European Journal of Epidemiology **10**: 507–508, 1994.

Role of the French drug licensing authority in the prevention of influenza pandemics

Michèle Aymard[1] & Jean-Paul Cano[2]
[1] *National Influenza Reference Centre, Lyon, France;* [2] *French Drug Licensing Authority, Saint-Denis, France*

Abstract. The French Drug Agency is responsible for the control and delivery of batch release certificates. In the case of an influenza pandemic, the use of inactivated vaccines, produced according to well-established procedures and controlled according to the European Pharmacopea and FDA requirements, will be strictly dependent on the necessary delays for production and controls. Mutual recognition between the National Control Laboratories in Europe might help in shortening the delays. If new, inactivated vaccines are produced either on cell cultures or by using genetically modified organisms, and if live attenuated vaccines are needed, it would be suitable to organize ad hoc working groups and international collaborative studies in fields of both research and regulation.

Key words: Licensing, Pandemic influenza, Vaccines control

Introduction

The objective of the French Drug Licensing Authority is to intervene rapidly and effectively:

1. In the formulation of vaccines, their control and the issuing of Marketing Authorization certificates, and
2. accomplish this action by applying the European procedure for the release of batches (Directive: 89/342/CE), applicable since January 1, 1992, to inactivated influenza vaccine.

This implies the need for planning and coordination on a European scale for the choice of vaccines and control procedures, but it also presents the advantage (because of mutual recognition) of possible redistribution of controls among different European laboratories as a function of their competence.

In the event of a pandemic, however, there will not only exist the *urgency* but also the necessity to produce large quantities of a monovalent vaccine, to diversify manufacturing processes (cell substrate/eggs) and types of vaccine (attenuated – inactivated), and to produce and control vaccines destined for non-European Community countries. For this to be successful, close, active international cooperation is necessary, with the WHO playing a predominant role.

The following comments refer to the responsibilities and functioning of the Drug Licensing Authority at the national level, and its recently restructured Control Laboratories.

Participation in decision making

- Nationally derived epidemiologic data are collected by the Department of Health, which maintains very close contacts with the European influenza surveillance network, the reference centres and the WHO.
- Participation in the EEC ad hoc working groups.

Decisions

- Vaccination, as a function of the urgency in making the vaccine available. A decision must be taken as to the type(s) of vaccine(s), the quantities needed (vaccination strategy?) and the controls to be demanded and carried out in order to allow batch release.
- Prophylactic medication (for example Rimantidine). Use need not be limited to the period prior to availability of a vaccine.

Do we possess the necessary technical knowledge?

Vaccines

Production

- Inactivated vaccine *rapidly* produced on *well-standardized* chicken egg embryo (< 6 months). Subject to the rapid availability of a strain possessing enhanced potency for multiplication.
- Inactivated vaccine produced on cell cultures. Characters have been defined of certain cell types

and these are used for production of other vaccines, but will the yield be sufficient?
- Live vaccine on cell cultures or chicken egg embryo. A live vaccine is being evaluated, but it is not known how long it will take to produce a correct strain and to assess its attenuation and its antigenic and genetic stability.

Control

For inactivated vaccines prepared on chicken egg embryo, all procedures have been defined, harmonized, and routine production of the necessary reagents ensured. This does not apply, however, to inactivated vaccines prepared on cell cultures or to the live vaccine. Working groups should now be created and collaboration established with international teams to coordinate the necessary research studies prior to the establishment of international consensus specifications.

Efficacy

With the object of enhancing the immunogenic and protective potency of vaccines, studies are ongoing on the adjuvants, the mode of administration (route and dose), and the association of inactivated-live vaccines. Results of these studies will assist in the choice of the best vaccine.

Much remains to be accomplished in the technological field to define the most effective criteria of efficacy, the test for anti-HA antibodies alone providing only a partial idea of the clinical protection obtained, even when assessed by the reduction of virologically documented influenza cases. Immunologic criteria of efficacy of live vaccines must differ, at least partially, from those used for inactivated vaccines, but few data exist and there is no international consensus on this subject.

Tolerance and adverse reactions

These must be examined very rapidly prior to commercialization of vaccines. Whereas our knowledge increases annually for the *inactived vaccine* produced on chicken egg embryo, using vaccines derived from the H1N1 and H3N2 variant strains, available for 16 and 25 years respectively, this is not the case for a 'new' unknown strain (cf, previous experience with H1swN1, New Jersey, 1976). Surveillance of efficacy and safety of this new vaccine must be instituted during its wide public distribution.

For the *live vaccine* derived from a new strain, our knowledge is currently very limited. Possible risks of 'sensitization', of recurrence of virulence (by mutation or genetic rematching), of sensitivity or resistance to antiviruses, of diffusion to persons at high risk (pregnant women, infants, the elderly, the immunodepressed, . . .) have not yet been evaluated and the virologic criteria allowing their detection or their prediction have not been established.

One can hope that the rapid development and mastery of molecular biology techniques will provide responses not only to the production of 'vaccinal' strains and the massive and rapid production of vaccines, but will also supply tests and reagents for the rapid and reliable control of vaccines to effectively complete the panoply of conventional tests.

References

1. Glezen WP, Taber LH, Gruber WC, et al. Family studies of vaccine efficacy in children: Comparison of protection provided by inactivated and attenuated influenza vaccines. In: Hannoun C, Kendal AP, Klenk HD, Ruben FL, eds. Options for the control Influenza II. Amsterdam: Excerpta Medica, 1993: 435–437.
2. Karzon DT. Cold adapted live vaccines: Conclusions and recommandations. In: Hannoun C, Kendal AP, Klenk HD, Ruben FL, eds. Options for the control Influenza II. Amsterdam: Excerpta Medica, 1993: 445–448.
3. Neustadt RE, Fineberg HV. 'The Swine Flu Affair' 1978. Washington, DC: US Department of Health Education and Welfare Publications, 1993.
4. Odelin MF, Pozzetto B, Aymard M, et al. Role of influenza vaccination in the elderly during an epidemic of A H1N1 virus in 1988–1989: Clinical and serological data. Gerontology 1993; 39: 109–116.
5. World Health Organization. Progress in the development of influenza vaccines: Memorandum from a WHO meeting – 1987. Bull WHO 1987; 65(3): 289–293.

Addresses for correspondence:
Prof. Michèle Aymard, National Influenza Reference Centre, 8 avenue Rockefeller, F-69373 Lyon-8, France
Phone: (78) 777 029; Fax: (78) 014 887

Prof. Jean-Paul Cano, French Drug Licensing Authority, 143–147 Boulevard Anatole France, F-93200 Saint-Denis, France
Phone: (1) 48 13 20 15; Fax: (1)