costs excluding R&D (with pre-qualification costs left in an uncertain category) represent 60 percent of total vaccine production costs. Costs that are essentially fixed per batch amount to roughly 25 percent of total costs. Fully variable costs are on the order of 15 percent. One implication would appear to be that if a plant produced fewer batches, it would avoid many of the fixed batch costs, making product-line-level costs somewhat less volume-dependent than would otherwise be the case.

The cost savings from operating larger plants per se, or from assigning more different products to a given plant (economies of scope), appear to be modest. This is shown in part by the fact that some companies operate multiple plants, most specialized in a narrower range of products than the company's whole portfolio, rather than concentrating their production at one location. In 2004 Chiron, for example, the fifth largest U.S. vaccine supplier, owned vaccine plants in California, Liverpool, England, two Italian cities, and India, along with leased plants in Germany and Sweden. The California, Liverpool, and German facilities were licensed to supply vaccines to the United States. Aventis-Pasteur had plants licensed for U.S. supply in Pennsylvania, Ontario, and Lyon, France.¹⁶ Three leading suppliers, on the other hand, concentrated their U.S. supply at a single plant -- Merck near Philadelphia, GlaxoSmithKline in Belgium, and Wyeth in New York State. It is possible that the multi-plant operations are the unrationalized remnants of prior mergers. If the economies of concentration were compelling, however, one would expect multi-plant operation to be eliminated fairly quickly, since transportation cost considerations for a high-value commodity such as vaccines do not favor geographic decentralization. See again Scherer et al. (1975).

According to a Mercer Management Consulting study cited in Rosegrant (1998, p. 5), vaccine production is subject to a learning curve; that is, unit costs fall over time as additional production experience is gained. This view is not shared by the Institute of Medicine study team (2004, p. 116), so the true situation remains unknown.

16. The source of this evidence is the Food and Drug Administration list of Licensed Establishments and Products, September 30, 2004, www.fda.gov/cber/ep/part1.htm.

How flexible production is in response to shocks depends on how fully plant and line capacity are being utilized and whether the plant is designed to include surge capability (which will not be maintained unless appropriate financial incentives are offered). Aventis Pasteur announced that it could only expand its output by 2.6 million doses above its originally planned 55 million doses to compensate for the 2004 shortfall of Chiron supply.¹⁷ A Canadian plant without formal authorization to supply the United States was reportedly able on short notice to supply 2 million doses in addition to the 10 million it was producing in Canada.¹⁸ Within a year, it could increase its output from 10 to 20 or 25 million doses. A principal hurdle to a major expansion was securing an additional supply of nutrient eggs.¹⁹ Similarly, when a tetanus vaccine shortage occurred in 2002, a State of Massachusetts-owned vaccine plant was able to double its output to 1 million doses in the course of a year and to quadruple it in two years time.

The Scale Economies - Shortage Tradeoff

It is clear qualitatively that significant economies of scale exist in the development, qualification, and production of vaccines. Their extent depends upon circumstances -- whether initial research and development are required, whether a plant has been pre-qualified to produce a particular well-known vaccine, and how much the production processes must be changed to deal with mutating viruses. The strongest scale economies, compelling natural monopoly at low to middling demand levels, exist for completely new vaccines. Greater precision is not possible with existing published data, although more careful estimates are very much to be desired. Nevertheless, by making heroic but plausible hypothetical estimates, additional insights, both qualitative and quantitative, can be extracted.

17. "Flu Vaccine Policy Becomes Issue for Bush," New York Times, October 20, p. A20.

18. "Washington Considers Purchasing Flu Vaccine," New York Times, October 15, 2004.

19. One might suppose that eggs could be air-lifted from a failed plant to one with surge capacity -- although trans-Atlantic distances could make this approach too costly.

We focus on an older vaccine in which the RDT&E have been sunk during the forgettable past, but process qualification costs must be incurred. Assume that they and other fixed costs, including capital carrying costs and depreciation on plant and equipment investments, amount to \$100 million per year. See Figure 1. There are also economies of scale in variable costs; average variable cost declines from \$8 per dose to \$5 at 50 million doses produced per season (i.e., year), after which it rises sharply, pulling average total cost up in tandem.²⁰ The fixed cost level and a 55 million dose maximum capacity assumption are chosen to approximate conditions in the recent production of influenza vaccines for the U.S. market, where each of two plants had capacities on the order of 50 million doses. Average variable costs are 2.5 times average fixed costs at a near-capacity output of 50 million doses -- the near reverse of the relationship reported in Institute of Medicine (2004, p. 114). This seems realistic given the relatively modest front-end fixed costs, the batch nature of the production process (with the possibility of avoiding fixed batch costs), the egg-intensive character of influenza vaccine production, and evidence on the prices actually charged (roughly, \$6-8 per dose) for influenza vaccines. If fixed costs were higher, the disadvantages of small-scale production would be greater.

On the demand side, we assume preliminarily, subject to a later sensitivity check, a demand function with constant elasticity of -0.85 over a considerable range sufficient to bring the market to equilibrium at a price of \$10.00 per dose with output of 50 million doses.²¹ Extending this curve above prices of \$50 per dose is problematic, since in the limit the price would be infinite, as would most measures of consumers' surplus, which is impossible. Therefore the demand curve is assumed conservatively to be linear from \$50 to \$75, with the quantity approaching zero at the higher of these prices. That the demand curve extends into this higher range is shown *inter alia* by the fact that black market prices of \$60 per dose for influenza vaccines during the 2004 shortages were observed.²² An alternative non-convex (e.g., linear or concave) demand curve would strengthen the case for multiplying production sources.

20. The equation is $AVC = 8.0 - .06 Q$, where Q is denoted in millions of doses per year. AVC is \$5.00 at an output of 50 million; marginal cost is \$2.00.

21. The function is $Q = 350 P^{-0.85}$ up to P of \$50, above which a linear slope of -0.50 is assumed.

22. "On Flu Lines, Signs of Fever and Headache," *New York Times*, October 14, 2004, p. A26.

Assuming a uniform price of \$10 per dose,²³ a single producer will produce 50 million doses at an average total cost of \$7.00 per dose, realizing a supra-normal profit of \$150 million.²⁴

Suppose now that the production assignment is divided equally between two distinct sources. Each is assumed to incur the front-end investment of \$100 million, maintaining a surge production capability allowing either firm to expand production over a relatively short period in crisis situations, including both failure of other plants' supply and unanticipated demand spurts. The volume over which fixed costs are spread declines, and so average total cost rises, indeed, above the previously assumed \$10 price. The price will have to be raised. Suppose it is raised to \$14. Then demand will be restricted to 37.14 million doses.²⁵ The mandate to produce this output is divided equally, so each producer supplies 18.57 million doses. At this still-lower volume, average total cost rises to \$12.27 per unit. Each producer's supra-normal profit is reduced to \$1.73 per dose -- a reduction that might be attributed to less concentrated bargaining on the supply side of what amounts to a bilateral monopoly relationship.²⁶ With a single producer realizing maximum scale economies at an output of 50 million doses, total production costs are \$350 million. With two producers, each supplying 18.57 million doses, total production costs are \$456 million (rounded). Thus, the excess production cost associated with double-sourcing and the maintenance of surge capacity amounts to \$106 million per year.

With a single producer supplying 50 million doses at a \$10 price, consumers' surplus (the area under the assumed demand curve and above the \$10 horizontal) of \$1,033 million is realized. The price increase to \$14 required to cover added production costs with dual sourcing reduces consumers' surplus to \$868 million. Thus, the consumers' surplus cost of dual sourcing is \$165 million.

23. Prices are lower to government procurement and reimbursement agencies than to private buyers. See Institute of Medicine (2004, p. 133). They were higher on average in 2004 than the \$5.53 and \$6.50 values reported for 2003.

24. Note that the economist's definition of fixed costs includes a normal competitive return on capital invested.

25. With a less convex demand function, the volume reduction would be smaller.

26. The \$10 price with output of 50 million is well below the monopoly profit-maximizing level, nor is it plausible that prices of less than \$10 per dose would maximize monopoly prices when black market prices of \$60 per dose can emerge.

Now we must consider the benefits of dual sourcing. As at Chiron's Liverpool plant and in many other cases historically, production sources fail. If there is only one source and it fails for an entire season, a whole season's consumers' surplus -- \$1,033 million -- is lost. For partial-season or fraction-of-output failures, the surplus estimation problem is more subtle. Normally, when one analyzes such phenomena in benefit/cost analysis, one assumes that only the marginal consumers -- those with the lowest willingness to pay -- are rationed out in a "shortage." But that requires prices to rise to clear the market. This is clearly not the normal case when vaccine supplies fail. Abstracting from occasional black market transactions, prices remain fixed at originally negotiated levels, and consumers with high willingness to pay are as likely to be rationed out of the market as consumers with low willingness to pay.²⁷ In this case, the consumers' surplus loss is proportional to total consumers' surplus in a complete season. With two sources and the assumptions taken here, sufficient excess capacity exists in each source to fill the gap left by the other source's failure. Assuming no price change from \$14 (which means that the continuing source with more widely spread overhead will realize windfall profits), we assume that the full 37.14 million dose demand will be satisfied -- three-fourths of the remaining source's maximum surge capacity.

The production cost and consumers' surplus penalties from having two sources supplying at a higher price have already been counted. How the benefits and costs balance out depends upon the probabilities that various sources will fail for an entire season, or, averaged over several years, the fraction of production lost on average over the entire period. We explore two sets of probabilities -- one $P(F_{.1})$ in which the probability that any given plant will fail for a full season is 0.1, and one $P(F_{.2})$ in which the single-source failure probability is 0.2. With two plants, both plants may fail simultaneously: if the failure odds are independent across plants, dual failure probabilities are 0.01 and 0.04 for 0.1 and 0.2 single-plant probabilities respectively. With two plants, the probability that both plants will be operating is $0.9 \times 0.9 = 0.81$ in the 0.1 failure case and $0.8 \times 0.8 = 0.64$ in the 0.2 case. By subtraction, the probability that one plant will be compensating for an output loss of the other is 0.18 in the 0.1 case and 0.32 in the 0.2 case.

A full benefit/cost analysis must count as benefits against which costs are weighed not only consumers' surplus, but also differences in producers' surplus. These are derived by integrating the area below price lines and above (declining) marginal cost functions. Benefits and costs must be probability-weighted to compare single and dual-source outcomes.

27. Newspaper accounts of the fall 2004 shortages make it clear that high reservation price consumers were rationed out to give preference to senior citizens, who tend to be less affluent and to have lower opportunity cost of work time lost to influenza than working blokes.

Table 1

Benefit/Cost Analysis

	One Plant Operates	One Plant Fails	Two Plants Operate	One of Two Operates	Two Plants Fail	Sum for	Sum for
Price per Dose	\$10	-	\$14	\$14	-		
Output (doses)	50.0	0	18.57 each	37.14	0		
Fixed cost	100	100	200	200	200		
Variable Cost	250	0	255.74	214.36	0		
Total Cost	350	100	455.74	414.36	200		
Consumers' surplus	1033	0	868	868	0		
Producers' surplus	250	0	264.22	305.60	0		
P(F ₁) Probabilities	.9	.1	.81	.18	.01		
Weighted Cost	315.0	10	369.15	74.58	2		
Weighted CS	929.7	0	702.08	156.24	0		
Weighted PS	225.0	0	214.02	55.01	0		
Weighted Consumers' plus Producers' Surplus minus Cost						<u>One</u>	<u>Two</u>
						829.7	681.6
Benefit/Cost Ratio: Two Plants vs. One							0.82
P(F ₂) Probabilities	.8	.2	.64	.32	.04		
Weighted Cost	280.0	20	291.67	132.60	8		
Weighted CS	826.4	0	555.52	277.76	0		
Weighted PS	200.0	0	169.10	97.79	0		
Weighted Consumers' plus Producers' Surplus minus Cost						<u>One</u>	<u>Two</u>
						726.4	667.9
Benefit/Cost Ratio: Two Plants vs. One							0.92

Table 1 reports the basic values obtained analyzing the cases specified above, with output reported in millions of doses per season and plant costs and surpluses reported in millions of dollars per year.

From the table, one sees that dual sourcing fails a benefits/cost test for the failure probabilities and surplus values considered thus far. The progression of values suggests that the test would be passed at higher failure probabilities, but they would probably be too high to be plausible.

However, a crucial further consideration remains to be addressed. Immunization benefits not only the consumer immunized, but also, by lessening the probability of contagion, the individuals with whom the immunized person comes into contact. In other words, immunization confers external economies or benefits. This point is emphasized in the 2004 Institute of Medicine report (pp.27-28), which summarizes 12 studies of immunization benefits and costs (not including influenza) and reports an average benefit/cost ratio of 8.7 to 1. The analysis in Table 1 evaluates only internal benefits -- that is, assuming limited altruism in individuals' health care purchase decisions, the surplus accruing mainly to the consumers immunized, and not to the individuals they might otherwise infect. The external benefits of immunization, like the probabilities that an epidemic disease will spread to others, probably follow a logistic-shaped curve, depending upon the fraction of the population immunized. If very few people have been immunized, and unless strict quarantines are enforced, each person who contracts a communicable disease is likely to infect several others, who in turn spread the disease widely to others. However, if 90 percent of the population has been immunized, a member of the remaining 10 percent is prevented from spreading the disease to 9 out of 10 random contacts, and so the disease spreads less widely and more slowly.²⁸

28. Obviously, encounters can be non-random -- e.g., within families that abjure immunization, or in day care centers when children are rationed out of vaccine distribution in shortages.

For many childhood diseases, especially since the U.S. Vaccines for Children program was initiated in 1993, immunization has progressed to high levels,²⁹ and as a result, the person who randomly encounters an infected individual is likely already to have been protected against the principal preventable diseases. This reduces the marginal external benefit from an additional immunization.³⁰ However, influenza, on which our benefit/cost analysis has focused, is different. The relevant viruses mutate rapidly. Vaccines administered several years ago are unlikely to provide protection against the most recent virulent strains. And with at most one-third of the population inoculated in any given recent year, contagion to unprotected citizens has a relatively high probability.³¹ The consequences of being infected are significant. On average, 36,000 Americans are said to die annually from influenza and the complications that can follow it, and some 100,000 are hospitalized.³² In the worst pandemic of the 20th Century, during 1918, there were 500,000 influenza-related deaths. Thus, the external benefits of assuring supply by maintaining multiple production sources with surge capacity cannot be insubstantial.

29. The Institute of Medicine (2004) reports, p. 4, that 74 percent of U.S. children now receive the recommended series of vaccines by age 2.

30. Although the assumptions are not made clear, the Institute of Medicine report appears to report total benefit/cost ratios rather than marginal ratios.

31. Cox and Subbarao (1999), p. 1278, observe that "a single infected person can transmit the virus to a large number of susceptible individuals." They report too, p. 1280, that the effectiveness of a single immunization in providing protection is in the range of 60 to 90 percent.

32. National Vaccine Program Office, "Pandemic Influenza Preparedness and Response Plan," August 2004. This estimate, which has been widely repeated in newspaper accounts, evidently places heavy stress on the complications, which can be minimized by early treatment and immunization against pneumonia. According to the Statistical Abstract of the United States: 2002, deaths attributed directly to influenza were in the range of 1,665 to 2,175, while pneumonia deaths were on the order of 62,000 to 65,000. For a more nuanced analysis, see Meltzer et al. (1999).

Let us estimate the effects conservatively. For the case of two production sources, with supply limited by the higher costs associated with the loss of scale economies, the single-year consumers' surplus has been estimated in Table 1 at \$868 million. Suppose no second source is available, or none has the capacity, to compensate for the failure of one source. Then half of those internal benefits, or \$434 million, are lost with probability 0.18 in the $P(F_{.1})$ case. The probability-weighted loss is \$78 million. If three additional infections could have been prevented by immunization of an average person counted within that loss figure, the additional external benefit from having the capacity to immunize the relevant cohort is \$234 million, which, added to internal consumers' surplus in the two-producer case, raises net probability-weighted benefits less costs from \$681.6 million in the $P(F_{.1})$ case to \$915.6, elevating the benefit/cost ratio for dual sourcing to 1.10.³³ Or in the $P(F_{.2})$ case, the resulting benefit/cost ratio is 1.49.

33. Breakeven with a benefit/cost ratio of 1.0 occurs when external benefits are 1.90 times internal consumers' surplus.

The numbers used in this example are hypothetical. An attempt has been made to assume plausible values while remaining within the rigorous framework of cost and demand function theory. However, it is worthwhile to consider sensitivity by viewing the demand and consumers' surplus problem from a different, less restrictive perspective. On average in recent years, roughly 7 percent of Americans contract influenza in a given season. The probability is of course higher for those who have not been vaccinated than for those who have. Assuming that one-third of the population has acquired immunity through vaccination, the conditional probability of infection for a person who has not been vaccinated but is considering doing so is roughly $0.07 / 0.667 = .105$. Assume that the person in this situation is one of 140 million employed Americans, earning an average wage of \$15.50 per hour.³⁴ On average, debility from influenza lasts an average of four days, with a long tail into longer intervals for cases with complications. Suppose being infected causes the person to miss four days of work. Given these assumptions, the loss of income or, when one can take sick leave, productive output, is \$496 (32 hours times \$15.50). Assume that for non-employed persons, roughly equal in number, the loss is one-half that figure. For the approximately 35 million in the non-employed group 65 years old or older, who experience a much higher higher probability of serious complications,³⁵ this loss estimate conservatively includes possible hospitalization costs and the intangible loss associated with death. For the 60 million under age 15, it includes earnings foregone by those who stay home to provide care. Thus, on average, the cost avoided through immunization - a first approximation to the consumers' surplus derived from immunization -- is $(496 + 248) / 2 = \$372$. Multiplying this by the 0.105 probability of infection times 50 million immunizations and subtracting \$900 million for vaccine and administration costs,³⁶ we obtain an estimate of \$1,053 million. This is sufficiently close to the \$1,033 consumers' surplus assumed in Table 1 to render a more detailed analysis unnecessary. For the two plant case, it is likely that the quantity of inoculations will be restricted less than in the -0.85 elasticity case, which raises the benefit/cost ratio of multiple sourcing without external benefits in comparison to our Table 1 examples.

With external infection effects taken into account, the benefit/cost analysis shows that insuring against plant failures by authorizing multiple sources with surge capacity can provide benefits in excess of its costs. This is more apt to be true for vaccines against influenza, with rapidly mutating viruses and relatively low rates of protection, high external benefits, and intermediate fixed cost levels, than for other vaccines and especially for newly-developed formulations. If in the actual base case there are two equal-size equal producers, as was true at the opening of the U.S. 2004-05 influenza season, each with severely limited ability to expand its output, the P(F_) analysis is a near-replica of the one presented here with all variables but prices and average costs doubled.³⁷ Dividing

34. The wage figure is taken from the 2004 Economic Report of the President.

35. See Meltzer et al. (1999), pp. 660-661.

36. We continue our assumption that the manufacturer's revenue per dose is \$10. According to Institute of Medicine (2004, p. 99), Medicare administrators have concluded that vaccination entails no incremental work over and above a routine office visit and allows an immunization fee of \$7.72. The patient's time and travel costs are assumed to be offset by value of reduced pain, suffering, and complication risk.

37. The probabilities are more complex. If $P(F) = 0.1$, the probability that all four plants will fail simultaneously is 0.0001, or one in ten thousand. The probability that all four plants will remain trouble-free at any moment in time is

up the output among four producers, each with surge capacity, leads to similar results, except that each of the four might be able to cover with its surge capacity slightly more than one-fourth of the interruption in market supply, raising the benefit/cost ratio. Others are urged to develop better data and use similar methodology to determine whether the conclusion remains robust for influenza vaccines and generalizes to a larger number of vaccines.

Conclusion

It seems clear that, despite the loss of scale economies when vaccine sources are multiplied and surge capacity is built into approved plants, benefits plausibly exceed costs, especially when one recognizes the substantial external benefits from immunization.³⁸ U.S. vaccine policy decision-makers should recognize this, encouraging whenever possible the maintenance of multiple sources possessing surge capacity. For injectable influenza vaccines, there should be at least three sources and quite possibly four. If private-sector producers do not respond favorably to government efforts to increase the number of sources because of questionable profit prospects and/or high front-end costs, it would be appropriate, given the existence of substantial externalities, for the government to subsidize additional sources' initial qualification costs.

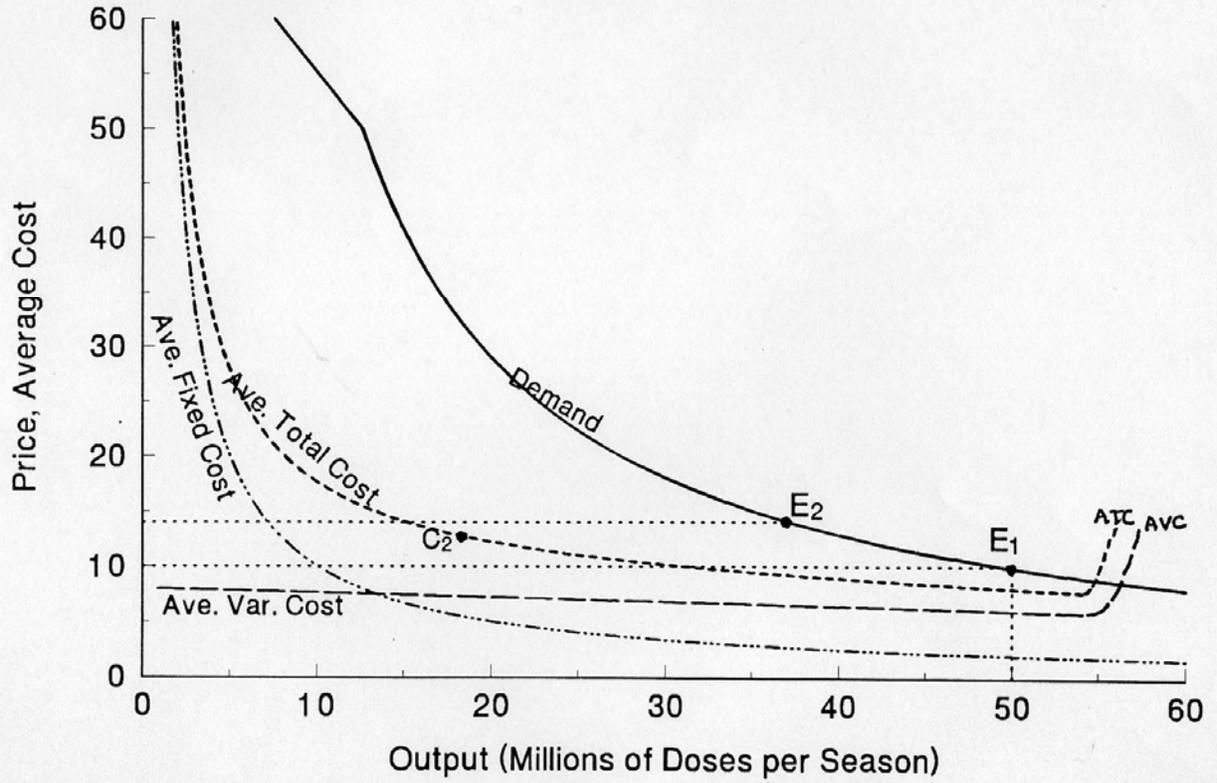
It is possible that the number of willing vaccine suppliers is too low because prices, set in part through government fiat or bargaining, are too low and hence, as some have claimed, that profits are insufficient. It would be irresponsible, however, to raise prices simply on the basis of such claims, unsubstantiated by solid information (denied the Institute of Medicine study group). To determine whether profitability is in fact as unattractive as it has been said to be, the Federal Trade Commission should use its subpoena power to obtain cost, revenue, asset, and profit data on the production of individual vaccines or clusters of vaccines and to publish a substantial analytic report on the results. To inform the public in this way was a principal reason for the Commission's creation in 1914. See Scherer (1990, pp. 466-467 and 476-477).

0.656.

38. In Great Britain, with much smaller population than the United States, five suppliers are said to be maintained. "With Few Suppliers of Flu Shots, Shortage Was Long in the Making," *New York Times*, October 17, 2000, p. 1.

Figure 1

Graph of Hypothetical Vaccine Supply and Demand Functions
Fixed Costs = \$1 00 Million



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