Development and evaluation of influenza pandemic vaccines: report of WHO expert meeting
Initiative for Vaccine Research, Global Influenza Programme

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Introduction and Meeting Objectives

The rapid spread of H5N1 viruses, considered the influenza strain with the greatest pandemic potential suggests that the world is closer to an influenza pandemic than at anytime since 1968. Several manufacturers have active programmes to develop and evaluate vaccines against H5N1 influenza virus, as well as against the H9N2 and H2N2 subtypes, from which it is anticipated that valuable information can be obtained. The current inter-pandemic period provides a window of opportunity to maximise and harmonize global efforts to expedite vaccine development and to augment supplies. To this end, the WHO has convened a meeting of regulators as well as manufacturers and researchers from as many as 13 countries (appendix 1) currently active in vaccine development and production. WHO strategy focuses on the development of global quality, safety and efficacy standards for influenza vaccines, as well as on promotion of antigen sparing techniques in vaccine development. Harmonizing regulatory pathways and bridging the gap between production capacity and potential pandemic vaccine demands is also a key focus. Each day saved in the development and registration process of future pandemic influenza vaccines will have a significant impact on the amount of vaccine available to confront and curtail such a potential pandemic.

Summary of Presentations

Matters discussed and issues arising:

1. Production of reference viruses by reverse genetics
2. Clinical studies: H5N1 & other strains
3. Antigen sparing approaches
4. Data & trial development needs
5. International standardisation and harmonisation

Production of Reference viruses by Reverse Genetics

Reverse Genetics has become a technique for generating reference strains through reassortment of genes from pathogenic influenza strains and attenuated host virus strains, coupled with the deletion of gene segments associated with pathogenicity. Such strains are provided to manufacturers for the development of vaccines. While an increasing number of laboratories are now capable in this technology, not all function at GLP/GMP or are members of the WHO Collaborating Centre network. Several speakers stressed that further optimisation of strains would be required for pandemic vaccine development, especially deriving strains which produced greater yields in

eggs. An expansion of the range of cell substrates in use was proposed for more efficient virus recovery. Exploration of the chicken Pol-I promoter system was suggested in addition to the currently most widely used cell line, Vero cells. Modification of one or more internal gene segments was discussed as a further enhancement to the reverse genetic process, notably the replacement of one or more PR8 gene segments with those from the target strain. Molecular analysis of manufacturers' seeds versus the reference virus produced by NIBSC, was suggested.

Expediting safety tests: With increasing experience, revision of WHO bio-safety guidance came under consideration with the aim of accelerating the release of reference strains to manufacturers. It was agreed feasible to consider preliminary release of reference strains following safety tests in ferrets. This has the potential to shorten the process to around 3 weeks instead of up to three months. Both USA and UK authorities were actively exploring ways of speeding up safety testing. Although an acceptable technique to licensing bodies Reverse Genetics brought with it additional GMO regulatory requirements, which differed from country to country and had an impact on time lines.

Clinical Studies

Inactivated vaccines: Studies with unadjuvanted, subunit influenza vaccines were currently the most advanced, but appeared only capable of inducing satisfactory antibody titres in healthy adults at significantly higher than usual antigen doses. A trial with the elderly was underway and a further study in children was about to begin.

Most studies employ the NIBSC reassortant virus NIBRG 14, from influenza A/Vietnam/1194/2004. Increasing knowledge on the value of standard and newer adjuvants was a key objective of clinical studies in several countries. Clinical studies of inactivated H5NI vaccines with or without adjuvant are being undertaken or planned in Australia, China, France, Hungary, Japan, the UK and the US, with additional evaluations of experimental H2N2 and H9N2 vaccines planned in Germany, Switzerland and the UK. Most investigations were assessing the safety and immunogencity of Aluminum (hydroxide or phosphate) adjuvanted vaccines. A range of experience with different antigen sparing formulations and dosing was presented (see antigen-sparing section below). Phase 1 studies evaluating low dose, Alum adjuvanted vaccines are due for analysis late 2005 or early 2006.

Updates from Japan, China, Russia, South Africa, and Thailand: Government support had proved pivotal in encouraging manufacturers to establish and plan to evaluate candidate H5 vaccines. The formulation and shape of the clinical trials will be influenced by the data generated by others over the next few months. Japan aims to facilitate the production of a single formulation by four manufacturers. Phase 1 and 2 studies were planned in China. Government support was also evident in Russia, where one institute was planning H5N1 trials and high protection against H2N2 in mice had been shown. Likewise, the South African Departments of Trade & Industry and Science & Technology were considering funding the development of an influenza vaccine manufacturing facility. Feasibility studies were being conducted with a view to vaccine production for the African region. Thailand was also reviewing the need

for its own production plant and the government was actively seeking partners interested in running H5N1 vaccine development trials in Thailand.

Live attenuated vaccine: A collaborative study (NIH and manufacturer), in the US is examining the safety and immunogenecity of an experimental H9N2 vaccine. The first clinical study in healthy young adults has been completed and further trials are planned in 2006.

Antigen sparing approaches

A limited range of experience with different antigen sparing formulations was presented. Alum is the most widely favoured adjuvant because it is available, cost effective, has an excellent safety record and is widely used in licensed vaccines. Little evidence is available to date for its use in naïve populations with the H5N1 virus. While there is encouraging Preclinical data to suggest that alum based influenza vaccine will be safe and immunogenic, whether or not a similar response will be seen in humans awaits the results of clinical studies by two companies, which are expected to be available in Q4/05 and Q1/06. Encouraging results on the immunogenicity of a single dose, AIP04 adjuvanted whole virus vaccine were presented by a small European manufacturer who was encouraged to organise collaborative studies to demonstrate whether or not its results are reproducible. Phase 1 studies had explored the use of MF59 adjuvant with the H5N3 and H9N2 viruses, and, likewise, found better hemagglutination-inhibition titres with adjuvanted vaccine at lower antigen doses. Further whole virus H9N2 investigations, with and without adjuvant, were planned in healthy adults. Studies are also underway to determine whether or not dose sparing can be achieved by administering candidate vaccines intradermally rather than intravascularly.

Data & trial development needs

Adjuvant data: A key step will be early sharing of safety and immunogenicity data from alum adjuvanted vaccines, which will allow modification of clinical protocols as knowledge accumulates. Head to head studies defining optimal regimens and formulations are now desirable and would require the support of manufacturers. With work still largely at Pre-clinical and Phase 1 stage, the need to move swiftly to the generation of data in ‘at-risk’ groups was evident.
Progression to registration: Regulators encouraged manufacturers to move rapidly in this interpandemic period. Several manufacturers had plans to progress to H5N1 trials in children and the elderly within the next 6-12 months, assuming positive results with current candidate vaccines in young, healthy adults. Dossiers were also in preparation by several manufacturers in response to accelerated ‘rolling review’ procedures set-up by the EMEA for pandemic influenza vaccines. This allowed for preliminary data submission pending full Phase 3 data. Mechanisms for implementation of Phase 3 trials for pandemic vaccines would need further exploration.
Information gaps: Evaluation of cross-reactive immune responses to newly emerging viruses of pandemic potential was highlighted as an important gap. Ideally, sera and PMBC from vaccine recipients should be collected, stored and made available for further assessment. Greater understanding of potential correlates of immune

protection was also required through assessment of candidate vaccine immunogenicity in a variety of assays. The Phase 1 work in the US with live attenuated vaccines warranted further exploration. Although complex and difficult to run, it was agreed that more trials with live attenuated vaccines would be highly informative both as vaccine studies and to assess protection with a 'mock challenge'.
Interpandemic infrastructure: The value of Government support for manufacturers during the inter-pandemic period - to enhance infrastructure to levels closer to those required to have adequate vaccine supply during a pandemic period - was recognised, as was provision of research funding. Government support was required to ensure effective flock management, availability of suitable bio-safety facilities and the development of staff training as well as robust bio-safety and bio-environmental procedures.

International standardisation and harmonisation

Many opportunities for expediting the development process emerged at an international level. Standardisation of immunogenicity assays would be important, including the use of standard protocols, reference laboratories and expression of antibody results in international units. Enhanced surveillance and standardisation of shipping and sharing of field virus samples was identified as a key enabler to antigenic analysis as well as periodic review to update vaccine composition. Significant delays were reported here by a number of countries. USA and European regulators were open to exploring ways of sharing data and resources. Although pathways differed between the two agencies, the required data sets were considered sufficiently similar to merit consideration of the opportunities for convergence of global licensure requirements. Two WHO meetings of regulators are scheduled. Meanwhile, both the FDA and EMEA were encouraging manufacturers of candidate vaccines to interact with them early and on an on-going basis. WHO would explore opportunities for creating a high level global task force to facilitate the required transparency and collaboration, as well as to manage public expectations during an imminent or actual pandemic.

General recommendations

1. Manufacturers who have utilized H5N1seed viruses based on the strain developed by NIBSC, to forward aliquots to NIBSC, so that reported differences in growth characteristics can be studied systematically.

2. Carry out future studies of adjuvanted vaccines with a comparator arm. If possible leading formulations should be compared head to head.

3. Assess safety and immunogenicity of candidate H5 vaccines in children and the elderly population in accordance with regulatory procedures using information from healthy adult studies.

4. Carry out studies to identify alternative cell lines suitable for use in reverse genetics and to explore the benefits of introducing additional genes from the target strain into the reference viruses.

5. Encourage further evaluation of the promising immunogenicity data reported by Hungarian manufacturers of an aluminium phosphate, adjuvanted whole virus vaccine.

6. Member States who planned to produce and use H5 vaccines should establish robust surveillance systems to monitor the safety and efficacy of the vaccine in the face of a pandemic.

Recommendations to WHO

1. Convene a meeting to share data on the immunogenicity of alum adjuvanted H5 vaccines, as soon as the data becomes available.

2. Consult with manufacturers to ensure that, wherever possible, sera and PBMC are collected from vaccine recipients and stored to enable exploration of potential correlates of protection and cross reactivity with emerging variant strains.

3. Ensure data generated by different laboratories is comparable by establishing standard testing protocols and by encouraging the expression of results in International Units.

4. Call on Member States to expand research efforts to develop live attenuated influenza vaccines with pandemic control potential.

5. Review the application of WHO Biosafety guidelines, to ensure reference strains generated by reverse genetics can be released to manufacturers as early as possible without compromising safety.

6. Encourage enhanced surveillance of influenza viruses and timely shipping of field samples to one of the WHO Centres for Influenza Reference and Research to enable prompt generation and provision of reference viruses to all manufacturers.

7. Support initiatives to increase research on influenza vaccines and to expand production capacity, especially in the developing world.

Appendix

1. **Presenting countries:** Australia, Austria, China, France, Germany, Hungary, Japan, Russia, South Africa, Switzerland, Thailand, United Kingdom, and United States of America.