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Understanding the Risk of an Avian Flu Pandemic: Rational Waiting or Precautionary Failure?

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The precautionary principle (PP) has been proposed as the proper guide for the decision-making criteria to be adopted in the face of the new catastrophic risks that have arisen in the last decades. This article puts forward a workable definition of the PP based on the so-called α-maximin expected utility approach, applying it to the possible outbreak of the avian flu disease among humans. Moreover, it shows how the shortage and/or lack of effective drugs against the infection of the virus A(H5N1) among humans can be considered a precautionary failure.

KEY WORDS: Ambiguity; avian flu; multiple priors; precautionary principle

1. INTRODUCTION

In September 2004, Thai and senior officials of the World Health Organization (WHO) announced the first documented case of human-to-human transmission of the A(H5N1) virus, more widely known as the avian flu, in a family cluster of cases. In Bangkok, a 26-year-old woman died of avian flu after having contracted the disease from her daughter.

This extremely worrying news opens before us terrifying scenarios, where lethal forms of avian flu are readily transmissible among humans. According to scientists and health authorities, we are facing the possibility of a global pandemic that could cause millions of deaths among humans, principally children. This nightmare—which recalls the Spanish flu, the most famous recombined avian flu virus—would not loom over us had proper precautionary actions been taken in due time by building of capacity for producing adequate quantities of specific antiviral drugs, which reduce the side effects of the disease, and starting the research and development of proper vaccines.

There has been much debate about the optimal strategies to control the epidemic of avian flu and to counter the risk that a genetic reassortment of the A(H5N1) virus will take place as a consequence of its matching with the human strain of a seasonal flu. The interpretation of the precautionary principle (PP) we propose can be a practical guide to rational decisions in facing possible catastrophic events like the expected human avian flu pandemic. Applying the PP as we interpret it, leads to the conclusion that proper steps taken in due time are the most effective strategy. In light of this conclusion, the present shortage of antiviral drugs and the delay in the production of the vaccine can hardly be considered as the result of a rational course of action.

The PP—which has become known worldwide after the 1992 Conference in Rio de Janeiro—has been advocated as the right response to a whole series of new extreme risks (global warming, genetically modified food, and unknown diseases such as acquired immunodeficiency syndrome (AIDS)), including the avian flu disease. Crucially, extreme risks

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have low or not fully reliable probability of occurring but catastrophic consequences. As a result, most rational decision-making models are inapplicable, since they are insensitive to low probability, as in the Allais Paradox (Allais, 1953), or are unable to represent not fully reliable probability, as in the Ellsberg Paradox (Ellsberg, 1961).

The impossibility of obtaining good estimates of the pandemic risk is the most frequently mentioned explanation for the delay in the design of containment strategies. Relying on the so-called α-maximin expected utility (α-MEU) approach, we suggest an interpretation of the PP that makes it possible to treat scientific uncertainty and to identify the optimal strategy against the possible A(H5N1) outbreak among humans. We adopt a nonexpected utility approach to define a criterion of choice in the presence of ambiguity or scientific uncertainty. We show how this criterion can make the PP much more operative than it has been considered until now. In the specific case of avian flu, we argue that its timely application would have prompted such action as to raise the current stocks of antiviral drugs to more reassuring levels and to advance the development of specific vaccines.

This article is organized as follows. A description of the origin and diffusion of the avian flu and its economic and social consequences is given in Sections 2 and 3. In Section 4, we present our interpretation of the PP. In Section 5, we analyze both the issue of the precautionary stockpile of antiviral and of the adequate production of a specific vaccine. The article ends with some concluding remarks.

2. THE AVIAN FLU: ORIGIN AND DIFFUSION

The avian influenza (fowl plague) was first identified as a disease of chickens in Italy in 1878. It is an infectious disease of birds and is now spread worldwide. There are three types of avian influenza virus, called A, B, and C. Types B and C are less aggressive. Virus B can cause human epidemics, but does not cause pandemics while virus C causes mild illness in humans but not epidemics or pandemics. Virus A can infect humans and animals.

Wild birds are the most prone hosts for this virus and domestic poultry, such as turkeys and chickens, can get very sick and die from type A flu.[3] Among the avian influenza virus subtypes, H5N1 is the worst: it mutates rapidly and acquires genes from viruses infecting other animal species. The virus H5N1 not only affects the respiratory tract but damages liver and kidney of infected humans and hurts central nervous systems in ferrets and some birds. Illness is characterized by fever, myalgia, severe malaise, rhinitis, otis, nausea, and vomiting.

Despite its seriousness, the avian flu did not raise alarm until it was believed that the virus could be contracted by human beings and, more worryingly, be transmitted from human to human. The mediation of mammals such as pigs was considered necessary.[4] It has been documented that bird flu jumped onto pigs in Vietnam in 2004 and since 1997 there has been growing evidence that human beings are exposed to this virus.

The first case that A(H5N1) infected both humans and poultry and transmitted itself from the latter to the former was in Hong Kong in 1997. About one-and-half million chickens were killed, 18 persons were infected, and six of them died. The destruction of almost the entire poultry population in Hong Kong is believed to have prevented the risk of a pandemic. In 1999, again in Hong Kong, two cases of avian influenza A(H9N2) were found in humans. In that same country, similar cases were detected in February 2003 when one person died of A(H5N1) after traveling to southern China. In 2003, avian flu A(H7N7) infected some poultry workers and their relatives (80 persons) and killed a person in the Netherlands. In mid-December 2003, a new outbreak of influenza A(H5N1) originated in the Republic of Korea and spread in 10 other Asian countries. In a few weeks, it infected humans in Vietnam and Thailand and by the end of October 2005 its costs were estimated as high as 140 million birds dead or culled and 123 humans infected, with 63 fatal cases.[5]

[3] Influenza type A viruses are classified into two categories on the basis of the proteins on the surface of the virus—hem agglutinin (HA) and neuraminidase (NA). Fifteen subtypes of influenza virus are known to infect birds, but all outbreaks of the highly pathogenic form have been caused by influenza A viruses of subtypes H5 and H7. Influenza viruses can change by antigenic drift (continuous small changes over time) or by antigenic shift (combination of one or both proteins in a form that has not been detected in humans).

[4] The great influenza pandemic known as Spanish flu, which occurred between 1918 and 1920 and caused around 50 million deaths, was so lethal because after the jump from birds to pigs both human and avian viruses swapped genes as the viruses reproduced.

[5] That includes 19 cases with 13 deaths in Thailand, 91 cases with 41 deaths in Vietnam, 9 cases with 5 deaths in Indonesia, and 4 cases, all of them fatal in Cambodia (October 2005). The majority of these cases involved individuals who had direct contact with sick or dead poultry. The majority of H5N1 cases involved children or

The United Nations has classified the epidemic of avian flu among poultry in Asia as a crisis of global importance. The U.S. Department of Agricultural and European Commission banned the import of all birds (class aves) from several countries: Cambodia, Indonesia, Vietnam, Thailand, Japan, Malaysia, People's Republic of China, Hong Kong SAR, South Korea, Russia.

Several suspect cases were reported but there was no evidence of human-to-human transmission of the virus. For instance, two sisters in Vietnam who died of the disease probably were infected by their brother and similar cases are believed to have taken place in Hong Kong. Indeed, until the summer of 2004, scientists deemed it highly unlikely that the A(N5H1) virus could spread from one person to another even though they feared that it could mutate into a subtype form readily transmissible to humans.[6]

Unfortunately, in September 2004, the first case of transmission of the virus A(H5N1) from humans to humans was documented. This episode opened a new and very disquieting season in the diffusion of the avian flu.[7]

In February 2005, another case of direct transmission of A(H5N1) from two brothers was documented in Vietnam, while the avian flu reached Europe where it contaminated plenty of birds (Romania, Croatia, and Turkey).

3. TERRIBLE RISKS AND INADEQUATE PRECAUTIONS

Looking at historical evidence, scientists warn that influenza pandemics may happen three or four times in a century (there were 31 pandemics in the last four centuries). In the last 100 years, there have been three cases of different seriousness: the Spanish flu of 1918–1919, the Asian flu of 1957–1958, and the Hong Kong flu of 1968–1969. The chances that the avian flu may spur the fourth pandemic in a century are not nil.

There are no reliable estimates of the cost of a possible pandemic A(H5N1) flu among humans, but public health systems around the world fear morbidity and decease rates so high that such costs may be huge indeed. WHO warned of a potential pandemic should the A(H5N1) strain of avian flu mutate and increase its ease of transmission, as in the case of severe acute respiratory syndrome[8] (SARS). Today, the WHO is very concerned about this chance. If the virus A(H5N1) acquires the ability to increase its rate of infection, it will have the potential to kill more humans worldwide than AIDS has killed in the last 25 years. According to conservative estimates by the WHO, there could be from 2 to 7 million human deaths, but no one can say what the real effects of the outbreak of a highly infective avian influenza virus subtype could be.[9]

As far as birds are concerned, we have some rough estimates of the costs involved and in particular of the market impact of the recent spread of avian flu in the Asian region, which hosts 40% of the world's chicken population. The principal measure to control an outbreak of A(H5Nl) in birds is the culling of sick and exposed birds. To date, many countries have banned imports of poultry from risky countries, like Thailand, China, and Russia. This makes for an increasing demand for the poultry of other producers (USA and Brazil) and inevitably leads to higher international prices with sensible effects on the welfare of consumers.

Thai poultry exports are estimated at U.S. $1 billion and Chinese poultry exports are around 500,000 tons for a total value of U.S. $900 million. The epidemic cost Vietnam's poultry industry about U.S. $192 million and 5 million chickens have been culled in Korea. In Taiwan and Japan, 1 million chickens were culled.[10] It is necessary also to consider that the estimates of the Food and Agriculture Organization

young adults. The H5N1 viruses isolated from both poultry as well as humans are resistant to the antiviral drugs amantadine and rimantadine, but they are susceptible to oseltamivir and zanamivir.

6 In April 2004, the Health Service reported that a man, who had never been in direct contact with poultry, in Westchester County (NY) contracted the A(H5N1) virus during the autumn.

7 Pranee Korngkaew, a 26-year-old woman, died on September 20. Thailand's Disease Control Department confirmed that the young woman had the A(H5N1) virus, but said that she was not known to have come into contact with suspicious birds. What is known is that this month she went to see her 12-year-old daughter, Sankuntala, who died in hospital on September 12 in the northern Kamphaengphet province. Both Sakuntala and her 32-year-old aunt, with whom she had been staying, had contact with dead chickens, the WHO reported. Sakuntala's mother, her aunt, and her 6-year-old cousin had the A(H5NI) virus.

8 Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a corona-virus. SARS was first reported in Asia. According to the WHO, 8,098 people worldwide became sick during the 2003 and 774 of them died.

9 A human flu pandemic could cause 20% of the world population to become ill and within a few months close to 30 million people would need to be hospitalized, a quarter of whom would die (Stohr & Esveld, 2004).

10 In Asia, avian flu induced losses from $10 to $15 billion up to April 2005 (Food and Agriculture Organization).

(FAO) about the effects on global animal feed markets are close to those of the mad cow disease.

There are other relevant economic effects of the avian flu outbreak: it could affect services-related businesses, such as tourism, and the domestic demand for restaurants and other outlets, with the loss of tens of billions of U.S. dollars. A conservative estimate of the general economic damage induced by a pandemic of avian flu disease only in Asia sets the total cost at $282 billion (Asian Development Bank, 2005) and more than $550 billion in developed countries (World Bank, 2005).

In this scenario, health services recommended as precautionary measures preparation of specific vaccines and, as a second best line of defense, huge stockpiling of antiviral drugs. Indeed, in the case of the A(H5N1) virus, the two main antagonists to its pandemic are vaccines and antiviral drugs. Conventional flu vaccines are not believed to act against avian flu. Only a few biotechnology firms have the skills and advanced genetic technology to develop proper vaccines,[11] among them Aventis Pasteur Inc. of Swift Water, Pennsylvania, the Chiron Corporation of Emeryville, California, and Sinovac Biotech Ltd. of Beijing, China.

Unfortunately, only two antiviral neuraminidase inhibitors—Tamiflu (oseltamivir) and Relenza (zanamivir)—seem to work against the A(H5N1) virus. To be effective, they are administrated within 36–48 hours from the symptoms of contagion. Tamiflu is a product of the Roche Group, Switzerland, and Relenza is produced by Glaxo-Smith-Kline (in the United Kingdom) that hold exclusive manufacturing rights. They retail prices are $60 and $40, respectively, for a treatment course for one adult.

The WHO and other National Institutes of Health (NIH) report an extremely short supply of Tamiflu and Relenza. In fact, it will be very hard to face a possible pandemic of avian flu, since no country, with the exception of the Netherlands, has a stockpile of drugs adequate to treat at least 25% of population, the minimum share to counter human-to-human transmission of avian flu, according to the WHO. The steps taken so far have been untimely and inadequate. Given this scenario, the specter of the terrible plagues of the three others pandemics in the last 100 years, which caused a lot of dead among humans, has begun to materialize.

Senior WHO officials have strongly criticized vaccine manufacturers[12] because they decided to develop vaccines against A(H5N1) only after receiving contracts from the U.S. NIH.[13] Aventis and Chiron delivered the first experimental vaccines during 2005 but have no plans for mass producing, while Sinovac Biotech signed an avian flu vaccine co-development agreement with the China Centers of Disease Control and Prevention only on December 16, 2004. Similarly, investments by Roche to expand the production of Tamiflu are inadequate and untimely; in fact, "at current rates of production, some reports suggest it would take a decade to produce enough to treat 20% of the world's population" (Economist.com, October 20, 2005). Roche answered its critics by saying that Tamiflu had been produced in the right amount to match market demand. Indeed, stockpiling costs and uncertain demand have kept production in check. The case of Relenza is even worse. It has been commercialized since 1999, but a limited market demand induced Glaxo-Smith-Kline (GSK) to reduce the production of Relenza to a very small quantity. A further obstacle is represented in both cases by the short expiration date, which could easily transform an investment into a sunk cost.[14] Moreover, national authorities planned to stockpile only modest quantities of drugs because they did not want to run the risk of overreaction, as in 1976, when 45 million Americans were vaccinated against a specific subtype of flu that did not occur.[15] As a result, despite its technical superiority, even "the US faces a major shortfall in manufacturing the right vaccine

[11] Estimated worldwide production of vaccines against flu is between 25 and 100 million courses a month.

[12] Reported by the *International Herald Tribune*, September 30, 2004.

[13] The National Institutes of Health awarded Chiron Corporation a $1.194 million contract to develop up to 40,000 doses of vaccine against the H9N2 avian influenza (August 17, 2004) and the Department of Health and Human Services (HHS) announced the awarding of a contract to Aventis Pasteur Inc. to manufacture and store 2 million doses of the avian influenza H5N1 vaccine. The amount of the contract is nearly $13 million (September 21, 2004).

[14] At the beginning of the outbreak of avian flu only Tamiflu was considered active against the virus A(H5N1). Further studies have proved that Relenza is also active in humans with induced avian flu. Tamiflu is considered more effective than Relenza and its administration is easier. In fact, Tamiflu is available as a capsule for oral use and Relenza is only available as powder for inhalation.

[15] The Centers of Disease Control and Prevention (CDC) of HHS, one of the main government agencies, has created an initial stockpile of 2.3 million treatment courses of oseltamivir to which more doses will be added.

and in stockpiling anti-influenza drugs. An estimated 89.000–207.000 Americans will die in the next pandemic" (Ho, 2005, p. 422).

Can this scenario, which looks like a clear failure *ex post*, be interpreted also as an *ex ante* failure in the application of the PP attributable to all the public and private institutions in charge of human welfare at large?

In the following sections, we take up all the issues related to this difficult question: What should have been an *ex ante* rational course of action? Which role should the several institutional actors have played in this rational course of action? Which specific features of the avian flu make a precautionary policy particularly difficult to define and implement? We come to the conclusion that there has been a serious precautionary failure with respect to the avian flu. Our first step is to clarify some important aspects of the PP itself.

4. THE PRECAUTIONARY PRINCIPLE: A SUGGESTED INTERPRETATION

The PP has been the subject of intense discussion among scholars in different fields and policymakers. As a consequence, opinions about its relevance in policy making vary markedly. Some people think that the PP is a misguided concept for regulating human activities, since it induces innovation and technology-development aversion among human beings. On the other hand, many environmentalists and politicians see the PP as the only protection against the many human activities that may endanger public health and the environment. Such conflicting views are due, at least to some extent, to the lack of a well-defined and widely agreed definition of the principle itself.[16]

To put some order in such a messy field, it has been suggested that a distinction should be made between a strong and a weak version of the PP. Unfortunately, neither version is fully satisfactory, mainly because they both fail to take seriously the issue of what rationality implies in the presence of uncertainty and irreversibility.

The distinguishing element of the strong version is the reversed burden of proof (Morris, 2000; Sunstein, 2003; Löfstedt, 2004): in practice, no action should be taken unless the actor—usually a firm—has demonstrated beyond any reasonable doubt that no harm will result. A margin of safety should be guaranteed in any decision: "better safe than sorry," as Sunstein (2003, p. 9) puts it.[17] However, the logical consequence of imposing a condition (certainty that no harms will follow) that in the given conditions (lack of full certainty) can never be fulfilled is to block almost any activity. In particular, human beings should refrain from using new technologies (no new technology is completely safe), giving up the benefits that such technology may bring. As Wildavsky (2000) has stated, the search for trials without errors, which the strong PP seems to encourage, may lead economic progress to a complete standstill.

The weak PP basically states that lack of full certainty is not a justification for preventing action that might be harmful. On the other hand, regulation can be justified even if we cannot establish a definite connection between, for example, low-level exposure to certain carcinogens and adverse effects on human health (Morris, 2000, p. 8). It would be rather disappointing to interpret the weak PP in terms of placing the burden of proving harm on the regulator, for we would reach an equally unrealistic conclusion as in the case of the strong version: since it is impossible to achieve certainty on harmful effects, any action shall be tolerated. A more convincing interpretation of the weak version is that regulation is admissible also when negative effects are uncertain. Unfortunately, it is not clear on the basis of which elements such decision should be taken. The conclusion to be drawn seems to be that everything is possible—uncertainty is neither necessary nor sufficient for regulation or *laissez faire*.

To make the PP a reliable guide to policy making, two problems should be addressed—both of which have received only limited attention.

As to the first problem, we should make it crystal clear that the PP refers to situations characterized by ambiguity[18] (more precisely: scientific uncertainty), irreversibility, and catastrophic events. Therefore, it is necessary to clarify what rationality entails in such situations and to suggest an interpretation of the PP as a specific rational behavior.[19]

[16] According to Sandin (1999) (quoted by Löfstedt, 2004, p. 10), there are at least 19 definitions of the PP. Majone (2002, p. 93) reminds us that also for the original German principle there are no less than 11 interpretations.

[17] See also European Commission (2001).

[18] There is ambiguity if there exists more than one additive probability distribution, or an interval of probability for each state is assumed to be possible. Both a nonadditive measure (capacity) and a fuzzy measure on the state space could be alternative representations of the epistemic state of the decisionmaker.

[19] Details are in Basili and Franzini (2006).

Rationality requires making use of all available information, but when ambiguity prevails, the available information is basically of the type Ellsberg pointed out with his seminal paradox. In particular, people attach different weights to various probability distributions. Under such conditions, subjectivity is all too important and rationality is compatible with a broad range of decisions. As a consequence, the PP can be seen as a criterion for selecting one of them. Interpreted in this way, the PP is neither coincident with rationality nor in conflict with it. Rather, it complements rationality as a normative criterion.

There is another aspect to be considered: standard evaluation criterion, such as mathematical expectation of consequences, fails in evaluating extreme risks like the avian flu pandemic. Unfortunately, the often-suggested alternative of maximin criterion (Wald, 1950) is a totally preservative method that systematically overvalues possible catastrophic consequences. Scientific uncertainty makes it impossible to attach a unique and reliable probability measure to the occurrence of an avian flu pandemic. Still, it is possible to keep ambiguity within an interval of probabilities coming from forecasts on relevant scientific data that experts around the world methodically collect and systematically scrutinize. In our view, behaving in a precautionary way means considering both the worst and the best probability distributions one is aware of, given the available information, that is, using a convex combination between maximin and maximax criteria. These conservative and dissipative evaluations are combined on the basis of the decision-maker attitude toward reliability of his or her assessment about possible events (ambiguity attitude), as in the so-called α-maxmin expected utility approach,[20] axiomatized[21] in Ghirardato *et al.* (2004).

In this article, we apply the notion of ambiguity attitude embodied in the α-MEU criterion, and evaluate the optimal choices against the menace of the human avian flu pandemic. In a nutshell, the α-MEU criterion as rationalization of the PP implies that dangers are taken as seriously as possible or we could also say that *early warnings* are given utmost attention.[22] There are good reasons to believe that worldwide scanty preparation with respect to the avian flu is the result of a failure in the application of the PP so defined.

In the next section, we set up a model that helps to understand what precaution would have suggested in particular with respect to the production of known antiviral drugs and the preparation of new specific vaccines.

5. THE PRECAUTIONARY PRINCIPLE: AN APPLICATION TO THE AVIAN FLU DISEASE

At the origin of this very critical and dangerous situation, there were a lot of mistakes and bad judgment on the part of the public and private agents on whose behavior social safety and welfare depend. Fauci (2005, p. 424) aptly blames national governments for failing to introduce "financial and economic incentives—including fair pricing, guaranteed purchase of unsold supplies, tax incentives—. . .[*because*] pharmaceutical companies are reluctant to enter or remain in the business of manufacturing vaccines—unpredictable consumer demands and lack of financial incentives make vaccine manufacture a risky business." Fauci sets the right scenario for our problem.

On the one hand, there is lack of certainty; on the other, there may be serious agency problems, especially insofar as the vaccine is concerned. More precisely, there is lack of certainty on several crucial aspects of the phenomenon, which makes it appropriate to base the analysis on the notion of ambiguity. As we have already seen in the avian flu case, there is ambiguity about the possibility of human-to-human transmission of the A(H5N1) virus, about the morbidity of the avian flu virus, about the subtype of influenza[23] and, finally, about the A(H5N1) ability to spread among people. Our problem is, first of all,

[20] Henry and Henry (2002) assume that incomplete scientific knowledge or scientific uncertainty is compatible with the representative decision-maker preferences encompassed into the Choquet Expected Utility (CEU) or the α-MEU approach.

[21] If S is a finite set of states of the world, Σ the set of all subsets of S, $X, Y \in \Im$ are acts such as $X: S \to H$, H is the set of consequences, $u: H \to R$ is a bounded utility function, and C is a unique nonempty, weak*-compact and convex set of countably additive probabilities on the measurable space (S, Σ), then a weak preference relation can be represented by the functional:

$$V(X) = \alpha \inf_{P \in C} \int_S u(X(s))\, P(s)\, ds + (1-\alpha) \sup_{P \in C} \times \int_s u(Y(s))\, P(s)\, ds \quad \text{for } \alpha \in [0,\ 1].$$

[22] The importance of early warnings is stressed in the volume by Harremoës and Gee (2002). To behave as an ambiguous adverse agent is, in our view, the best (or, probably, the only) manner for giving proper consideration to those pieces of information that are "early warnings."

[23] There are two subtypes of avian flu: Highly Pathogenic (HPAI), associated with high mortality in poultry (kills 90–100% infected chickens), and Low Pathogenic (LPAI), less severe or no illness in poultry.

to define rational decision-making processes in the presence of ambiguity and to single out, within the set of rational decisions, those that embody a precautionary attitude.

Another crucial feature is the presence of agency problems in the supply of vaccine. As we have seen, market signals are unreliable as a precautionary guide. Therefore, it is necessary to set up an institutional system whereby the governments enter into a contractual relation (broadly defined) with the pharmaceutical industry in order to make the latter's behavior with respect to the production of vaccines consistent with the requirements of a precautionary course of action. Let us now analyze separately the antiviral drugs and the vaccine decisions.

5.1. Precautionary Antiviral Demand under Ambiguity

The decision to stockpile antiviral drugs against the human-to-human transmission of A(H5N1) is to be taken by the National Health Service under ambiguity and irreversibility. Ambiguity relates both to the possible outbreak of an avian flu pandemic and to the antiviral drug's efficacy against an avian flu attack. Irreversibility arises from the future lack of adequate stock of antiviral drugs due to market shortage and queues.[24] The NIH should implement the PP notion as related to ambiguity and it would act considering its ambiguity attitude. The NIH has to evaluate costs and benefits of purchasing antiviral drugs, including severe harm and hospitalization, reduction of illness and death, and likely remission of the disease, as a consequence of therapeutic treatment of infected people.

Formally, the NIH has to compare two lotteries, X and Y. Lottery X represents the strategy of buying a fair amount of antiviral drug, while lottery Y represents the strategy involving the collection of more information about the relevant phenomena. The two lotteries are represented in Fig. 1.

Probability p is the occurrence of pandemic and probability υ is the efficacy of the antiviral drug. More precisely, due to ambiguity, the probability υ of the antiviral drug efficacy is between $[\nu; \upsilon]$, such that $0 \leq \nu \leq \upsilon \leq 1$ and the probability of its inefficacy is $[(1-\nu);(1-\upsilon)]$. CT is the cost of the antiviral drug, PAF is the cost of an avian flu pandemic, and INF is the cost of a standard influenza to be borne in case of the antiviral drug efficacy. Due to ambiguity, PAF can take any value between a minimum and a maximum.

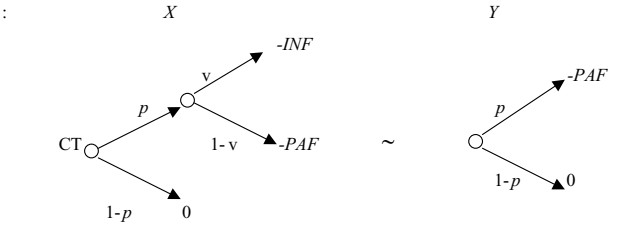

Fig. 1. Decision tree illustrating the NIH choice between a pair of equivalent strategies about antiviral drugs.

The NIH has to find the minimum compound probability of efficacy that makes the purchase of antiviral drugs the optimal strategy. Roughly speaking, the NIH has to determine the compound probability of the antiviral drug efficacy that makes the two strategies equivalent (Fig. 1). In the first period, the NIH buys the antiviral drug and estimates the damage of avian flu disease among humans in the second period. The latter varies between INF, the cost of a pandemic controlled by the antiviral drug, and PAF, the cost of uncontrolled avian flu pandemic in case of the antiviral drug inefficacy.[25] As already stated, PAF is itself characterized by a range of possible values.

Following the α-MEU approach, the NIH solves the following maximization problem, considering both the worst- and the best-case scenarios:

$$\begin{aligned}\max V &= \alpha\left[(-CT)+\frac{(-INF)\upsilon p+(-PAF_{\max})(1-\upsilon)p+pPAF_{\max}}{1+r}\right]\\ &\quad+(1-\alpha)\left[(-CT)\right.\\ &\quad\left.+\frac{(-INF)\upsilon p+(-PAF_{\min})(1-\upsilon)p+pPAF_{\min}}{1+r}\right], \qquad (1)\end{aligned}$$

where r is the discount rate and $\alpha \in [0;1]$ is the degree of confidence in the probability assessment of different scenarios.

To evaluate compound probability distributions, we consider the two extreme cases:

- If $\alpha = 1$, the NIH faces the worst-case scenario (pessimism). The compound probability that makes the two strategies indifferent is the following:

[24] In March 2005, the United Kingdom announced the purchase of 10 million Tamiflu courses, but it only receives 800,000 courses a month, even if Roche quadruples Tamiflu production.

[25] In a more general model, quasi-option value should be considered into evaluation. Details in Appendix.

$$(-CT) + \left(\frac{PAF_{\max}}{1+r}\right) vp = 0 => vp = \frac{CT(1+r)}{PAF_{\max}}. \quad (2)$$

- If $\alpha = 0$, the NIH faces the best-case scenario (optimism):

$$(-CT) + \left(\frac{PAF_{\min}}{1+r}\right) vp = 0 => vp = \frac{CT(1+r)}{PAF_{\min}}. \quad (3)$$

Equations (2) and (3) set the minimum compound probabilities of the antiviral drug efficacy against an avian flu attack in the worst and best scenarios, respectively, which make the stockpiling of the antiviral drug the best strategy.

Let us apply those equations to the present situation in the United States. The relevant data are as follows. Tamiflu and Relenza are drugs that everyone knows could be effective and efficient against the side effects of seasonal flu: protective efficacy is estimated (74%) for oseltamivir (Hayden *et al*., 1999) and (68%) for zanamivir (Monto *et al*., 1999). Recently, research and studies have enlarged these coefficients of efficacy to human avian flu (Tamiflu is being used to treat human cases in Thailand and Vietnam). Roche produces Tamiflu at \$60 a course and GSK produces Relenza at \$40 a course. The WHO suggested that buying antiviral drugs for 25% of the population of a country would be a safe strategy. Therefore, the NIH faces the following choice: buy antiviral drugs for 25% of the population or wait for more information about the outbreak of the disease. The cost of Tamiflu for 70 million humans, that is 25% of the U.S. population, is \$4 billion. The cost of a controlled avian flu epidemic is \$41 billion, that is, \$12 billion per year in direct medical costs and loss of productivity, plus \$29 billion in losses inflicted on the U.S. poultry sector production.[26] The worst-case evaluation is based on a World Bank study of high pathogenic flu pandemic that could induce losses between \$100 and \$200 billion. The discount rate $r = 5\%$, U.S. T-bond rate 30 years. Taking account of these data, Equations (2) and (3) yield the following results:

$$(-4) + (151.4)vp = 0 \;\; => \;\; vp = \frac{4}{151.4} = 2.64$$

$$(-4) + (56.1)vp = 0 \;\; => \;\; vp = \frac{4}{56.1} = 7.13. \quad (4)$$

The interval of minimal compound probability of antiviral efficacy against avian flu attack, which makes stockpiling of Tamiflu to cover 25% of the population the optimal strategy in the United States, is, therefore, (2.64; 7.13).[27]

These results are consistent with the cost-benefit analysis for stockpiling drugs for avian influenza pandemic in the United States carried out by Balicer *et al*. (2005). On the assumptions that Tamiflu has an efficacy of 71% and the probability of avian flu is 3%, they show that therapeutic treatment and postexposure prophylaxis is "cost-saving with a cost-benefit ratio of 2.44–3.68 . . . Even under the most unfavorable estimates, prepandemic stockpiling remained cost-saving as long as the estimated probability of a pandemic remained >1 every 80 years" (Balicer *et al*., 2005, p. 1281).

Recently, the actual efficacy of Tamiflu has been questioned but the available evidence seems inadequate to reach negative results.[28] Indeed, this is a difficult question to answer definitely in light of possible future mutations of the virus. However, the best strategy is not renunciation of antiviral stockpiling. Instead, it would be safe to adopt a strategy involving the diversified stockpiling of both Tamiflu and Relenza and the continuous monitoring of the avian influenza viruses. This is precisely what any ambiguity hedging strategy would require.

5.2. Ambiguity and Agency Problems in Vaccine Production

Let us now analyze the problem of research and production of new specific vaccines. Unlike antiviral drugs, vaccines do not exist and they have to be synthesized and produced. In order to take as rational a decision as possible, the NIH first of all has to try to estimate the value it can attach to the vaccine. A useful

[26] The United States is the world's leading producer and exporter of poultry meat. About 75% of that comes from chicken production, the rest from the sales of eggs and turkey.

[27] Evaluating Relenza, you have to substitute \$3 billion as cost and interval of compound probability efficacy.

[28] To the best of our knowledge, it has been demonstrated (Mai Le *et al*., 2005) that virus A(H5N1) could become resistant to an antiviral drug. Key facts are as follows: the infected patient received a therapeutic dose of oseltamivir (Tamiflu) and was discharged from hospital without virus. Samples from the patient were later sequenced and some of the virus particles found had developed into a form of the virus resistant to oseltamivir. Oseltamivir resistant A(N5H1) virus was sensitive to zanamivir (Relenza).

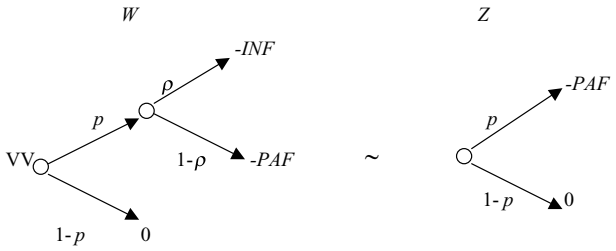

Fig. 2. Decision tree illustrating the NIH choice between a pair of equivalent strategies about a new specific vaccine.

framework for analyzing the problem is one that replicates, with adaptations, the decisional framework for the best choice of antiviral drugs, as discussed below.

The NIH has to determine the compound probability of vaccine efficacy that makes lottery W (buy vaccine) indifferent to lottery Z (waiting strategy). The meaning of the symbols is as follows: p is the probability of the occurrence of a pandemic and ρ is the probability that the vaccine will be effective. PAF is the cost of an avian flu pandemic and INF is the cost of a standard influenza, which here is assumed to be the cost to be borne when the vaccine is efficacious. Roughly speaking, the value of the vaccine VV is the amount that the NIH would have to pay to make the two lotteries equivalent (Fig. 2).

The problem is rendered difficult by the ambiguity that affects several variables. There is ambiguity because the individuals have a perception of incompleteness, i.e., they are aware that there could be unforeseen contingencies.[29] Knowledge of the A(H5N1) virus is ambiguous; there is not a unique and fully reliable probability of the magnitude of its diffusion among humans, there is not certainty about the magnitude of the costs in case of a pandemic or about the effectiveness of the vaccine, which depends on its "quality," its quantity, and also the time of its availability. However, given its attitude to ambiguity, the NIH will set the value of the vaccine on the basis of the pandemic probability, of its additional costs with respect to known costs of a standard influenza, and of the efficacy of the vaccine. Other things being equal, the value of the vaccine will in general increase with its own efficacy, as well as the occurrence and cost of a pandemic. Formally:

$$VV = VV(p, PAF, \rho) \quad \text{such that } \frac{dVV}{dp} > 0;$$

$$\frac{dVV}{dPAF} > 0; \quad \frac{dVV}{d\rho} > 0. \tag{5}$$

[29] See Henry and Henry (2002).

There are good reasons to believe that the market will attach a much lower value to the vaccine and therefore will underproduce it or will not produce it at all. Vaccine discovery involves huge and specific cost in R&D (sunk cost) and the expectations of future demand may not be considered a sufficient incentive. Future costs may be underestimated by the market, as may be the probability of the pandemic. Moreover, pharmaceutical firms are market-risk averse and invest in new production only if they can rely on a sure demand (market-risk sharing). As a consequence, pharmaceutical firms will manufacture a new vaccine if they have sufficient *ex ante* purchasing contracts, or monetary transfer from the NIH or stakeholders.

The second step in a NIH rational strategy is precisely the overcoming of this weak incentive to pay for the discovery and the production of the vaccine. Whether the vaccine will be produced, at what cost, and at what level of efficacy depends on the NIH. It should act as a principal entering an agency relation with pharmaceutical firms, in the familiar scenario of incentive contracts. The object of the contract is the efficacy of the vaccine and the NIH has to devise to this end a compensation scheme for pharmaceutical firms. The cost of the compensation can be taken as the actual cost of the vaccine of given expected efficacy. A rational NIH would maximize the difference between the value of the vaccine, which we know is positively related to its efficacy, and its actual cost, represented by the compensation paid to the producers. As in the standard agency models, the principal and the agent hold asymmetric information on the latter's effort. However, unlike the standard models (Grossmann & Hart, 1983; Hart & Moore, 1988, 1999; Maskin & Tirole, 1999), the principal does not have a complete and fully reliable description of all future possible states of nature because the efficacy of the vaccine is characterized by ambiguity. Therefore, an optimal incentive scheme has to take this very important aspect into account. Our model aims at offering a solution to this problem.

The above discussion helps clarify the basic assumptions of the model. The utility of the principal (NIH) is positively related to the expected efficacy of the vaccine ϕ, that is, $U = u(\phi)$. Here, efficacy is taken to mean a timely availability of adequate quantities of vaccines. According to the time of its availability and to the produced quantity, ϕ can take a low or a high value: $\phi \in [\phi^{\circ}, \ \phi^{*}]$. Moreover, to make our analysis as simple as possible, we assume that the principal is neutral with respect to the risk associated with

the efficacy of the vaccine. This implies that its utility function is linear and, without loss of generality, can be written as follows: $u(\phi) = \phi$.

Let e be the agent's effort level upon which, alongside a stochastic variable, the efficacy of the vaccine is dependent. Our simplifying hypothesis is that e can take two values only: e^* (high effort) or e° (low effort), with e^* more likely leading to higher efficacy; e° is normalized as zero and e^* as a positive effort of one, that is, $e = \{0,\ 1\}$.

Since the effort is not observable and the outcome depends also on a stochastic variable, the relationship between ϕ and the agent's effort level is described by the conditional density function $f(\phi \mid e)$, with $f(\phi \mid e) \geq 0$ for all e and $\phi \in [\phi^\circ,\ \phi^*]$. As a consequence, the cumulative distribution functions are such that $F(\phi \mid e^*) \leq F(\phi \mid e^\circ)$, for all $\phi \in [\phi^\circ,\ \phi^*]$, with strict inequality for some ϕ. This implies that the expected utility of the principal is larger when the agent supplies the effort e^*.[30]

The agent is risk averse, with a separable utility function $u(s, e) = g(s) - \gamma(e)$, where s is the compensation paid by the principal and $\gamma(e)$ represents the cost of the effort to the agent. Obviously, $\gamma(e^*) > \gamma(e^\circ)$, such that $\gamma(e^\circ) = \gamma_0 = 0$ and $\gamma(e^*) = \gamma_1 = \gamma$. The agent's utility increases with s and decreases with e, at a decreasing rate; moreover, $u(s, e^\circ) > u(s, e^*)$, for all s. This makes it clear that there is a conflict between the target of the principal and the purpose of the agent. The principal's problem is to design a compensation scheme $s(\phi)$ that is sufficient to induce the agent to supply the high effort, and maximize its own net utility, which depends on the difference between the utility of the efficacy of the vaccine and the compensation paid to the agent. The search for such a scheme is made more complex by the presence of ambiguity, which makes the principal feel that there are several probability distributions linking the effort by the agent to the efficacy of the vaccine. In this model, ambiguity arises from the incomplete knowledge about the variables affecting the efficacy of a vaccine besides the agent's effort. In order to make ambiguity compatible with a maximizing behavior, we assume that the principal maximizes a weighted average of the worst- and the best-case scenarios, where the weight is the parameter α, as in the α-MEU approach.

Therefore, the principal's optimal contract solves the following problem:

$$\max_{s(\phi)} I = \alpha \int_{\phi^\circ}^{\phi^*} (\phi - s(\phi))\, f^\wedge(\phi \mid e)\, d\phi + (1-\alpha) \int_{\phi^\circ}^{\phi^*} (\phi - s(\phi))\, f(\phi \mid e)\, d\phi \qquad (6)$$

such that

$$(i)\ \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid e)\, d\phi - \gamma(e) \geq \bar{u}$$
$$(ii)\ \arg\max_{\bar{e}} \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid \bar{e})\, d\phi - \gamma(\bar{e}),$$

where $f^\wedge(\phi \mid e)$ and $f(\phi \mid e)$ are the minimum and the maximum conditional density functions with respect to e, such that $e = \{e^\circ;\ e^*\}$, in the set of conditional density functions. The condition (i) is a *participation constraint*, which exhibits the agent's expected utility to be at least equal to its reservation utility level $\bar{u}$, while the condition (ii) is an *incentive constraint*, which assures that the agent will supply the optimal effort level under the monetary transfer $g(s(\phi))$.

Since the contract specifies the effort level e, in order to maximize Equation (6), the principal has to minimize the expected value of the agent's monetary transfer, that is,

$$\max_{s(\phi)} I = \alpha \int_{\phi^\circ}^{\phi^*} -s(\phi)\, f^\wedge(\phi \mid e)\, d\phi + (1-\alpha) \int_{\phi^\circ}^{\phi^*} -s(\phi)\, f(\phi \mid e)\, d\phi \qquad (7)$$

or

$$\min_{s(\phi)} I = \alpha \int_{\phi^\circ}^{\phi^*} s(\phi)\, f^\wedge(\phi \mid e)\, d\phi + (1-\alpha) \int_{\phi^\circ}^{\phi^*} s(\phi)\, f(\phi \mid e)\, d\phi \qquad (8)$$

such that

$$(i)\ \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid e)\, d\phi - \gamma(e) \geq \bar{u}$$
$$(ii)\ \arg\max_{\bar{e}} \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid \bar{e})\, d\phi - \gamma(\bar{e}).$$

Let us consider the case in which the principal maximizes its utility when the effort level is e^*. In this case, Constraint (ii) can be written as:

$$(iii)\quad \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid e^*)\, d\phi - \gamma(e^*) \geq \int_{\phi^\circ}^{\phi^*} g(s(\phi))\, f(\phi \mid e^\circ)\, d\phi - \gamma(e^\circ). \qquad (9)$$

[30] $F(\phi \mid e^*) \leq F(\phi \mid e^\circ)$ implies first-order stochastic dominance.

Considering the problem of Equation (7) and assuming strictly positive co-state variables,[31] $s(\phi)$ must meet the *Kuhn-Tucker first-order conditions*[32] at every $\phi \in [\phi^{\circ},\ \phi^{*}]$:

$$\alpha(-1)\, f^{\wedge}(\phi \mid e^{*}) + (1-\alpha)(-1)\, f(\phi \mid e^{*}) + \lambda g'(s(\phi))\, f(\phi \mid e^{*}) + \mu g'(s(\phi)) \times [\, f(\phi \mid e^{*}) - f(\phi \mid e^{\circ})] = 0, \tag{10}$$

where λ is the optimal monetary transfer if the agent's effort is observable.[33] Equation (10) can be reformulated as follows:

$$\alpha\left(-\frac{1}{g'(s(\phi))}\frac{f^{\wedge}(\phi \mid e^{*})}{f(\phi \mid e^{*})}\right) + (1-\alpha)\left(-\frac{1}{g'(s(\phi))}\right) + \lambda + \mu\left[1 - \frac{f(\phi \mid e^{\circ})}{f(\phi \mid e^{*})}\right] = 0 \tag{11}$$

or

$$\frac{1}{g'(s(\phi))}\left[\alpha\frac{f(\phi \mid e^{*})}{f^{\wedge}(\phi \mid e^{*})} + (1-\alpha)\right] = \lambda + \mu\left[1 - \frac{f(\phi \mid e^{\circ})}{f(\phi \mid e^{*})}\right]. \tag{12}$$

Equation (12) discloses a very interesting relationship: the optimal monetary transfer is not constant and could differ from the agent's reservation utility level $\bar{u}$.

Consider the case in which $\alpha = 0$: the principal faces ambiguity but is certain about the correctness of its best probability assessment (optimism). If the principal is ambiguity seeking or an optimist:

$$\frac{1}{g'(s(\phi))} = \lambda + \mu\left[1 - \frac{f(\phi \mid e^{\circ})}{f(\phi \mid e^{*})}\right]. \tag{13}$$

The transfer is larger for outcomes that are statistically more likely to occur under e^{*} than under e° and it is smaller for outcomes that are statistically more likely under e° than under e^{*}. Note that the optimal monetary transfer is at least equal to the optimal monetary transfer when the agent effort is observable, other things being equal.

Consider the case in which $\alpha = 1$: the principal faces ambiguity and considers its probability assessments unreliable, then it applies the most conservative rule only taking its worst probability distribution (pessimism) into account. If the principal is ambiguity averse or pessimistic:

$$\frac{1}{g'(s(\phi))}\frac{f(\phi \mid e^{*})}{f^{\wedge}(\phi \mid e^{*})} = \lambda + \mu\left[1 - \frac{f(\phi \mid e^{\circ})}{f(\phi \mid e^{*})}\right] \tag{14}$$

or

$$\frac{1}{g'(s(\phi))} = \frac{f^{\wedge}(\phi \mid e^{*})}{f(\phi \mid e^{*})}\left\{\lambda + \mu\left[1 - \frac{f(\phi \mid e^{\circ})}{f(\phi \mid e^{*})}\right]\right\}. \tag{15}$$

The above result shows that the optimal monetary transfer depends on the principal's ambiguity attitude. Due to ambiguity, in order to maximize its utility, the principal will associate higher or lower monetary transfers, the amount of which will depend on $f^{\wedge}(\phi \mid e^{*})/f(\phi \mid e^{*})$, or the ratio between the minimum and maximum conditional density function with respect to e^{*}. From Equation (15) it follows that when the principal is ambiguity averse ($\alpha = 0$), the optimal monetary transfer could be lower or higher than λ (the optimal monetary transfer with observable agent effort), if $f(\phi \mid e^{*}) > f^{\wedge}(\phi \mid e^{*})$ or $f(\phi \mid e^{*}) < f^{\wedge}(\phi \mid e^{*})$, respectively. Whether $f^{\wedge}(\phi \mid e^{*})/f(\phi \mid e^{*})$ is greater or smaller than one will depend on ambiguity: the larger the interval of probability distributions that represents the principal's scientific uncertainty, the larger the ratio and, perhaps, the larger the monetary transfer.

Thus, ambiguity aversion does not systematically cause agency costs to rise by a nonmonotonic monetary transfer scheme; what is crucial is the degree of confidence α and how the probability of good and bad outcomes changes when it is evaluated on the basis of the minimum and maximum conditional distributions. This result plays a significant role in order to establish whether there was a precautionary failure as far as the research and the production of vaccines are concerned. In fact, the agency costs to be borne in order to overcome the incentive problems outlined above are not necessarily higher when a precautionary attitude is chosen. This implies that in this important respect, precaution may very well cost no more than a more optimistic approach, while its expected benefits are very likely to be higher. Therefore, precaution may be a fully rational choice and any other course of action can be blamed as a failure to behave precautionarily and rationally.

[31] Co-state variables equal to zero are either impossible or induce the violation of the constraints.

[32] The first-order condition for $s(\phi)$ is obtained from making the derivate of the Lagrangian function respect the monetary transfer for every effort.

[33] If the set of possible probabilities only includes singleton, there is no ambiguity and the degree of confidence does not matter. When effort is observable, the optimal monetary transfer is $1/g'(s(\phi)) = \lambda$, payment is constant, and the agent receives exactly its reservation utility level $\bar{u}$.

6. CONCLUDING REMARKS

In this article, we have put forward a working interpretation of the PP that tries to eschew the severe limitations of other approaches normally disregarding either the costs of this strategy or the presence of ambiguity—a crucial feature of the problems to which the principle is to be applied. The procedure we suggested takes proper account of ambiguity and is nonetheless rooted in rational calculations of a cost-benefit type.

We applied our approach to the two most important measures that could have been adopted in order to prevent the huge damages expected in case of a human avian flu pandemic: the provision of adequate production capacity for antiviral drugs and the timely research and production of specific vaccines.

We have argued that the two cases are rather different. In particular, the research and production of vaccines, unlike the purchasing of antiviral drugs, engender some thorny incentive problems and, therefore, give rise to agency costs that may make this kind of precautionary behavior quite costly.

Our analysis of the problem of antiviral stockpiling yielded the main conclusion that the precautionary decision of purchasing antiviral drugs covering at least 25% of the population (a safety threshold according to the WHO) was not rationally justifiable only under very low, and quite unrealistic, probabilities of a pandemic and of antiviral efficacy. This result is consistent with the conclusion reached in some rare epidemiological and biomedical studies on the problem. On this basis it seems appropriate to talk about precautionary failure.

As to the vaccine problem, we have put forward a scheme for taking rational decision under ambiguity and we have also clarified what precaution would imply in such a scheme. In particular, we argued that the value, in social terms, of a vaccine depends positively on its efficacy given other variables subject to ambiguity, like the probability of a pandemic outbreak or the damages it would bring about.

A rational approach is, therefore, to compare the value of the vaccines of given efficacy with their cost. The latter is to be determined within a principal-agent framework, given the implied incentive problems and asymmetry of information. We have shown how a rational compensation scheme should be designed when the principal faces not only risk but also ambiguity, as in this case. An interesting result is that under ambiguity and hidden action, the incentive scheme is not monotonic with respect to the quantity or quality of vaccine and the optimal compensation could be even smaller than under conditions of symmetric information. This result can be taken to mean that being precautionary does not necessarily involve higher agency costs while benefits in the form of a vaccine of better expected efficacy may be substantially greater. Therefore, precaution and rationality may easily go hand in hand. We believe that there are good reasons to conclude that also with respect to vaccine research and production there has been a precautionary failure: years ago, well-designed and financially adequate incentive contracts—concerning research and production of specific vaccines—had to be offered to pharmaceutical firms.

As other authors have also stressed (Gollier & Treich, 2003), there are very good reasons for believing that the market is not the right institution for taking a precautionary course of action. In this article, we have shown that in the avian flu case, as in many similar cases, public bodies contributed to a sort of general institutional failure in precaution. The reasons for such failure could probably justify an additional chapter in an updated handbook on the so-called nonmarket failures. What really matters, however, is that the joint market and nonmarket failures may have catastrophic consequences in terms of social and human costs. This is enough to take precaution very seriously.

APPENDIX

In a more general decisional framework, the NIH has to consider quasi-option value in buying antiviral drugs, that is, the induced benefit of avoiding the cost of avian flu pandemic. As a consequence, in the two-stage lottery, X has to consider this opportunity benefit (Fig. A.1).

Other things being equal, the NIH solves the following maximization problem:

$$\begin{aligned}
&\max V \\
&= \alpha \left[(-CT) \right. \\
&\left. + \frac{[(-INF) - (-PAF_{\max})]\upsilon p + (-PAF_{\max})(1-\upsilon)p + pPAF_{\max}}{1+r} \right] \\
&+ (1-\alpha) \left[(-CT) \right. \\
&\left. + \frac{[(-INF) - (-PAF_{\min})]\upsilon p + (-PAF_{\min})(1-\upsilon)p + pPAF_{\min}}{1+r} \right],
\end{aligned} \tag{A.1}$$

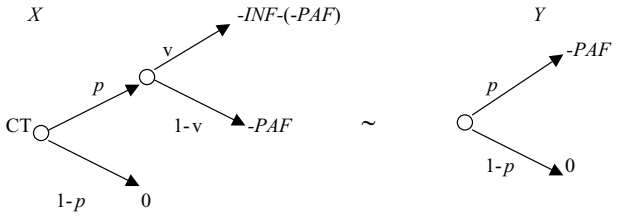

Fig. A.1. Decision tree illustrating the NIH choice between a pair of equivalent strategies about antiviral drugs, including quasi-option value as a cost.

that is,

$$\max V = \alpha\left[(-4)+\frac{[(-41)-(-200)]\upsilon p+(-200)(1-\upsilon)p+200p}{1+0.05}\right] + (1-\alpha) \times\left[(-4)+\frac{[(-41)-(-100)]\upsilon p+(-100)(1-\upsilon)p+100p}{1+0.05}\right]. \quad (A.2)$$

Consider the extreme scenarios:

1. If $\alpha = 1$, the NIH faces the worst-case scenario (pessimism):

$$(-4)+\frac{[(-41)-(-200)]\upsilon p+(-200)(1-\upsilon)p+200p}{1+0.05} = (-4)+\frac{(+359)\upsilon p+(-200)p+200p}{1.05} = (-4)+\frac{(+359)\upsilon p}{1.05} = (-4)+(341.9)\upsilon p. \quad (A.3)$$

As a result, the compound probability that makes the two strategies indifferent is:

$$(-4)+(341.9)\upsilon p = 0 \text{ then } \upsilon p = \frac{4}{341.9} = 1.16. \quad (A.4)$$

2. If $\alpha = 0$, the NIH faces the best-case scenario (optimism):

$$(-4)+\frac{[(-41)-(-100)]\upsilon p+(-100)(1-\upsilon)p+(100)p}{1+0.05} = (-4)+\frac{(+59)\upsilon p+(100)\upsilon p-100p+100p}{1.05} = (-4)+\frac{(+159)\upsilon p}{1.05} = (-4)+(151.4)\upsilon p. \quad (A.5)$$

As a result, the compound probability that makes the two strategies indifferent is:

$$(-4)+(151.4)\upsilon p = 0 \text{ then } \upsilon p = \frac{4}{151.4} = 2.64. \quad (A.6)$$

The interval of minimal antiviral drug efficacy (1.16; 2.64) is smaller and stockpiling Tamiflu is the optimal strategy.

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