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The global strategy to cope with H5N1: the property rights caveat

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The global strategy to cope with H5N1: the property rights caveat

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Abstract

Shortage of stockpiled antiviral drugs and insufficient production capacity of vaccines make the possible avian flu pandemic a global disaster. Catastrophic consequences in social and economic losses loom over the near future of humans but they derive from a wrong business model based on private production granted by patent rights and price discrimination. In this paper a new sustainable economic model for vaccines and antiviral drugs production based on liability rule and trust fund is advanced.

KEYWORDS: avian flu, ambiguity, incomplete rights, market failure

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1. INTRODUCTION

Since December 2003, at least 383 cases of H5N1 influenza have been reported in humans, resulting in 241 deaths (63% fatality/case ratio) in many countries around the world, mostly among Less Developed Countries (LDCs).

What makes highly pathogenic avian flu A subtype viruses (H5N1; H9N2) very dangerous is the fact that they are potential pandemic ones. As a matter of fact H5N1 has not only crossed the species barriers from avian to mammals (tigers, cats, pigs etc) then to humans, but it has also induced more than thirty family clusters and there is statistical evidence that strain of it was spread from human-to-human (Thailand and Indonesia). Family clusters of H5N1 suggest that a viral or epidemiologic change has been occurring and it could reflect adaptation to the human host, that is a viral mutation resulting in an efficient human-to-human spread.

A recent research shows that the household secondary attack rate (SAR) of avian flu, that is the probability that an infectious person infects a member of her family, is 29%. Crucially, the avian flu "SAR is similar to statistical estimates for interpandemic influenza A in the United States (12.7%–30.6%). The mean incubation period of this strain appears to have been ≈5 days, nearly twice as long as for past pandemic strains and current interpandemic strains of influenza" [1].

According to the World Health Organization (WHO), that uses a series of six phases of the Pandemic Alert Period to classified the global threat of an avian flu pandemic, the World is presently at Phase 3: "a new influenza virus subtype is causing disease in humans, but is not yet spreading efficiently and sustainably among humans". Crucially, each new human case increases the opportunity of H5N1 to evolve towards a pandemic strain since this virus has been shown to mutate rapidly and has a documented propensity to exchange genes with influenza viruses from other species. As a consequence, "experts at WHO and elsewhere believe that the world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics occurred".

As a consequence, WHO has established a strategy to contain the avian influenza pandemic threat based on three pillars: an early warning system, a rapid containment plan and a coordinated global scientific development. The first pillar is based on WHO Global Influenza Surveillance Network (GISN) and the Global Outbreak Alert and Response Network (GOARN). The second pillar was detailed in WHO protocol of rapid operations to contain the initial emergence of pandemic influenza [2]. The third pillar is based on WHO

coordination about the development of representative H5N1 candidate vaccines (actually, modified clade 1 and clade 2).

In the global strategy to contrast a possible avian flu pandemic there is a very dangerous bug: possible shortage of effective antiviral drugs and vaccines, that could transform a pandemic influenza in a catastrophic event.

WHO recommends as precautionary measures preparation of vaccines and huge stockpiling of antiviral drugs. In fact, vaccines are considered the best available protection against the H5N1 virus, but at least two problems undermine the first best strategy: constant evolving nature of influenza viruses makes impossible to select a certain H5N1 virus as vaccine virus and induces frequent reformulation of the vaccine strain candidates. Global monovalent seasonal influenza vaccine doses production capacity is 1.0/1.5 billion a year, but there are six billion people all susceptible to infection in the World and available pandemic vaccines require two doses.

The second line of the containment strategy for reducing morbidity and mortality during an influenza pandemic is based on extensive antiviral prophylaxis and treatment. Recommended duration of antiviral prophylaxis is 20 days, but it could be extended for longer periods. Unfortunately, only two antiviral neuraminidase inhibitors: *Tamiflu*© (oseltamivir) and *Relenza*© (zanamivir) are active against the A(H5N1) virus. Tamiflu is a product by Hoffmann-La Roche Ltd and Relenza is produced by Glaxo-Smith-Kline (GSK) that hold exclusive manufacturing rights. WHO currently has an antiviral stockpile of 5 million treatment courses (i.e. 2 doses per day for 5 days) of oseltamivir donated by La Roche. As a matter of fact, an elevated resistance of seasonal H1N1 viruses to oseltamivir have been identified in Norway and other countries in 2008, even if the neuraminidase protein in human H1N1 viruses is different from that in avian H5N1 and then implication appears uncertain, "viruses oseltamivir resistance due to the same mutation has been reported in three patients with H5N1 infection who were treated with oseltamivir" [3].

Summarizing. People face the terrible threat of a pandemic flu that has a very high mortality rate. None is able to predict if this pandemic will occur, but scientists consider it probable, as a consequence they suggest a complex strategy to contain the disease based on medical and non medical options. A rational decision-maker should make a cost-benefit-analysis of this strategy and implement the optimal solution. Unfortunately the decision-making process is characterized by ambiguity and irreversibility and adoption of precautionary policy induces very huge expenditure, mostly for LDCs. Critically large part of this potential expenditure is due to property rights and patents.

In this paper it is suggested to remove financial and legal obstacles to prepare medical barriers against possible pandemic flu. In light of the catastrophic threat, if the impact of the actual patent cost on the spread of vaccines and antiviral drugs stockpiling is considered unsustainable, it will be rational to change the legal mechanism that permits the transfer of the entitlement a part from approval of the owner. In liability rule, it is not relevant the kind of entitlement, but the mechanism of protection is only considered, indeed given inalienability, a legal entitlement can be also protected by imposing a compensation for infringement [4]. As a consequence, if irreversibility, incomplete contracts, harmful externalities, agency problems, strategic behavior, information asymmetries and ambiguity prevent efficient bargaining to work, then liability rule should be employed. It should be rational to provide a compensation, or the payment for a fixed amount of damages, for patents of antiviral drugs and permit others to manufacture them. In the case of vaccines price discrimination, patent rights and liability exposure do not permit private efficient production, both market and institutional failures occur. It is suggested introducing a trust fund financed through *earmarked taxes* that makes sure the global supply of vaccines at administrated prices.

The paper is as follows. Section 2 describes some aspect of potential avian flu disease and gives an economic evaluation of a possible outbreak. Section 3 puts in evidence characteristics of the decision-making process involving vaccine and antiviral drug productions. Section 4 describes the effect of substitution of property rule with liability rule in antiviral drugs production. Section 5 introduces a trust fund for vaccine production. Concluding remarks are in Section 6.

2. AVIAN FLU OUTBREAK COSTS AND CONSEQUENCES

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 spread worldwide now. There are three types of avian influenza virus, called A, B, and C, all but A can infect animals and/or humans and cause epidemics or pandemics. What makes an influenza pandemic a very dangerous event is that once a fully human transmissible virus emerges it will be impossible to stop it and a global infection, that is a simultaneous and generalized disease, will occur within a few months.

Historical evidence shows that influenza pandemic may appen three or four times in a century (there were 31 pandemics in the last four centuries). In the XX century there were

three cases of pandemic: the Spanish flu of 1918-1920, the Asian flu of 1957-1958, and the Hong Kong flu of 1968-1969. Avian flu could be the next influenza pandemic.

There are not fully reliable estimation of cost induced by an outbreak, but a conservative assessment of the general economic damage induced by an avian flu pandemic sets the total cost at $282 billion [5] in Asia and "the World Bank has estimated that a pandemic could cost the world economy between 800 billion dollars and 2 trillion dollars, depending on the virulence of the virus" [6].

Potential mortality from an avian flu pandemic is also very uncertain and epidemiologic models produce estimates from 2 million to 360 million of deaths.[1] A study based on a quantitative analysis of vital registry data from the 1918-1920 Spanish flu pandemic puts in evidence that "excess mortality data show that, even in 1918-20, population mortality varied over 30-fold across countries. Per-head income explained a large fraction of this variation in mortality. Extrapolation of 1918-20 mortality rates to the worldwide population of 2004 indicates that an estimated 62 million people (10^{th}-90th percentile range 51 million-81 million) would be killed by a similar influenza pandemic; 96% (95% CI 95-98) of these deaths would occur in the developing world. If this mortality were concentrated in a single year, it would increase global mortality by 114%.....This analysis of the empirical record of the 1918-20 pandemic provides a plausible upper bound on pandemic mortality. Most deaths will occur in poor countries- i.e., in societies whose scarce health resources are already stretched by existing health priorities" [7].

If it is not possible to stop the ability of an influenza pandemic to spread among people, there exists a strategy to contain its morbidity and mortality and transform it in a bad seasonal influenza with limited economic effects and low mortality rate. Antiviral drugs and vaccines are the most important devices for reducing morbidity and mortality during an influenza pandemic.

About effective and efficient antiviral drugs, i.e. Tamiflu and Relenza, WHO suggested that buying antiviral drugs for 25% of the population of a country would be a safe strategy. A recent study on the cost-effectiveness of stockpiling antiviral drugs for potential influenza pandemic and the use of near-patient testing in the management of antiviral drugs in the United Kingdom, shows that: "stockpiling antiviral drugs for a treat-only program is likely to be a cost-effective strategy in preparation for a potential influenza pandemic, even if the

[1] The economic value of the human life can be measured by the so-called *value of statistical life* (VSL), that is the relevant parameter for the valuation of accidents. VSL recommended for policy decisions in Europe and North America, is in the range of 1 to 5 million euros.

pandemic occurs many years from now, assuming that antiviral drugs provide some protection against death. However, under current UK planning assumptions (CAR- clinical attack rate 25%), the antiviral stockpile would be too small (at 14.6 million courses) to treat all cases of influenza-like illness. Near-patient testing is unlikely to be a cost-effective approach to conserving antiviral stocks but might be considered early in a pandemic. A more cost-effective strategy would be to increase the stockpile of antiviral drugs. Since CARs in excess of 30% have been observed in pandemics, increasing the stockpile to cover this possibility may be both prudent and cost-effective" [8].

WHO considers "vaccines the single most important medical intervention for reducing morbidity and mortality during an influenza pandemic This creates our most difficult ethical dilemma. The dilemma has two dimensions. One is a technical problem, related to vaccine manufacturing. The second is a resource problem, related to money. One touches science. The other touches policy". Technical problems derive from two main characteristics of the H5N1 virus: continuous evolving nature, that requires frequent reformulation of the vaccine strains, and rapid spread during epidemic that collapses the steps in the vaccine process of production and delivery into a tight time. A rational strategy to cope with shortage of human H5N1 influenza vaccines is to increase production by reducing the total time of provision and increasing global supply. WHO is going to create a global stockpile of human H5N1 vaccines and "currently, at least 16 different manufacturers have an H5N1 vaccine in relatively advanced development based on a range of approaches (including egg and cell culture grown viruses, live virus and inactivated virus vaccines, whole and split antigen, and vaccines with and without different adjuvants). Additional technologies are also under consideration and development" [2]. But legal and patent problems prevent cooperation among vaccine firms. With respect to the global vaccines supply, WHO estimates a human H5N1 vaccine production from 500 million to 1500 million of doses in one year. Crucially, not only vaccine production is vastly insufficient to immunize global population, but also finite manufacturing capacity is concentred in Europe and North America and it is plausible that sharing of vaccines does not take place during a pandemic and LDCs could not access to vaccines. In LDCs, there exists a possible solution, at least with respect to manufacturing capacity, in fact the Developing Countries Vaccine Manufactures' Network (DCVNM) "is a voluntary public health driven alliance of vaccine manufacturers owned by and located in developing countries that offer a consistent and sustainable supply of quality vaccines that are affordable and accessible to developing countries" [9]. Recent success of the DCVNM in vaccine

production[2] puts in evidence that the real question is how to permit easy access and transfer of technologies from the European-based influenza vaccine industry to the South of the World.

3. AVIAN FLU CONTAINEMENT: A DECISION UNDER AMBIGUITY

The shortage of stockpiled antiviral drugs and inadequate production of human H5N1 vaccines are consequences related to extreme events, indeed the outbreak of a pandemic flu. Extreme events are disasters and catastrophes that are characterized by very low and/or ambiguous probabilities of occurring and very dangerous and large consequences; "failures in response to catastrophic emergencies demonstrate the difficulty of assessing, managing, and communicating these risks. Misinterpretation of extreme risks is a consequence of an unsolved theoretical question, in other words, the implementation of an optimal choice rule in the face of unlikely events with serious consequences"[10].

WHO defines strategic actions to contain the initial emergency of pandemic and those actions invoke the application of the Precautionary Principle as the rational decision rule. The core of WHO Interim Program is based on stockpiling antiviral drugs and vaccines to intervene near the start of a pandemic and all around the World to protect enough people in time and avoid leaving vast population vulnerable to the H5N1 virus.

Unfortunately even if potential losses are catastrophic, this strategy induces very large expenditure for countries, given budget constraints, and buy antiviral drugs and options on vaccines can appear not rational under uncertain outbreak and ambiguity about efficacy of stored medicines. As a consequence, this containment strategy is not fully implemented and there are not efficient stockpiling of antiviral drugs and sufficient production capacity to manufacture vaccines supporting the potential global demand.

This undesirable outcome derives from some problems that this paper would like to disentangle.

A critical question refers to rational decision rules that should be implemented facing an global human health threat under irreversibility (should antiviral drugs and vaccines be produced and stockpiled?) and uncertainty (will influenza pandemic occur? will drugs be efficient and effective?). It has been known, since the Allais paradox [11], that human beings

[2] For example, "the DCVMN contribution in vaccine doses to PAHO's 2007 tenders ranged from 5 to 100%, the average being 70%. In fact, two out of every three children born in the world get immunized with at least one vaccine that comes from a manufacturer from the DCVMN" [9].

are not able to distinguish among very small probabilities. It has been proven that the standard approach to choice under risk fails to induce the optimal act when extreme events are involved; in fact the standard evaluation method induces misevaluation of catastrophic events because of insensitivity to very low probabilities. This behavior is outlined in Cumulative Prospect Theory[3] that assumes the existence of an inverse S-shape of probability weighting function and shows a positive correlation between the decision-maker's attitude and unusual outcomes. Basili *et al* [14] put in evidence that it is possible to introduce "an operational notion of the precautionary principle that encompasses both customary and extreme events. Differently from all the previous characterizations, the new notion of the precautionary principle is not a simple convex combination between maximin and maximax criterion, but it is a combination between the mathematical expectation of all the possible outcomes and the most extreme ones…..our decisional rule is suitable for useful implementations in situations that entangle both more reliable (risky) consequences and less known (uncertain), extreme outcomes. As a consequence uncertainty should not be inflated and evoked as a proper justification for inaction, since our operational measure of the precautionary principle describes how to act".[4]

The second problem is related to very large expenditure induced by buying antiviral drugs and writing options on future pandemic vaccines. Storage of antiviral drugs is prohibitive for LDCs and could be ineffective since avian flu could evolve in antiviral resistant strains or because of short shelf life (five years). Nevertheless epidemiological studies and statistical models show that antiviral drugs could be effective in preventing or treating diffusion of an avian flu pandemic. In fact, "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…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.[16]" [17].[5]

In 2006 and 2007, Roche expanded its capacity to manufacture Tamiflu by contracting (sublicensing) with 19 external production partners in nine countries up to 400 million treatments for a year, but crucially production exceeds existing orders from governments and

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[3] Cumulative Prospect Theory was introduced in [12] and axiomatised in [13].

[4] Basili and Chateauneuf [15] introduce a more general decision rule under risk and ambiguity based on the quantile utility maximization method.

[5] On the assumptions that Tamiflu has an efficacy of 71% and the probability of avian flu is 3%, Balicer *et al*. show that therapeutic treatment and post-exposure 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" [16].

corporations. Prohibitive cost for authentic Tamiflu from $80 to $100 for a 10-pill treatment makes present manufacturing capacity larger than global market demand, but current production is not enough to treat 20%-30% of the world's population, that is the minimum number of treatment required by a pandemic influenza containment strategy.

Finally in 2008, the main seasonal flu virus circulating in the United States and Canada as well as parts of Europe has shown higher resistance to Tamiflu. Even if cases of resistance remain relatively rare, experts suggest to diversify stockpiling of flu drugs. In order to provide an adequate cover governments need to store both Tamiflu and Relenza, that is countries have to face new huge expenditure to buy Relenza.

The third critical question is the existence of ambiguity and agency problems in vaccine production that induce market failures. Vaccine discovery involves huge and specific cost in R&D (sunk cost) and liability exposure. In this condition the expectations of future demand for avian vaccines 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 adverse and invest in new production only if they can rely on a sure demand (market-risk sharing). Estimated costs to bring a new vaccine to markets are $900 million but low prices deriving from demand deep discounts make many vaccines unprofitable. Moreover vaccine firms face huge legal expense in vaccine liability cases. As a consequence, pharmaceutical firms manufacture new vaccines only if they have sufficient *ex-ante* purchasing contracts, or monetary transfer from national health services or stakeholders. Crucially, to address vaccine shortages national health services and/or International Organisms have to devise compensation scheme through monetary and non-monetary incentives. It was proved that "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" [17]. Finally national health institutes run the risk of over-reaction, in fact if pandemic influenza does not occur vaccine will be useless.[6]

[6] In 1976, 45 million Americans were vaccinated against a specific subtype of flu (swine flu) that did not occur: The CDC campaign of mass vaccination cost $134 million and caused Guillain-Barré syndrome in some vaccine recipients.

4. NEW RULES FOR ANTIVIRAL DRUG PRODUCTION

Access to antiviral drugs is affected by intellectual property rights, in this case patent rights, and it is crucial to examine their effects during public health crises.

The number of sales of Tmaiflu and Relenza worldwide has been growing steadily according to data since 2005. Roche and GSK have been reported to experience a double digit jump in annual profits (Roche +34% in 2006).[7] In May 2008, Reuters reported that "Tamiflu had sales of $1.8 billion in 2007, making it a major profit driver for Swiss group and Relenza sold $510 million last year".[8] Moreover price stock of Roche and GSK have been growing more than for other Big Pharma since 2005, when pandemic avian flu alert was launched and antiviral efficacy was declared. Capital gain was exceptional for Roche whose stock price moved from 94.55 CHF in 2005, to 241.40 CHF in 2007 up to 185 CHF in June 2008.

It is worth remembering that Relenza royalties paid to Biota, the original inventor that licensed the antiviral drug to GSK in 1990, grew to $39,9 million in 2006 from $5,2 million in the previous year and, in 2005 Roche and Gilead Sciences Inc, that invented Tamiflu in 1996, reached a new agreement by which Roche paid $81 million as an adjustment and royalty from 14% to 22% depending on sales.[9]

Summarizing, since 2005 revenues and profits of Roche and GSK have been boosted by sales of antiviral drugs. Roche and GSK have a very limited production capacity unable to match the global demand in case of an outbreak. Even if Roche agreed to reduce the price of Tamiflu for LDCs, high prices of antiviral drugs make market demand lesser than current production. As a result there are not enough Tamiflu and Relenza stockpiled. Crucially Gilead and Biota, the two small biotechnogical firms that invented Tamiflu and Relenza obtained small lump sum when they transferred their property rights and limited royalties during the patent life.

Patent law is devoted to provide economic incentives to develop new products or processes. Preventing free-riding, patent rights grant inventors with a time limited (usually 20 years) monopoly in exploiting new discoveries. Patent rights prevent from unauthorized uses protected discoveries. Patent infringements are sanctioned with injunction to cease and/or

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7 Roche said net income in 2006 rose to 9.17bn CHF from 6.86bn CHF in 2005.

8 In May 2008, British experts suggested to stockpile different sort of flu drugs, i.e. Tamiflu and Relenza, since the exact mutation in protein structure that can make some flu virus resistant to Tamiflu makes Relenza still effective.

9 Gilead Sciences Inc. licensed all its rights to Roche for a $50 million license fee and royalty payments during the life of the drug's patent.

prohibit offending activity and monetary compensations. Since patent rights are considered like other property rights, the patent holder may sell, transfer or license her patent rights.

The Patent Cooperation Treaty (PCT) is a mechanism for administrating international patent applications and publications under the PCT gives a rough indication of the trend in patent activity: referred to avian flu or H5N1 virus "….of all relevant international applications since the first instance recorded in 1983, some 35% were published in the first 9 months of 2007. These publications therefore disclose relatively recent research and development activity, in the form of inventions that were first applied for between late 2005 and early 2006. There is considerable diversity in this activity, with publications from over 100 different actors representing a mix of private firms, individual inventors, public sector institutions and government agencies" [18].

Patent rights have a local characteristic (national and regional legal effects) and "national patent laws differ considerably on what is considered fit subject matter for a patent. International standards exist, but leave open considerable latitude (or flexibility). The WTO TRIPS Agreement, while requiring in principle that patents *shall be available for any inventions, whether products or processes*, provides for several exceptions that WTO members may apply in their patent laws" [18].[10]

Patent and property rights are protected by WTO, but "compliance with TRIPS is a prerequisite for WTO membership and article 31 of the TRIPS Agreement address the right of WTO member states to award compulsory licenses……Notably, Article 31 does not discuss the circumstances under which compulsory licenses would be justified. However, for national emergencies and other circumstances of extreme urgency, Article 31 provides that a compulsory license may issue without the proposed user having to first make an effort to obtain a voluntary license from the patent holder" [19]. Moreover Declaration on the TRIPS Agreement and Public Health (Doha Declaration) affirms that: "we recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement" [20].

Beside compulsory licenses granted by an international treaty, there are also national legal mechanisms that confer a government's statutory authority to issue a compulsory

[10] Agreement on Trade-Related Aspects of Intellectual Property Rights - TRIPS Agreement - is an international agreement on intellectual property that is one component of the treaties that created the World Trade Organization - WTO - in 1995.

license, such as the Section 1498(a) of Title 28 of the US Code that authorizes the federal government to take private property for public use.[11]

Under the threat of the issue of compulsory licenses for Tamiflu, in April 2007 Roche signed voluntary licensing agreement with external contractors to produce the antiviral. Voluntary licensing agreement can partially solve the problem of a scarce supply, but can not answer the problem of an insufficient demand because of the high price of drug. What the pharmaceutical industry objects to a compulsory license is the fact that it would "take away incentives for other companies to undertake the difficult and costly work of searching for new antivirals and vaccines for this possible health crisis. Because drug products are time-consuming and expensive to develop but relatively easy to copy, the pharmaceutical industry is particularly dependent upon the patent system" [19]. Crucially, even if the drug was subject to a compulsory license, firm could receive royalties, but it would have no control on the sale price of the drug that could be sold as a cheaper generic version.

Licensing agreement can not be considered an efficient solution and could be of interest to move toward a liability rule.

In the case of antiviral dispute, a court intervention could be invoked to solve the dispute. Following [3] a judge could confirm the patent right for the pharmaceutical firm or could suspend the patent right and permit production to generic firms. Moreover the court could settle the dispute by defining a new right and correlated duties, for example the judge might define a right for the specific use of the drug formula for generic firms and include that generic firms will pay a price equal to patent holder opportunity costs to avoid compulsory licenses.

This arrangement could be obtained by a liability rule, that appears the appropriate strategy to protect legal entitlements under ambiguity and strategic behavior. In fact property rules give to the owner of the entitlement the exclusive power to exclude, through the market price mechanism, the others from using it, i.e. property rules prevent all non-consensual transfers; on the contrary liability rules give to non-holder the possibility to take the entitlement at a determined (judge or legislator) price with or without the approval of the owner. As a matter of fact, the approach based on property rules (patent rights of antiviral drug licensers) assumes that "market through price mechanism is able to coordinate productive activities and allocate resources to their most productive use….From the supply-side by introducing private incentives to invest in creation, development and

[11] The Takings Clause of the Fifth Amendment to the U.S. Constitution authorizes the federal government to take private property for public use.

dissemination…..from demand-side, the market is generally seen as an efficient system for aggregating, processing, and responding to information about what people want….The market may fail to allocate resources efficiently in cases where consumers' willingness to pay understates societal demand….Simply put the demand signalling function of the price mechanism does not necessarily work well when purchasers use a resources as an input to produce public goods and merit/non-market goods" [21].

The crucial question is the existence of incomplete property rights that derives from relevant unforeseen contingencies and transaction costs. The existence of unforeseen contingencies means that human beings have incomplete, fuzzy or vague knowledge of all possible future states of the world related to their actions, that is they face ambiguity. Ambiguity makes states of the world included in decisional models not exhaustive and incomplete. Ambiguity induces very large transaction costs that prevent the existence of complete contracts.

Incomplete contracts originate in the Coase's view a *bundles of rights*, in fact "function other than to serve as the baseline for contracting or for collectively imposing use rights in resources, and he modelled conflicts over the use of resources exclusively in terms of bipolar disputes between A and B. Wittingly or not, this gave rise to a conception of property as a cluster of *in personam* rights and hastened the demise of the *in rem* conception of property" [22]. Differently from Blackstone that considers the property as being a right *in rem*[12] that entails "that sole and despotic dominion which one man claims and exercises over the external things of the world, in total exclusion of the right of any other individual in the universe" [23], the legal realists[13] promoted the concept of property as bundles of legal relations and Coase's view by which "we may speak of a person owning land and using it as a factor of production but what the land-owner in fact possesses is the right to carry out a circumscribed list of actions" [25]. Coase considered property as a list-of-uses of a given resource or collections of use rights that induce social costs and externalities. Coase observes that "the rights of a land-owner are not unlimited…[in fact] …. A system in which the rights of individuals were unlimited would be one in which there were no rights to acquire….[then].. We may speak of a person owning land and using it as a factor of production but what the land-owner in fact possesses is the right to carry out a circumscribed list of actions" [25]. In this perspective Coase considers property rights in terms of permitted uses resulting from

[12] Smith and Bentaham accept the notion of property as a *right in rem*.

[13] Holfeld [24] can be considered as the intellectual noble father of the metaphor *bundle of rights* to design property that became the core of legal realist's theory and then of the Coase's law and economics.

juridical resolutions of conflicts whose costs can exceed the gains deriving from legal transactions. For long the logic consequence of this interpretation of Coase's approach was the superiority of market allocation (price regulation) of permitted uses with respect to government regulation. Crucially, Coase sets that when there is an increasing number of parties involved in a dispute that overwhelms bilateral contract, it could be necessary to come back to public regulation.

By resting on the notion of entitlement, Calabresi and Malamed move from Coase's approach, distinguish between property rule and liability rule and introduced "forced exchange as the preferred option for dealing with large-number problems where contractual exchange of use rights is infeasible" [22]. In Calabresi and Malamed's perspective, large numbers cases do not induce question about the *in rem* nature of property rights and do not involve government regulation, as in Coase, but illustrate "the need for liability rules, i.e., a mode of protection of entitlements that permits forced exchange in return for the payment of just compensation. The presence of large numbers of affected individuals is the occasion for shifting from voluntary exchange to forced exchange of *in personam* entitlements, not for shifting the analysis from *in personam* to *in rem* rights" [22].[14]

It appears reasonable an interpretation of the disputes about antiviral drugs in terms of post-Coasean theory of property rights. Original agreements between Gilead-Roche and Biota-GSM produced incomplete contracts and induced the possibility to sue Roche and GSM claiming breaches of contract and fiduciary duties, indeed for failing [26]. The dispute between inventors and Big Pharma is a question about the agent's effort and residual claimant, "a farmer who leases land at a fixed rent is a residual claimant of the attributes of the land over the period of the lease; the greater the farmer's ability to affect the long-term value of the land, the more likely lease terms will be longer (or that full ownership will be transferred)"[22]. The voluntary agreement based on a monetary adjustment and new royalties confirms the perspective of incomplete assignment of all elements of economic value in a contract.

Differently, the dispute about Big Pharma and Governments about generic producers originates from a market failure, i.e. insufficient production of antiviral drugs to contain a pandemic avian flu. This failure is due to the "world of incomplete rights, externalities over undefined uses call for a court intervention aimed at defining a new property right through either a property rule or a liability rule. Independently of whether new rights are created by

[14] A quite different approach to property rights is the seminal paper of Hansmann and Kraakman [27].

property or liability rules, the nature and the extent of future externalities over conflicting undefined uses could generate new processes of rights' definition"[28]. If externalities, insufficient protection of the world population and possible catastrophic consequences induced by an uncontained pandemic flu derive from the incompleteness of rights, liability rules are alternative ways for a court to define new property rights and correlated duties. If property rights are incomplete bundles of uses means then there are alternatives ways to define new property rights "in turn, these newly created rights are protected by a property rule until a new externality over undefined uses bundled in those rights does emerge. At that point courts might be called for a decision which may involve again either a property or a liability rule"[28]. In debated antiviral case, given high transaction costs and potential catastrophic damage to victims, the court can use a liability rule and permit generic producers to manufacture antiviral drugs at administrated prices that include royalties paid to Roche and GSK. Royalties should be at least equal to the royalties paid with compulsory licenses (opportunity cost of the owner). Patent rights give a temporary monopoly power to the owner, administrated prices can be derived as in a monopoly by considering marginal price and applying a low mark-up.

5. A TRUST FUND FOR AN EFFICIENT VACCINE PRODUCTION

If the application of liability rules can potentially solve the market failure, notably it is unable to correct no-market or institutional failures.

Vaccines are supplied by a bunch of distributors and humans are dependent on a small number of companies for the major vaccines with a sharp downward trend in new product introductions. Vaccine production requires sophisticated production plans and very large expertise that are difficult to replicate: if a firm exits from market its substitution is improbable. Vaccine producers face: distorted incentive, that is demand pattern (price and amount) that does not reflect the true benefit from medicines, extreme liability exposure and difficulty to obtain adequate insurance premiums to cover risks.

Institutional failures are very dangerous in vaccine productions. Unlike antiviral drugs, vaccines do not exist and they have to be synthesized and manufactured. Vaccine preparation is affected by incompleteness and there is ambiguity about occurrence of pandemic flu, vaccine effectiveness, cost of a pandemic and so on. Basili and Franzini give a formal representation of this problem and put in evidence a possible solution through an optimal

incentive scheme in a principle-agent framework. Crucially, Basili and Franzini show that "ambiguity aversion does not systematically cause agency costs to rise by a non-monotonic monetary transfer scheme...This implies that 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"[17].

Vaccine production is also affected by liability for vaccine related injuries such as the occurrence of adverse reaction to immunization. Side effects or serious rejections are rare and ambiguous, but vaccine producers have been exposed to huge legal expenses for liabilities that have induced much of them to suspend production.

Differently from individual risks, such as car accident, that are independent and have known frequencies, then they can be insured, extreme events induce correlated risks whose frequencies are ambiguous or unknown and involve very large population and geographic areas at once. Chichilnisky and Heal [29] propose to combine insurance and derivatives in catastrophe bundles. Catastrophe bundles "consists of an insurance instrument and a novel derivative security for betting on the frequency itself. .....The combination of both instruments ensures that the reinsurer is not exposed to more risks than it anticipates whatever the pattern of the hazards. Alternatively, we can use a modified and more complex form of insurance, with contracts conditional on the frequency of the observed event. In this case no separate securities transactions are needed. A third possibility is to use what is called mutual insurance, together with the securities" [29]. Even if in principle it is possible to span an efficient private insurance market for extreme risks based on catastrophic bundles, because of ambiguity, moral hazard and high correlated losses could be impossible to obtain adequate insurance at premium considered acceptable by vaccine firms that will not invest the time and money to develop the products.[15]

Nevertheless it could be of interest to introduce avian flu pandemic and large-scale risks (natural disasters etc.) in a commercial coverage mechanism with private and public

[15] The first catastrophe indexed bond - *catastrophe bonds* or *cat bonds* - providing coverage against terrorism was issued on the capital markets in August 2003 (the 18th Football World Cup). FIFA issued a cat bond (Golden Goal Finance Ltd) covering its investment up to $262 million. The financial cover, however, is not specific to terrorist action since it provides coverage for FIFA for all kinds of catastrophes, natural, terrorist, or others. The second catastrophe bond (Vita Capital) was created in December 2003 by Swiss Re to transfer to financial markets exposure to mortality risk amounting to $400 million under a stop loss provision [30].

partnership, such as TRIPRA, to face catastrophic economic and social consequences induced extreme events.[16]

In vaccine industry there are some problems: compensation of injured persons, incentive to produce vaccines and increase the number of producers. Solutions require direct actions of government and private sector to:

- ensure an adequate supply by becoming *manufactured of the last resort* or introducing incentive scheme;
- institute a global insurance and compensation system for vaccines, able to ensure liability protection, assure an adequate supply and stabilize costs.

A pandemic flu looks like a public good (bad), indeed non-rivalry and non-exclusion, but mass vaccination induces a positive externality. In a seminal paper Demsetz considers private production of public goods as a problem of joint production and under competitive conditions he declares that "payment of different prices for the same good is consistent with competitive equilibrium….the geometry of equilibrium shows that the vertical summation of the demand prices equals the marginal cost" [31]. In Demsetz's view price discrimination is able to conduct to a competitive equilibrium, given ability of identifying and separating submarkets, that is perfect exclusion is socially efficient. What happens if strategic behavior, incomplete information and irreversibility affect the private production of a public good? The world faces the spectre of an influenza pandemic without a sufficent capacity of producing vaccines. Crucially the Demsetz'z solution works well if producers have a complete and fully knowledge of market demands, but vaccine demand depends on an extreme event (ambiguous and catastrophic in consequences) that may prevent efficient allocation.

Agents act with a coarse representation of all possible contingencies that could influence outcomes. The awareness of the incomplete description of possible states of the world affects their behavior, makes the standard approach based on maximization of expected utility inappropriate and inefficient incomplete contracts can emerge if agents are non-

[16] On November 26, 2002 the US Congress adopted the Terrorism Risk Insurance Act (TRIA) which established a system of risk sharing between the federal government, the insured and insures. TRIA was adopt because of such a catastrophic event is capable of inflicting high human and financial losses able to curtail he prospect of economic development for involved sectors. TRIA is a special terrorism insurance program that overcomes failures of private insurance markets to develop capacity to write terrorism risk insurance coverage. TRIA requires that insurers make available commercial lines coverage against certain certified acts of terrorism on terms and was extended through December 31, 2014 as TRIPRA.

expected utility maximizers.[17] Unforeseen contingences can prevent (no-trade) a Pareto optimal allocation ([33]; [34]) and non-neutral ambiguity attitude may generate an incomplete market economy that does not converge to a Pareto optimal equilibrium ([35]). Finally, Harsanyi [36] seminal result of possible linear aggregation of expected utility maximizers (social utility is a convex combination of the consumers' utilities) is not true under ambiguity, in fact "any behavior that is not neutral towards uncertainty leads to the impossibility of linear aggregation. As a consequence, it is not possible that society's preferences be, say, uncertainty averse, unless there is a dictator" [37].

As a result there is room for public and private sector in providing protection against possible pandemic disease. In the case of vaccine manufactures, a possible model for private and public partnership could be a Global Vaccine Injury Compensation and Production Program (GVICPP) financed by pharmaceutical industry and Governments. It is possible to imagine GVICPP as a generalized version of the US Vaccine Injury Compensation Program (VICP) created in 1986.[18] The VICP "has succeeded in providing a less adversarial, less expensive and less time-consuming system of recovery than the traditional tort system that governs medical malpractice, personal injury and product liability cases" (VICP-HRSA). Notably, VICP is funded by an excise tax imposed vaccine doses.[19]

Differently from the US VICP, the GVICPP should be a system able to assure an adequate global supply of vaccines at low prices and ensure a global liability protection. It is a wide program that causes very large expenditure.[20] As a consequence GVICPP could not be funded through an excise tax on vaccines like in the case of VICP, but more properly by *hypothecated* (*earmarked*) *taxes* on drug and medical sales. A hypothecated tax is a clear mechanism to finance the provision of public goods. There are a lot of virtuous examples such as in environmental conservation (tax on CO2 emission) or health service (tax on tobacco). Hypothecated taxes on medical and drug sales may be suggested when information is imperfect or other market mechanisms to allocate revenues across public service fail. GVICPP should have the role of promoting production and diffusion of vaccines among humans and providing liability protection to vaccine makers. Crucially GVICPP could be

[17] Formal treatments of the coarse contingencies problem is in Epstein *et al*. [32]

[18] VICP derived from the National Childhood Vaccine Injury Act is a no-fault, i.e. the claimant need not prove negligence on the part of the physician or the manufacturer of vaccine, alternative to the traditional tort system for resolving vaccine injury.

[19] VICP is funded by a $0.75 excise tax on each dose of vaccine purchased. The Department of Treasury collects the excise taxes, and oversees and manages the investing activities for the Trust Fund. As of January 31, 2007, the Trust Fund balance was nearly $2.5 billion [39].

[20] Estimated insurance premium to spend for containing to the next influenza pandemic ranged from $48 million to $2,184 million per year.

considered for developing medical remedies for neglected diseases, that affect a billion of persons in low-income populations and cause up to one million of deaths annually. There is a large academic debate about incentive effects of earmarked taxation with respect to a price mechanism[21], but market failures and lack of vaccines for not profitable diseases, make clear that price mechanisms are ineffective and inefficient. The hypothecation of revenues for vaccine production may introduce rigidity in expenditure for drugs and create vicious circle between health taxes and expenditures, but there is a huge experience in health and environmental economics that can be easy transferred in this context to ameliorate possible inefficiencies.

6. CONCLUDING REMARKS

Shortage of antiviral drugs and insufficient production of vaccines are not accidents, but consequences of market and institutional failures. Patent and property rights that were introduced to promote the social welfare may induce catastrophic events with terrible social and economic consequences. It is necessary to remove legal impediments to the development of efficient medical remedies without destroying pharmaceutical industry. This paper shows that this ambitious target is possible by transforming property law in liability rule in antiviral market and substituting price differentiation with administrated prices in vaccine market financed by a trust fund.

[21] Price differentiation and patent rules are invoked as proper instruments to promote R&D in pharmaceutical industry; "R&D costly roughly $1 billion for each new drug approved in 2007, including the cost of failures and necessary return on capital invested over the 8-12 years required for R&D" [38]. Crucially antiviral drugs able to contrast avian flu were invented by two small bio-firms that sold effective drugs to Roche and GSK for a bunch of money and vaccine industry has a very limited production capacity. Probably it is necessary to change the business model, such as in music and entertainment industry, because it is impossible to recover the cost of an inefficient industrial organization with the revenues from a few blockbuster products.

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