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The H1N1 Pandemic Flu. Some Critical Remarks from a Legal Point of View

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Commentary

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ABSTRACT

Aim: This paper analyses the global and European responses to the break out of the H1N1 virus in 2009 and highlights the major deficiencies of the European authorization procedure of vaccines against H1N1 pandemic flu.
Study Design: The study analyses the institutional reactions to the spread of the H1N1 pandemic flu (commonly called swine flu). The study reports the fundamental steps undertaken by global and European Institutions since 2009 to face the spreading of the H1N1 flu.
Methodology: The study applies a legal methodology proceeding from formal rules towards the substantial effects taking place in the specific health protection field

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considered.
Results: The analysis of the European authorization procedure of vaccines against H1N1 pandemic flu shows the lack of coordination between Member States and the European Union, as well as coordination between the European Medicines Agency (EMA) and the European Office of the World Health Organization (WHO); moreover, a fundamental violation of the precautionary principle emerged. In the European context, in fact, the principle does not coincide with the temporary nature of the measures, but reflects the fundamental distinction between assessment and risk management.
Conclusions: The supranational mediation of the European Union has offered in many cases the guarantee of health protection within contexts in which the multiplicity of involved interests increases the level of conflict. That mediation has definitely failed in the case of swine flu because of the lack of supranational constituency representation within the European Medicines Agency that allows the intergovernmental component and the underlying unilateral protection of economic interests to resurface.
In the case of swine flu, the trust relationships between global and European bodies have been affected by the lack of transparency of the responsible organizations (WHO and EMA) and the lack of pluralistic openness to different interests in the decision-making procedures.

Keywords: H1N1 pandemic flu; health protection; authorization procedure of vaccines; mediation of interests at European level.

1. INTRODUCTION

The current emergence at supranational and international level of the alert regarding the spread of pandemic influenza constitutes a recurring pattern. The flu virus subtypes appear to be an evolution of the previous ones and, therefore, an effective response in the sense of prevention and pharmaceutical care must be developed each time *ab initio*.

From the years 2009-2010 three main subtypes of A type flu appeared jointly: H1N1 swine flu, H5N1 bird flu, and the traditional seasonal influenza H3N2.

With regard to the H1N1 flu, its impact is characterized in a specific way: its spread also in temperate countries; its diffusion in different seasons from those typical of influenza; the large use within developed and developing countries of both antiviral drugs and vaccines.

In a medium-intensity flu season, some concerns derive from the 'backlash' of the former pandemic H1N1 virus, which in some countries was recalled for the deadly effects recorded especially among young and middle-aged adults.

While, more recently, in Greece there occurred 40 dead and over 140 infected, U.S. health officials have issued an appeal urging the mass vaccination: injection shield for everyone, including pregnant women.

In particular, the recent warnings issued by the Greek authorities propose some questions regarding the quality of the alarm system built at global and supranational level.

2. THE VACCINES FOR THE H1N1 FLU PANDEMIC

A highly significant and interesting case, which has highlighted the structural deficiencies of the overall process of dissemination and of the European procedure for the authorization of medicines, was that of vaccination in view of the spread of the H1N1 flu in 2009.

2.1 The Global Context

In April 2009, the World Health Organization (WHO) launched the alarm, since the virus began to be transmitted directly between individuals (without contact with the infected animals), towards defining a possible pandemic global flu alert of level 5 [1]. On the 3rd of June, the WHO announced the raising of the alert to level 6, which is the maximum degree of the pandemic scale. On the 14th July, the WHO declares the H1N1 flu unstoppable, recommending to all countries to obtain supplies of the vaccine, indicating as priority objectives the vaccination of healthcare workers and those most at risk, such as pregnant women and people aged more than 65 years.

The technical-scientific opinion on vaccination policies promoted by the WHO has been elaborated by the Strategic advisory group of experts (Sage), a group of experts composed of 15 members to represent mainly 3 instances: that of scientific expertise through members of research institutes, universities, governmental organizations such as public health departments and independent agencies; to find the main areas of existing expertise in medical research (monitoring programs of spread of infectious diseases, respiratory diseases, heart diseases, dysenteric diseases); the sum of the three major areas of intervention of the WHO in the fight against pandemic influenza (innovation, quality assurance and safety of care, integration of vaccination policy with other policy areas).

The selection of members of Sage is made through a public competition, on the basis of qualifications and previous experience, for a period of three years, renewable only once. Members must be and appear independent from the economic and political interests concerned by the policies of the WHO and to this end shall sign before the official appointment a declaration stating the absence of conflicts of interest. As observers, members of non-governmental organizations, professional organizations, representatives of technical agencies, associations of vaccines industry may be invited to attend meetings of the Sage, which take place in ordinary session twice a year.

In the case of the spread of H1N1 influenza, the Sage was supported by an ad hoc established committee, the *Policy Advisor working group on influenza A vaccines*, and to ensure regional representation, the conference of leaders of the WHO regional committees responsible for this field [2].

In February 2010, the WHO has admitted before the Parliamentary Assembly of the Council of Europe that was influenced by pharmaceutical laboratories when the pandemic of the virus H1N1 was declared, after that an investigation by the French newspaper *Le Parisien* had spoken of “relations of interest among six experts from the WHO and some pharmaceutical industries” [3].

Wolfgang Wodarg, German chairman of the Health Committee of the Council of Europe, spoke of a “false pandemic”, publicly accusing that pharmaceutical companies of having influenced the decisions of the World Health Organization to declare a pandemic: “to

promote their patented drugs and vaccines against flu, pharmaceutical companies influenced scientists and official agencies, responsible for health, and, so alarmed governments around the world, have led them to squander the restricted financial resources for ineffective and needlessly strategies vaccination and exposed millions of people to the risk of unknown side-effects of insufficiently tested vaccines" [4].

2.2 The European Context

The European Union has authorized so far different types of vaccines [5]: three types containing an adjuvant substance, the Celvapan (Baxter AG multinational), the Pandemrix (Glaxosmithkline), the Focetria (Novartis) [6] which was chosen by the Italian Medicines Agency for distribution in Italy [7], and two types of vaccine that do not contain adjuvants (Daronrix of Glaxo and Sanofi of Aventis) [8]. The main problems related to the vaccine detected in the scientific community dealt largely with the safety of adjuvants used to boost the immune response of the organism. The "exceptional circumstances" that have occurred in Europe, justified by the elevation of the influence of the degree of pervasiveness (from level 5 to level 6 alert) by the WHO in June 2009 [9], led to the marketing authorization of the vaccines under a simplified procedure [10].

Firstly, the prior authorization of the clinical trial concerned the so-called H5N1 bird flu antigen (virus of the same strain of H1N1 but not identical) and, secondly, the reports of clinical information have been updated through the surveillance after the placing on the market [11].

The evaluation process of the vaccines has therefore resulted not always linear and threw some shadows on the European Agency responsible for.

In December 2009, the European Medicines Agency (European Medicines Agency - EMA) passes from the reference of the Directorate General "Enterprise and Industry" to the influence of DG "Health and Consumer Protection" of the European Commission. The reasons that prompted this change are manifold. The connection of the EMA to the DG Industry certainly assumed that the center of gravity of the European Agency was especially the protection of business interests in the field of medicines.

Moreover, it had been pointed out that the European Medicines Agency failed to ensure the separation of the evaluation phase and the phase of health risk management.

In fact, the functions of representation and scientific advice were combined within the Scientific Committee for Medicinal Products Agency [12] differently from what happens in the European Agency for Food Safety (European Food Safety Authority - EFSA) [13], an agency more recently instituted than the EMA.

The Institution Regulation of the EFSA provides that the staff of the Scientific Committee and Scientific Panels shall be appointed by the Board of Directors upon proposal of the Executive Director following a public competition [14]. The organizational rules of the EMA seems to be capable of destabilizing the already precarious balance of European integration. Without the privileged position of the European administration [15], the traditional ways of the intergovernmental co-operation resurface weakening the position arising from the representation of the European institutions in scientific committees.

3. THE AUTHORIZATION PROCEDURE

The European Medicines Agency [16], through its Committee for Medicinal Products for human use, adopts an opinion which is transmitted in the centralized authorization procedure, to the Commission, to the Member States, to the applicant.

The opinion is not binding. However, the Commission must state precise reasons when distances from the opinion are taken [17]. In the decentralized procedure and the mutual recognition procedure, in case of persistent disagreement, the opinion is always necessary and States are obliged to report the matter to the Committee [18].

Within the measure of approval of the EMA it is reported that the Focetria was approved only after the trial in healthy subjects, while ordinarily the drugs before they are marketed are subject to three experimental phases: in the first one the drug is tested on a small number of healthy volunteers; in the second one on hundreds of patients suffering from the disease that the drug is called to eradicate; in the third one the sample is larger in order to identify the more frequent adverse reactions and side effects.

While in France and the United Kingdom two adjuvanted (Pandemrix and Focetria) and two non-adjuvanted vaccines (Celvapan and Sanofi) [19], in Germany one adjuvanted and one without adjuvants were authorized, Poland refused permission to vaccines claiming insufficient clinical trial and the contrasts of the clauses imposed by manufacturers on liability for adverse events with the internal rules in Poland.

The coordination between Member States and the European Union was ultimately lacking, as well as coordination between the EMA and the European Office of WHO [20].

Within the context of a trust relationship that characterizes the relationship between the European Union and other global bodies (in this case the WHO), the lack of appropriate scientific control mechanisms on global decisions, the insufficient transparency of the European institutions appointed to ensure a proper coordination between the European and global decisions, the insufficient participation of private actors, not directly linked to the pharmaceutical industry, but expression of the associations of physicians, practitioners, patients, contributed to an approval decision in which the only validated point of view was that of the pharmaceutical companies directly involved in the proceedings, affecting the necessary pluralism of information required by the European processes of policy-making.

In addition, there has emerged a fundamental violation: the breach of the precautionary principle. In the European context the principle does not coincide with the temporary nature of the measures, but reflects the fundamental distinction between assessment and risk management.

First, the scientific data held by the Committee for Medicinal Products did not exclude the potential harmful of the vaccine, in such a case the inaction would have been more respectful of the principle of precaution than the authorization.

Moreover, the risk management is entitled to the Commission taking the measure of the marketing authorization of the vaccine[21].However, it should be emphasized that the composition of the Intergovernmental Committee for Medicinal Products for Human Use of the EMA, reduces the scope for the intervention of the Commission in the preliminary activity, making it even ineffective in decisional phase because it may lack the specialist skills required by the reliability of scientific statements made in the opinion of the European Agency.

4. CONCLUSION

The case of the so-called swine flu (H1N1), which developed from the spring of 2009 shows a singular short circuit occurred between the regulatory mechanisms of the European Union and the process of alert triggered by the WHO, caused by some structural deficiencies of the organisms involved.

The supranational mediation of the European Union has offered in many cases the guarantee of health protection within contexts in which the multiplicity of interests involved increases the level of conflict. That mediation has definitely failed in the case of swine flu because of the lack of supranational constituency representation within the European Medicines Agency that allows the intergovernmental component and the underlying unilateral protection of economic interests to resurface.

In the case of swine flu, the trust relationships between global bodies have been affected by the lack of transparency of the responsible organizations (WHO and EMA) and the lack of pluralistic openness that has affected the decision-making procedures. Given the substantial economic interests that exist in the field of pharmaceutical industry regulation, the structures of the WHO and the EMA should certainly be reformed to ensure transparency and pluralism of participation in the proceedings.

While the WHO should ensure the independence of its scientific experts [22], the EMA should define more precisely the separation of the functions carried out in the interest representation and risk evaluation within the system of scientific committees.

The strategic interaction between European and global level frequently shed light on the specific European health protection, which by virtue of supranational component resizes the neoliberal global expectations and the state protectionist intents, assigning a mandatory character to the need to protect health-related issues.

Where, as in the case of so-called swine flu, the supranational constituency was under-represented, the private interests of the pharmaceutical industry have affected unilaterally the management of the pandemic at European level, causing a prevalence of the reasons of the market on the needs for health protection, which has not been slow to arouse widespread uproar.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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1. See available link: www.who.int/csr/disease/swineflu/.
2. See Sage, Report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic. 2009;301(9). Available: www.who.int/wer/2009/wer8430.pdf.

3. In 2010, the International Health Regulations Review Committee proceeds to assess the ways of the global response to the pandemic and recommends WHO to revise guide lines on the evaluation process and response (Implementation of the International Health Regulations: Report of the Review Committee on the functioning of the International Health Regulations of 2005 in relation to pandemic H1N1 2009. Geneva: World Health Organization; 2011. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_10-_en.pdf). See also What are the dangers of mandatory swine flu vaccination? Dr. Mercola, June 2009, http://blogs.mercola.com/sites/vitalvotes/archive/2009/07/15/What-are-the-Dangers-of-MandatoryMandatory-Swine-Flu-Vaccination.aspx.
4. In the Report of 4 June 2010 of the Health Committee of the Parliamentary Assembly of the Council of Europe (Rapporteur Paul Flynn) the serious lack of transparency in the process of declaration of the pandemic at global level is denounced, in particular the existence of major conflicts of interest of some experts collaborating with the WHO, and the consequent major investment of public money.
5. The centralized procedure used for the case of the swine flu has provided the use of shorter time limits for the placing on the market to meet the impending emergency (pursuant to art. 14.9 of Regulation 726/2004), available: cfr.www.emea.europa.eu/pdfs/human/press/pr/46856809en.pdf; cf. Finally, Annex 3 of the Communication SEC (2009) 1191 final., p. 15 ff.
6. On 30 September 2009 the EMA has authorized the last two vaccines on the basis of the positive opinion of the Scientific Committee on Medicinal Products for Human Use on 24 September 2009. Both contain an adjuvant. Pandemrix contains MF59 and Focetria contains AS03. Both adjuvants contain a substance, squalene (fish oil, derived in particular from the shark), considered harmful to human health.
7. Once the authorization process was completed at European level (EMA) and at national level (Italian Medicines Agency), the use of vaccines in each Member State has depended on the national recommendations, the availability of vaccines, the economic resources that every State has had to invest. The Italian Corte dei Conti has approved by resolution no. 16/2009/P the contract concluded on 21 August 2009 by the Novartis noting “the exceptional nature and the urgency of the intervention”, despite the excessively favourable conditions granted by the Ministry of Health for the multinational company related to the risks’ assumption, responding only in the Novartis case of manufacturing defect, and the compensation ordered in favour of the company in the event of losses (Article 4.6 of the resolution).
8. Cfr. Commission staff working document, Regulatory process for the authorisation of the antiviral medicines and vaccines in the protection against pandemic influenza H1N1 2009, Sec (2009) 1191 final, p. 7.
9. With the declaration of a pandemic on 11 June 2009, the WHO has clarified that the seriousness of the situation was mainly due to the rapid spread of the infection rather than to the virulence of the virus, which appears in most cases very limited. The WHO alert system, which does not distinguish between low and high pathogenic virus, is therefore open to criticism in terms of its specificity.
10. See supra note n. 9.
11. See the report on the EMA pharmacovigilance activities, published on December 23 of 2009. See also the Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, The pandemic H1N1 2009, COM (2009) 481 final of 15 September 2009, p. 12. During the post-marketing surveillance many actors were involved: the national competent authorities, the owners of licences and patents, health care providers WHO

administer or have responsibility for the care, cf. Directive 2005/61 implementing Directive 2002/98 and the provisions of Regulation 726/2004.

12. The Committee for Medicinal Products for Human Use of the EMA is composed of two representatives, one member and one alternate member for each member country, who are appointed after consultation with the Board of Directors, for a period of three years, renewable once, two representatives, one member and one alternate, Iceland and Norway, parts of the European Free Trade Association (Efta), and five members selected from among experts are appointed by Member States or the Agency and recruited, if necessary, to provide expertise in certain scientific areas, pursuant to art. 61 of Regulation 726/2004, amending the Regulation 2309/1993 establishing the Agency. The Committee has, along with the competence to provide the EMA with the advice in the context of the centralized procedure of authorization of drugs, even the expertise relevant to the granting, variation, and suspension or revocation of a marketing authorization in accordance with the provisions of the rules on pharmacovigilance. The Scientific Committees of the EMA, responsible for the elaboration of scientific advice on the basis of Regulation 726/2004, are currently 6: in addition to the above-mentioned committee, there are the Committee for Medicinal Products for Veterinary Use, the Committee for Orphan Medicinal Products, the Committee on Herbal Medicinal Products, the Committee for Pediatric Medicinal Products, the Committee for Advanced Therapies.
13. While within the EMA the function of interest representation has been combined with the function of the scientific advisory of scientific committees, in the EFSA they are completely different, being provided for connecting functions and representing the Member States the Advisory Forum.
14. Article 28.5 of Regulation 178/2002 establishing the EFSA. The Board of Directors in June 2005 decided that the renewal of the mandate of the scientific staff takes place every three years and may be renewed twice, regardless of the actual duration of the individual mandate, cfr. EFSA Management Board at 27-10-2005. At the end of these three terms, the expert may be transferred, if eligible, in another scientific body of which s/he has never taken part. The EFSA Scientific Committees are composed of experts appointed following a public selection procedure which may also include third-country nationals, not being provided national quotas and being taken into consideration only the scientific expertise.
15. The supranational component is not represented in the Scientific Committee for medicinal products for human use but only in the Board of Directors, which basically checks the validity of the procedures for issuing the scientific opinion. The Board of Directors consists of one representative from each Member State, two representatives of the Commission and two representatives of the European Parliament. The Council also appoints, in the Board of Directors, in consultation with the European Parliament and on the basis of a list drawn up by the Commission, representatives of organizations of patients, physicians and veterinarians.
16. The Agency was established by Council Regulation n. 2309/93 replaced by Regulation no. 726/2004 of the European Parliament and the Council of 31 March 2004. The main task of the organization is to provide the European institutions and Member States with scientific advice to allow the exercise of the powers conferred on them by European legislation for the authorization and supervision of medicinal products. The Board of Directors consists of one representative from each Member State, two representatives of the Commission and two representatives of the European Parliament. The Council also appoints, in the Board of Directors, in consultation with the European Parliament and on the basis of a list drawn up by the Commission, representatives of organizations of patients, physicians and veterinarians (Article 65 of

Regulation 726/2004). The Director is appointed, after his hearing by the European Parliament, the Council of Administration upon the proposal of the Commission and on the basis of a list drawn up through a selection process. The opinions of the Agency are prepared by the six special committees.

17. The centralized procedure, which is used for technologically advanced medicinal products, medicinal products obtained through biotechnology, orphan medicinal products, medicinal products containing a new active substance and therapeutic indications in the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative diseases, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases, is described in the Council Regulation 2309/93, replaced by Regulation 726/2004.
18. The procedures for marketing authorization of drugs include, in addition to the centralized procedure provided in Regulation 2309/93, the EC Regulation n. 726/2004 in conjunction with Regulation 1394/2007 (on the drugs used in advanced therapies), the mutual recognition procedure and the decentralized procedure (now codified as Directive n. 2001/82, relating to veterinary medicinal products, as amended by Directive 2004/28 and Directive n. 2001/83, relating to medicinal products for human use, as amended by Directives no. 2004/24, 2004/27, 2004/28 which introduced the distinction between mutual recognition and decentralized procedure.
19. The French government decided to cancel 7 million doses of vaccine already ordered. The British government has ordered 132 million doses of vaccine (two for each citizen). Only 13 million doses were delivered, while the remaining 119 million were stored. The government has negotiated with GlaxoSmithKline and Baxter International to reduce the order, when the alert was ceased. However there have been controversies about the waste of public money.
20. In compliance with art. 27 of Regulation 726/2004, the Agency is working with the WHO as regards pharmacovigilance and exchange of information on measures taken.
21. On the draft decision of the Commission a standing committee of the comitology must give an opinion, as expression of governmental experts of the States. The opinions of the Scientific Committee must be ratified by the comitology procedure, as well as the opinions of the EFSA (Art. 10 and Art. 87 Regulation 726/2004). Where the draft decision is not in accordance with the opinion of the Agency, the Commission justifies its own different opinion in an annex which must be forwarded to the Member States and the applicant. The Commission shall take a final decision in accordance with the procedure by fifteen days of the completion of the procedure.
22. The effectiveness of independence should be provided by rules that specify the obligations relating to the exercise of outdoor activities of the experts in order to better determine the extent of the obligation of independence imposed to them. A total ban should apply to the exercise of professional functions, paid or unpaid, during the performance of the tasks as scientific experts. Moreover, the rules should ensure transparency, integrity and fairness in the exercise of the functions and in the period following the resignation of the experts.

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