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Vaccination under pessimistic expectations in clinical trials and immunization campaigns*

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Abstract

We provide one of the first formalizations of a vaccination campaign in a decision-theoretic framework. We analyse a model where an ambiguity-averse individual must decide how much effort to invest into prevention in the context of a rampant disease. We study how ambiguity aversion affects the effort and the estimation of the vaccine efficacy in clinical trials and immunization campaigns. We find that the behaviours of individuals participating in a clinical trial differ from individuals not participating. Individuals who are more optimistic toward vaccination participate more in trials. Their behaviours and efforts are also affected. As a result, because vaccine efficacy depends on unobserved behaviours and efforts, the biological effect of the vaccine becomes difficult to evaluate. During the scale-up phase of a vaccination campaign, provided that vaccine efficacy is established, we show that vaccine hesitancy may still be rational.

Keywords*: Decision Theory, Vaccination, Clinical Trials, Immunization Campaigns*

JEL: D7, D81, I12. *Data sharing not applicable to this article as no datasets were generated or analysed during the current study.*

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1 Introduction

The coronavirus vaccines approved in Europe are considered as remarkably effective. Several studies undertaken in real-world conditions indicate that overall, COVID-19 vaccination has reduced the number of new SARS-CoV-2 infections, with the largest benefit received after two vaccinations and for symptomatic and high viral burden infections (Chodick et al., 2021; Haas et al., 2021; Lustig et al., 2021; Milman et al., 2021; Pritchard et al., 2021). However, there is continuing concern about vaccine hesitancy in some countries and some communities within them (Kluge & McKee, 2021). Proving that a COVID-19 vaccine is safe and effective can only be a turning point if the uptake of the vaccine is high enough to stop the circulation of the virus (Chevallier, Hacquin, & Mercier, 2021). Therefore, there is an urgent need to better understand how to reach out to those who have the opportunity to be vaccinated but refuse to do so. Previous research has identified several promising levers for reducing vaccine hesitancy. These include the motivation to be altruistic (Shim, Chapman, Townsend, & Galvani, 2012), emphasis on the dangers of the disease (Horne, Powell, Hummel, & Holyoak, 2015), rational calculation of pros and cons, and anticipated regret at not having been vaccinated (Betsch, Böhm, & Chapman, 2015; Brewer, DeFrank, & Gilkey, 2016). However, analysing cepticism about vaccination is difficult, because of the critical issue of disentangling so many factors involved in vaccination decisions.

In this paper, we provide one of the first formalizations of a vaccination campaign in a decision-theoretic framework. We build a model that can be used to compare self-protection and behaviours before a vaccine trial is implemented, during the trial and when immunization is scaled-up. In a nutshell, we analyze a model in which an ambiguity averse individual must decide how much effort to invest in prevention in the context of a rampant disease. The individual may decide to participate in a randomized vaccination clinical trial and later in a vaccination campaign. The main objective is to study how ambiguity aversion affects the effort exerted by the individual and the estimation of the vaccine efficacy. The model shows that individuals participating in clinical trials behave differently than individuals not participating, with behavioural differences owing to risk attitude. These differences may in turn compromise the validity of the vaccine efficacy calculation. The paper also finds that vaccine hesitancy may persist even if vaccination has beneficial effects. Specifically,

our benchmark model in the absence of a vaccine simply starts by showing that efforts (to invest in prevention) increase with income and decrease with exogenous improvements in the probability of not developing a severe form or dying from COVID-19.

The extension of this simple model includes vaccination and adverse effects during a clinical trial. As perceived adverse events may differ across individuals, we introduce a certain degree of pessimism related to vaccination. We show that when individuals participate in a clinical trial, the more pessimistic they are, the more they will invest in prevention, whereas optimists make fewer efforts. This is indeed crucial in clinical trials as informed participation is on a voluntary basis. Another consequence of voluntary participation is that the utility of participating in a clinical trial is greater than not participating. Clearly, this may depend on the health system. Participating in a trial may mean access to free care in the US, whereas in France, this type of motivation does not exist. This may generate selection bias and also differential efforts between optimists and pessimists in an endogenous way. Put differently, only people with relatively low pessimism may participate in the trial. We show that the share of pessimists in the trial may in turn affect vaccine efficacy. When the probability of catching COVID-19 and the probability of developing a severe form after being infected, are two independent features, we show that it is indeed possible to identify the treatment (vaccine) effect. Otherwise, the treatment effect remains undetermined. Whether these events are independent is debatable (Chidambaram et al., 2020; Izcovich et al., 2020; Liu et al., 2020; Pijls et al., 2021; Rozenfeld et al., 2020). There are probably some joint confounding factors and the availability and evolution of screening guidelines, individual factors, or clinical judgement may also affect who is tested (Rozenfeld et al., 2020). The amount of evidence remains limited on this question, though comparing age groups, children seem to be infected in large numbers without developing such severe symptoms as the elderly.

Lastly, we examine widespread inoculation in society. We show that during an immunization campaign, when the risk premium associated with wealth, expressed in terms of effort, is lower than the level of effort without any vaccine, then the individual may get vaccinated under certain conditions related to factors that are exogenous to individual behaviours. We therefore provide a discussion on vaccination hesitancy between genders.

Section 2 relates our work to the literature. Section 3 provides a benchmark model before an infectious threat is introduced to society and therefore before any clinical trial is

undertaken. Section 4 extends this model during an experimental phase aiming at finding new vaccines. The optimal effort (to invest in prevention) during the vaccination clinical trial is examined. Section 5 examines optimal efforts and vaccine efficacy during the vaccination campaign. Section 6 discusses the COVID-19 vaccine's gender paradox to illustrate the model and concludes.

2 Background literature

This paper contributes to several strands of the literature. First, various approaches have been used in economics to model vaccination decisions. In deciding whether to get vaccinated or not (a binary choice), individuals consider the risk of morbidity from vaccination, the probability of becoming infected, and the risk of morbidity or mortality from that infection. The decisions of individuals are indirectly influenced by externalities, i.e. the decisions of all other individuals, because the sum of these decisions yields the vaccine coverage levels in the population and hence the course of epidemics. One interesting prediction from this literature is that it is impossible to eradicate a disease through voluntary vaccination when individuals act according to their own interests (Geoffard & Philipson, 1997; May, 2000). Game theory has also explored vaccination decisions in such settings (Bauch & Earn, 2004; Bauch, Galvani, & Earn, 2003). Interestingly, Auld (2003) indicates that a partially effective prophylactic vaccine (one which reduces probability of infection) may alter incentives and induce perverse behaviours (see Peltzman (1975) for a similar discussion on car safety and traffic accidents). In particular, pessimistic expectations over the future of the epidemic induce more current risky behaviour. Medical researchers recognize that such reactions can occur, and this concern has contributed to some existing vaccines not being made available (Blower & McLean, 1994). Direct evidence from clinical trials of prophylactic vaccines also suggests that vaccination leads to increased risk behaviours (Chesney, Chambers, & Kahn, 1997; Johnson, 1999).

Second, a key factor in explaining vaccination success is the perception of risks associated with infection and vaccination (Brewer et al., 2007; Streefland, Chowdhury, & Ramos-Jimenez, 1999; Wheelock, Thomson, & Sevdalis, 2013). Voinson, Billiard, and Alvergne (2015) show for instance that sceptical individuals (negative opinion) overestimate infec-

tion cost, while pro-vaccine individuals (positive opinion) overestimate vaccination cost. In decision theory under risk, vaccination is similar to self-protection. In both cases, the individual's objective is to reduce the probability of occurrence of an undesirable event. The literature on health risk attitudes has explored self-protection and prevention following the seminal paper by Ehrlich and Becker (1972). Health models in health economics have also used a similar framework (Brianti, Magnani, & Menegatti, 2018; Courbage & Rey, 2016). However, for vaccination there is a new cost that may be important, namely the risk of side effects (Crainich, Eeckhoudt, & Menegatti, 2019).

Risk assessment is likely to be related to many factors that may or may not be related to the infection. These factors are psychological and social: media coverage, salient past experiences, beliefs about contagion and information, family and peers, trust in health care providers, health care professionals, and the state. The link between the environment and the cognitive or meta-cognitive mechanisms underlying decisions - rather than the health outcomes of decisions - has also been highlighted as a critical factor (Oraby & Bauch, 2015). We argue rather that in the case of COVID-19, the overall picture is better described as one of ambiguity than of risk. In particular, the informational structure can be represented by a set of available scenarios that describe the effect of vaccination and the possible negative side effects due to vaccination, each associated with a distribution function. Among models that have been put forward to represent preferences under uncertainty, we have opted for the widely used α-Maxmin Expected Utility criterion (α-MEU) that generalizes the Hurwicz criterion (1951) and whose properties have been studied by Ghirardato and Marinacci (2002).[1] This model has the advantage of allowing a separation between ambiguity and ambiguity attitudes, and also between risk and ambiguity attitudes.[2] Moreover, the α-MEU model is of great interest for the applied decision-theoretic literature as it can model ambiguity aversion and ambiguity seeking.

Third, in the experimental context, vaccination has also been shown to be an efficient way of reducing infection, and this is naturally the first step before market authorization. However, some authors have warned about the effects of behaviours in experimental con-

[1] See Etner, Jeleva, and Tallon (2012) or Gilboa and Marinacci (2013), for a survey on ambiguity literature.

[2] Although the α-MEU model is one of the most popular models in decision making under ambiguity, there is no known axiomatic characterization in a general domain of preference actions. However, axiomatic foundations have recently been better understood (Klibanoff et al., 2021).

texts. Malani (2006) focuses on these beliefs. By manipulating an individual's beliefs while holding constant the pharmacological effects, he shows that it is possible to generate and identify placebo effects. Indeed, Malani (2006) points out a neglected feature of clinical trials, namely that they manipulate patient expectations, and suggests that this feature can be used to identify the effects of expectations on outcomes, that is, placebo effects. He next uses variation in probability of treatment to identify placebo effects in several trials, and also advocates for incorporating variation in treatment probabilities into randomized trials (Malani, 2006, 2008). Similarly, Chassang, Snowberg, Seymour, and Bowles (2015) address complementarity between treatment and behaviour. They show that the gold standard double-blind randomized controlled trial (DBRCT) fails to fully account for the efficacy of treatment if there are interactions between treatment and behaviour, for example, if a treatment is more effective when patients change their exercise or diet. The decision to drop out of a trial may also be affected. Chan and Hamilton (2006) exploit drop-outs to estimate the subject's utility associated with the receipt of treatment, as revealed by drop-out behaviour, and evaluate treatment effects.

Fourth, some exogenous characteristics may be particularly important in vaccination decisions. This is the case of gender for instance. Gender heterogeneity with respect to preferences, risk and ambiguity has been widely debated in the economic literature. In general, most results from abstract gamble experiments indicate that women are more risk averse than men (Croson & Gneezy, 2009; Eckel & Grossman, 2008a). With respect to ambiguity aversion, the results are inconclusive on whether women are more ambiguity averse than men (Aggarwal & Damodaran, 2020; Agnew, Anderson, Gerlach, & Szykman, 2008; Borghans, Golsteyn, Heckman, & Meijers, 2009; Kray & Gelfand, 2009; Yang & Zhu, 2016). Borghans et al. (2009) find that women initially respond to ambiguity much more favourably than men (i.e. their reservation price does not decline), but as ambiguity increases, men and women show similar marginal valuations of ambiguity. While the evidence from abstract gamble experiments suggests greater risk aversion among women, the evidence from experiments with a contextual environment is less conclusive (among others, see Eckel and Grossman (2008b); Schubert, Gysler, Brown, and Brachinger (2000)). With respect to ambiguity aversion, Schubert et al. (2000) find that women are more ambiguity averse in an investment context but not in an insurance context. Kocher, Lahno, and Trautmann (2018) find that ambiguity

attitudes depend on the outcome domain and likelihood range, and no evidence for universal ambiguity aversion as is assumed in many applications in economics. Most of the ambiguity aversion evidence involves money, and there is little evidence on ambiguity and health. Curley, Eraker, and Yates (1984) found ambiguity aversion for health, which differed from ambiguity aversion for money. This domain specificity of ambiguity preferences is consistent with studies on risk and time preferences, which found that findings for money cannot be directly translated to health (Attema, Bleichrodt, L'Haridon, Peretti-Watel, & Seror, 2018; Chapman, 1996; Weber, Blais, & Betz, 2002). Attema, Bleichrodt, and L'Haridon (2018) show that individuals are more pessimistic under ambiguity in the loss domain, but little is said on gender heterogeneity.

3 A benchmark model prior to vaccination

We start with a model where individuals decide about their optimal behaviour in the presence of an epidemic disease that may have an impact on their health.

3.1 Definitions and notations

Let us consider two health states, H_i with $i \in \{0, 1\}$, which are such that $H_1 > H_0$. In state H_0, individuals are infected and have a severe form of the disease, while in H_1, they have not been infected or do not have a severe form of the disease. The probability of being in good health (i.e. in H_1 state) is given by a function $\lambda(e, \mu)$, which increases with the preventive behaviour of individuals, denoted e, and with an exogenous biological factor, denoted μ; both e and μ are positive real numbers. We thus have $\lambda_e(e, \mu) > 0$ and $\lambda_\mu(e, \mu) > 0$. Prevention may be interpreted as the effort such as physical distancing, wearing a mask, etc. Parameter μ combines all factors that are, by nature, exogenous to individual behaviour such as age, sex, immunity characteristics and also the existence of an efficient preventive treatment or vaccine. To keep the model general, we allow for substitution effects between behaviour and biological factors in the probability function. We do not at this stage impose a sign on $\lambda_{e\mu}$, even if it is reasonable to think that a more efficient biological parameter reduces the efficiency of the preventive behaviour. Taking the example of age as a proxy for the biological parameter, this means that the effect of preventive behaviors on the probablility

to be in good health increases with age. This appears to be true for COVID-19 as suggested by the efficiency of vaccination. It mostly benefited to old and very old adults (Bernal et al., 2021; Heaton, 2020; Soiza, Scicluna, & Thomson, 2021). However, this assumption can be discussed and is certainly not valid in all settings (Burton, Shapiro, & German, 1999; Levy & Myers, 2004).

Individuals derive utility from consumption, $c := w - e$, where $w > 0$ is the endowment, and from their health status, H_i. We suppose that the utility function, denoted $U(c, H_i)$, is an increasing function of consumption and health, $U_c(c, H_i) > 0$, $U_H(c, H_i) > 0$, and is strictly concave with respect to both arguments, $U_{cc}(c, H_i) < 0$, $U_{HH}(c, H_i) < 0$. Hence, individuals are risk averse towards health risk. Moreover, we suppose that the second cross derivative is non-negative, $U_{cH}(c, H_i) \geq 0$, which corresponds to correlation loving, namely the complementarity between wealth and health. This relationship has been empirically supported by Viscusi and Evans (1990), Sloan, Kip Viscusi, Chesson, Conover, and Whetten-Goldstein (1998) and Finkelstein, Luttmer, and Notowidigdo (2009) among others.

3.2 Optimal effort

We assume that the epidemic has been present for a sufficiently long time and that the value of the biological parameter μ is known. In the case without vaccination, we set it equal to μ_0. The expected utility of a non-vaccinated person is:

$$W(e) = \lambda(e, \mu_0) U(w - e, H_1) + (1 - \lambda(e, \mu_0)) U(w - e, H_0). \tag{1}$$

We denote by e^* the optimal effort, that is the solution of $\max_e W(e)$.

Proposition 1 *There exists a unique* e^* *if* $\lambda_{ee}(e, \mu_0) \geq 0$. *Moreover,* $e^* \in (0, w)$ *if* $\lim \lambda_e(0, \mu_0) = \lim U_c(0, H_i) = +\infty$.

As the effort is costly, there is an optimal effort that is obtained provided that its marginal effect on the probability of being in the good health state is infinite at the origin and decreasing. Moreover, an infinite marginal utility when consumption tends to zero makes it possible to ensure that the effort is lower than the endowment. One could extend this framework to a pure utility cost of the effort, but the results we derive below will be unchanged.

Proposition 2 *The optimal effort increases with the endowment and, provided that* $\lambda_{e\mu} \leq 0$*, decreases with the biological parameter.*

Proposition 2 is intuitive. We find that effort increases with income and decreases with exogenous improvements in the probability of not developing a severe form. For example, wearing a mask will certainly increase with income (the poorest households cannot afford to buy several masks per day even subsidized) and will also decline with the probability of dying from COVID-19 or developing a severe form. As a result, older individuals are more likely to wear a mask (Haischer et al., 2020). If $\lambda_{e\mu} > 0$, the effort may increase with μ, but this is less intuitive.

4 Randomized vaccination clinical trials

When a new epidemic emerges, the research community immediately looks for treatments and preventive solutions. Vaccine development during COVID-19 is one such example, as they reduce the likelihood of developing a severe form of infection with COVID-19. More specifically, vaccination makes it possible to act on the value of the biological parameter μ, and possibly improve it by increasing the immune defences of vaccinated people. But, we do not know the new value of μ before testing the vaccine. The gold standard in clinical trials is the double-blind placebo control clinical trials. This is a medical study involving human participants in which neither side knows who is getting treatment and who the placebo. In pragmatic trials, people who participate are not the same as those who do not participate (Schwartz & Lellouch, 2009). The trial population also differs from the non-enrolled population, especially in randomized, blinded trials (much more so than in observational studies). This may be assimilated to the Hawthorne effect, in which the results of an experiment are due not to the experimental factors but to the fact that subjects are aware that they are participating in an experiment in which they are being tested, which usually results in greater motivation.

Below, we propose to characterize the behaviour of participants in such a test using a decision theory framework. To our knowledge, there is in the literature no model of this type under uncertainty and ambiguity.

4.1 The optimal effort of participants in a trial

We consider here that μ is likely to increase with vaccination. We consider it as a random variable, $\tilde{\mu}$, of support $[\mu_0, 1]$. A the lower bound, μ_0, vaccination does not modify the probability of suffering from a severe form. At the uppur bound $\mu = 1$, the vaccination means never undergoing a serious form, which is translated into $\lambda(e, 1) = 1$. However, prior to the trial, the distribution of μ is not known.

COVID-19 vaccines validated in Europe and North America are considered safe globally but negative side effects or adverse events, such as arterial thromboembolic and haemorrhagic events, have been observed for some vaccines. Moreover, even if adverse effects are relatively low in practice, individuals may overweight them. In the case of vaccination, one may experience an adverse reaction that reduces health; it is noted that one experiences the adverse reaction whether infected with COVID-19 or not, and that this adverse effect depends on one's health status. Adverse effects on health are measured with the random variable $\tilde{\varepsilon}$ of support $[0, \varepsilon]$ if one is in state H_1 and by $\theta\tilde{\varepsilon}$ with $\theta \geq 0$ if one is in state H_0. Again, we assume that the distribution of $\tilde{\varepsilon}$ is unknown. The probability of experiencing an adverse event (regardless of health status) is noted $\tilde{q}_\varepsilon$. It is also a random variable of support $\Omega_q = [0, q_\varepsilon^{\max}]$ whose distribution is not known. We are aware that drop-outs induced by adverse effects may generate selection bias and imbalance in randomized average characteristics (Chan & Hamilton, 2006), thus revealing preferences. But we do not consider this here, as we are studying a static framework.

We consider the α-MEU model of preferences representation under ambiguity. This model evaluates decisions as a weighted sum of the highest and the lowest expected utility compatible with the set of priors. The weight granted to the lowest expected utility measures the DM's ambiguity aversion. To this end, we compute the worst possible expected utility of a participant. It is characterized by a vaccine that has no effect (when the realization of $\tilde{\mu}$ is μ_0) and adverse effects that are the highest possible (when the realization of $\tilde{\varepsilon}_1$ is ε) and that occur which the highest probability (when the realization of $\tilde{q}_\varepsilon$ is $q_\varepsilon^{\max}$). This state of nature provides the following expected utility:

$$\begin{aligned} U^{\min}(e) &= q_\varepsilon^{\max}\left[\lambda(e,\mu_0)U(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))U(w-e,H_0-\theta\varepsilon)\right] \\ &\quad +(1-q_\varepsilon^{\max})\left[\lambda(e,\mu_0)U(w-e,H_1)+(1-\lambda(e,\mu_0))U(w-e,H_0)\right]. \end{aligned} \tag{2}$$

Conversely, the best possible expected utility is given for a vaccine whose effect is maximal (when the realization of $\tilde{\mu}$ is 1) and has no adverse effects (when the realization of $\tilde{q}_\varepsilon$ is 0). This gives the following satisfaction:

$$U^{\max}(e) = U(w - e, H_1). \tag{3}$$

Each individual displays a degree of ambiguity aversion (or pessimism) about vaccination, which is denoted by $\alpha \in [0, 1]$. Some articles of the literature document a differential vaccination hesitancy across genders, hesitancy being higher among women despite the fact that they are more likely to perceive the pandemic as a very serious health problem and to agree and comply with restraining measures (Galasso et al., 2020). This might partly explain, along with sex-based immunological differences, the share of women in specific sectors, or other health-related behaviours such as smoking (Wenham, Smith, & Morgan, 2020), why women die less than men of COVID-19. Still vaccine hesitancy is higher amongst women, an observation that has been called the COVID-19 vaccine's gender paradox (Galasso, Profeta, Foucault, & Pons, 2021), as women are more concerned about COVID-19 and more likely to believe themselves to be infected and become seriously ill. We note that gender might not be the only source of heterogeneity in the aversion towards vaccination. In France, where vaccination hesitation is historically high (Neumann-Böhme et al., 2020), Hacquin, Altay, Araujo, Chevallier, and Mercier (2020) show that vaccine-hesitant individuals are more likely to be women, young, less educated, vote for political extremes, be dissatisfied with the government's response to the COVID-19 crisis, and feel less at risk of COVID-19. In our framework, those differences translate as different α.

The objective function of a person who is vaccinated is given as the convex combination of the expected utilities in the worst and best cases:

$$V(e; \alpha) = \alpha U^{\min}(e) + (1 - \alpha) U^{\max}(e). \tag{4}$$

Since we are considering double-blind placebo control clinical trials, not all participants in the trial are vaccinated. Let p be the probability of being vaccinated during the trial, which is known by the participant as it is defined by the trial organizer and usually has to be disclosed. The problem of an individual with a degree of ambiguity aversion α who

participates in the trial is:

$$\max_{e} pV(e;\alpha) + (1-p)W(e). \tag{5}$$

Let $e^{**}(\alpha)$ be the solution of this problem. We first show this solution exists.

Proposition 3 *There exists a unique* $e^{**}(\alpha) \in (0,1)$ *if the conditions in Proposition 1 are satisfied and if* $H_1 - H_0 \geq \varepsilon(1-\theta)$.

The conditions that guarantee the existence of an optimal effort for the participants in the trial are the same as those that prevail in the benchmark model, except one that is related to the adverse effects associated with the trial. More precisely, it is required that minimal health in the good health state, $H_1 - \varepsilon$, should be better than that in the bad health state, $H_0 - \theta\varepsilon$. We observe that it is always the case for $\theta \geq 1$, which means that the maximal adverse effect is greater in the bad health state than in the good one. Notice that if $H_1 - H_0 < \varepsilon(1-\theta)$, the optimal effort might be equal to zero.

We now assume that the conditions stated in Proposition 3 are satisfied and propose some comparative statics.

Proposition 4 *The optimal effort* e^{**} *decreases with* μ_0 *if* $\lambda_{e\mu}(e,\mu_0) \leq 0$, *increases with* θ, *and increases with* ε *and* $q_{\varepsilon}^{\max}$ *if* $\theta \geq 1$. *Moreover, the effort increases with ambiguity aversion,* α.

Since $U_{cH}(w,h) \geq 0$, the marginal utility of wealth is lower in the disease state. First, the reduction in the probability of disease, by changing μ_0, raises the expected marginal utility of wealth and thus lowers the level of effort. Second, when μ rises, it changes the efficiency of effort on probability of disease, $1 - \lambda_e$. If it increases efficiency, $\lambda_{e\mu} < 0$, this second effect reinforces the first one and the effort increases with μ_0. Otherwise, we cannot conclude.

When θ increases, the side effects on bad health status increase, as does the gap between good and bad health status. This incites individuals to increase their effort.

The effect of side effects, ε, on optimal effort depends on the way it impacts initial health status, whether bad or good health. First, when ε rises, $U_c(w-e, H_1-\varepsilon)$ and $U_c(w-e, H_0-\theta\varepsilon)$ fall since we assume that $U_{cH}(w,H) \geq 0$, lowering the expected marginal

utility of wealth and thus the marginal cost of effort. This incites the individual to increase the level of effort. Second, an increase in ε raises the gap between being sick and being healthy, $H_1 - H_0 + \varepsilon(\theta - 1)$ if $\theta \geq 1$. Thus, it raises the marginal benefit of effort. If $\theta < 1$, an increase in ε decreases the gap between being sick and being healthy, decreases the marginal benefit of effort and goes in the opposite direction to the first effect. Therefore, we cannot conclude.

$q_\varepsilon^{\max}$ is the worst scenario in the sense that it is the highest probability of adverse side effects occurring. In our set-up, a change in the degree of ambiguity/model uncertainty corresponds to a change in the size of the set Ω_q without affecting the probability distributions that already belong to the set. The arrival of a new worst scenario potentially alters the optimal level of effort. If $q_\varepsilon^{\max}$ increases, the worst scenario is even worse, and this "bad news" encourages individuals to raise their level of effort if $\theta \geq 1$ (else we cannot conclude). Similarly, if $q_\varepsilon^{\max}$ decreases, the worst scenario is less severe, and this "good news" encourages individuals to reduce their level of effort (if $\theta \geq 1$).

Finally, ambiguity aversion encourages individuals to increase their level of effort. This result is similar to the ones obtained by Alary, Gollier, and Treich (2013) or Berger and Bosetti (2020) in different contexts.

We now characterize the behaviour of those who participate in the trial with respect to the average behaviour e^* observed prior to the trial.

Proposition 5 *There exists* $\bar{\theta} \in (1 - (H_1 - H_0)/\varepsilon, 1)$ *such that (i)* $e^{**}(\alpha) < e^*$ *for all* $\alpha \in [0,1]$ *if* $\theta \leq \bar{\theta}$*; (ii) there exists a unique* $\widehat{\alpha} \in (0,1)$ *such that* $e^{**}(\alpha) \geq e^* \Leftrightarrow \alpha \geq \widehat{\alpha}$ *if* $\theta > \bar{\theta}$.

As a result, the most optimistic individuals (or least ambiguity-averse) make less effort during the trial. We note that they may still make an effort because they do not know if they received the vaccine dose during the trial or only a placebo. They are just doing less than what was observed before the clinical trial.

If θ is sufficiently high, that is, the adverse effect is larger in the bad health state than in the good one, the more pessimistic individuals are, the more they will invest in prevention and make efforts. If θ is low, all the participants will invest less in prevention whenever their level of pessimism.

The level of ambiguity aversion (or seeking) is a major determinant of the effort made by individuals participating in the trial. In addition, it is a determining factor in the decision whether or not to participate in these trials. Since the participants are volunteers, we introduce a participation constraint, that is the utility of participating in the trial is greater than the one of not participating:

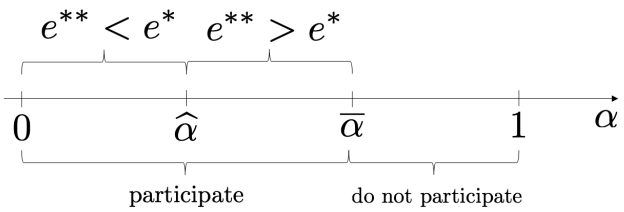
$$pV\left(e^{**}\left(\alpha\right);\alpha\right)+\left(1-p\right)W\left(e^{**}\left(\alpha\right)\right)\geq W\left(e^{*}\right). \tag{6}$$

Proposition 6 *For sufficiently high p, there exists a unique $\overline{\alpha}\in(0,1)$ such that agents with relatively low pessimism $\alpha\in[0,\overline{\alpha}]$ participate in the trial whereas those with relatively high pessimism $\alpha\in[\overline{\alpha},1]$ do not participate.*

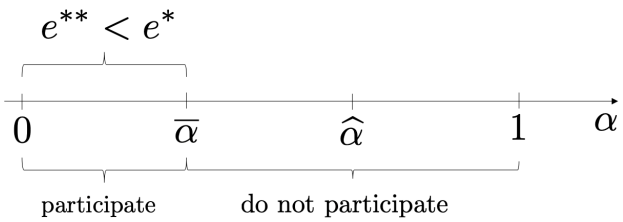
We show that only the less pessimistic will participate in the trial. Since effort increases with pessimism, one may expect that those who participate will not do much prevention and particularly less than those who do not participate. Actually, this intuition is not entirely correct. Indeed, there are two cases. Either, $\widehat{\alpha}\geq\overline{\alpha}$: all participants involved in a clinical trial have a lower level of effort compared to the one that prevailed before the trial, i.e. we have $e^{**}\leq e^{*}$. Or, $\widehat{\alpha}<\overline{\alpha}$: some participants (those with $\alpha\in[0,\widehat{\alpha}]$) have a lower level of effort and some (those with $\alpha\in[\widehat{\alpha},\overline{\alpha}]$) have a higher level of effort. The difficulty here is that both $\widehat{\alpha}$ and $\overline{\alpha}$ are endogenous variables. We thus claim that the amount invested in prevention does not only depend on ambiguity aversion but also on the adverse effect size. The change in behaviour according to whether or not individuals participate in the trial is thus linked to an external effect, ε, and preferences, α. We highlight the role of adverse effect in the following.

Proposition 7 *If the adverse effect ε is sufficiently weak, then $\widehat{\alpha}<\overline{\alpha}$. If ε is sufficiently large, it is possible to have $\widehat{\alpha}>\overline{\alpha}$.*

Importantly, the behaviour of the participants in the trial does not necessarily imply a lower effort than in the population that does not participate in the trial. Combining the results of propositions 6 and 7, we obtain that there are two thresholds to note for ambiguity aversion. First, only the most optimistic participate in the vaccine trial ($\alpha\leq\overline{\alpha}$). On the other hand, the most optimistic of them decrease their level of effort by participating ($\alpha\leq\widehat{\alpha}$). Figure 1 summarizes these results.



(a) A weak ε



(b) A high ε

Fig. 1: *Participating in trial and effort*

However, many concerns have been raised about the heterogeneity of vaccine hesitancy, vaccine efficacy and vaccine side effects, most notably across genders. Although COVID-19 vaccines have been demonstrated to be safe and effective in both clinical trials and widespread inoculation for both males and women with limited side effects, our model proposes a potential framework and explanation to fuel this debate. It might not be so surprising that vaccine-hesitant individuals are more likely to be women rather than men, at least declaratively, as men may be more optimistic or less adverse to ambiguity. In our model, optimistic individuals participate more in a trial. However, our model suggests that it will be difficult to predict efforts and vaccine efficacy, a result that has been partly explored in the literature. Malani (2006) argues that "*more optimistic patients may modify their behaviour - like the ulcer patient who reduces their consumption of spicy food or the cholesterol patient who exercises more often - in a manner that complements their medical treatment. If an investigator does not measure these behavioural changes (as is commonly the case), the more optimistic patient will appear to have a better outcome, that is, to have experienced placebo effects.*" Understanding how women differ from men in response to treatment is clearly critical for enhancing treatment efficacy. However, gender-specific efforts and behaviours are rarely measured during clinical trials, where only the medical outcome is measured. One avenue for research might be to develop protocols and measures of efforts that would help

to understand this gender paradox.

We now turn to the evaluation of vaccine efficacy.

4.2 Estimating Vaccine Efficacy

Let $z(\alpha)$ be the share of persons with ambiguity avecrsion α within the population, with $\int_0^1 z(\alpha)\, d\alpha = 1$. In a clinical trial, the vaccine is considered effective if the proportion of uninfected is higher in the treated group than in the control group. Let us note $\hat{\mu}$, the true value of μ in case of vaccination, it is enough that $\hat{\mu} > \mu_0$ for it to be the case because the probability of not having a severe form of COVID-19 in the treated group is $\lambda(e^{**}, \hat{\mu})$ while the same probability in the control group is $\lambda(e^{**}, \mu_0)$.

At the end of the clinical trial, the efficacy of the vaccine is determined by counting the infected among the treated and among the controls. We note that, a priori, we observe neither the e^* behaviours of the participants, nor the '*true*' state of nature $\widehat{\mu}$.

Vaccine efficacy VE is defined as the (number of people in the control group developing a severe form - number of people in the vaccinated control group developing a severe form) / number of people in the control group developing a severe form . If the distribution of α is the same among the controls and the vaccinated -which is justified if the samples are large enough and nobody drops out -, we obtain:

$$\begin{aligned} VE &= \frac{\int_0^{\overline{\alpha}} z(\alpha)\left(1-\lambda\left(e^{**}(\alpha),\mu_0\right)\right)d\alpha - \int_0^{\overline{\alpha}} z(\alpha)\left(1-\lambda\left(e^{**}(\alpha),\widehat{\mu}\right)\right)d\alpha}{\int_0^{\overline{\alpha}} z(\alpha)\left(1-\lambda\left(e^{**}(\alpha)\right),\mu_0\right)d\alpha} \\ &= \frac{\int_0^{\overline{\alpha}} z(\alpha)\left[\lambda\left(e^{**}(\alpha),\widehat{\mu}\right)-\lambda\left(e^{**}(\alpha),\mu_0\right)\right]d\alpha}{\int_0^{\overline{\alpha}} z(\alpha)\left(1-\lambda\left(e^{**}(\alpha)\right),\mu_0\right)d\alpha} \end{aligned}$$

Remark. Let us assume that $1-\lambda(e,\mu) = (1-\pi(e))(1-\mu)$, which can be interpreted as the product of two independent probabilities: $1-\pi(e)$ is the probability of catching COVID-19 and $(1-\mu)$ is the probability of developing a severe form if one is infected by COVID-19, then we have:

$$VE = \frac{\widehat{\mu}-\mu_0}{1-\mu_0}.$$

But if λ is not separable, we cannot deduce $\widehat{\mu}$ because we do not observe e^*. As a result, after clinical trials and during the scale-up phase of a vaccination campaign, precise

vaccine efficacy may be unknown, and we revert to the previous trial case. This may happen because vaccine efficacy depends on unobserved behaviours and efforts, but also for many other reasons, including ,for instance, fake news that will introduce noise around vaccine efficacy. In this case, our results show that preventive efforts are extremely difficult to predict, a result that is consistent with the literature (Courbage, Rey, & Treich, 2013). This may call for further trials connected with real clinical practice.

Thus, provided that λ is separable, the trial enables researchers to determine the values of ε and θ and the probability of occurrence of an adverse reaction, noted $\widehat{q}$. Because this case differs from the trial case, the next section discusses this option.

5 Optimal efforts during the vaccination campaign

As explained above, in this section, we assume that the probabilities λ are separable, which implies that the uncertainties associated with vaccination have been removed. The biological parameter and side effect characteristics are now assumed to be known and given by the triplet $(\widehat{\mu}, \widehat{\varepsilon}, \widehat{q}_\varepsilon)$. The expected utility of an agent vaccinated during the vaccination campaign is:

$$\begin{aligned} EU\left(e;\widehat{\mu},\widehat{\varepsilon},\widehat{q}_\varepsilon\right) &= \widehat{q}_\varepsilon\left[\lambda(e,\widehat{\mu})U(w-e,H_1-\widehat{\varepsilon})+(1-\lambda(e,\widehat{\mu}))U(w-e,H_0-\theta\widehat{\varepsilon})\right] \\ &\quad +(1-\widehat{q}_\varepsilon)\left[\lambda(e,\widehat{\mu})U(w-e,H_1)+(1-\lambda(e,\widehat{\mu}))U(w-e,H_0)\right]. \end{aligned} \tag{7}$$

Let e^{***} be the solution of: $\max_e EU\left(e;\widehat{\mu},\widehat{\varepsilon},\widehat{q}_\varepsilon\right)$ while e^* is the effort of a non-vaccinated agent, who solves $\max_e W\left(e\right)$ where $W\left(e\right)$ is given by (1).

Let us now examine under what conditions an individual will come forward for vaccination. The condition for voluntary participation in the campaign is:

$$EU\left(e^{***};\widehat{\mu},\widehat{\varepsilon},\widehat{q}_\varepsilon\right) \geq W\left(e^*\right). \tag{8}$$

Let us define the wealth risk premium in a bi-dimensional environment, expressed in terms of effort, $\bar{e}$, as the difference between the initial health and the global certainty equivalent

of health risk. $\bar{e}$ is therefore the solution of the following equation:

$$(1-\widehat{q_\varepsilon})\,U(w,H_1)+\widehat{q_\varepsilon}U(w,H_1-\widehat{\varepsilon})=U(w-\bar{e},H_1). \tag{9}$$

We can state that:

Proposition 8 *If the wealth risk premium, expressed in terms of effort, is lower than the level of effort without any vaccine, i.e. if $\bar{e}<e^*$, then individuals get vaccinated if $\widehat{\mu}$ is high enough.*

The relationship between the demand for vaccination and the degree of risk aversion is unclear. This is consistent with the well-known results on the ambiguous impact of risk aversion on self-protection (Dionne & Eeckhoudt, 1985). However, in the context of vaccination, our result is close to the one obtained by Crainich et al. (2019). In our set-up, the vaccination trial reveals the value of the effect of vaccines on the probability of having a severe form of the disease. We show that if the risk premium is relatively low, that is for weakly risk-averse individuals, then individuals decide to get vaccinated if the impact of vaccines is sufficiently high. Otherwise, they prefer not to get vaccinated and make more effort (e.g. protective measures). Our setting extends standard cost-benefit analysis, which considers only the health impacts of vaccination, by introducing risk aversion toward the possible adverse effects induced by vaccination. This may help in understanding why some individuals may still be reluctant about vaccination even if the balance between health benefits and costs is positive.

6 Conclusion

In this paper, we propose a novel theoretical framework to analyze vaccination trials and campaigns. It emphasizes the role of ambiguity and ambiguity attitudes by using a α-MEU model of preferences that captures the ambiguous nature of adverse effects of vaccination. This attitude is assumed to be heterogeneous within the population. We show that individuals enrolled in a clinical trial are not likely to be representative of the total population in terms of risk exposure to the disease and, during the trial, will behave differently according to their own attitude towards ambiguity. After the trial, we characterize the condition

that establishes the biological effect of the vaccine. Under that latter condition, we analyse whether the general population is likely to participate in the vaccination campaign and we show the crucial role of the degree of risk aversion of the population.

What are the implications of these findings for how to design clinical trials and vaccination campaigns? Although we do not yet have a toolkit, this article could motivate an entire research agenda on how to anticipate the expansion of clinical trials to vaccination campaigns from a behavioral perspective. Chassang et al. (2015) for example, proposes a research design when there are interactions between treatment and behaviours. Optimism bias has previously been studied in clinical research, but not in relation to ambiguity aversion (Chalmers & Matthews, 2006; Sharot, 2011). Innovative research designs accounting for ambiguity-aversion could thus be one avenue for research. Clinical trials should also aim at estimating and classifying the bias in vaccine efficacy more systematically so that the vaccination campaign could adjust this bias in information campaigns. This may be anticipated at an early stage of randomized controlled trials (RCTs) - when patients are invited to participate - by improving data collection on ambiguity measurements (Izhakian, 2020; Jewitt & Mukerji, 2017). Finally, vaccination campaigns could naturally run out of steam if vaccine hesitancy persists despite the effectiveness of the treatment. Recently, some studies have shown the efficiency of nudges on vaccination decisions (Dai et al., 2021; Patel, 2021). Experimenting different ways to nudge decision making and communicating risks in such context is certainly crucial (Kahneman, 2017).

Last but not least, this paper complements other frameworks that have e.g. studied the political economy of vaccination (Iverson, Karp, & Peri, 2022; Manski, 2017; Nganmeni, Pongou, Tchantcho, & Tondji, 2022). Our model is used to illustrate the vaccination episode of the COVID-19 pandemic but do not consider other preventive behaviors such that antibody testing (Guimarães, 2021) or self-isolation (Baril-Tremblay, Marlats, & Ménager, 2021). Moreover, our work could be usefully extended by introducing a dynamic framework in which uncertainty evolves over time. This would make it possible to characterize the waiting strategies of part of the population. It could also be extended to a more economic framework that would evaluate the cost and benefits of vaccination, and their consequences for firms and markets (see, e.g. Morimoto and Suzuki (2022)).

7 Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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8 Appendices

A Proof of Proposition 1

The first order condition is $W'(e) = 0$, where $W'(e)$ can be written as:

$$\begin{aligned} W'(e) &= \lambda_e(e, \mu_0)\left[U(w-e, H_1) - U(w-e, H_0)\right] \\ &- \left[\lambda(e, \mu_0) U_c(w-e, H_1) + (1 - \lambda(e, \mu_0)) U_c(w-e, H_0)\right]. \end{aligned} \tag{A.1}$$

The second order condition is $W''(e) < 0$, where $W''(e)$ can be written as:

$$\begin{aligned} W''(e) &= \lambda_{ee}(e, \mu_0)\left[U(w-e, H_1) - U(w-e, H_0)\right] \\ &-2\lambda_e(e, \mu_0)\left[U_c(w-e, H_1) - U_c(w-e, H_0)\right] \\ &+\lambda(e, \mu_0) U_{cc}(w-e, H_1) + (1 - \lambda(e, \mu_0)) U_{cc}(w-e, H_0). \end{aligned} \tag{A.2}$$

Given the assumptions $U_c(c, H_i) > 0$, $U_H(c, H_i) > 0$, $U_{cH}(c, H_i) \geq 0$ and $U_{cc}(c, H_i) < 0$, a sufficient condition for $W''(e)$ to be negative is $\lambda_{ee}(e^*, \mu_0) \geq 0$. Moreover, $e^* > 0$ if $W'(0) > 0$, which is obtained if $\lim \lambda_e(0, \mu_0) = +\infty$ and $e^* < w$ if $W'(w) > 0$, which is obtained if $\lim U_c(0, H_i) = +\infty$. □

B Proof of Proposition 2

We use equation (A.1) as an implicit function and derive the following relation:

$$sign\frac{de^*}{dw} = sign\begin{bmatrix} \lambda_e(e^*, \mu_0)\left[U_c(w-e^*, H_1) - U_c(w-e^*, H_0)\right] \\ -\left[\lambda(e^*, \mu_0) U_{cc}(w-e^*, H_1) + (1 - \lambda(e^*, \mu_0)) U_{cc}(w-e^*, H_0)\right] \end{bmatrix}, \tag{B.3}$$

which is positive since $U_{cH}(c, H_i) \geq 0$ and $U''_{cc}(c, H_i) < 0$. Similarly, we have:

$$sign\frac{de^*}{d\mu_0} = sign\begin{bmatrix} \lambda_{e\mu}(e^*, \mu_0)\left[U(w-e^*, H_1) - U(w-e^*, H_0)\right] \\ -\lambda_\mu(e^*, \mu_0)\left[U_c(w-e^*, H_1) - U_c(w-e^*, H_0)\right] \end{bmatrix}, \tag{B.4}$$

which is negative since $\lambda_{e\mu} \leq 0$. □

C Proof of Proposition 3

The first order condition is:

$$
\begin{aligned}
&p\alpha\left\{-q_{\varepsilon}^{\max}\left[\lambda(e,\mu_0)U_c(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))U_c(w-e,H_0-\theta\varepsilon)\right]\right.\\
&-(1-q_{\varepsilon}^{\max})\left[\lambda(e,\mu_0)U_c(w-e,H_1)+(1-\lambda(e,\mu_0))U_c(w-e,H_0)\right]\\
&+\lambda_e(e,\mu_0)\left[q_{\varepsilon}^{\max}\left(U(w-e,H_1-\varepsilon)-U(w-e,H_0-\theta\varepsilon)\right)\right.\\
&\left.\left.+(1-q_{\varepsilon}^{\max})\left(U(w-e,H_1)-U(w-e,H_0)\right)\right]\right\}\\
&-p\left(1-\alpha\right)U_c(w-e,H_1)+(1-p)\,W'\left(e\right)=0. \qquad \text{(C.5)}
\end{aligned}
$$

We note that the left-hand side of the above expression is strictly positive for $e=0$ if $\lim\lambda_e'\left(0,\mu_0\right)=+\infty$ and $U(w,H_1-\varepsilon)>U(w,H_0-\theta\varepsilon)$, which reduces to $H_1-H_0\geq\varepsilon\left(1-\theta\right)$. It is strictly negative for $e=w$ if $\lim U_c'\left(0,H_i\right)=+\infty$. Moreover, the second order condition is

$$
\begin{aligned}
&p\alpha\left\{-2q_{\varepsilon}^{\max}\lambda_e(e,\mu_0)\left[U_c(w-e,H_1-\varepsilon)-U_c(w-e,H_0-\theta\varepsilon)\right]\right.\\
&-2(1-q_{\varepsilon}^{\max})\lambda_e(e,\mu_0)\left[U_c(w-e,H_1)+U_c(w-e,H_0)\right]\\
&+q_{\varepsilon}^{\max}\left[\lambda(e,\mu_0)U_{cc}(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))U_{cc}(w-e,H_0-\theta\varepsilon)\right]\\
&+(1-q_{\varepsilon}^{\max})\left[\lambda(e,\mu_0)U_{cc}(w-e,H_1)+(1-\lambda(e,\mu_0))U_{cc}(w-e,H_0)\right]\\
&+\lambda_{ee}(e,\mu_0)\left[q_{\varepsilon}^{\max}\left(U(w-e,H_1-\varepsilon)-U(w-e,H_0-\theta\varepsilon)\right)\right.\\
&\left.\left.+(1-q_{\varepsilon}^{\max})\left(U(w-e,H_1)-U(w-e,H_0)\right)\right]\right\}\\
&+p\left(1-\alpha\right)U_{cc}(w-e,H_1)+(1-p)\,W''\left(e\right), \qquad \text{(C.6)}
\end{aligned}
$$

which is negative if $\lambda_{ee}(e,\mu_0)\leq 0$ and $H_1-H_0\geq\varepsilon\left(1-\theta\right)$. □

D Proof of Proposition 4

We use equations (A.1) and (C.5) as implicit functions and compute the following:

$$\begin{aligned} sign\frac{de^{**}}{d\mu_0} &= sign\left[p\alpha\left\{-q_\varepsilon^{\max}\lambda_\mu(e,\mu_0)\left[U_c(w-e,H_1-\varepsilon)-U_c(w-e,H_0-\theta\varepsilon)\right]\right.\right. \\ &\quad -(1-q_\varepsilon^{\max})\lambda_\mu(e,\mu_0)\left[U_c(w-e,H_1)-U_c(w-e,H_0)\right] \\ &\quad +\lambda_{e\mu}(e,\mu_0)\left[q_\varepsilon^{\max}\left(U(w-e,H_1-\varepsilon)-U(w-e,H_0-\theta\varepsilon)\right)\right. \\ &\quad \left.\left.+(1-q_\varepsilon^{\max})\left(U(w-e,H_1)-U(w-e,H_0)\right)\right]\right\} \\ &\quad +(1-p)\,\lambda_{e\mu}\left(e,\mu_0\right)\left[U\left(w-e,H_1\right)-U\left(w-e,H_0\right)\right] \\ &\quad -(1-p)\,\lambda_\mu\left(e,\mu_0\right)\left[U_c\left(w-e,H_1\right)-U_c\left(w-e,H_0\right)\right]\right], \end{aligned} \tag{D.7}$$

which is negative if $\lambda_{e\mu}(e,\mu_0)\leq 0$ (as in Proposition 2). We also have:

$$sign\frac{de^{**}}{d\theta} = sign\left[(1-\lambda(e,\mu_0))U_{cH}(w-e,H_0-\theta\varepsilon)+\lambda_e(e,\mu_0)U_H(w-e,H_0-\theta\varepsilon)\right], \tag{D.8}$$

which is positive. Moreover, we have:

$$\begin{aligned} sign\frac{de^{**}}{d\varepsilon} &= sign\left[\lambda(e,\mu_0)U_{cH}(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))\theta U_{cH}(w-e,H_0-\theta\varepsilon)\right. \\ &\quad \left.-\lambda_e(e,\mu_0)\left[U_H(w-e,H_1-\varepsilon)-\theta U_H(w-e,H_0-\theta\varepsilon)\right]\right], \end{aligned} \tag{D.9}$$

which is positive if $\theta\geq 1$ (as we have $U_{cH}\geq 0$ and $U_{HH}<0$). Finally, we have:

$$\begin{aligned} sign\frac{de^{**}}{dq_\varepsilon^{\max}} &= sign\left[\lambda(e,\mu_0)\left[U_c(w-e,H_1)-U_c(w-e,H_1-\varepsilon)\right]\right. \\ &\quad +(1-\lambda(e,\mu_0))\left[U_c(w-e,H_0)-U_c(w-e,H_0-\theta\varepsilon)\right] \\ &\quad -\lambda_e(e,\mu_0)\left[\left(U(w-e,H_1)-U(w-e,H_1-\varepsilon)\right)\right. \\ &\quad \left.\left.-\left(U(w-e,H_0)-U(w-e,H_0-\theta\varepsilon)\right)\right]\right]. \end{aligned} \tag{D.10}$$

The latter expression is equal to 0 for $\varepsilon=0$ and is increasing with ε if $-U_H(w-e,H_1-\varepsilon)+\theta U_H(w-e,H_0-\theta\varepsilon)\geq 0$, which is the case if $\theta\geq 1$. We therefore conclude that the sign is positive if $\theta\geq 1$.

Finally, the sign of $\frac{de^{**}}{d\alpha}$ is given by the sign of $\frac{\partial V_e(e^{**};\alpha)}{\partial \alpha}$.Using equation (A.1), we obtain:

$$\begin{aligned}\frac{\partial V_e\left(e^{**};\alpha\right)}{\partial \alpha} &= U_c(w-e^{**},H_1)+q_\varepsilon^{\max}\lambda_e(e^{**},\mu_0)\left[U(w-e^{**},H_1-\varepsilon)-U(w-e^{**},H_0-\theta\varepsilon)\right]\\ &\quad -q_\varepsilon^{\max}\left[\lambda(e^{**},\mu_0)U_c(w-e^{**},H_1-\varepsilon)\right.\\ &\quad \left.+(1-\lambda(e^{**},\mu_0))U_c(w-e^{**},H_0-\theta\varepsilon)\right], \qquad \text{(D.11)}\end{aligned}$$

or equivalently:

$$\begin{aligned}\frac{\partial V_e\left(e^{**};\alpha\right)}{\partial \alpha} &= \left[U_c(w-e^{**},H_1)-q_\varepsilon^{\max}U_c(w-e^{**},H_0-\theta\varepsilon)\right]\\ &\quad +q_\varepsilon^{\max}\lambda_e(e^{**},\mu_0)\left[U(w-e^{**},H_1-\varepsilon)-U(w-e^{**},H_0-\theta\varepsilon)\right]\\ &\quad +q_\varepsilon^{\max}\lambda(e^{**},\mu_0)\left[U_c(w-e^{**},H_0-\theta\varepsilon)-U_c(w-e^{**},H_1-\varepsilon)\right]. \qquad \text{(D.12)}\end{aligned}$$

In the previous equation, the first expression in brackets is positive since $q_\varepsilon^{\max}\leq 1$ and $U_{cH}\geq 0$; due to $U_H>0$ the second is also positive if one assumes that $H_1-H_0\geq\varepsilon\left(1-\theta\right)$, as required in Proposition 3; finally, due to $U_{cH}\geq 0$, the third is also positive under the same assumption. We conclude that $\partial V_e\left(e^{**};\alpha\right)/\partial\alpha>0$. □

E Proof of Proposition 5

To characterize the difference between $e^{**}\left(\alpha\right)$ and e^*, we use the concavity of both optimization problems to state that $V_e\left(e^*;\alpha\right)\geq 0\Leftrightarrow e^{**}\left(\alpha\right)\geq e^*$. It is thus sufficient to analyse the sign of $V_e\left(e^*;\alpha\right)$, noting that e^* is independent of α,ε and θ. We have:

$$V_e\left(e;\alpha\right)=\alpha\Delta\left(e\right)-U_c(w-e,H_1), \qquad \text{(E.13)}$$

where:

$$\begin{aligned}\Delta\left(e\right) &= U_c(w-e,H_1)-q_\varepsilon^{\max}\left[\lambda(e,\mu_0)U_c(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))U_c(w-e,H_0-\theta\varepsilon)\right]\\ &\quad -(1-q_\varepsilon^{\max})\left[\lambda(e,\mu_0)U_c(w-e,H_1)+(1-\lambda(e,\mu_0))U_c(w-e,H_0)\right]\\ &\quad +\lambda_e(e,\mu_0)\left[q_\varepsilon^{\max}\left(U(w-e,H_1-\varepsilon)-U(w-e,H_0-\theta\varepsilon)\right)\right.\\ &\quad \left.+(1-q_\varepsilon^{\max})\left(U(w-e,H_1)-U(w-e,H_0)\right)\right]. \qquad \text{(E.14)}\end{aligned}$$

The proof proceeds in three steps. First, we note that $V_e(e;0) < 0$ whatever e, which implies that $V_e(e^*;0) < 0$ and therefore that $e^{**}(0) < e^*$. Second, following the previous proposition, we know that $\partial V_e(e^*;\alpha)/\partial\alpha > 0$.

Third, we examine the sign of $V_e(e^*;1)$. If $V_e(e^*;1) < 0$, we can conclude that $e^{**}(\alpha) < e^*$ for all $\alpha \in [0,1]$. If $V_e(e^*;1) > 0$, we can conclude that there exists a unique $\widehat{\alpha} \in (0,1]$ such that $e^{**}(\alpha) \geq e^* \Leftrightarrow \alpha \geq \widehat{\alpha}$. We have:

$$\begin{aligned} V_e(e^*;1) &= q_\varepsilon^{\max}\lambda_e(e^*,\mu_0)\left[U(w-e^*,H_1-\varepsilon)-U(w-e^*,H_0-\theta\varepsilon)\right] \\ &\quad -q_\varepsilon^{\max}\left[\lambda(e^*,\mu_0)U_c(w-e^*,H_1-\varepsilon)+(1-\lambda(e^*,\mu_0))U_c(w-e^*,H_0-\theta\varepsilon)\right]. \end{aligned} \tag{E.15}$$

Let us compute

$$\frac{\partial V_e(e^*;1)}{\partial\theta} = q_\varepsilon^{\max}\varepsilon\left[\lambda_e(e^*,\mu_0)U_H(w-e^*,H_0-\theta\varepsilon)+(1-\lambda(e^*,\mu_0))U_{cH}(w-e^*,H_0-\theta\varepsilon)\right], \tag{E.16}$$

which is positive due to $U_H > 0$ and $U_{cH} \geq 0$. Let us now evaluate:

$$\begin{aligned} V_e(e^*;1)|_{\theta=1} &= q_\varepsilon^{\max}\lambda_e(e^*,\mu_0)\left[U(w-e^*,H_1-\varepsilon)-U(w-e^*,H_0-\varepsilon)\right] \\ &\quad -q_\varepsilon^{\max}\left[\lambda(e^*,\mu_0)U_c(w-e^*,H_1-\varepsilon)\right. \\ &\quad \left.+(1-\lambda(e^*,\mu_0))U_c(w-e^*,H_0-\varepsilon)\right]. \end{aligned} \tag{E.17}$$

Since $V_e(e^*;1)|_{\theta=1,\varepsilon=0} = q_\varepsilon^{\max}W'(e^*) = 0$ and since

$$\frac{\partial V_e(e^*;1)}{\partial\theta} = q_\varepsilon^{\max}\lambda_e(e^*,\mu_0)\varepsilon U_H(w-e^*,H_0-\varepsilon)+q_\varepsilon^{\max}(1-\lambda(e^*,\mu_0))\varepsilon U_{cH}(w-e^*,H_0-\varepsilon) > 0$$

and

$$\begin{aligned} \frac{\partial V_e(e^*;1)|_{\theta=1}}{\partial\varepsilon} &= -q_\varepsilon^{\max}\lambda_e(e^*,\mu_0)\left[U_H(w-e^*,H_1-\varepsilon)-U_H(w-e^*,H_0-\varepsilon)\right] \\ &\quad +q_\varepsilon^{\max}\left[\lambda(e^*,\mu_0)U_{cH}(w-e^*,H_1-\varepsilon)+(1-\lambda(e^*,\mu_0))U_{cH}(w-e^*,H_0-\varepsilon)\right], \end{aligned}$$

is positive due to $U_{HH} < 0$, we can conclude that $V_e(e^*;1) > 0$ for $\varepsilon > 0$ and $\theta \geq 1$. Now,

the minimal value for θ is $\max\{1-(H_1-H_0)/\varepsilon, 0\}$. Let us first compute:

$$V_e(e^*;1)|_{\theta=1-\frac{H_1-H_0}{\varepsilon}} = -q_\varepsilon^{\max} U_c(w-e^*, H_1-\varepsilon) < 0. \tag{E.18}$$

Moreover, we have:

$$\begin{aligned} V_e(e^*;1)|_{\theta=0} &= q_\varepsilon^{\max}\lambda_e(e^*,\mu_0)\left[U(w-e^*,H_1-\varepsilon)-U(w-e^*,H_0)\right] \\ &\quad -q_\varepsilon^{\max}\left[\lambda(e^*,\mu_0)U_c(w-e^*,H_1-\varepsilon)+(1-\lambda(e^*,\mu_0))U_c(w-e^*,H_0)\right], \end{aligned} \tag{E.19}$$

which is equal to 0 for $\varepsilon = 0$ and is negative for the maximal value of ε, i.e. for $\varepsilon = H_1 - H_0$. Thus, $V_e(e^*;1)|_{\theta=0} < 0$ if ε is sufficiently large. Therefore, there exists $\bar{\theta} \in (1-(H_1-H_0)/\varepsilon, 1)$ such that $V_e(e^*;1) \geq 0 \Longleftrightarrow \theta \geq \bar{\theta}$.

F Proof of Proposition 6

Let the function $f(\alpha)$ be defined as:

$$f(\alpha) = pV(e^{**}(\alpha);\alpha) + (1-p)W(e^{**}(\alpha)) - W(e^*). \tag{F.20}$$

The agent participates in the trial if and only if $f(\alpha) \geq 0$. Since we have:

$$f'(\alpha) = p\left[U^{\min}(e^{**}(\alpha)) - U^{\max}(e^{**}(\alpha))\right] < 0, \tag{F.21}$$

it is sufficent to evaluate $f(0)$ and $f(1)$ to conclude. We have

$$\begin{aligned} f(1) &= pU^{\min}(e^{**}(1)) + (1-p)W(e^{**}(1)) - W(e^*) \\ &= pq_\varepsilon^{\max}\left[\lambda(e^{**}(1),\mu_0)U(w-e^{**}(1),H_1-\varepsilon)\right. \\ &\quad \left.+(1-\lambda(e^{**}(1),\mu_0))U(w-e^{**}(1),H_0-\theta\varepsilon)-W(e^*)\right] \\ &\quad +(1-pq_\varepsilon^{\max})\left[W(e^{**}(1))-W(e^*)\right]. \end{aligned} \tag{F.22}$$

The first term in square brackets is negative since:

$$\begin{aligned} & \lambda(e^{**}(1),\mu_0)U(w-e^{**}(1),H_1-\varepsilon)+(1-\lambda(e^{**}(1),\mu_0))U(w-e^{**}(1),H_0-\theta\varepsilon) \\ < \;& \lambda(e^{**}(1),\mu_0)U(w-e^{**}(1),H_1)+(1-\lambda(e^{**}(1),\mu_0))U(w-e^{**}(1),H_0)=W(e^{**}(1)) \end{aligned}$$

and by definition, $W(e^{**}(1)) < W(e^*)$. As a result, $f(1) < 0$. Moreover,

$$\begin{aligned} f(0) &= pU^{\max}(e^{**}(0)) + (1-p)\,W\left(e^{**}(0)\right) - W\left(e^*\right) \\ &= p\left[U(w-e^{**}(0),H_1) - W\left(e^*\right)\right] + (1-p)\left[W\left(e^{**}(0)\right) - W\left(e^*\right)\right] \end{aligned} \tag{F.23}$$

The first term between brackets is positive because $e^{**}(0) < e^*$ implies $U(w-e^{**}(0),H_1) > U\left(w-e^*,H_1\right) > W\left(e^*\right)$. The second term between brackets is negative by definition. We conclude that $f\left(0\right) > 0$ if p is sufficiently high. In that case, there exists $\overline{\alpha} \in (0,1)$ such that $f(\overline{\alpha}) = 0$ and: $f(\alpha) \geq 0 \Leftrightarrow \alpha \leq \overline{\alpha}$. □

G Proof of Proposition 7

We evaluate in $\alpha = \widehat{\alpha}$ the sign of $pV\left(e^{**}\left(\alpha\right);\alpha\right) + (1-p)\,W\left(e^{**}\left(\alpha\right)\right) - W\left(e^*\right)$; In $\widehat{\alpha}$, we have $e^{**}\left(\widehat{\alpha}\right) = e^*$, which implies that one must evaluate the sign of $V\left(e^*;\widehat{\alpha}\right) - W\left(e^*\right)$. We get:

$$\begin{aligned} V\left(e;\alpha\right) - W\left(e\right) &= \alpha U^{\min}(e) + (1-\alpha)\,U^{\max}(e) - W\left(e\right) \\ &= \alpha q_\varepsilon^{\max}\left\{\left[\lambda(e,\mu_0)U(w-e,H_1-\varepsilon)+(1-\lambda(e,\mu_0))U(w-e,H_0-\theta\varepsilon)\right]\right. \\ &\quad \left. -\left[\lambda(e,\mu_0)U(w-e,H_1)+(1-\lambda(e,\mu_0))U(w-e,H_0)\right]\right\} \\ &\quad +(1-\alpha)\left(1-\lambda(e,\mu_0)\right)\left[U(w-e,H_1)-U(w-e,H_0)\right]. \end{aligned} \tag{G.24}$$

We note that this expression is positive for $\varepsilon = 0$ (no adverse event) and that it is decreasing in ε. This implies that if ε is sufficiently small, then $\widehat{\alpha} < \overline{\alpha}$. On the other hand, if ε is large, it should be possible to have $\widehat{\alpha} > \overline{\alpha}$. This can be shown for a specific case such that $\theta = 0$, i.e. there is no adverse reaction for those who got the disease, and, $\varepsilon = H_1 - H_0$ the adverse reaction leads to a deterioration in the health of a healthy person as much as the disease

would do. Then, equation (G.24) rewrites:

$$V(e;\alpha) - W(e) = \left[(1-\alpha)(1-\lambda(e,\mu_0)) - \alpha q_\varepsilon^{\max}\lambda(e,\mu_0)\right]\left[U(w-e,H_1) - U(w-e,H_0)\right]. \tag{G.25}$$

Thus, we have $\widehat{\alpha} \leq \overline{\alpha}$, for all $\varepsilon \in [0, H_1 - H_0]$ if $\lambda(e^*,\mu_0) \leq 1/\left(1 + \widehat{\alpha} q_\varepsilon^{\max}/\left(1-\widehat{\alpha}\right)\right)$. Otherwise, there is a value, $\overline{\varepsilon}$ in $]0, H_1 - H_0[$, such that $\varepsilon > \overline{\varepsilon} \Leftrightarrow \widehat{\alpha} \geq \overline{\alpha}$. □

H Proof of Proposition 8

Let us define $g(\mu) := EU\left(e^{***};\mu,\widehat{\varepsilon},\widehat{q}\right) - W\left(e^*\right)$, or

$$\begin{aligned} g(\mu) \;=\; & \widehat{q}_\varepsilon\left[\lambda(e^{***},\mu)U(w-e^{***},H_1-\widehat{\varepsilon}) + (1-\lambda(e^{***},\mu))U(w-e^{***},H_0-\theta\widehat{\varepsilon})\right] \\ & +(1-\widehat{q}_\varepsilon)\left[\lambda(e^{***},\mu)U(w-e^{***},H_1) + (1-\lambda(e^{***},\mu))U(w-e^{***},H_0)\right] \\ & -\left[\lambda\left(e^*,\mu_0\right)U\left(w-e^*,H_1\right) + \left(1-\lambda\left(e^*,\mu_0\right)\right)U\left(w-e^*,H_0\right)\right]. \end{aligned}$$

We have $g(\mu_0) < 0$ and $g'(\mu) > 0$. Therefore, if $g(1) > 0$, there exists $\overline{\mu} \in (\mu_0, 1)$ such that agents participate in the vaccination campaign $\mu \geq \overline{\mu}$ and do not participate otherwise. If $g(1) < 0$, agents do not participate in the vaccination campaign. Since $\lambda(e,1) = 1$, and $e^{***} = 0$ for $\mu = 1$, we can write:

$$\begin{aligned} g(1) \;=\; & \widehat{q}_\varepsilon U(w,H_1-\widehat{\varepsilon}) + (1-\widehat{q}_\varepsilon)U(w,H_1) \\ & -\left[\lambda\left(e^*,\mu_0\right)U\left(w-e^*,H_1\right) + \left(1-\lambda\left(e^*,\mu_0\right)\right)U\left(w-e^*,H_0\right)\right]. \end{aligned} \tag{H.26}$$

Thus, a sufficient condition for $g(1) > 0$ is:

$$\widehat{q}_\varepsilon U(w,H_1-\widehat{\varepsilon}) + (1-\widehat{q}_\varepsilon)U(w,H_1) > U\left(w-e^*,H_1\right). \tag{H.27}$$

Or using (9), $U(w-\bar{e},H_1) > U\left(w-e^*,H_1\right)$, which is equivalent to $\bar{e} < e^*$. □