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Supply Chain Coordination and Influenza Vaccination

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Billions of dollars are being allocated for influenza pandemic preparedness, and vaccination is a primary weapon for fighting influenza outbreaks. The influenza vaccine supply chain has characteristics of the classic news vendor problem, but possesses several key differences from typical supply chains, such as a nonlinear value of sales (caused by nonlinear health benefits of vaccination due to infection dynamics) and vaccine production yield issues. We show that several contracts that can coordinate buyer (governmental public health policy) and supplier (vaccine manufacturer) incentives in other supply chains are not able to fully coordinate the influenza vaccine supply chain. We then demonstrate a variant of a cost-sharing contract that is able to do so.

1. Influenza, Vaccines and Operational Challenges

Influenza is an acute respiratory illness that spreads rapidly in seasonal epidemics (`http://www.cdc.gov/flu`). Globally, annual influenza outbreaks result in 250,000 to 500,000 deaths. The World Health Organization reports that costs in terms of health care, lost days of work and education, and social disruption have been estimated to vary between $1 million and $6 million per 100,000 inhabitants yearly in industrialized countries. A moderate, new influenza pandemic could increase those losses by an order of magnitude (WHO, 2005). For reference, the "Spanish flu" (H1N1) pandemic of 1918 killed 20–40 million people worldwide.

Vaccines are a key tool for controlling influenza (WHO, 2005). Vaccines can reduce the probability of infection of a susceptible individual, and the infectiousness of an ill individual and are known to reduce the direct and indirect costs of infection (Weycker et al., 2005).

Gerdil (2003) describes the challenging and time-constrained vaccine production and delivery process for the predominant method of vaccine production, the inactivated virus vaccine. There are several key operational challenges in the influenza vaccine value chain.

A challenge at the start of the value chain is due to the constant mutation of the virus (antigenic drift and shift), which requires that influenza vaccines be reformulated each year. Influenza vaccines are therefore one-time news-vendor products, as opposed to all other vaccines, which closely resemble (perishable) EOQ-type products. Not only are production volumes hard to predict, but the selection of the target strains is a challenge. Wu et al. (2005) develop an optimization model of antigenic changes. Their results suggest that the current selection policy is reasonably effective. They also identify heuristic policies that may improve the selection process.

Another challenge occurs toward the end of the value chain, after vaccines are produced. That involves the allocation of vaccines to various subpopulations, and the logistics of transhipment to insure appropriate delivery. Hill and Longini (2003) describe a mathematical model to optimally allocate vaccines to several supbopulations with potentially heterogeneously mixing individuals. Weycker et al. (2005) use a different, stochastic simulation model to illustrate the benefits of vaccinating certain subpopulations . Those articles do not discuss the logistics of delivery. Yadav and Williams (2005) propose an information clearinghouse for vaccine supply and demand to provide a market overview and help to eliminate order gaming and price gouging, demand forecasting tools, and regional vaccine redistribution pools to shift supplies from areas with surpluses to areas experiencing shortages.

This paper is concerned with a challenge in the middle of the value chain: the design of contracts that align manufacturer choices for production volume and the need for profitability, and governmental choices that balance the costs and public health benefits of vaccination programs. The importance of the problem is clear. US President Bush recently met with industry leaders to improve pandemic preparedness, and requested $7.1 billion in emergency funding to that intent. Vaccines are a significant part of that plan.

Special characteristics of the influenza vaccine supply chain that differentiate it from many other supply chains include a nonlinear value of a sale (the value of averting an infection by vaccination depends upon nonlinear infection dynamics), and a dependence of production yields on the virus strains selected for the vaccine. We therefore present a model of a government's decision of purchase quantities of vaccines, which balances the public health benefits of vaccination and the cost of procuring and administering those vaccines, and a manufacturer's choice of production volume. We characterize the optimal decisions of each in both selfish and system-oriented play. Due to special features of the influenza value chain, wholesale price and payback contracts are shown to be unable to fully coordinate decisions. We then demonstrate a variation of a cost-sharing contract that can coordinate concerns for both public health outcomes and production economics.

2. Joint Epidemic and Supply Chain Model

This work unites two previously separate streams of literature. The epidemic literature provides epidemic models and cost benefit analysis for interventions such as vaccination (Diekmann and

Heesterbeek, 2000; Hill and Longini, 2003), but does not address logistical and manufacturing concerns. The supply chain literature does not yet adequately address the special characteristics of the influenza vaccine supply chain highlighted above.

We use simplified epidemic and supply chain models to focus on contractual issues between a single government and a single manufacturer. The government initially announces a fraction f of a population of N individuals to vaccinate. Given the demand by the government, the manufacturer then decides how much to produce. Production volume decisions are indexed by the number of eggs, n_E, a critical factor in influenza vaccine production. Production costs are c per egg. The actual amount produced, $n_E U$, is a random variable that is indexed by a yield, U. We assume that the yield U has a continuous probability density function $f_U(u)$ with mean μ and variance σ^2. This assumption means that the yield is affected by the specific strain of the virus, and may vary from year to year, more so than from one batch to the next within a given production campaign.

The manufacturer then sells whatever vaccine is produced, up to the amount initially requested by the government (a maximum of Nfd doses, where N is the population size, and d is the number of doses per individual). Unmet demand is lost, and excess vaccines are discarded (due to antigenic shift). The **manufacturer problem** for a given f announced by the government is:

$$\begin{array}{lll} \min\limits_{n_E} & MF = \mathrm{E}\left[cn_E - p_r Z\right] & \text{(net manufacturer costs)} \\ \text{s.t.} & Z = \min\{n_E U, fNd\} & \text{(doses sold} \leq \text{yield and demand)} \\ & n_E \geq 0 & \text{(nonnegative vaccine quantity)} \end{array} \tag{1}$$

So that the optimal $n_E^* > 0$, we assume expected revenue exceeds the cost per egg, $p_r \mu > c$.

When acting separately, the government seeks to minimize the variable cost of procuring, p_r, and administering, p_a, each dose, plus the total social cost of the outbreak, $bT(f)$. $T(f)$ is the total number of infected individuals by the end of the outbreak, and b is the average direct and indirect cost of influenza infection per outbreak (Weycker et al., 2005, provides estimates of such costs). Define $\bar{f}$ to be the maximum fraction of the population for which the marginal cost of administering more vaccination is negative,

$$\bar{f} = \sup\{f : bT'(\bar{f}) + p_a Nd < 0, \text{ for } f \text{ such that } T'(f) \text{ exists}\}. \tag{2}$$

The **government problem** is to select a fraction f that indexes demand, knowing that the manufacturer will behave optimally, and may deliver less, in expectation, than what is ordered due to yield losses. We assume that the government purchases up to the amount it announced, but will administer only those doses that have a nonnegative cost-health benefit.

$$
\begin{array}{lll}
\min\limits_{f} & GF = \mathrm{E}\left[\ bT(\frac{W}{Nd}) + p_a W + p_r Z\ \right] & \text{(net government costs)} \\
\text{s.t.} & Z = \min\{n_E U, fNd\} & \text{(doses bought} \leq \text{yield and demand)} \\
& W = \min\{n_E U, fNd, \bar{f}Nd\} & \text{(doses given} \leq \text{doses bought, cost effective level)} \\
& \int_0^{\frac{fNd}{n_E}} u f_U(u) du = \dfrac{c}{p_r} & \text{(manufacturer acts optimally for Equation (1))} \\
& 0 \leq f \leq 1 & \text{(fraction of population)} \\
& n_E \geq 0 & \text{(nonnegative vaccine quantity)}
\end{array}
\tag{3}
$$

The above *game setting* is a two-actor game that can be shown to have a Nash equilibrium.

The following *system setting* assesses whether the government and manufacturer can jointly improve system-wide costs. This base model helps assess whether contracts can align the incentives of the game setting to obtain system optimal behavior.

$$
\begin{array}{lll}
\min\limits_{f, n_E} & SF = \mathrm{E}\left[bT(\frac{W}{Nd}) + p_a W + c n_E\right] & \text{(total system costs)} \\
\text{s.t.} & W = \min\{n_E U, fNd, \bar{f}Nd\} & \text{(doses given} \leq \text{yield, demand, cost effective level)} \\
& 0 \leq f \leq 1 & \text{(fraction of population)} \\
& n_E \geq 0 & \text{(nonnegative vaccine quantity)}
\end{array}
\tag{4}
$$

This formulation does not explicitly link f and n_E together, since the objective is system optimal behavior rather than local profit-maximizing behavior.

The epidemic model determines the number of individuals, $T(f)$, that are infected by the end of the outbreak. While vaccine effects and health outcomes may vary by subpopulation, and vaccination programs can take advantage of that fact (Weycker et al., 2005), we simplify the model in order to focus on contract issues for production volume, rather than including details about optimal allocation of a given volume. In a deterministic compartmental model of N homogeneous and randomly mixing individuals (Diekmann and Heesterbeek, 2000), a fraction S_0 of the population is initially Susceptible and a fraction I_0 is initially Infected and infectious. This represents an initial seeding due to exposure from exogenous sources. After recovery, individuals are Removed and no longer infectious. This so-called SIR epidemic model is consistent with the natural history of infection of influenza.

We assume that vaccination removes some fraction ψ of individuals from the pool of susceptibles, where ψ is interpreted as a combination of vaccine effects. If $S_0 = 1 - I_0 - \psi f$, then $T(f) = Np$, where the so-called attack rate p, see Longini et al. (1978), satisfies

$$p = S_0(1 + \frac{I_0}{S_0} - e^{-R_0 p}). \tag{5}$$

Here, the critical vaccination fraction required to prevent a nonlinear system dynamic that leads to an outbreak is $f^0 = (R_0 - 1)/(R_0 \psi)$ when $R_0 > 1$ (Hill and Longini, 2003).

3. Results

In this work we first characterize optimal strategies for both system, see 4, and game setting, see 3, namely we determine production levels and the fraction of the population to be vaccinated for each case. We first relate the production level in global optimization to the one determined when the manufacturer maximizes its expected profit.

Theorem 1 *If n_E^S and n_E^G denote the production levels under the system setting and game setting respectively, then $n_E^S > n_E^G$*

The theorem thus implies that when the manufacturer maximizes its own profit, production level is strictly below the one appropriate for the entire system. The reason is that under the game setting, which represents the current supply practice, the manufacturer bears all the risk of production yield resulting in a more conservative production levels.

The key to coordinating the supply chain is to transfer some of the production risk from the manufacturer to the government. Unfortunately, traditional contracts such as wholesale or payback contracts can not coordinate this supply chain. However, we show that a variant of the cost sharing contract can achieve this goal.

For this purpose, consider a cost sharing contract where $p_r(f)$ is a wholesale menu that depends on f, the fraction of population to be vaccinated. This unit price $p_r(f)$ must be decreasing with f and satisfy some other mild conditions. Let $p_e(f)$ be the cost share payment made by the government to the manufacturer for each unit (egg) produced. $p_e(f)$ is an increasing function of f and is directly related to $p_r(f)$. Interestingly, a variety of cost sharing contracts, $p_r(f), p_a(f)$, that satisfy the conditions specified in the paper, exist.

Theorem 2 *For any $p_e(f), p_r(f)$ satisfying the conditions in the paper, the optimal production levels and the fraction of the vaccinated population under the cost sharing contract are equal to the optimal values in global optimization.*

This suggests that to coordinate the supply chain, the government should pay a portion of the manufacturing cost and this payment is proportional to the fraction of the population the government intend to vaccinate. Interestingly, in this cost sharing contract, the higher the fraction of the population targeted by the government for vaccination, the higher their cost sharing payment and the lower the per unit vaccine price.

4. Discussion

There are several limitations of this model. One, an epidemic model with homogeneous and homogeneously mixing populations ignores the potential to target specific critical subpopulations, such as children or the elderly. Two, the model assumes that health consequences can be quantified by direct and indirect monetary costs, but a multi-attribute approach might be desired to more fully examine issues like the number of deaths or hospitalizations. Three, the model assumes that the government can precisely specify the number of individuals to vaccinate. This is potential drawback of the other vaccine models mentioned in this paper, too. Four, the model currently examines a single manufacturer and a single government, and that all parameters are known to all parties. The cost per dose is not likely to be public information. The full version of the paper indicates how some of these limitations might be addressed practically. Still, each of these limitations could lead to interesting future work to extend the insights about contract design for governmental/industry collaboration for inuenza preparedness.

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