

Swine Flu: to Vaccinate or not ?

Marc GIRARD, MSc, MD

Consultant in drug monitoring and pharmacoepidemiology
European expert (AEXEA)
76 route de Paris, 78760 Jouars-Pontchartrain – France
(agosgirard@free.fr)

site: <http://www.rolandsimion.org>

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1. Rationale

Projects of forced flu vaccination certainly raise serious issues regarding fundamental liberties, but more simply, they also raise significant health issues, which require a factual analysis.

Basically, **vaccines are drugs amongst others** (and, as will be demonstrated below, far more complicated agents as compared to most available drugs). From my professional experience in drug development and pharmacoepidemiology, I have got a quite simple conceptual frame of relevant issues to be analysed:

1. which benefit?
2. which risk?
3. which cost?

2. Which benefit ?

2.1. Vaccines against seasonal flu

The Cochrane collaboration¹ is a non-profit network dedicated to performing systematic reviews of health care interventions, including a number of drug treatments. Independent in principle, its reviews are not always above any criticism² – as everybody of us... However, there is a general agreement that the “Cochrane reviews” are amongst the most reliable assessments available in the field of medical care.

As it happens, the Cochrane collaboration has recently published thorough reviews on flu vaccines: the significance of these retrospective assessments is even greater since, in addition, they have been subjected to quite recent updates.

As opposed to the implacable promotional activism of health authorities (WHO included), their conclusions are damning.

- In the elderly (65 years and more)³ : *“according to reliable evidence the usefulness of vaccines in the community is modest”*.

¹ <http://www.cochrane.org/>

² Girard M. Meta-analysis on recombinant versus urinary follicle stimulating hormone. *Human Reproduction* 2000; 15: 1650-1651

³ Rivetti D, Jefferson T, Thomas RE, Rudin M, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in the elderly. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD004876. DOI: 10.1002/14651858.CD004876.pub2.

- In healthy adult⁴ : “ *There is not enough evidence to decide whether routine vaccination to prevent influenza in healthy adults is effective*”
- In healthy children⁵ : “ *If immunisation in children is to be recommended as a public health policy, large-scale studies assessing important outcomes and directly comparing vaccine types are urgently required.*” Not without irony, the authors add the following comment: “It was surprising to find only one study of inactivated vaccine in children under two years, given current recommendations to vaccinate healthy children from six months old in the USA and Canada.”
- In healthcare workers who work with the elderly⁶ : “ *There is no credible evidence that vaccination of healthy people under the age of 60, who are HCWs caring for the elderly, affects influenza complications in those cared for*”.

No need of being an epidemiologist to grasp the problem raised by this series of reviews which included all the available relevant studies (randomized controlled trials, cohort and case-control studies) performed from 1966 to 2006: during 40 years, **nobody (in particular neither the manufacturers, nor any health agency) has proved able to produce any convincing evidence of a significant benefit related to vaccines against influenza⁷!**

Incidentally and to be fair, it may be noted that the manufacturers of antiviral treatments do not seem more demanding than vaccine makers as far as pharmacoepidemiological evidence is concerned. In a recent correspondence sent to the *British Medical Journal*, Roche’s medical director was not afraid of writing: “The product summary for oseltamivir *shows* that it is effective and well tolerated in children”⁸ (my italics). In more than 27 years of professional life devoted to the assessment of drugs, this is the first time that I hear of a product summary likely to “show” any kind of scientific evidence...

⁴ Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD001269. DOI:10.1002/14651858.CD001269.pub3.

⁵ Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD004879. DOI: 10.1002/14651858.CD004879.pub3

⁶ Thomas RE, Jefferson T, Demicheli V, Rivetti D. Influenza vaccination for healthcare workers who work with the elderly. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD005187. DOI: 10.1002/14651858.CD005187.pub2.

⁷ Even more paradoxical since, as everybody knows, available studies are rather skewed towards an overestimation of benefits, because of the publication bias. To say the same in more mathematical way: if an overestimation of benefits proves to be near zero, at which level may be the *real* benefits?...

⁸ Rashford M. *BMJ* 2009; 339: 650

To sum up:

- within 40 years, the manufacturers have never made any effort to get any scientific evidence of the efficacy of their flu vaccines;
- within the same period, the health agencies have never requested any scientific evidence of efficacy for the flu vaccines they had the responsibility to register or not;
- in spite of this depressing state of the art, these vaccines are more and more promoted (and, quite often, reimbursed) with the active participation of regulatory bodies: as rightly pointed out by the leading authors of these Cochrane reviews⁹, their activism in promoting flu vaccines places health agencies as well as their "experts" in a quite objective conflict of interest¹⁰.

2.2. Vaccines against swine flu

For health agencies as well as their experts, this is a leitmotiv that a longstanding past experience with vaccines against seasonal flu is clearly relevant for the development of new vaccines against swine flu and justifies the frightening swiftness of their current development. But as demonstrated in the previous section, a thorough assessment of this past experience is now available – and it is disastrous.

Even worse, the manufacturers and health agencies do not contend themselves with using this disastrous precedent as a shield: they search to take advantage of a supposed pandemic emergency to get rid of time-consuming regulatory prerequisites regarding major pharmaceutical innovations such as new adjuvants or new processes of viral cultures (each of them likely to require *years* of research).

If, in some 40 years of anti-flu routine, the responsables have not proved to be able to produce any sound evidence of efficacy for their vaccines, who would be ready to believe that they will do better under the pressure of emergency ?...

2.3. Swine flu per se

The *intrinsic* efficacy of a drug against a disease is not the last word of the benefit assessment: it remains to be demonstrated whether the risks of this disease are

⁹ Jefferson T, Demicheli V. Influenza vaccination for elderly people and their care workers. *Lancet* 2007; 369:1857-8.

¹⁰ This may be the place to pick out that, in April 2007, US Representatives Dave Weldon and Carolyn Maloney have introduced a new bill that aims to allocate responsibility for vaccine safety in the US to an independent agency within the Department of Health and Human Services. The Vaccine Safety and Public Confidence Assurance Act of 2007 will remove most of the vaccine safety research from the Centers for Disease Control (CDC), which currently has responsibility for both vaccine promotion and safety, posing a conflict of interest that has been receiving public criticism (*Reactions Database*, AN: 809074716). Such a move largely confirms the criticism of Jefferson and Demicheli regarding the credibility of health agencies "experts" in assessing retrospectively the benefit/risk ratio of vaccines.

significant enough to require any treatment. To be specific, the question is whether, on the basis of objective available data, swine flu appears threatening enough to require an *extraordinary* wealth of preventive measures.

The answer is obviously NO.

- Professional or not, even the most alarmist medias agree that, for the time being, the new virus seems rather less virulent than its seasonal predecessors.
- As modest as it appears now, the severity of swine flu as currently assessed is markedly biased towards an overvaluation.
 - Obviously, the death toll has been exaggerated: at the end of April, within one single day, the number of Mexican deaths ascribed to swine flu dropped from some 200 to 7 only ; similar examples could be multiplied.
 - World area where the rate of presumed deaths was highest were also those with the less performing health systems, so that one may wonder about: 1/ the baseline health status of patients with a fatal outcome; 2/ the adequacy of medical care in case of respiratory complications; 3/ the reliability of aetiological diagnosis (it is perfectly possible to suffer from a mild flu and to die from an infarction – or an assassination for unrelated reasons...).
 - In contrast with an hysterical mediatisation of most deaths, newspapers as a matter of rule remained quite discrete on underlying diseases and medical history: yet, a trivial cold – not even influenza – may be sufficient to kill a patient suffering from immunodepression... That is not a scoop.
 - For objectively low it was, the rate of fatal cases was exaggerated by an underestimation of the total number of cases, as the symptoms were so mild in many of them that they did not feel the need to visit a doctor: if, amongst 10,000 recorded cases, death occurred in 10 cases, the apparent mortality is 1/1,000; however, if in addition, 90,000 patients did not display significant symptoms, the real mortality will drop to 1/10,000, that is ten times less.

Once established that swine influenza currently corresponds to a fairly mild form of influenza, health agencies retort that their concern is not the virus as it is now, but as it *could* become in near future after a mutation. However:

- propensity to mutate is a strong characteristic of any virus in general, and of influenza viruses in particular: there is nothing new with that;
- if this swine virus is supposed to mutate in the future:

- this could be in the direction of an even *lower* virulence ;
- as the vaccine is currently prepared against the current strain of the virus, it could be ineffective against a mutated strain (this unexpectedness of a mutation is the classical excuse of the manufacturers each time the efficacy of the vaccines against seasonal flu proves to be obviously poor).

3. Which risk?

3.1. Risks of drugs in general

3.1.1. Benefit/risk ratio

Any drug, even targeted towards trivial symptoms, carries a potential of hazards, some of them may be severe: just think of the precedent of thalidomide, a product normally used to relieve pregnant women from their nausea... As *drugs amongst others*, vaccines against swine flu will therefore induce hazards whose frequency and severity will be difficult to anticipate, as is usually the case when drug exposure has not been large enough.

The natural correlate of that inherent drug-induced toxicity is the **benefit/risk** ratio, which may be considered from two complementary standpoints in the case in point.

- Having regard to the average mildness of swine flu, it might be that, by their frequency or their severity, the unwanted effects of a vaccine could surpass the risk inherent to the disease that it is supposed to prevent.
- Relevant for any kind of drug, the significance of the previous warning is enhanced in proportion of the *preventive* target of a vaccine – taking into consideration that a majority of the vaccinated subjects were not supposed to contract influenza. Thus, for “collective” the benefit might be, who would be stupid enough to take even a small risk of adverse effect from a drug which carries no *personal* benefit? In other terms: inasmuch as the expected *personal* benefit decreases, the potential risk must decrease in parallel. At the end, **for a drug whose personal benefit is negligible, the sole acceptable level of iatrogenic risk must be zero or something quite close.**

Thus, on the basis of available data, is it possible to contend that the level of risk related to the new vaccines against swine flu is near zero? Clearly NO, and this will be demonstrated below.

But before, I would add a word on the hypocrisy of the argument about the collective benefit of flu vaccination. As already said, there is a general agreement about the average mildness of this new flu: therefore, this could be the right time to facilitate the dissemination of the virus in order to allow a “natural” vaccination of populations (a strategy whose financial could be far more advantageous than a mass vaccination with products sold at indecent prices...) No doubt that there will be some kind souls to retort that such an ecological vaccine policy would have a cost in terms of

individual complications occurring mainly in fragile subjects: that is clear, but why, in that case, the priority of “collective” benefit should become irrelevant?¹¹

3.1.2. Past experience with the therapeutic class

One major argument of health authority to justify the urgent development of a new vaccine in the setting of a regulatory anarchy is that in their pharmacological principle, the vaccines against A/H1N1 have nothing new: their development may benefit from the acquired 40-year experience with seasonal flu.

Apart from the intrinsic contradiction of a virus new enough to justify a panic but classical enough to require only experience acquired with traditional virus (!), let us summarize our past experience with vaccines against seasonal flu.

To be short, it suffices to go back to the previous Cochrane reviews (see 2.1): according to the authors, there is a lack of evidence regarding the safety of flu vaccines, esp. in children. Therefore, defective as it appears after appropriate review, **the past experience with the vaccines against seasonal flu can, in no way, be used as a reassurance regarding the safety of the new vaccines.**

From this statement of fact, it is also possible to get a remark parallel to that made about the efficacy parameter: if, within some 40 years, the manufacturers or regulatory bodies have not been able to gather any convincing evidence about flu vaccines, who could believe in their credibility to assess the safety of new vaccines in a climate of methodological hurry and regulatory anarchy?

An additional remark may be of significance. As everybody knows, the marked involvement of the biggest pharmaceutical firms in vaccine sectors is fairly recent. Thus, if one refer to documents published *before* this self-seeking involvement (with all its impact on the integrity of medical publications...), it is easy to record that in that time, the adverse effects of flu vaccines were acknowledged as an obvious fact. To take only one example, the 30th edition of the reference book Martindale¹², in 1993, reads that adverse effects were “as for vaccine in general” (including anaphylaxis and effects on the nervous system), with an additional mention of pericarditis, Henoch-Schönlein purpura and acute polyarteritis. Finally: “An epidemiologic and clinical evaluation of these cases suggested a definite link between vaccination and the onset of the syndrome [of Guillain-Barré] with extensive paralysis (...) Influenza virus which lack a swine influenza virus component seem not to raise the risk of paralysis above background levels”.

¹¹ Taking into consideration the additional fact that, because of the current mildness of swine flu, the overall cost (mortality, morbidity and resulting financial cost) of such an epidemics would be probably less than the cost normally accepted every year with seasonal flu.

¹² Martindale . *The Extra Pharmacopoeia*, 30th edition. London, The Pharmaceutical Press, 1993.

Five years before, the 11th edition of Meyler's Side Effects of Drugs, another book of reference¹³, listed amongst the adverse reactions reported with influenza vaccine: "neurological reactions [ranging] from polyneuropathy to meningoencephalitis and Guillain-Barré syndrome", optic neuritis, myocardial infarction and pericarditis, interstitial lung disease, as well as drug interactions...

This acknowledged evidence from the past of a significant toxicity of flu vaccines downgrades to lies or ignorance the contrary statements of most "experts" now.

3.2. Risk of vaccines

3.2.1. Duration of action

Usually, when a drug is administered, it has a limited duration of action; within the fluctuations of its elimination (which may take some weeks with some drugs), the duration of its pharmacological action is more or less restricted to the time of administration.

In contrast, vaccines have a quite unusual particularity: for only *one* administration (sometimes followed by some few boosters), the expected effects are supposedly lasting for years, decades or even the whole life span.

Yet, strangely enough and still in contrast with usual drugs, the safety trials performed with most vaccines are extremely short: from the *Physician Desk Reference*, for example, one may learn that those carried out during the development of the hepatitis B vaccine Engerix did not last *more than 4 days*...

For accepted as it is by regulatory authorities, this design is obviously defective – esp. to assess delayed adverse effects... But in addition and as exemplified by the abovementioned Cochrane review or by experience, these trials are, in practice, quite often carried out in a fairly lax manner, to be polite. It seems taken for granted that, as compared to other drugs, vaccine *cannot* induce significant risks, so that monitoring their safety to not require either effort or rigour.

Engerix case once again gives an eloquent illustration of this paradox. It appears from the summary of product characteristics that some 8 years were necessary to see the mention of a risk of "anaphylaxis"¹⁴. Thus, it took no less than 8 years to the manufacturer or the health agencies to record *the most immediate* drug-induced reaction that could be imagined. Hard to rely on the same "experts" to assess properly:

- delayed adverse effects such as auto-immune diseases, multiple sclerosis or lateral amyotrophic sclerosis;

¹³ Dukes MNG (ed). Meyler's Side Effects of Drugs. An Encyclopaedia of Adverse Reactions and Interactions, 11th edition. Amsterdam, Elsevier, 1988

¹⁴ That is a shock (possibly severe or even fatal) of immunological determinism within the seconds or minutes following injection.

- the safety profile of the new influenza vaccines which, in contrast with Engerix (whose development took several years), will have been developed within a maximum of a few weeks.

Here is the appalling illogicality of vaccine development: whereas these drugs are supposed to exert their beneficial immunological effects on a *very* long term, they are never conscientiously suspected (and, in any case, never conscientiously assessed) regarding their potential to exert adverse immunological effects within the same long term.

This blatant illogicality justifies a re-appraisal of the ferocious antagonism between supporters of vaccines and antivaccinationists. Unlike any other domain in therapeutics¹⁵, vaccination *cannot* be a matter of academic controversy: either you have no doubt about the *obvious* benefits of *every* vaccine and you are on the side of "Reality"; or you are inevitably on the side of "myth", "misinformation", "misconception", "falsehood", "archaism", etc.¹⁶ Actually, evidence is more balanced. To be frank, it is clear that antivaccinationism is on the agenda of a number of sects – to say nothing about paranoiacs. No doubt also that most antivaccinationist groups have vested interests in the marketing of "alternative" medicines as opposed to "allopathic" products, with contributions, journals or sites closer to sales promotion than to scientific communication. For a professional in pharmaceutical development, however, it is no less true than vaccine promotion – be it performed in the most prestigious journals (like NEJM, The Lancet or BMJ) – is distinguished by *a distressing amateurism* – to say nothing about latent conflicts of interests. Marked in particular by gross inconsistencies and a rare illogicality, this pro-vaccine amateurism feeds anti-vaccine movements, making every person endowed with a minimum of cultural background and elementary logic able to point out its most blatant failures¹⁷.

In my papers devoted to the vaccines against hepatitis B, I gave a number of amazing examples of this amateurism of pharmaceutical firms, experts or health agencies as soon as vaccination is concerned¹⁸. Additional evidence will be given at the end of this paper.

¹⁵ L. Lasagna (ed). *Controversies in Therapeutics*. Philadelphia, Saunders, 1980.

¹⁶ Kimmel SR. Vaccine adverse events. Separating myth from reality. *Am Fam Physician* 2002; 66: 2113-20

MacIntyre CR, Leask J. Immunisation myths and realities: responding to arguments against immunization. *J Paediatr Child Health* 2003; 39: 487-91

Wolfe RM, Sharp LK. Anti-vaccinationists past and present. *BMJ* 2002; 325: 430-3

Begg N, Nicoll A. Myths in medicine – Immunisation. *BMJ* 1994 ; 309 : 1073-5

¹⁷ Girard M. Being or not being an "activist", that is the question. *Medical Veritas* 2006; 3: 1214-5

¹⁸ Girard M. When evidence-based medicine (EBM) fuels confusion: multiple sclerosis after hepatitis B vaccine as a case in point. *Medical Veritas* 2007; 4:1436-51

3.2.2. « The mosaic of autoimmunity »¹⁹

Each vaccination corresponds to the introduction in a human organism of antigenic material which has been subjected to a more or less precise identification²⁰ and which carries *per se* a potential for inducing reactions of autoimmunity, for example by a mechanism of molecular mimicry (if there is a similarity between this antigenic material and any physiologic structure of the self²¹).

In addition and *as with every drug*, even a minute contamination²² or impurity during the manufacturing process is likely to trigger an unwanted immune reaction and, in particular, an autoimmune one. Overall, there is a strong record of the potential of vaccines to produce autoimmune diseases (such as rheumatic disorders)²³.

Already significant – if not frequent – from an epidemiological standpoint, this autoimmune risk is obviously magnified by the use of adjuvants.

As acceptable as it may be in some preventive indications precisely targeted against significant infectious risks (which, let me remind, are not uniformly distributed all over the world...), this risk of autoimmune hazard is statistically correlated to the number of administrated vaccines. Thus, it is not exaggerated to assert that the continuous reinforcement of immunization schedule, with its mathematical increase in the autoimmune risk, is certainly not offset by a parallel effort to extend or deepen the epidemiological assessment of these new recommendations. To take only one example, since the time of my medical training, the targeted population for the immunization against seasonal influenza has shifted from fairly small “at risk” groups to everybody every year, which means on average an additional burden of some **80 new immunisations** in each person over his/her life span: to the best of my knowledge (and as confirmed by the recent Cochrane reviews), progress in the safety assessment of these vaccines has not been in keeping with this dazzling increase.

¹⁹ Shoenfeld Y, Aharon-Maor A, Sherer Y. Vaccination as an additional player in the mosaic of autoimmunity. *Clin Exp Rheumatol* 2000; 18:181-4.

²⁰ If the linear structure of antigenic molecules may be identified, it is far more difficult to anticipate their spatial disposition : yet, it is precisely this spatial disposition which will determine the main part of immune reactions in the host.

²¹ Selmi C, Battezzati PM, Tishler M, Shoenfeld Y, Gershwin ME. Vaccines in the 21st century: the genetic response and the innocent bystander. *Autoimmun Rev* 2005; 4(2):79-81.

²² Faure E. Multiple sclerosis and hepatitis B vaccination: Could minute contamination of the vaccine by partial Hepatitis B virus polymerase play a role through molecular mimicry? *Med Hypotheses* 2005; 65:509-20

²³ Shoenfeld Y, Aharon-Maor A, Sherer Y. Vaccination as an additional player in the mosaic of autoimmunity. *Clin Exp Rheumatol* 2000; 18:181-4.

Le lecteur intéressé pourra trouver bien d'autres références sous la plume de Y. Shoenfeld et de ses collaborateurs.

3.2.3. Associations

As illustrated by the *Physician Desk Reference* or any equivalent book, the issue of **drug interactions** is a crucial one with any pharmaceutical product. As compared to this baseline, concerns about interactions seem quite diluted as soon as the product in question is a vaccine.

Yet, as exemplified by note 13, there is not convincing reason to believe that vaccines do not expose immunized subjects to significant problems regarding interactions with other drugs.

In addition, there is no reliable evidence that the risk of multiple immunizations has been seriously considered: to take only one example, it does not seem that the frightening issue of sudden infant death syndrome (SIDS) – which cannot be ignored on the basis of anecdotic evidence (as reflected by experience or by the VAERS, amongst other data) – has received the epidemiological attention it deserves²⁴.

This poverty of clinical or epidemiological research on drug interactions induced by vaccines is all the more paradoxical since, as stressed above, the duration of action is normally far more prolonged with vaccines as compared with any other drug subjected to a far more rigorous screening in this regard.

3.3. Risks of vaccines against influenza

As compared to vaccines in general, those targeted against influenza have two additional drawbacks.

- As already said (cf. 3.2.2), these vaccines require an additional immunization every year: it must be born in mind that these yearly injections are not booster doses, but correspond each time to *a new active principle*. If the current recommendations of health authorities were to be followed, it is clear that over a life span, flu vaccines would be major contributors to the mosaic of autoimmunity. From a simple Hippocratic standpoint, the imprudence of these recommendations is vertiginous.
- Each year, depending on the characteristics of the virus isolated as responsible of the epidemics, the new influenza vaccines are prepared in an incredible rush, which has no equivalent in pharmaceutical development (I will come back to this important point: see 3.4.4.2). Here is most probably the genuine cause of the disastrous results of the Cochrane review: **it is simply not**

²⁴ When the vaccine Hexavac was registered, the summary assessment posted on the site of the European Agency (EMA) showed that, *simply during the development*, the rate of SIDS (7 amongst some 3905 infants exposed) was **35 times higher** in those exposed to the vaccine than normally expected: the Agency contended itself with claiming placidly that these deaths were unrelated to the vaccine. Later, the Agency never undertook the slightest epidemiological assessment and completely ignored unusually alarming signals of postmarketing experience such as that by Zinka B. et al (Unexplained cases of sudden infant death shortly after hexavalent vaccination. Vaccine 2005 May 18).

possible to develop drugs within 2-3 months. And contending the contrary is both irresponsible and deceitful.

3.4. Additional risk related to the case in point

3.4.1. Prevention and its risks

In evolution, immunity is not a stock given once and for all to individuals: this is a dynamical system which requires periodic reactivations, especially as far as "non specific immunity" is concerned.

Although it might be difficult to find reliable epidemiological evidence on this topic, there are a number of good reasons to take as a serious hypothesis that trivial viral infections such as cold or flu have the adaptive function to maintain the reactivity of our non specific immunity. In other words, even if these infections may carry an undisputed burden in terms of individual casualties, they are most probably beneficial at the scale of a population.

It is striking that a number of scholars who are certainly not antivaccinationists recognize that natural infections could have, overall, a protective role against autoimmune diseases and that anti-infectious prevention (with vaccines or, in some cases, with antibiotics) may have a harmful impact on the risk of diseases such as asthma²⁵ or diabetes. This should be taken into consideration when assessing the benefit/risk of immunisations.

3.4.2. Scale effect

There is a large agreement that, even when clinical trials are properly carried out (which is certainly not the case with those on the new influenza vaccines), the probability of recognizing a hazard is near zero if it occurs at a frequency of 1 in 1,000 exposed patients²⁶. Incidentally, let me remind that this lack of statistical power inherent to the clinical development is the classical plea of the manufacturers once the toxicity of their products can no longer be denied, as was the case in the Vioxx affair.

For the time being, a number of experts claim that swine flu could hit one third of the population with a mortality of 0.1% (which, in my opinion, is probably an overestimation). Applied to the USA population, these estimates correspond to 100 millions of affected person, with a maximum death toll of 100,000 persons, mainly in elderly or in patients made vulnerable by severe underlying diseases: overall, this mortality would not have much impact on the average life expectancy in this country.

²⁵ *J Allergy Clin Immunol* 2008 ; 121 : 626-31

²⁶ Schneiweiss F, Uthoff VA. Sample size and postmarketing surveillance. *Drug Information Journal* 1985 ; 19 : 13-6.

Inasmuch as most of the alarmism regarding swine flu is based on “the worst case hypothesis”, let me for a while adopt the same rhetoric: so, let us suppose that the “clinical trials” on the new influenza vaccines will miss 1 adverse reaction in 1,000 exposed patients, and that this reaction will be fatal (a pessimistic hypothesis, of course, but not extravagant from a statistical standpoint: there are precedents...). Thus, if forced or improperly alarmed, the whole of the US population was vaccinated, there would be 300,000 deaths: three times the death toll due to influenza and, this time, in babies, children, young adults, all of them in perfect health – with a major impact on average life expectancy.

And to say nothing about the *other* adverse reactions of these new vaccines (e.g. Guillain-Barré syndromes), as it never happens that a drug carries the risk of *one* hazard only...

3.4.3. The “protected species” of pharmaceutical development

Pharmaceutical development has always considered as “protected species” four categories of persons: elderly, pregnant women, children and patients with underlying diseases (cancer, autoimmune disease, diabetes...). As a matter of policy and allowing for exceptions (e.g. to develop a treatment against Alzheimer’s disease or metastatic cancer), study protocols exclude these subjects: as a consequence and as it is easy to verify, the summary of product characteristics of new drugs usually includes severe warnings about prescription in pregnant women or below a certain age.

Once an additional postmarketing experience is available, it becomes possible to envisage a progressive extension of the drug indications, but always at the price of a new development with appropriate clinical trials leading to a new drug application. Experience shows that the regulatory authorities are often overcautious regarding such extensions and that the probability for the application to be rejected is far from being negligible.

Yet, in the case in point and according to health agencies, who will be the subpopulations to be first and foremost exposed to these flu vaccines developed in an incredible technical and regulatory anarchy? As it happens: elderly, pregnant women, children and patients with underlying diseases – and even the newborns according to some experts.

This has to be said without any political correctness: that is a criminal nonsense.

As a single counter-example, let me remind that no less than 20 years – and a fantastic exposure – were necessary before the neonatal hazards of serotonergic antidepressants (such as Prozac) were identified²⁷, whereas these products – unlike the new influenza vaccines – were developed according to a standard way, including very long studies in animals and over a duration incommensurable comparatively: it

²⁷ Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. *Pediatrics* 1993; 92: 721–2

took some 15 years or more to introduce Prozac²⁸ on the market. Yet, in its principle, this drug is far simpler than products which may contain several antigenic parts added to adjuvants... Of note also: the risk of foetal toxicity is still debated with these antidepressants²⁹.

3.4.4. Bypassing the regulatory process

Although quite restrictive legally and highly significant as far as public health is concerned, the process of a new drug application (NDA) and registration is widely ignored by most people, including most health professionals. As such, it justifies a minimum of basic development below.

3.4.4.1. Usual duration of drug development

As opposed to the public declarations of some "experts" clearly unfamiliar with drug making, the development of a new drug is not confined to clinical studies only. Besides of heap of administrative data, it includes three main parts³⁰.

- Chemical, pharmaceutical and biological documentation: composition of the drug, method of preparation, control of starting material, control tests on intermediate materials, control tests on the finished product, stability testing, bioavailability/bioequivalence, data related to the environment risk assessment for products containing genetically modified organisms...
- Pharmacotoxicological documentation: toxicity, reproductive function, embryo-fetal and perinatal toxicity, mutagenic potential, pharmacodynamics, pharmacokinetics, local tolerance, environment risk assessment...
- Clinical documentation: clinical pharmacology, clinical experience...

Without entering in more details, it is already more palpable for anybody why it is simply not possible to develop a new drug within one, two or three months. According to the author referred to in note 30: "Prior to the introduction of high-density computer storage media (e.g. CD-ROMs), the physical size of a marketing authorisation application could be daunting".

This is my current guess that the physical size of the applications regarding the new vaccines against swine flu authorised is, in no way, "daunting"...

²⁸ Early development started at the very beginning of the 1970s (Wong D et coll. "A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine". *Life Sci* 1974 ; 15 (3): 471–9). The first registration was given in Belgium in 1986 ; in the US, it was not given before 1988.

²⁹ <http://www.medicinescomplete.com/mc/martindale/current/12763-x.htm?q=%22prozac%22#r12763-a5-7-d-8> (consulté le 25/08/09)

³⁰ The brief summary is mainly inspired from RJ Harman, *Development and Control of Medicines and Medical Devices*, London, Pharmaceutical Press, 2004.

Just to vividly evoke what a drug development *should* be, let me sketch the usual timing of an usual clinical trial (to say nothing of the pharmacotoxicological prerequisites prior any introduction in man).

- Protocol redaction: this normally takes several months.
- Choosing the investigators, having their feedback on the protocol and integrating their suggestions if any: this may take some time, especially if the centres are distributed all over the world, as is often the case as soon as a certain sample size is required. Before, of course, you took the time to write the “investigator brochure” which summarizes available data on the new drug (esp. animal prerequisites) as well as on the therapeutic class (i.e. 40-year experience with flu vaccines...)
- Submitting the protocol to an ethical committee as well as to the regulatory agencies (several of them if the study is international): you can count a minimum of several months (and more if these guys have the idea of criticizing your protocol and to request modifications).
- At a moment or another, you have to manufacture a placebo or a comparator in exactly the same form as your drug under investigation: you may have some technical problems – as pharmacy is a tricky cookery...
- In some countries like mine, you have to get the agreement of the medical association on the contract between any investigator and the sponsor: usually, it is not a matter of a few days.
- Then, you have to recruit the patients, which may be a long process – esp. with a new vaccine people are often afraid of (remember that you have to get their informed consent...)
- You will have to follow the patients over the treatment duration specified by the protocol: if it is 2 months and if the last patient is recruited some 2 months after the first (which is an unusual promptness), the overall duration of the treatment phase cannot be less than 4 months.
- Once the last dose administered, a minimum follow-up of one month is normally required – for each patient.
- Then, you will have to carefully check that the data entry in your base has been strictly consistent with the patients case report form. You will also have to check that, for each patient, every prescription of the protocol was respected. For every detected mistake (spelling of a name, error on a date or on a dose, etc.) you have to get it corrected by *the investigator* who usually has other concerns than your study in his professional life (hospital activity, other clinical trials with other manufacturers, continuous medical education, litigations with past patients...)

- This will be the time of the statistical analysis: you can count some months, if your statisticians are diligent – and if you do not detect retrospectively problem in the protocol conception or in the way data were entered.
- Once the statistical results are available, it is time to write the study report: if you go on internet to get available templates (e.g. those of the International Conference on Harmonisation), you can easily understand the inherent burden...
- Once the report has been completely written, then you have to enter into the process of internal approval – actually a nightmare (*the* moment where those who did nothing thus far take the opportunity to show that: 1/ they exist, 2/ they have some degree of power in one way or another). Regarding the last report I was commissioned to write (in a major firm, on a project labelled as “very urgent”), the medical director alone asked for a 2-month time limit for his approval: challenged on that duration in view of emergency, he answered that this was “incompressible” – and everybody in the firm seemed to agree...

That was just an average sketch. But I am sure that everybody understands that, for any clinical trial, the natural units to measure the duration of the process are *years* and not months, and certainly not weeks or days... In addition, one single study is not sufficient for a drug development. Finally, when you have performed all the required studies, you have to assess them *on the whole* in an “expert report” – once again a quite complicated document normally structured by pernickety guidelines and templates: of course, such an expert report has to be done for each part of the dossier (pharmaceutical quality/ pharmacotoxicological data/ clinical data). I say nothing of the *physical* making of the application, which includes amongst other a scanning of all individual data (that of the patients, but also of the animals included into the toxicological studies).

It is now up to the vaccine manufacturers and governmental agencies to justify how such an enormous burden may be compressed within a few weeks...

3.4.4.2. Which registration?

Normally, the introduction of a new drug on the market is conditioned by a **registration process**, which corresponds to the scientific assessment performed by regulatory authorities of a marketing authorisation application (or: a new drug application): this application includes all the investigations carried out by the manufacturer during the drug development to comply with quality, safety and efficacy criteria required by pharmaceutical regulations.

Yet, it is not difficult to document from media that quite early in the summer months, the governments of developed countries such as the US, the UK, Germany or France (which are not supposed to lack legislation or regulatory bodies) have prided themselves on having ordered (and even paid) huge amounts of vaccines against

swine flu and on being ready to trigger (or even: to force) massive campaigns of immunization.

It is not difficult either to document that for the time being (end of Sept, 2009), these vaccines are still in their phase of development – which, in the process described by the current legislations, normally corresponds to a step *preceding* the making-up of a new drug application (which precedes itself the process of registration involving a careful assessment of this application).

From which one may raise an interesting question (to my knowledge, never brought up before): how is it possible to buy, pay and administrate a drug *before* the health authorities have complied with their duty of protecting consumers by carefully assessing the quality, safety and efficacy of this new agent?

In a country like mine where I pride myself on having introduced this regulatory issue into the public debate, the government, obviously shaken by this unexpected objection, tries to justify itself by making up now a retro-planning tending to demonstrate that – of course – the marketing authorisation will be available *before* any significant campaign of immunization.

With such fancy claims, however, the government is getting itself in deeper and deeper water: if, depending on local regulations, the timing of the registration *process* may be scheduled (with a deadline for the final decision, in particular), the *authorisation* cannot be subjected to any *a priori* schedule.

A useful metaphor for the registration process is that of a school examination: you can success if you are good, be subjected to an additional examination if you are borderline, but also... be flunked if you aren't up to standard. In the process of a drug application, the drug maker is like a student: his new drug may be approved, he can get blocking questions ("measure of investigation") which may require clarifications, additional checks or even new investigations, and of course the application *may be rejected* by the regulatory authority.

Therefore: how is it possible to have a pre-specified schedule of approval in a process where the approval may be delayed or even rejected? And how is it possible for governments to spend public funds by paying *in advance* products whose introduction on the market may never be granted? The answer is clear: **our health authorities have never been seriously thinking of genuinely assessing the new influenza vaccines.**

And while giving by their orders a strong signal to the manufacturers that they were ready to co-operate for transforming into a blockbuster *any* dirty kind of vaccine mixture, our governments put the finishing touches by making sure that no judicial litigation could hit the formers.

This is a scandal and a tragedy.

4. Which cost?

On the question of financial cost, I will be shorter as I have no special competence in pharmaco-economy. But as brief as they will be, the following remarks may be of relevance.

Vaccine prices – The leitmotiv of the manufacturers to justify the exorbitant price of their drugs has always been the time spent in their development³¹: years, and sometimes more than a decade. Thus, if you follow the same line, you should expect that the cost of vaccines developed within a few weeks only should be lowered accordingly: this does not seem to be the case...

Number to treat – Having regard to the enormous population targeted by an immunisation, as compared to the current mildness of swine flu, the relevant parameter to assess the cost/benefit of the vaccination should be the number to treat: how many persons should be vaccinated to avoid *one* fatal case of influenza? And in the prospect of a massive campaign: how many persons *will* be vaccinated to avoid one fatal case of influenza?

Indirect costs - To the direct cost of the vaccines (and of the remuneration of the health professionals who would perform the injections), indirect costs should be added. That of the anarchy inherent to the extravagant preventive measures taken by the governments, and of course that of the side-effects of the vaccines: according to some medical sources, up to 30% of adults developing a Guillain-Barré syndrome may have neurological sequels, and the proportion could be higher in children (and of course, Guillain-Barré syndrome is not the only hazard one can expect with vaccines developed in an unprecedented rush – some by firms which already have their previous history of malpractices...)

Resource allocation – From a scientific point of view, this is a safe bet to claim that the swine virus *can* mutate and become exceedingly naughty, as no serious professional can deny such a possibility: but the relevant question is rather *the probability* of such a mutation. In a world where money is limited, once you focus on one issue, you take resources which will not be devoted to other issues. Therefore, our responsibility as experts is not to cry wolf under any pretext: it is rather to *rank* priorities in health problems on the basis of *available* data in order to enlighten the politicians about resource allocation. Until the contrary is proven, I maintain that thus far, available data do not make swine flu as a health priority: neither at the scale any country considered individually, neither at an international scale.

Profitability – At the end of the 1990s, it was not a secret that drug makers were becoming nervous about the persistence of the indecent profitability of their business because of blockbusters coming out of patent and, more seriously, their lack of innovation. Since then, it suffices to skim through economical press to note that

³¹ Angell M. The Truth about the Drug Companies. How they deceive us and what to do about it. New York: Random House, Inc, 2004.

vaccines have become *the* providential sector to maintain this profitability. In spite of their depressing lack of imagination to create valuable new chemical entities, it did not take drug manufacturers a long time to understand that from a pure question of profitability, vaccines offer two major advantages: 1/ with adequate lobbying (thanks to the WHO experts³² and to those of governmental agencies with their vested interests), it is not difficult to widen to everybody³³ the target population; 2/ with their slapdash development, vaccines are not expensive to make. This should have been an eminent priority for health agencies to protect citizen against such prospects: for the time being, they have preferred to serve the manufacturers interest, giving credibility to the tales of pharmaceutical promotion by their outrageous alarmism and supporting the amateurism of vaccine makers by ignoring the regulations they should have the duty to enforce.

³² Girard M. World Health Organization Vaccine Recommendations: Scientific Flaws, or Criminal Misconduct. American Journal of Physicians and Surgeons 2005; 11:22-3

³³ Just consider the current tragicomic fuss made by the manufacturer and its experts to justify the administration of Gardasil (normally aimed at preventing cancer of the *uterus*) to men, under the pretext of dirty sexual practices that any moral person should reprove... Even the inescapable determinants of anatomy are not serious obstacles for the « experts » of drug makers !

5. Conclusion

As mentioned above, a positive consequence of the swine flu story could be a radical reappraisal of the ferocious antagonism between vaccine promoters and antivaccinationists. This time, by dint of ignoring the basics of drug development, things went too far – and everybody may notice. It is time now to go back, to understand that **vaccines are drugs amongst others**, with their potential of hazards and the inherent requirement of a cautious assessment regarding their benefit/risk ratio. It is time now to stop considering that vaccines *must* be beneficial and that they *cannot* be risky. It is time to require that the elementary principles of drug development cannot be so grossly ignored as they are nowadays as far as vaccines are considered. It is time to recognize that human body is not a bin for the dangerous gadgets that, through lack of professionalism, Big Pharma develops instead of useful drugs.

In April 2007, on the site of the French *Association des médecins de l'industrie pharmaceutique*, an association of professionals working for pharmaceutical firm, one of the major vaccine makers posted a job advertisement in English (attached). This was for an appointment of "clinical team leaders, global clinical development, vaccines" – typically the kind of guys that may be now in charge of the development of influenza vaccines. After emphasizing an "excellent salary, bonus and benefits package (including 53 days annual leave)", the ad turned to the candidate profile: "An understanding of the clinical aspects of infectious diseases – virology, immunology or microbiology would be very useful *but is not essential*. You need to demonstrate the core interpersonal skills, including international outlook, excellent presentation and communication skills, team leadership, impact and influence (...)" (my italics). The ad was *strictly silent* on any requirement of a past experience in drug development...

This should be a serious concern for any health professional – and beyond: for any citizen – that, in the vaccine sector, things went so far that manufacturers are not ashamed of publicly advertising that, to develop new vaccines, even a simple "comprehension" (not an expertise!) of infectious disease "is not essential" as compared to smartness ("excellent presentation"), a personal gift for chatter ("communication skills") and good manners with people ("impact and influence": preferably with opinion leaders and experts of the governmental agencies?).

No wonder that on the basis of such amateurism, vaccine makers are just able to develop *defective* products. But, perfectly illustrated by the current story of swine flu, the problem is that they are actively encouraged by health authorities to introduce and *maintain* their defective products, in blatant contradiction with laws in force³⁴.

How to explain this contradiction between the law on the one hand, and the regulatory practice on the other? In its Directive 65/65/EEC (26/01/65), the Council of the European Economic Community was not afraid to write:

³⁴ For example in Europe, the Directive 85/374/EEC (25/07/1985)

Whereas the primary purpose of any rules concerning the production and distribution of medicinal products must be to safeguard public health;

Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community

At least in Europe, this was probably *the first time in the whole history of pharmacy* that a mercantile target was put exactly at the same level as the primacy of public health: when laws are so hypocritically ambivalent in their inspiration, no wonder if their enforcement is schizophrenic in practice³⁵...

By contrast, let us compare the Royal Charter granted by King James I of England to the Society of Apothecaries, in 1614:

(...) very many Empiricks and unskilful and ignorant men do abide in the City of London, which are not well instructed in the Art or Mystery of Apothecaries, but do make and compound many unwholesome, hurtful, dangerous and corrupt medicine and the same do sell (...) to the great peril and daily hazards of the lives of the King's subjects³⁶

"Unskilful and ignorant" drug makers, "unwholesome, hurtful, dangerous and corrupt medicines", "great peril and daily hazard" for citizens: which of the royal concerns was not sadly exemplified by the story of swine flu?

Conflicts of interests: *Dr Girard works as a consultant for pharmaceutical firms, including manufacturers likely to have an interest in influenza pandemic and (at least until recently...) a number of vaccine makers.*

³⁵ I suppose that similar ambivalence may be found in American regulations.

³⁶ Quoted in Dukes G, *The Law and Ethics of the Pharmaceutical Industry*, Amsterdam, Elsevier, 2006, p. 87