THE ROYAL SOCIETY

The Academy of Medical Sciences

Summary of oral evidence: Dr John Wood and Dr James Robertson, National Institute for Biological Standards and Control (NIBSC)

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Dr John Wood and Dr James Robertson are Principal Scientists in the Division of Virology at NIBSC. Dr Wood and Dr Robertson lead the NIBSC's influenza group and their responsibilities include the control and standardisation of influenza vaccines. On behalf of the World Health Organisation (WHO) the NIBSC is involved in the serological testing of vaccine trials; the preparation and distribution of influenza viruses to vaccine manufacturers; and the coordination of EU strain selection process.

Members of the working group present were: Sir John Skehel, Professor Glynis Breakwell, Professor Neil Ferguson, Professor Barry Furr, Dr John McCauley, Professor Andrew McMichael, Professor Karl Nicholson, Dr Geoffrey Schild and Richard Stubbins.

Key points

NIBSC is a government funded agency which acts as an interface between public health and the vaccine industry to control and standardise biological products. Reverse genetics technology is used to modify virulent strains before they are given to vaccine manufacturers. The NIBSC also supplies industry with standards and reagents to measure vaccine potency and is responsible for the official testing of new vaccines. In summary, the NIBSC is involved in many stages of the life cycle of seasonal vaccine production and is constantly looking at new methods to speed up pandemic vaccine production.

Obtaining sera

Drs Robertson and Wood told the group they face no restrictions in obtaining supplies of sera after vaccine manufactures have completed their trials of seasonal influenza vaccines. However, H5N1 sera have been more closely guarded. They have just begun a project with Professor Maria Zambon (Health Protection Agency, HPA) to examine vaccine cross reactivity in H5N1 but this has just started as it has been hard to obtain the necessary permission. Vaccine manufactures are reluctant to release their sera in case regulators require more experiments in the future.

Pandemic vaccines

Drs Robertson and Wood consider that pandemic vaccine development in the EU has been slow due to limited public funding. This is in contrast to the situation in the USA. Dr Wood told the group that the NIBSC collaborate with the vaccine industry, for example on an H9N2 vaccine. The EMEA have helped to persuade industry to invest in pandemic vaccines with the introduction of the mock up files and by waiving the regulatory fees and several pandemic vaccines are now in clinical trials. However, this is a slow process and they believe that public funding (from Department of Health (DH) or the EU) should have been used to kick start the process as industry would not initially release funds to develop a product which may not be marketable.

Intellectual property (IP)
Drs Robertson and Wood were asked about the effect of IP on the production of novel vaccines. They agreed that patents for technology, such as gene rescue for (H5N1) virus production have slowed down the process, particularly obtaining material transfer agreements. The IP holders have waived ownership of the reverse genetics technology used in vaccines in the research phase, but want an agreement when the vaccine is commercialised. It was considered that a generic MTA for the technology would be useful, rather than a separate one for each virus. This may be an area where WHO should provide guidance and be involved in the negotiations.

Virus production and strain variance
H5N1 vaccines are proving difficult to generate, achieving acceptable immunogenicity is a challenge and the immunological correlates of protection are not well understood. The way ahead appeared to be use of functional serological tests such as virus neutralisation, but the protective levels of neutralising antibody are currently not known. The group discussed the plasmid-based system used in reverse genetic techniques to produce a safe pandemic virus strain for the manufactures.

Drs Wood and Robertson told the group that antigenic drift of H5N1 has been seen in 2005/6 and two distinct genetic groups now exist, clades 1 and 2. Clade 2 viruses are genetically heterogeneous and appeared 6 months ago. NIBSC obtained samples of a clade 2 virus from Turkey and the US Center for Disease Control and Protection has obtained an Indonesian virus. Vaccine viruses are now being generated by reverse genetics.

NIBSC have looked at cross protection of vaccines produced from 1997, 2003 and 2004 H5N1 viruses in mice and have found that despite antigen differences, they protect mice against infection with a 2004 H5N1 virus.

Communication with the Department of Health
Drs Wood and Robertson were asked how their knowledge feeds into DH and if they think it is done sufficiently. Together with Dr Stephen Inglis (Director, NIBSC), they are members of several government committees and also hold more casual meetings with DH to talk through issues. These meetings are either arranged by NIBSC or DH and included a brainstorming meeting held about 6 months ago to look at how processes can be made quicker, especially for H5N1 vaccine development. It was highlighted that they often provide information to DH but often are uncertain about what DH does with it.

Research and funding sources
Drs Wood and Robertson considered that there is a lack of vaccine research in the UK compared with the US. They told the group that NIBSC has made submissions to DH and to the EU for pandemic vaccine, but they have not been funded. They were asked by the group if they are given the freedom and resources to look at new approaches. They told the group that they have the freedom at NIBSC to initiate their own research programmes, but not the resources. They were unaware if the situation is likely to improve with the forthcoming amalgamation with the HPA.

Dr Robertson's research work for the last three years has been predominately directed at improving the reverse genetics technology. His group is also looking at ways to improve the low viral yield of H5N1 in vaccine manufacturing. The NIBSC has had some funding from the EU for pandemic vaccine research, but they both agreed that funding resources are a big issue.

Facilities for experimental animals
Facilities in the UK are not considered as good as those in the US. Experiments with mice at high biocontainment can be done at NIBSC and HPA facilities at Porton Down are being upgraded for ferrets, but

are currently not up and running. Dr McCauley told the group that the Institute of Animal Health has 16-18 rooms available for experiments using ferrets.

Use of live vaccines

Drs Wood and Robertson were asked their opinion on priming the population for a pandemic using live vaccines and if they consider it to be a good idea. However the timing is critical; if live H5N1 vaccines are used now it would be considered too dangerous, but if a pandemic is imminent the risk may be justified. A stockpile of live vaccine, with the cleavage site removed, could be used to prime the population in advance of the pandemic reaching the UK. Even without an exact match in virus strain, it is predicted that this would provide a broad immunity to the population.

Surge capacity

A process evaluation is currently being conducted at NIBSC to identify areas to improve surge capacity in a pandemic. It is anticipated that the Institute's essential functions will be preserved but some functions will be minimised.

The NIBSC is not involved with diagnostics for influenza, or any other infectious disease.