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Eurosurveillance, Volume 8, Issue 25, 17 June 2004

Articles

Citation style for this article: Wood JM, Robertson JS. Development of a vaccine for humans against highly pathogenic avian influenza virus. Euro Surveill. 2004;8(25):pii=2489. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2489

Development of a vaccine for humans against highly pathogenic avian influenza virus

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In the past eight years there have been three pandemic 'false alarms' caused by avian H5N1 viruses. The first of these in 1997 was a turning point in our understanding of the difficulties of vaccine development from a lethal avian virus. It took 7 months to produce the first vaccine and even this was not an ideal candidate, due to antigenic differences from the 1997 H5N1 virus and poor growth properties. Since 1997, we have become much better equipped to respond, mainly due to increased sophistication and more widespread use of reverse genetics technologies. The important features of reverse genetics for pandemic influenza vaccine development are as follows:

- Ability to genetically modify a highly pathogenic avian virus so that the molecular basis for pathogenicity is removed. This dramatically reduces the danger associated with the virus.
- Ability to produce reassortants between a modified safe avian virus and a human vaccine virus such as A/PR/8/34. A PR8 reassortant will grow well in mammalian cells and in eggs and it is likely to be attenuated for man, thus improving the safety profile of a pandemic vaccine virus.

Since 1997, more experience has been gained with rescue of reassortant viruses in Vero cells, which was an important advance because Vero cells are widely used for production of human viral vaccines. This provided an opportunity to rescue an avian virus: PR8 reassortant in a cell line approved by regulatory authorities.

These advances prompted a European initiative to develop pandemic influenza vaccines, which was sponsored by the European Commission. The project, FLUPAN, started in 2001 with the aim to construct a safe vaccine virus from a highly pathogenic avian H7N1 virus using reverse genetics. The reassortant H7N1 virus would then be used to produce and clinically evaluate an experimental mammalian cell-grown vaccine. This project aimed to provide a 'proof of concept' that safe and immunogenic vaccines could be produced from highly pathogenic avian influenza viruses.

However, in 2003 the work of FLUPAN was overtaken by events in Hong Kong. Two human cases of H5N1 [1] prompted the World Health Organization (WHO) to request WHO Collaborating Centres to prepare a safe vaccine strain. As there were no non-pathogenic H5N1 strains available, the only option for vaccine virus development was to modify one of the highly pathogenic avian viruses by reverse genetics. Incredibly, within the space of less than four weeks an H5N1:PR8 reassortant was rescued in Vero cells by researchers in the United States (US) [2]. A few days later, a further reverse genetics H5N1:PR8 reassortant was produced in the European Union at the United Kingdom's National Institute for Biological Standards and Control (NIBSC, http://www.nibsc.ac.uk) and for the next two months, it was important to establish whether these newly constructed viruses were safe for vaccine development. The objectives of the safety testing programme were to establish non-pathogenicity of the reassortant viruses in chickens and in man. There were already internationally agreed procedures for chicken pathogenicity tests [3], but such procedures were obviously not possible in man. Consequently, the WHO Collaborating Centres produced a protocol to assess virus pathogenicity in ferrets [4], which is probably the best available animal model for influenza infection in man.

In 2004 we faced a third and possibly more serious pandemic threat, when highly pathogenic H5N1 infections of man were confirmed. These cases were associated with widespread H5N1 disease in domestic birds in South East Asia [5]. Once more, the WHO requested the development of candidate vaccine viruses and it was disappointing that the H5N1:PR8 reassortants produced in 2003 were not suitable, due to antigenic differences between the haemagglutinin protein of the 2003 and 2004 viruses [2]. It was therefore necessary to start once more with vaccine virus development. A reassortant was produced in Vero cells within four weeks at NIBSC and just over two months later, the virus was available to vaccine manufacturers after passing pathogenicity tests. At the time of writing, H5N1:PR8 reassortants produced in the US will also become available shortly.

Meanwhile, despite delays in FLUPAN while responding to H5N1 threats, an H7N1:PR8 reassortant has recently been rescued in Vero cells and is now awaiting safety tests and vaccine development

has recently been rescued in Vero cells and is now awaiting safety tests and vaccine development.

A further significant event in pandemic vaccine development was the publication of an EU regulatory framework for pandemic vaccines in the past year [6]. Recent research has shown that in naïve populations, conventional influenza vaccine formulations are unlikely to provide adequate protection and alternative vaccination strategies are needed. It is therefore likely that pandemic vaccines will be significantly different from those currently licensed and unless the licensing protocol is addressed in advance, they will cause administrative delays in availability of pandemic vaccines. The EU Committee for Proprietary Medicinal Products thus encouraged and provided guidance to vaccine manufacturers to prepare a core dossier for a pandemic vaccine, which could be licensed in advance of a pandemic. Such core dossiers would contain clinical data on the use of a 'mock' pandemic vaccine strain such as an H5N1 or an H7N1 virus. In the event of a pandemic, the vaccine could then be rapidly licensed by an update procedure.

The key steps in pandemic influenza vaccine development are illustrated in the table. It is envisaged that candidate vaccine viruses will be generated by reverse genetics when WHO declares Phase 0 level 2 of their Pandemic Preparedness Plan (two or more human cases, but no efficient person to person transmission) [7]. If pandemic activity does not follow such alerts, the vaccine viruses are unlikely to be used for large scale vaccine production, but they provide ideal candidates for pandemic vaccine clinical research. Such research is crucial in order to explore different vaccination strategies, so that manufacturers know in advance how to formulate an immunogenic, antigen-sparing and safe pandemic vaccine. Once such information has been generated, manufacturers can seek to obtain an EU licence for this concept, as described above. In the event of pandemic activity, manufacturers can then go into full scale vaccine production as soon as the vaccine virus is available, confident in the knowledge that their pandemic vaccine can be licensed in the EU very quickly, without further clinical evaluation.

Table. Key steps in pandemic influenza vaccine development

Event	Comments
More than one human case of infection with novel influenza virus	WHO pandemic phase 0 level 2WHO requests vaccine strain development
Construction of vaccine virus by reverse genetics	Takes place in WHO Collaborating Centres
Safety tests of vaccine virus	Only needed if novel virus is highly pathogenic
Vaccine production	The scale of production depends on level of pandemic activity and national needs
Vaccine formulation	Dose, need for adjuvant etcIf data not already available, vaccine enters research phase (Phase 1 / 2 clinical trials) to evaluate safety and immunogenicity
Quality control data including animal immunogenicity data	Manufacturers will work closely with national control authorities
Vaccine licensing	EC fast track procedure (2-3 days) envisaged. This is unique in not requiring clinical data, but depends on prior clinical research, submission and licensing of a pandemic vaccine concept
Vaccine in general use	Post marketing data on vaccine safety and efficacy will be accumulated

Thus, in the space of one year, candidate vaccine viruses have been produced from two H5N1 viruses and one H7N1 virus. This is ample proof that reverse genetics technologies have potential for rapidly generating pandemic vaccine viruses. It is now important for vaccine manufacturers to gain experience in vaccine production from such viruses, for clinical trials to be undertaken and for progress in EU licensing of pandemic vaccines to be initiated.

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