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Swine influenza and vaccines: an alternative approach for decision making about pandemic prevention

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Abstract

Background: During the global pandemic of N1H1 (2009) influenza, many Governments signed contracts with vaccine producers for a universal influenza immunization program and bought hundreds of millions of vaccines doses. We argue that, as Health Ministers assumed the occurrence of the worst possible scenario (generalized pandemic influenza) and followed the strong version of the Precautionary Principle, they undervalued the possibility of mild or weak pandemic wave.

Methodology: An alternative decision rule, based on the non-extensive entropy principle, is introduced and a different Precautionary Principle characterization is applied. This approach values extreme negative results (catastrophic events) in a different way than ordinary results (more plausible and mild events), and introduces less pessimistic forecasts in the case of uncertain influenza pandemic outbreaks. A simplified application is presented through an example based on seasonal data of morbidity and severity among Italian children influenza-like illness for the period 2003-2010.

Principal Findings: Compared to a pessimistic forecast by experts, who predict an average attack rate of 15% for the next pandemic influenza, we demonstrate that, using the non-extensive maximum entropy principle, a less pessimistic outcome is predicted with a 20% savings in public funding for vaccines doses.

Conclusions: The need for an effective influenza pandemic prevention program, coupled with an efficient use of public funding, calls for a rethinking of the Precautionary Principle. The non-extensive maximum entropy principle, which incorporates vague and incomplete information available to decision makers, produces a more coherent forecast of possible influenza pandemic and a conservative spending in public funding.

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Introduction

On June 14 2009, the Director-General of the World Health Organization (WHO) declared a global pandemic of N1H1 influenza and suggested the application of the WHO Interim Program (2007) to mitigate the pandemic emergency. Given the constant evolving nature of influenza viruses, the frequent reformulation of the vaccine strain candidates coupled with the possible shortage in the supply of these vaccines due to constrained production capacity, the WHO suggested combining vaccination and an extensive campaign of antiviral prophylaxis and treatment.

There was uncertainty about the nature of a influenza pandemics and its economic impacts, but all studies (global, continental, regional) on the possible human and economic costs of an influenza pandemic agreed in considering global consequences catastrophic: uncountable deaths and economic losses of about a trillion US dollars (World Bank suggested 4.8% of global GDP). Many governments signed pre-pandemic contracts with vaccine producers for a universal influenza immunization program and hundred million of doses of vaccine were bought, or subscribed options to buy, (e.g in spring 2009 the US government signed contracts for 251 millions of doses and UK and Netherlands bought vaccines for the 30% of all population). [1-5] Curiously, some countries were so pessimistic with respect to the evolution of the pandemic that they bought enough vaccines to give double doses to each citizen. Others, like Poland in Europe, were less pessimistic and did not sign pre-pandemic contract. The adopted containment strategy, whom ended in February 2010, (with more than 213 countries reported cases of pandemic influenza H1N1 at least 16,226 deaths), may appear to be a success. However, millions of short-running antiviral does and a large number of pandemic vaccine doses remained on the shelves, as millions of people refuted vaccination (e.g. only 60 million Americans had been vaccinates). These undesired outcomes induced some critical questions on the role of the WHO in declaring the pandemic alert, and the function of pharmaceutical industry in the management of such emergencies. Cohen and Carter (2010) published the paper 'WHO *and the pandemic flu conspiracy*' [6] where they supported the conspiracy theory charging the WHO to cover "troubling questions about how the WHO managed conflicts of interest among the scientists who advised its pandemic planning, and about the transparency of the science underlying its advice to governments". Moreover, Cohen and Carter reported doubts about the manner in which the pandemic risk was estimated and communicated. Wilson (2011) [7] offered a different view and interpreted the difference between predicted and observed effect of the pandemic H1N1 as a problem of " how …deaths are estimated, counted and compared" [7, pp.7]. In this paper we contribute to this discussion by considering the management of H1N1 pandemic as a problem of decision making rules. In the puzzling and ambiguous scenario of the pandemic influenza, the WHO and Health Ministers decided to contain the H1N1 (2009) influenza by adopting the strong version of the Precautionary Principle (PP) which dictates '*better safe than sorry*'. This decision corresponds to the application of Wald's *maximin criterion*[8], that evaluates acts according to the worst possible scenario and almost everywhere induces the most conservative choice. We argue that the H1N1 pandemic could have been managed with a less conservative rule. This paper suggests that the application of the full conservative notion or strong version of the PP induces overreaction. We propose the application of a less conservative PP based on the notion of non-extensive entropy, which reduces the degree of preventive actions required. In order to demonstrate the application of this principle, a simplified example based on Italian data about influenza-like-illnesses (ILI) among children for the period 2003-2010 is presented.

Method: non-extensive entropy maximization

In the global pandemic of N1H1 influenza,[9] Health Ministers faced conflicting and not necessarily independent opinions of experts and scientists due to the absence of epidemiological data testing the severity of pandemic influenza. Therefore, opinions available to decision-makers appeared to be incomplete and generally uncertain. Nevertheless, since experts and scientists opinions were expressed as probability measures, densities, mass functions or odds, their probability distributions could be used to form a *consensus distribution*, that is a combination of all probability distributions. Such a consensus distribution can be used to develop a rational decision rule can be based. In the standard decision theory, Bayesian pooling methods, experts' opinions and personal judges exist as methods for eliciting a consensus distribution. These methods faces problems (i.e. arbitrariness of the pooling weights, the dependence between the decision-maker's information and the experts' information, dependence among experts' probability distributions or stochastic dependence, and calibration of experts' opinion) and crucially they don't leave room for ambiguous attitude. Nevertheless, the ambiguity attitude, that is the attitude about the reliability of available information on the underlying uncertainty, that emerges when individuals face vague and incomplete statistical data, influences perception of risky events and induces human beings to elicit probabilities and apply decision rules that violate the standard rational paradigm.

As an alternative to the Bayesian pooling methods, this paper introduces a decision rule based on the *non-extensive entropy*, which portraits the concept of generalized entropy as a quantitative criterion for measuring uncertainty in estimations. The decision-makers assess extreme negative results (catastrophic events) in a different way than ordinary results (more plausible events).[10, 11]

Crucially, since extreme events lay on the tail of the ordinary probability distribution, the non extensive entropy principle considers their divergence in order to forecast the pandemic events. Ambiguity attitude of the decision-maker is represented through the non-extensive statistical mechanics, indeed a non-additive generalization of quantum information theory based on the non-extensive entropy, and the maximum entropy solution is defined.

Formally, let S be the set of states of the world and $i = 1,...,n$ be a finite number of information or experts' judgments and let P^i the probability distribution i on S, then the non extensive entropy is defined as follows:

> ***Definition 1***. $H_q^* = \frac{1}{1-q}\left(1-\int P(x)^q dx\right)$ *is known as the Tsallis entropy where* $q \in R$ *such that if* $q < 1$ or $q > 1$ *then super-extensivity and sub-extensivity occurs, respectively.* H_q^* *is concave for* $q > 0$ *(and convex for* $q < 0$*), hence q-entropy maximizing distributions, given specific constraints, are uniquely defined for* $q > 0$.

The non-extensive entropy is a parametric entropy that depends on the factor q, the entropic index that represents the dependence degree among experts opinions is $q \to 1, \lim H_q^* = H_{BGS} = -\int_{q\to 1} P(x)\log P(x)dx,$ which is the usual concave and extensive Boltzman-Gibbs-Shannon entropy.[12] This form of entropy was first introduced by Tsallis in 1988, as a generalization of the standard entropy, and has been used in many applications, such as solar wind, high-energy physics, financial markets etc.

In decision-making, the ordinary risk distribution (P) and the chance of the catastrophic event (Q) may be observed. They satisfy properties in *Definition 2* and are used in finding the distribution of risk H^*(P) as the solution of the following Problem 1.

Definition 2. *Let P and Q be two probability distributions, such that* $Q(x)$ *is absolutely continuous with respect to* $P(x)$, *then the Kullback-Leibler or relative entropy of* $Q(x)$ *and* $P(x)$ *is* $H_{KL}(P(x) \| Q(x)) = \int P(x)\log\frac{P(x)}{Q(x)}dx$ *and it exhibits the divergence between* $P(x)$ *and* $Q(x)$.

The probability distribution $Q(x)$ represents the excess of a randomness over the distribution $P(x)$, and the H_{kl} , which is the Kullback-Leibler distance, measures the maximum feasible divergence between the two probability distributions. It is worth noting that the measure of distance between distributions represents the constraint that has to be satisfied by the distribution *H*(*P*) which is the optimal solution of the following *Problem 1*:

Problem 1.

$$MaxH(P) = -\int P(x)\log P(x)dx$$

$$s.t. \quad H_{KL}(P(x) \| Q(x)) = \int P(x)\log\frac{P(x)}{Q(x)}dx = \theta$$

Crucially, *H**(*P*), the solution of this constrained maximum entropy problem, is "the Renvyi entropy of distribution $Q(x)$ with index q, minus a linear function of the constrained"[13].

Definition 3. *The Renvy entropy is* $H_q^R = \frac{1}{1-q}\log\int Q(x)^q dx$, *with* $q \neq 1$, *and it is concave only for* $0 < q \leq 1$

Results: an example of the non-extensive entropy in influenza pandemic forecast

Let suppose that in preparing the pandemic prevention program the decision-maker wants to model all information available about influenza attack rates but she/he also wants to be as neutral as possible about what is unknown. Therefore, calling *H* the model for the pandemic influenza attack rate we need to assign a level of severity to the next influenza wave *H(p)* in order to find the most "uniform" decision model. The parameter p is the level of severity. Observing influenza time series data, the level of severity may be broadly grouped into five levels, called Very Low (*VL*), Low (*L*), Medium (*M*), High (*Hi*), Very High (*VHi*). With this information, the first constraint in modeling H is

(a) $H(VL)+ H(L)+ H(M)+H(Hi)+ H(VHi)=1$

and we can search a suitable model which obeys this constraint. The constraint is satisfied if model H always predicts that the attack rate is very low, $H(VL)=1$, or if the model predicts that *VL* and *L* occurs with probability ½, and so on. Infinite solutions are possible. Based on available information about previous pandemics we know that very high attack rate also can occur, such as with the pandemic flu of 1918. We can assume that the total probability is evenly distributed among events, $H(VL)=H(L)=H(M)=H(Hi)=H(VHi)=1/5$, and this sort of model is the *most uniform model*, subject to the assumption that all levels of severity can occur. However, further information may be available, for example that levels *VL* and *L* appear 30% of the time. Therefore this extra piece of information, together with constraint (*a*), reduces the number of solutions but again different models can be consistent and the most uniform model *H,* which allocates probabilities as evenly as possible given the two constraints, is

(b) $H(VL)=H(L)=3/20$ and $H(M)=H(Hi)=H(VHi)=7/30$.

Proceeding by adding piece of information the model H is getting complex and two problems are envisaged: what exactly is meant by uniform model? How does one find the most uniform model subject to a set of constraints?

The maximum entropy method answers both questions predicting to model all that is known and assume nothing about what is unknown. Therefore, given a collection of influenza events[15-19], it chooses a model which is consistent with all these previous observable events, but otherwise is as uniform as possible. This intuitive principle of building the maximum-entropy decision rule is followed in our numerical example where we assume that distribution $P(X)$, $Q(X)$ and θ, as in *Problem 1*, are known and based on simplified assumptions.

The ordinary attack rates of influenza come from the Italian annual influenza-like-illnesses (ILI) morbidity and severity data, provided by the surveillance system which collects epidemiological and virological data from national networks.[14] Data refer to the period 2003-2010 for the following age classes: 0-4, 5-14, 14-64 and over 65. Data span from week 42th in 2003 to week 17th in 2010 and are based, on average, on over one million people. For the year 2009, data are also available for the weeks 17th-42th, defined as the *'non ordinary influenza season'*. An overview of influenza attack rate and a breakdown for age classes in ordinary and non-ordinary flu season is reported in *Table 1*.

[*Table 1 about here*]

In the ordinary season, the period 2004-2005 presented on average the highest attack rate to all age classes, except for the young group (5-14 years) for which the worst period was 2009-2010, with an attack rate of almost 10%. On average, the swine flu period shows lower attack rates for all age classes except 5-14. Similarly, in the non ordinary influenza season the influenza attack rate is lower than in any of the ordinary seasons for each age class. Contrasting the ordinary and swine flu season attack rates, we find some statistically significant differences as shown in the last row of *Table 1*. In the swine flue season, the young group experienced a higher attack rate than the ordinary season (*p-value*=0.04), while the Adult and Senior group show a statistically lower attack rate than the ordinary season (*p-value*=0.002 and *p-value*=0.0001). No difference is found for the Children group.

Based on these results, this *post-pandemic* estimate suggests very mild effects. However, at the beginning of 2009, the Italian Health Minister could not know the impact of swine flu, but had to decide which quantity of vaccines to buy. Following the strong version of the PP, the Health Minister could sign a pre-influenza contract for buying millions of vaccines doses according to international forecast of the attack rate. Alternatively, the maximum entropy rule suggests using the international prediction and the ordinary influenza attack rates for obtaining a less pessimistic view.

Let's assume that the influenza attack rate variable is broadly summarized in five levels as:

1. *Very Low-VL* (less than 10/1000 people);
2. *Low-L* (11-50/1000 people)
3. *Medium-M* (51-100/1000)
4. *High-Hi* (101-200/1000)
5. *Very High-VHi* (201-350/1000)

Therefore, counting the proportion of times that each age class registers an attack rate in one of the 5 levels in the ordinary influenza season, we get the severity of influenza distributions as in *Figure 1*.

[*Figure 1 about here*]

As expected for all age classes, the seasonal attack rate distribution is concentrated in the first two categories (*L* and *VL*) and each of these distributions may be used as a proxy for the distribution $P(x)$ in *Problem 1*. In developing *Problem 1,* let us consider a $P(x)$ distribution for children which predicts that level *VL* occur in the 80% of cases and *L* with probability 20%. The average seasonal attack rate is 10/1000. For the distribution $Q(x)$ of *Problem 1,* we assume that experts' forecast for the next influenza pandemic predicts an average attack rate of 15% with the distribution concentrate between levels *M* and *Hi*. Applying the strong version of the PP, the government should buy doses of vaccine for 15% of children which at a cost of €21 per dose, implies a spending of about €3 millions. However, the decision-maker may observe that:

- the seasonal distribution $P(x)$ in *Figure 1* for children,
- distribution $Q(x)$, is as the tail of the seasonal or ordinary influenza distribution,
- and the relative entropy of $Q(x)$ and $P(x)$ is within the range 10-20. This assumption reflects the fact that the level of uncertainty (θ) is fixed in this range in order to reflect a medium level of knowledge. In fact, according to the maximum entropy theory there is no uncertainty when $\theta = 0$ and maximum for $\theta = \infty$ uncertainty.

Solving *Problem 1* numerically,[20] we get the $H^*(P)$ distribution of the next influenza attack rate that is largely flat but heavier tails than the seasonal influenza. This distribution predicts and average attack rate of 12%, which is less pessimistic than expert's forecast. Further, using a Tsallis distribution in decision making for the pandemic influenza, we explicitly take into account uncertainty and we acknowledge that the distribution for decision-makers' choice is quite broad as in *Figure 2*.

[*Figure 2 about here*]

In conclusion when using this decision rule, the decision-makers could rationally decide to buy vaccines doses for only 12% of the children, which implies a public saving of around 500,000 € (17% of expenditure) compared to the strong PP rule.

Concluding remarks

The (H1N1) 2009 influenza pandemic highlighted the need for a rational decision rule to assist policy makers and planners with effective health system responses to epidemics. We introduce a decision rule capable of taking explicitly into account the uncertainty about the pandemic infection of H1N1. We considered the selection of the best containment strategy given ambiguous and incomplete information for the pandemic H1N1 (2009), and we concluded that one critical drawback of the containment strategy was the application of a strong version of the PP. In fact, different Health Ministers assumed the occurrence of the worst possible scenario and undervalued the possibility of mild or weak pandemic wave. This over-pessimistic view resulted in billions of Euros/dollars allocated to vaccines stockpiling. We argue that by applying a different decision rule, based on the maximum entropy principle, decision-makers may smooth out misevaluation and induce less pessimistic choices.

Given the state of information at the beginning of 2009, if the new functional form of pandemic influenza distribution, based on constrained Tsallis entropy, had been applied, a target vaccination program would have emerged as a more sensible choice, with respect to a universal program, and billions of Euros/dollars would have been saved. Finally, as the pandemic virus of H1N1 (2009) was first recognized in North America as a reasserting of the influenza A (H1N1) subtype and then confirmed in Australia and New Zealand in May 2009, the influenza distribution observed in one hemisphere could have been used as a proxy in the maximum entropy setting for predicting the attack rate in other hemispheres.

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Table 1 The average Italian ILI rate in the season 2003-2010/1,000 people

ILI-season	**Children** (0-4)	**Young** (5-14)	**Adult** (15-64)	**Senior** (over 65)	**All**
2003-2004	5.33	3.77	1.74	1.07	2.04
2004-2005	8.44	7.43	3.23	2.57	3.91
2005-2006	4.20	2.91	1.15	0.66	1.44
2006-2007	6.91	4.62	1.73	0.93	2.23
2007-2008	7.69	5.73	2.33	1.21	2.83
2008-2009	6.58	4.75	2.04	1.20	2.48
Total in ordinary season	**6.52**	**4.87**	**2.04**	**1.27**	**2.49**
2009-2010	*8.35*	*9.71*	*2.31*	*0.96*	*3.50*
Non ordinary influenza season	*1.59*	*0.84*	*0.34*	*0.16*	*0.43*
Total in swine flu period	**5.04**	**5.36**	**1.34**	**0.57**	**2.00**
P-value: H_0: ordinary=swine flu Kruskas Wallis test	***0.08***	***0.04***	***0.002***	***0.0001***	***0.01***

Figure 1 The severity of influenza distribution obtained by the Italian weekly ILI attach rate for age classes (P(x)).

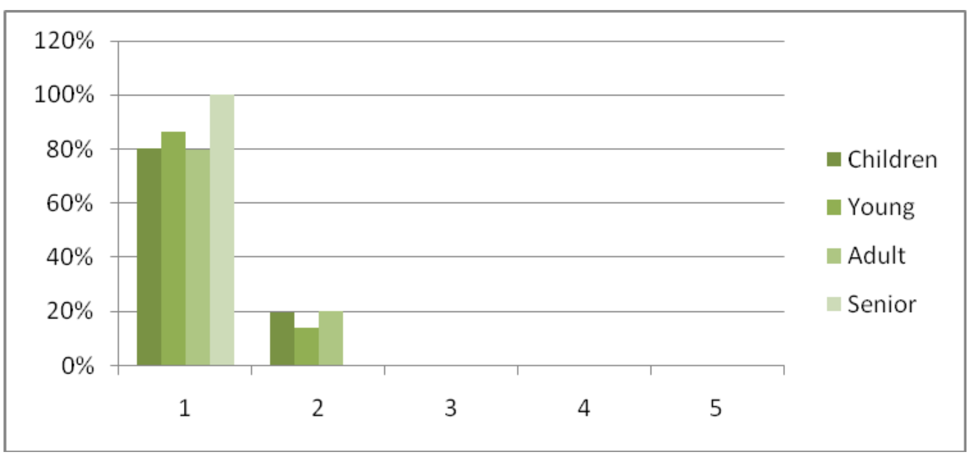

Figure 2 Smoothing distribution of season influenza distribution P(x) and expected attack by experts Q(x) and resulting Tsallis distribution H*(P) for next influenza attack rate forecast