VACCINE APPROVALS AND MANDATES UNDER UNCERTAINTY:
Some Simple Analytics

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Preamble

When studying collective decision problems, economists have long asked how a planner should act.

A standard exercise specifies a set of feasible policies and a welfare function.

The planner is presumed to know the welfare achieved by each policy.

The objective is to characterize the optimal policy.
Planners often have only partial knowledge of the welfare achieved by alternative policies. Hence, they may not be able to determine optimal policies.

Elementary decision theory suggests a two-step choice process.

The first step is to eliminate dominated policies.

The second is to apply some criterion to choose an undominated policy.

There is no uniquely "optimal" way to choose among undominated alternatives.

There are various "reasonable" ways.
A planner might assert a subjective distribution on unknowns and maximize subjective expected welfare.

However, a subjective distribution is a form of knowledge and a planner may have no credible basis for asserting one.

Then the planner may face a problem of decision under ambiguity (Knightian uncertainty).

Considering planning under ambiguity, I have focused attention on the maximin and minimax-regret criteria.

Introduction

Social interactions make communicable disease a core concern of health policy.

Preventive administration of vaccines, therapeutic administration of antimicrobial drugs, and quarantine of infected persons may reduce disease transmission.

In a decentralized health care system, infected and at-risk persons may not internalize the external implications of their actions.

Hence, there may be a rationale for government to seek to influence treatment of communicable disease.
A prevalent problem is scarcity of empirical evidence about how alternative vaccination policies affect population behavior and illness.

Randomized clinical trials may reveal whether vaccination generates an immune response in a vaccinated person. (*direct effects*)

In a connected world, RCTs cannot reveal the disease transmission that would occur with alternative vaccination policies. (*indirect or herd immunity effects*)
Researchers have used epidemiological models to forecast outcomes with counterfactual vaccination policies.

They have commonly assumed that the planner has sufficient knowledge to determine an optimal policy.


Two studies of vaccination under uncertainty are Tanner, Sattenspiel, and Ntaimo (2008) and Manski (2010).
The present paper studies the decision problems faced by health planners who choose whether to approve a new vaccine or mandate an approved one, but who do not know the indirect effect of vaccination.

Approval is a choice between a zero vaccination rate and the vaccination rate the health-care system will yield if the vaccine is approved.

Mandate of an approved vaccine is a choice between vaccinating the entire population and the vaccination rate generated by decentralized decisions.

In the United States, the Food and Drug Administration (FDA) makes approval decisions while states make mandate decisions.
I show that it may be possible to determine optimal policies in some cases where the planner can only bound the indirect effect of vaccination.

When optimal policy is indeterminate, I pose several decision criteria—expected utility, minimax, and minimax-regret—and derive the policies they yield.
Background: Unconstrained Choice of Vaccination Rate


I study choice of vaccination rate by a planner who wants to minimize the social cost of illness and vaccination.

The planner observes the realized vaccination and illness rate in a study population.

He assumes that the illness rate of unvaccinated persons decreases with the vaccination rate.

He does not know the magnitude of the indirect effect.
Optimal Vaccination

The planner must choose the vaccination rate for a large population of observationally identical persons.

Vaccination (or intent-to-vaccinate) generates a preventive immune response in a person with probability $\lambda$.

Let $v$ be a vaccination rate. $\lambda v$ is the effective rate. $1 - \lambda v$ are susceptible.

Let $p(\cdot)$ be the indirect-response function. $p(\lambda v)$ is the fraction of unvaccinated persons who become ill when the effective vaccination rate is $\lambda v$.

The fraction of the population who become ill is $p(\lambda v)(1 - \lambda v)$. 
The planner wants to minimize a social cost function with two components: the harm caused by illness and the cost of vaccination.

Let $a > 0$ denote the mean social harm caused by illness.
Let $c > 0$ denote the mean social cost per vaccination.

The social cost of vaccination rate $v$ is $a \cdot p(\lambda v)(1 - \lambda v) + cv$.

The planner wants to solve the problem $\min_{v \in [0, 1]} a \cdot p(\lambda v)(1 - \lambda v) + cv$.

This static optimization problem expresses the core tension of vaccination policy: a higher vaccination rate is more effective in preventing illness but is more costly.
Partial Knowledge of Indirect Effects

Let the planner observe the vaccination rate \( r \) and the illness rate \( q = p(\lambda r) \) of susceptibles in a study population with \( r < 1 \).

He assumes that the study population and the treatment population have the same indirect-response function \( p(\cdot) \).

He assumes that \( p(\cdot) \) is weakly decreasing.

He makes no other assumption about the shape of \( p(\cdot) \).

It follows that \( v \leq r \Rightarrow p(\lambda v) \geq q \),

\[
 v \geq r \Rightarrow p(\lambda v) \leq q.
\]
Findings

Fix the scale of social cost by setting \( a = 1 \).

A candidate vaccination rate \( v \) is strictly dominated if any of these conditions hold:

(a) Let \( c < \lambda q \). Then \( v \) is strictly dominated if \( v < r \).

(b) Let \( c > \lambda q \). Then \( v \) is strictly dominated if \( v > r + \lambda q(1 - r)/c \).

(c) Let \( c > \lambda \). Then \( v \) is strictly dominated if \( \lambda(1 - q)/(c - \lambda q) < v \leq r \) or if \( v > \max (r, \lambda/c) \).
I derive the minimax and minimax-regret vaccination rates.

The minimax rate is one of the three values (0, r, 1), depending on the values of the known parameters (c, λ, r, q).

The minimax-regret rate is a fraction whose value depends on (c, λ, r, q).
Approvals and Mandates as Constrained Optimization Problems

Approval and mandate decisions pose constrained optimization problems.

I assume that decentralized vaccination decisions are statistically independent of relevant personal attributes (cost of vaccination, ability of vaccination to generate an immune response, susceptibility to disease, infectiousness).

Then the decision to mandate an approved vaccine presents a choice between vaccinating the entire population and the vaccination rate, say $v_d$, that would be generated by decentralized decision making in the absence of the mandate.
The optimal mandate decision is

mandate if \[ p(\lambda)(1 - \lambda) + c \leq p(\lambda v_d)(1 - \lambda v_d) + cv_d, \]
do not mandate if \[ p(\lambda)(1 - \lambda) + c \geq p(\lambda v_d)(1 - \lambda v_d) + cv_d. \]
Vaccine approval presents a choice between a zero vaccination rate and the vaccination rate that the health-care system will yield if the vaccine is approved.

The latter rate is either 1 or \(v_d\), depending on whether approval would or would not be followed by imposition of a mandate.

Let \(v_a\) denote the vaccination rate that would occur following approval.

The optimal approval decision is

- approve if \(p(\lambda v_a)(1 - \lambda v_a) + cv_a \leq p(0)\),
- reject if \(p(\lambda v_a)(1 - \lambda v_a) + cv_a \geq p(0)\).
This formalization of the planning problem poses approval and mandate as separate binary decisions. The FDA approves vaccines and states impose mandates.

Why might society make constrained decisions way when unconstrained choice of the vaccination rate may yield greater social welfare?

A possible answer is that having a planner choose a vaccination rate other than 0 or 1 would violate a version of the ethical principle of "equal treatment of equals."

Vaccinating a fraction of the population is consistent with equal treatment in the *ex ante* sense that all persons have the same probability of vaccination.

It violates equal treatment in the *ex post* sense that only some persons ultimately are vaccinated.
Mandates with Partial Knowledge of Indirect Effects

Maintain the assumptions of Manski (2010). Let the study population be a regime with decentralized vaccination. A mandate is optimal iff

\[ p(\lambda)(1 - \lambda) + c \leq p(\lambda v_d)(1 - \lambda v_d) + cv_d. \]

Observation of \( p(\lambda v_d) \) and the assumption of monotone treatment response imply that \( 0 \leq p(\lambda) \leq p(\lambda v_d) \). This bound on \( p(\lambda) \) suffices to determine the optimality of a mandate if either of two conditions hold:

\[ p(\lambda v_d)(1 - \lambda) + c \leq p(\lambda v_d)(1 - \lambda v_d) + cv_d \Rightarrow \text{mandate is optimal,} \]
\[ c > p(\lambda v_d)(1 - \lambda v_d) + cv_d \Rightarrow \text{mandate is not optimal.} \]
Equivalently,

\[
\begin{align*}
    c & \leq \lambda p(\lambda v_d) & \Rightarrow \text{mandate is optimal,} \\
    c & > p(\lambda v_d)[(1 - \lambda v_d)/(1 - v_d)] & \Rightarrow \text{mandate is not optimal.}
\end{align*}
\]

The optimality of a mandate is indeterminate if

\[
\lambda p(\lambda v_d) < c \leq p(\lambda v_d)[(1 - \lambda v_d)/(1 - v_d)].
\]

Indeterminacy is impossible if $\lambda = 1$ but may occur if $\lambda < 1$. 
Decision Making When the Optimal Policy is Indeterminate

Minimization of Subjective Expected Cost

Let $S$ denote the set of states of nature, indexing feasible values of $p(\lambda)$.
Let $p_s(\lambda)$ denote the value of $p(\lambda)$ in state $s$.
Let $\pi$ denote the subjective distribution placed on $S$.
Let $f(\cdot) : \mathbb{R} \to \mathbb{R}$ be an increasing function expressing the planner's risk preference.

Then

mandate if \[ \int_S f[p_s(\lambda)(1 - \lambda) + c] d\pi \leq f[p(\lambda v_d)(1 - \lambda v_d) + cv_d], \]
do not mandate if \[ \int_S f[p_s(\lambda)(1 - \lambda) + c] d\pi \geq f[p(\lambda v_d)(1 - \lambda v_d) + cv_d]. \]
Minimax Criterion

The planner acts as if increasing the vaccination rate from $v_d$ to 1 has no indirect preventive effect. That is, he acts as if $p(\lambda) = p(\lambda v_d)$. The result is

mandate if $p(\lambda v_d)(1 - \lambda) + c \leq p(\lambda v_d)(1 - \lambda v_d) + cv_d$,

do not mandate if $p(\lambda v_d)(1 - \lambda) + c \geq p(\lambda v_d)(1 - \lambda v_d) + cv_d$.

This simplifies to

mandate if $c \leq \lambda p(\lambda v_d)$,

do not mandate if $c \geq \lambda p(\lambda v_d)$.

The minimax criterion resolves indeterminacy in favor of no mandate.
Minimax-Regret Criterion

Let $S_m$ and $S_d$ be the subsets of $S$ in which a mandate yields strictly lower and higher social cost than decentralized decisions. Maximum regret in $S_m$ and $S_d$ are

$$
R_m \equiv \max_{s \in S_m} [p(\lambda v_d)(1 - \lambda v_d) + c v_d] - [p_s(\lambda)(1 - \lambda) + c]
$$

$$
= p(\lambda v_d)(1 - \lambda v_d) - c(1 - v_d),
$$

$$
R_d \equiv \max_{s \in S_d} [p_s(\lambda)(1 - \lambda) + c] - [p(\lambda v_d)(1 - \lambda v_d) + c v_d]
$$

$$
= (1 - v_d)[c - \lambda p(\lambda v_d)].
$$
The MMR decision is

mandate if \[ R_d \leq R_m, \]
do not mandate if \[ R_d \geq R_m. \]

That is,

mandate if \[ c \leq p(\lambda v_d)[1 - 2\lambda v_d + \lambda]/[2(1 - v_d)], \]
do not mandate if \[ c \geq p(\lambda v_d)[1 - 2\lambda v_d + \lambda]/[2(1 - v_d)]. \]

The minimax and minimax-regret decisions generally differ but coincide if \( \lambda = 1. \)
Approval with Partial Knowledge of Indirect Effects

Analysis of the decision to approve a new vaccine is straightforward if the planner knows the vaccination rate that would occur after approval.

I maintained this idealized assumption.
Approval Followed by a Mandate

If approval would be followed by a mandate, approval is equivalent to enacting a mandate when the observed decentralized vaccination rate is $v_d = 0$ and the observed decentralized illness rate is $p(\lambda v_d) = p(0)$.

\[
p(0)(1 - \lambda) + c \leq p(0) \implies \text{approval is optimal,}
\]

\[
c > p(0) \implies \text{approval is not optimal.}
\]

The optimality of approval is indeterminate if

\[
\lambda p(0) < c \leq p(0).
\]
The minimax approval decision is

approve if \( c \leq \lambda p(0) \),
reject if \( c \geq \lambda p(0) \)

The minimax-regret approval decision is

approve if \( c \leq p(0)(1 + \lambda)/2 \),
reject if \( c \geq p(0)(1 + \lambda)/2 \).
Approval Followed by Decentralized Vaccination

Suppose that approval would be followed by decentralized decision making and the planner knows the value of $v_d$ that would occur. Then approval is optimal iff

$$p(\lambda v_d)(1 - \lambda v_d) + cv_d \leq p(0).$$

Monotonicity of $p(\cdot)$ implies that $0 \leq p(\lambda v_d) \leq p(0)$. Hence,

$$c \leq \lambda p(0) \quad \Rightarrow \quad \text{approval is optimal},$$

$$c > p(0)/v_d \quad \Rightarrow \quad \text{approval is not optimal}.$$

The optimality of approval is indeterminate if $\lambda p(0) < c \leq p(0)/v_d$. 
The minimax decision is

approve if $c \leq \lambda p(0)$,
reject if $c \geq \lambda p(0)$.

The minimax-regret decision is

approve if $c \leq p(0)(1 + \lambda v_d)/(2v_d)$,
reject if $c \geq p(0)(1 + \lambda v_d)/(2v_d)$. 
Prevailing Vaccine Approval and Mandate Procedures

The American processes for approving new vaccines and mandating approved ones differ in numerous respects.

The federal FDA decides approvals. State agencies decide mandates.

The FDA approval process focuses on the direct effect of vaccination. Concern with indirect effects is a central rationale for state mandates.

FDA approval decisions ignore the monetary costs associated with vaccination and illness. State mandate decisions consider these costs.
FDA Approval

The FDA vaccine approval process is similar to the one used for drug approval.

Approval of new vaccines rests primarily on evidence from RCTs administering the vaccine, as does FDA approval of drugs.

RCTs are uninformative about the indirect effect of vaccination on illness.
The FDA description of the vaccine approval process refers to performance of a "risk/benefit assessment" en route to an approval decision.

The word "risk" refers to the possibility that administration of a vaccine to a person may have deleterious side effects while "benefit" refers to the direct preventive effect of vaccination on illness.

To an economist, "risk/benefit assessment" suggests quantification of risks and benefits and weighing the two to measure the net value of approving a vaccine.

However, the FDA does not quantify the tradeoff between risks and benefits.

Indeed, the FDA has rejected use of formal decision analysis in drug and vaccine approval in favor of what it calls a "structured qualitative approach."
A 2012 amendment to the federal Food, Drug, and Cosmetic Act called on the FDA to institute a "structured benefit-risk assessment framework," stating:

"Section 505(d) (21 U.S.C. 355(d)) is amended by adding at the end the following: 'The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision making, and the communication of the benefits and risks of new drugs."

In response, the FDA released to the public a draft document that is so revealing of current FDA thinking that I will quote from it at length.
The FDA document begins this way:

"In the past, some FDA stakeholders have indicated that there is room for improvement in the clarity and transparency of FDA’s benefit-risk assessment in human drug review. When FDA approves a new product, the agency publishes the various relevant documents, such as discipline reviews . . . and decision memoranda, on its website. While FDA takes great care to clearly explain the reasoning behind a regulatory decision in these documents, the clinical analysis may not always be readily understood by a broad audience who may wish to understand FDA’s thinking. In addition, some have argued that drug regulatory decisions should be based on more formalized and quantitative approaches to benefit-risk assessment, including the assignment of weights to benefit and risk considerations. Others, however, are skeptical of fully quantitative approaches, and consider such attempts to be a highly subjective exercise that would add little clarity to regulatory decision making."
It goes on to side with those who are skeptical of quantitative approaches, stating:

"In the last few years, as other disciplines such as decision science and health economics have been applied to drug regulatory decision-making, there has been much discussion among regulators, industry, and other stakeholders regarding “qualitative” versus “quantitative” approaches to benefit-risk assessment. The term “quantitative benefit-risk assessment” can have various meanings depending on who is asked. Some hold the view that a quantitative benefit-risk assessment encompasses approaches that seek to quantify benefits and risks, as well as the weight that is placed on each of the components such that the entire benefit-risk assessment is quantitative. This approach is typical of quantitative decision modeling. It usually requires assigning numerical weights to benefit and risk considerations in a process involving numerous judgments that are at best debatable and at worst arbitrary. The subjective judgments and assumptions that would inevitably be embodied in such quantitative decision modeling would be much less transparent, if not obscured, to those who wish to understand a regulator’s thinking. Furthermore, application of quantitative decision modeling seems most appropriate for decisions that are largely binary. Many benefit-risk
assessments are more nuanced and conditional based on parameters that could be used to effectively manage a safety concern in the post-market setting. There is significant concern that reliance on a relatively complex model would obscure rather than elucidate a regulator’s thinking.

These concerns have led FDA to the conclusion that the best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately. FDA believes that this can be accomplished by a qualitative descriptive approach for structuring the benefit-risk assessment that satisfies the principles outlined earlier in this section, while acknowledging that quantification of certain components of the benefit-risk assessment is an important part of the process to support decision-making. FDA considers it most important to be clear about what was considered in the decision, to be as quantitative as possible in characterizing that information, and to fully describe how that information was weighed in arriving at a conclusion. Quantitative assessments certainly underpin the qualitative judgments of FDA’s regulatory decisions, but FDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA’s benefit-risk assessment and how that information led to the regulatory decision.
FDA Approval Reconsidered

The "structured qualitative" approval approach of the FDA is not transparent.

The agency makes public only a "Summary of Basis for Approval" when a new vaccine or drug is approved.

It does not make public even a summary of its rationale when it rejects an application for drug or vaccine approval.

The qualitative decision process of the FDA shields the agency from scrutiny.

Analysis of approval as a planning problem would make explicit the full social costs and benefits of vaccination.