European Journal of Epidemiology **10**: 487–490, 1994.

Vaccine manufacture at the time of a pandemic influenza

Hervé P. Chalumeau
Pasteur Mérieux, Sérums et Vaccins, Marcy l'Etoile, France

Abstract. In the event of a major influenza epidemic, the availability of a potent and safe vaccine would be a major concern. The following presentation describes the main features of a flu vaccine manufacturing campaign: beginning with the supply of embryonated eggs, in which the flu viruses are cultivated, through the different steps of vaccine production – egg harvest, purification, inactivation, splitting – down to the final vaccine formulation and aseptic filling in the appropriate containers. In usual times, such a production cycle takes over 70 weeks. In an emergency situation, the manufacturers and the authorities would have to take innovative approaches to minimize such delays. This will inevitably translate into an enormous strain on all the players in such a project, from the egg suppliers to the organisers of the vaccine dispatching and administration. It will result in suboptimal yields and costs. However, facing a massive and urgent need of vaccine, both the authorities and the vaccine manufacturers must work together to supply the necessary doses in time.

Key words: Flu vaccine manufacturing, Pandemic influenza

Emergency production is more often than not the lifestyle of international vaccine manufacturers. Unexpected epidemic outbreaks or large, sudden orders of national or international organisations have long-driven the producers to build strategic stocks of millions of doses of vaccines, in the form of intermediate, or ready-to-ship products. Flu vaccine is quite a different business: first, the yearly epidemics are, in a way, foreseeable; second, the flu virus strains change from year to year and, thus, the manufacturer cannot set up stocks of vaccine. Every year, the new vaccine doses must be prepared from start to finish. In our developed world, the swift spread of influenza viruses is well known; a pandemic is likely to catch off-guard manufacturers devoid of any vaccine stock. And while the influenza vaccine has been credited with a major role in the struggle against a pandemic, the inevitable time constraints brought by the manufacturing and testing of biologicals are often unknown to the general public and even to some essential partners of the healthcare system. In an emotional atmosphere, any delay in delivering the vaccine could soon be ascribed to listless, routine-minded manufacturers or, who knows, to deliberate attempts to create an effect of shortage.

I do hope that the few following comments will describe what the vaccine manufacturers can contribute, in the case of a major crisis such as the one we have been considering for these last three days. And I can assure you without a doubt that these manufacturers will all contribute their share in the huge endeavour that would then be necessary.

Let us first see briefly how the vaccine is made. To manufacture the vaccine, one first needs influenza virus. These last years, most national and international authorities have recommended the use of a trivalent vaccine including two type A strains and one type B strain. With a few exceptions, these strains are the same for most countries. The seeds are provided by reference laboratories such as the British NIBSC or the American CDC.

The virus is grown in the allantoic cavity of embryonated hens' eggs and incubated for 10 to 12 days. Large quantities of eggs are required every year. The incoming embryos are inspected and must comply with stringent quality criteria. A virus suspension is then injected, through the shell of each egg, into the allantoic cavity of the embryo, so that the virus can multiply, invading the epithelial tissues nearby, and be released into allantoic fluid. The viral culture lasts two or three days while the eggs are placed in incubators.

Whereupon, the eggs are harvested. The allantoic fluid is collected from each embryo, representing around 10 ml per egg. This crude viral suspension is next purified, concentrated, inactivated and split. The order in which these steps take place, as well as the exact nature of these processes, vary according to the producers. Purification most often resorts to ultracentrifugation, inactivation is achieved with formaldehyde or beta-propiolactone, and virus splitting is made with detergents.

Nowadays, the vast majority of the vaccines obtained after these numerous manufacturing steps

are much less reactogenic than those of the sixties; they contain minimal amounts of ovalbumin, they are of very little pyrogenicity. This entire process ends with the production of bulk monovalent vaccines for each viral strain.

The more conventional, pharmaceutical operations are next, which consist of mixing the vaccines prepared from the different strains, filling the batches into syringes, ampoules and vials, and labelling and packing the final lots, i.e. putting them in boxes and cartons. All the manufacturing steps are interspersed by laboratory analyses, in order to test the quality of the in-process products and to decide, for each batch, whether one can proceed with the next production steps.

With such a manufacturing process in mind, one can try and find the constraints which would surface if we were to produce, on short notice, vaccine doses in much larger amounts than those usually needed: (1) the appropriate viral strains and immunological reagents should be made available, (2) large quantities of fertilized eggs should be obtained, (3) there could be a limited supply of filling containers, (4) the production cycle time, (5) the current regulatory procedures could slow down our response, and (6) our manufacturing capacities would most likely reach saturation.

Let us go over these points one by one again. The pandemic would most probably originate from a type A virus strain. The producers should thus be provided with certified seeds of this strain, along with standard immunological reagents (antigens, antisera) in order to assay and calibrate the vaccine.

Another major point is the supply of the millions of eggs which are necessary each year. The egg outputs are huge: yearly, Europe produces over 100 milliards of eggs. Worldwide, 700 milliard eggs are made each year. However, for vaccine manufacturing, only embryonated eggs can be used. These come from poultry farms including roosters, which are the minority of the breeding plants, those producing chickens and laying hens. Additionally, large incubator capacities are necessary to develop the embryos. European incubators have room for 60 million eggs. The Americans, who are big chicken-eaters, have incubation room for 200 million eggs. In terms of daily egg output, these figures must be grossly divided by 21 for chickens and by 11 for chick embryos used in flu vaccine production. In the event of a general, urgent demand for vaccination by every population, vaccine manufacturing could mobilize over 10% of these incubation capacities. Clear arbitrations should probably be pronounced by the authorities upon the use of the egg incubators, to divert such capacity levels toward vaccine production, at the expense of the cheap and popular source of proteins, which the chickens constitute.

The vaccine manufacturers generally deal with egg producers whom they have long known and audited, and from whom they require high quality standards. Facing highly increased demand, one would have to use eggs from any origin. The flu vaccine is fortunately a chemically inactivated, sterile filtered product. A possible microbial contamination does not translate into a contaminated final vaccine. For proper production, the vaccine manufacturers would, however, have to agree upon a minimum set of quality criteria with egg vendors who are unfamiliar with pharmaceutical standards. With variable sources of eggs, suddenly diverted from their regular users – and, therefore, obviously more expensive – the production yields would decrease, batches unfit for vaccine production would appear more frequently, putting a serious burden on the vaccine manufacturers.

In Europe, to foster the quality of vaccination, the vaccines are most often delivered in unit doses, in the form of pre-filled, ready-to-use syringes. These containers must be sterilised at the manufacturer's just before filling; to withstand sterilisation, they are made of glass. These syringes are costly, in limited supply and, because of their bulk and costs, large stocks cannot be built up. In case of a large epidemic, one may want to turn more often to other containers, such as ampoules or vials. The vaccine could be filled in multidose containers, for mass immunisation sessions. The syringes used to deliver these doses could then be plastic items, which are widely used for many drugs, thus available in large supply. With multidose containers, the filling capacities of the manufacturers would be increased, which could reduce the response time of the production.

However fast the pace imposed on production, there will still remain some lag from the time when all raw materials are available to the day of vaccine distribution to the market. Virologists, after all, are familiar with this notion which they would christen 'latent period', a phenomenon which the cellular machinery itself undergoes when it comes to producing viruses.

In Figure 1, the different steps of the manufacturing of the flu vaccine are shown. In regular production, it can be seen that it takes around 80 weeks from the first contract negotiations with the egg vendors to the launching of the first doses of vaccines in September. As a matter of fact, the poultry farms must be informed of the quantities of eggs that are required for the production campaign very early. Applying the old chicken and egg principle, the farmer must order, from the breeder of poultry stocks, the eggs which will give birth to the hens and roosters which will produce the eggs which will produce the vaccine. . . . Therefore, for the flu vaccine that will protect people in 1994–1995, most agreements between the egg vendors and the vaccine producers were discussed in the summer of 1993.

In times of pandemic, things of course should go faster; we have already seen that embryonated eggs

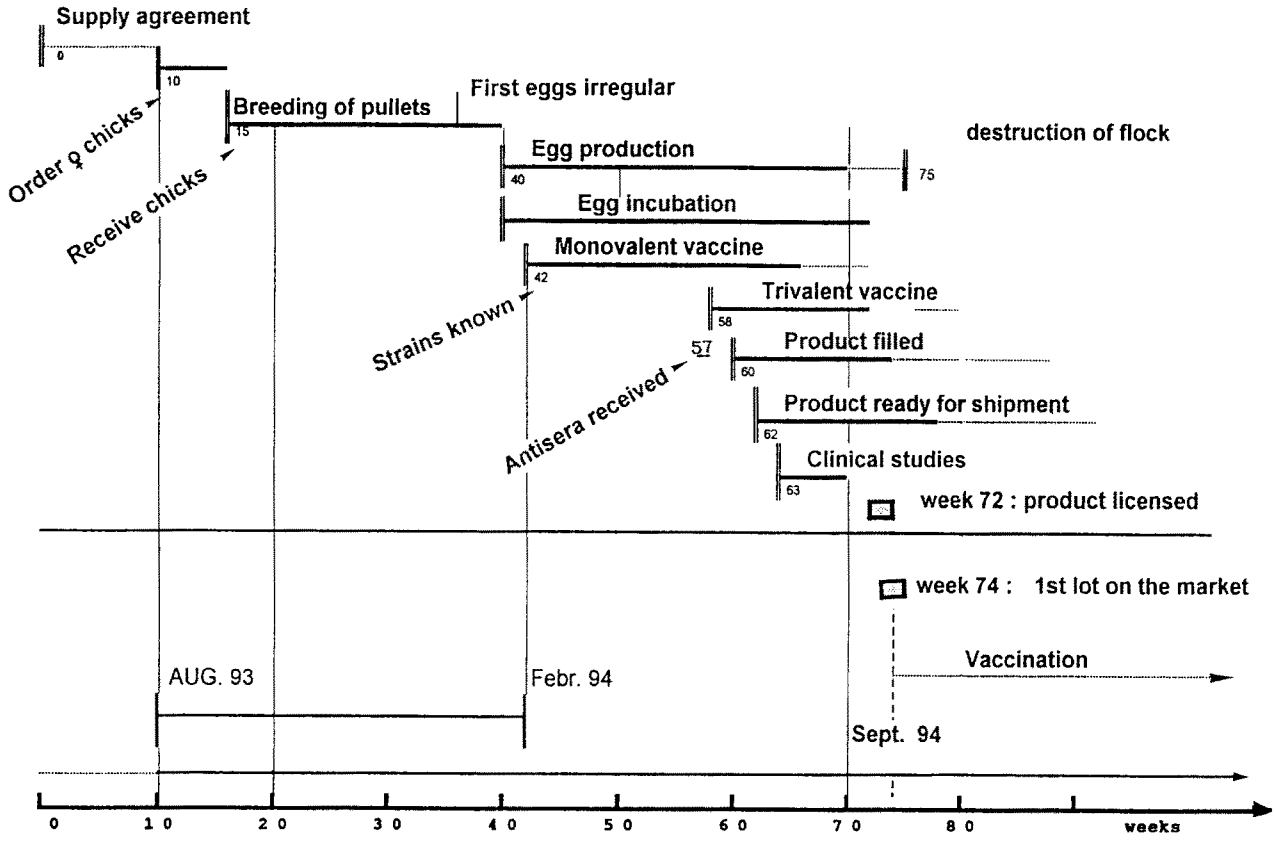

Figure 1. The planning of a flu campaign.

could be readily obtained. We have run a study to see whether we could further accelerate a manufacturing process which everyone knows is already quite tense each year. Assuming that all the production factors are available, i.e. the viral seeds, a trained staff, 11-day-old embryos, the necessary equipment and raw materials, the filling containers, the packaging items, the standard reagents; and assuming that a vaccine with only one valence would be necessary (and God forbid that we face a two-strain pandemic!) we could establish that in seven weeks, we would be able to drive a production batch from the egg inoculation to the dispatching of the finished product.

For the manufacturers, the implications would be heavy: one would have to continuously produce, without waiting for quality control tests to be performed at each step, which, at the end of the process, would bring a significant discard risk, i.e. a certain number of batches would be unacceptable. Also, the size of some installations, such as incubators, would have to rapidly increase and be able to work around the clock, day in, day out. Staff and equipment would have to be diverted from other vaccine productions, which could soon translate into loss of orders, if not customers, in a trade where the reliability of the vaccine supplier is cardinal for the organisations who rely on him. Working with eggs of varied sizes, which should be handled by finely tuned machinery, and sometimes staffs with little training, to manufacture a vaccine based on a new, little known viral strain, will only result in poor yields; but, in a pandemic, all these emergency measures no doubt would be worth trying.

The determination of the regulatory authorities, whether national or international, would have a major impact on the success of such manufacturers' efforts. The authorities should be advised to:

1. adopt more flexible regulatory procedures: product licensing procedures should accommodate the emergency situation, accepting, for instance, limited clinical studies before the product can be distributed;
2. make public the clear decision to launch an extended vaccination campaign, decide which parts of the population to immunize, assume the responsibility of having a sufficent number of doses made and of immunising so many people;
3. contribute to defining and organising the distribution of the vaccine;
4. coordinate national health measures with the policies of neighbouring countries.

Governments, as well as the media, have a major role to play in the responsible information of a conceivably very anxious public. Vaccine manufacturing can be represented as a oceanliner: slow to move off, it is also slow to stop; a social and mediatic environment, avoiding ups and downs, controversies, orders and counter-orders, would be the only context which would allow continuous and timely production of the necessary doses of vaccine.

Producing vaccines is a craft; it is also a passion. Passion for biology, for sure, but also conviction that we manufacture essential products for public health. No doubt that, with everyone's help, we, the vaccine manufacturers shall take up, with all our might and all our heart, this huge challenge that would, that will represent one day, a severe pandemic of influenza.

Address for correspondence: Hervé Chalumeau, Pasteur Mérieux Sérums & Vaccins, 1541 avenue Marcel Mérieux, F-69280 Marcy l'Etoile, France
Phone: (78) 873 666; Fax: (78) 873 016