Evidence for the Royal Society and the Academy of Medical Sciences study on pandemic influenza

Submitted on behalf of the National Institute for Biological Standards and Control (NIBSC) by:

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March 30 2006

NIBSC role

NIBSC has, on behalf of the WHO, been responsible for developing and distributing appropriate vaccine strains to industry for several decades. Recognising the need for a more rapid and robust approach to strain production in a pandemic, the NIBSC team has in recent years developed a 'reverse genetics' approach in which the desired virus strain is rescued directly from DNA plasmids encoding the HA and NA genes from the outbreak strain together with DNA plasmids representing the other six genome segments of the laboratory strain PR8[1]. This approach provides the additional advantage that the HA gene from a highly pathogenic virus can also be genetically modified at the cleavage site to reduce its pathogenic potential[2].

We have used this technology so far to generate over 20 novel virus strains, most recently in response to the threat posed by H5N1 strains circulating in the bird population in S.E. Asia and Europe. In 2004, NIBSC was asked by WHO to develop a potential vaccine strain from a human Vietnamese isolate of A/H5N1 virus. The resulting strain, NIBRG-14, was constructed in just three weeks, and following safety testing, has now been distributed worldwide to over 30 vaccine manufacturers. Several vaccines based on NIBRG-14 are now in clinical trials. More recently a new vaccine strain has been generated from a clade 2 avian H5N1 virus circulating in Turkey using the same methodology.

NIBSC is working closely with WHO, the Health Protection Agency, vaccine manufacturers and other stakeholders to help minimise the response time for vaccine development in an emergency through advance planning and preparation of materials.

In response to the call for evidence, we have focused on vaccine development, supply and clinical use in responding to a pandemic

Background to submission and problem statement

1. Vaccine development and supply should be a key element in dealing with an influenza pandemic. There are advantages in developing a vaccine prior to the pandemic, focusing on potential pandemic strains, for use either in pre-vaccination of the population or in advance vaccine stockpiling. However, this is not a perfect solution because of the possibility that an emerging pandemic strain may differ significantly from a pre-prepared vaccine.

2. The most efficacious vaccine will be one based on the pandemic strain itself. The time needed to move from identification of a new and dangerous isolate emerging in the human population to

availability of vaccine to protect the population is crucial and must be minimized. This is dependent on a number of factors, the most significant of which is vaccine manufacture itself.

3. Global vaccine manufacturing capacity, based on current dosage requirements, appears wholly insufficient to meet vaccine needs and capacity needs to be increased as a matter of urgency.

4. A pandemic vaccine strain is likely to require two doses at least 1 month apart, doubling the number of doses required to protect a given population[3]. Furthermore recent clinical trials in the USA with a standard H5 influenza vaccine have indicated that six times the usual vaccine dose was needed to generate an adequate immune response whilst a recent French trial of alum-adjuvanted H5 vaccine showed that twice the usual vaccine dose was needed.

5. Feedback from vaccine manufacturers has indicated that the yield of HA antigen from NIBRG-14 virus is only 30% of that found normally with seasonal influenza vaccines. This is a great concern and compromises most of the plans for pandemic vaccine supply.

6. Data generated from H5N1 vaccine clinical trials and from current (unpublished) WHO and EU collaborative studies have shown inadequacies in current serological techniques used to assess the potential efficacy of vaccines. The tests appear to be insensitive for antibody to H5N1 vaccines and more sensitive tests such as virus neutralization are difficult to interpret as there are no accepted correlates of protection.

Need for improvement

1. At a recent WHO meeting, several vaccine manufacturers reported low yields of NIBRG-14 HA antigen despite satisfactory infectious titres during virus growth. We examined the HA content of virions by PAGE and found the HA content of NIBRG-14 virions was <20% of total virion protein, compared with a more usual figure of 35-40% of the virion protein[4]. This requires urgent investigation to greatly improved production capacity of influenza vaccine.

2. An important preparation measure should be the development of a 'library' of vaccine seed strains and reagents against potential pandemic strains. We should not neglect the pandemic potential posed by influenza viruses from other subtypes i.e. H7, H2, H9. Though such strains might not turn out to be identical with actual emerging strains, they may be close enough to provide some protection, would quite probably provide effective immune 'priming' (see paragraph 7) and could buy time for preparation of a fully matched vaccine. Availability of 'ready made' seeds developed up to a point where they could be put directly into production by manufacturers would significantly speed up the overall response time. An added benefit from the library in that matched reagents to assess pandemic vaccine potency can also be made. Approximately 1 month could be saved by use of library vaccine viruses for vaccine production and 2 months by use of library reagents developed in advance.

3. A consequence of developing a library of potential pandemic strains is the need to understand the basis of vaccine-induced protection and in particular the ability of a 'mis-matched' vaccine to provide cross protection. In studies with seasonal influenza vaccines, it is known that the antibody responses and the resulting protection against clinical illness are relatively strain specific[5]. However the requirement of a pandemic vaccine may in the short term be to protect against the worst consequences of a highly pathogenic pandemic virus i.e. to preserve life. Studies performed at NIBSC and elsewhere[6] have indicated that mice immunized with a 'mis-matched' vaccine can survive lethal infections of a highly pathogenic H5N1 virus. Such studies need to support the development of library viruses.

4. In order to increase the availability of vaccines and to insure against the vulnerability of egg based vaccine supply there should be research on vaccine manufacture based on cell culture systems. Currently each dose of seasonal influenza vaccine manufactured requires one fertilized hen's egg. While this system is tried and tested, and appears to represent the only viable option at present to produce sufficient vaccine on a global scale, in the long term the potential vulnerability of egg supply in an emergency represents a very substantial risk. There are three cell culture systems being pursued by industry, MDCK cells, Vero cells and Per.C6 cells. It is important to develop, license and expand cell culture manufacturing facilities.

5. In the long term there should be investment in a vigorous programme of research aimed at identifying new approaches to vaccine development. This could include DNA vaccines and recombinant protein vaccines. Each of these vaccine approaches uses fermentation technologies and can potentially deliver many fold more doses than a conventional vaccine within weeks of a pandemic being declared. Although two veterinary DNA vaccines are now licensed for use, there appear to be practical problems with efficient delivery to the human immune system. Intradermal delivery may be more immunogenic[7] and this needs exploring in a pandemic context. Recombinant H5 HA protein vaccines do not appear to be very immunogenic and efforts to improve immunogenicity should be made.

6. We need to develop a better understanding of immunological correlates of protection as measured by virus neutralisation tests. Data could be obtained from cases of human H5N1 infections and also from infections with seasonal influenza.

7. A further crucial area for research in the short and medium term should be to explore opportunities for generating a degree of broad protection against pandemic influenza strains through advance vaccination. It is well recognised that the human immune system can react much more rapidly and effectively to an infectious assault if the system has been 'primed' in advance through encounter with a similar agent. There are a number of possibilities and they should be evaluated further.

    a. An inactivated vaccine administered routinely would 'prime' the immune system so that in the event of a pandemic outbreak vaccinated individuals would enjoy a limited degree of protection, or would require only a single vaccine dose. If this strategy proved effective, routine seasonal influenza vaccines could be regularly adapted to include one or more components in order to prime the population against potential pandemic influenza strains.

    b. A live attenuated pandemic vaccine stockpiled in advance would be administered on declaration of a pandemic. Such a vaccine should be capable of stimulating a broad spectrum of priming, so an exact antigenic match with the pandemic virus would not be needed.

8. It is unrealistic to imagine that demand for a pandemic vaccine could be met simply by investing in additional manufacturing plant. In order to meet demand it is clear that highly efficient 'antigen sparing' strategies will be required, in order that a much larger number of effective vaccine doses can be generated in a shorter space of time from the manufacturing capacity that does exist. This is likely to be achieved only by using adjuvants that are already in use for human vaccines i.e. alum, MF59, liposomes. There is thus need for urgent clinical trials of adjuvanted pandemic vaccines.

9. It is recognized that current influenza vaccines are inefficient in promoting local secretory IgA and CD8+ T lymphocyte responses, both of which play a role in immunity against influenza infections

and which are effective against a broad spectrum of viruses[8]. In the medium to long term there needs to be research into strategies to improve and broaden the immune responses induced by conventional influenza vaccines, so that vaccination against pandemic influenza does not wholly depend on developing strain specific immune responses.

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