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H1N1 'SWINE FLU' VACCINE

A novel strain of influenza (flu) virus subtype H1N1, originating from Mexico, is currently spreading across the globe. A vaccine against the strain could reduce its global impact but would take time to develop and manufacture. Different claims have been made about the time it would take to develop and produce a vaccine. This note describes how a pandemic vaccine for UK use would be manufactured, and alternative techniques for vaccine development and manufacture.

Development of an H1N1 Vaccine

A vaccine against the newly emerging strain of H1N1 could stop or slow its spread, and thus reduce its impact on health services, workplaces, schools and the economy. Since this virus differs markedly from previous strains of H1N1, existing flu vaccines will not work against it and a new vaccine needs to be developed.

Several different companies have the technology necessary to develop such a vaccine. This involves making a preparation of the flu virus that will cause an immune response without leading to symptoms of the disease. This is done either by using killed flu viruses, or by using proteins isolated from the virus (Box 1). Vaccine development begins with a sample of the virus responsible for the disease outbreak. Samples of the H1N1 virus have been received by The Health Protection Agency's National Institute of Biological Standards and Control (NIBSC), which is developing a strain of the virus suitable for use in vaccine development (see page 2), with the aim of passing it on to vaccine manufacturers.

The Vaccine Manufacture Process

The main process in vaccine manufacture involves growing large quantities of viruses. The rate at which doses of vaccine can be made depends on how fast the virus can be grown, and on how much viral material is needed in each dose. Therefore, vaccine manufacture techniques are tailored to:

- grow the virus as quickly as possible;
- maximise the number of doses that can be obtained from a given quantity of virus (for example by adding an adjuvant, see Box 1).

Box 1. What is in a Vaccine?

The purpose of a vaccine is to prime the body's immune system so that it is able to respond rapidly if it is later exposed to that particular disease. The immune system fights viral diseases such as flu by recognising proteins (antigens) on or in the virus. A flu vaccine contains either a safe version of the virus, or copies of its proteins. It causes the immune cells that recognise these proteins to replicate so that they are primed to respond to a later attack by this virus. The vaccine does not itself cause flu, as it does not contain a virus which could replicate within the body – if a whole virus is used, it is killed before the vaccine is created.

Using a whole virus, rather than just isolated proteins, typically leads to a stronger immune response. It can also lead to 'cross-protection' - protection against strains of virus whose proteins differ slightly. This is useful if the virus infecting the population undergoes a mutation, in which its structure changes. For these reasons, vaccines made from isolated proteins may also contain an adjuvant – a chemical designed to enhance the immune system's response to the viral protein, and to maximise cross-protection.

UK Pandemic Vaccine Suppliers

The Department of Health (DH) has 'sleeping contracts' with two manufacturers (Baxter and GSK) which reserve a certain number of doses of any vaccine developed against a pandemic flu strain. These two companies each use a different method of vaccine manufacture.

In GSK's vaccine production process, the quantities of virus needed are grown in hens' eggs - a traditional method of growing viruses, still used by most vaccine manufacturers. The viruses are then split into their constituent proteins, some of which are included in the vaccine. In contrast, Baxter grows the virus in cultured mammalian cells, which is a newer technique requiring a high containment facility. The Baxter vaccine includes a whole, killed virus rather than isolated proteins.

The starting point for a vaccine is a sample of the virus responsible for the disease outbreak. The disadvantage of using eggs for vaccine production is that this sample virus needs to be 'tamed', so that it can be grown in large amounts in eggs, and so that it does not itself pose a

health risk. This taming process is currently under way at NIBSC in the UK, and at the Centers for Disease Control and Prevention (CDC) in the USA. It involves creating a new virus which is based on a safe strain of flu virus but has surface proteins identical to the pandemic strain. This is estimated to take approximately 5-6 weeks. Baxter, which uses cultured cells, can work directly with the 'wild' virus, so can start vaccine production sooner. However, the rate of production is also important, and GSK can produce more doses per week than Baxter once production has started[1]. The DH deliberately chose two companies with very different methods of production to make it less likely that both would be affected by any barrier to production which arose, such as a shortage of hens' eggs.

Timescale for Obtaining Vaccine Supplies

Once the vaccine manufacturers have access to a virus sample, the first doses of a vaccine are estimated to be produced in 12-15 weeks[1], depending on the manufacturing technique (see above). However, it will take some time for all of the UK's reserved doses to be produced. The DH has sleeping contracts for 72 million doses of pandemic vaccine from Baxter, and 60 million doses from GSK (based on the expectation that each person will need two doses of the vaccine). However, this does not mean the UK will have access to the entire first batch of vaccine produced, as the companies also have contracts with other countries. The first doses produced will be shared out amongst all countries with sleeping contracts, in proportion to the number of doses which each has reserved. It will take approximately one year for the UK to obtain all of its reserved doses.

Starting Vaccine Production

A vaccine manufacturing plant can only produce one type of vaccine at any one time. Therefore, before pandemic vaccine production can start a decision needs to be made to stop production of other vaccines. Manufacturers are currently producing doses of seasonal flu vaccine, and it is likely that all of the required doses will have been produced by the time a pandemic vaccine has been developed and is ready for production[1].

The decision to activate the UK's sleeping contract for pandemic vaccine rests with the Secretary of State for Health. However, as the manufacturers have contracts with more than one country, the UK may not have the final say on when vaccine production will start. Also, vaccine manufacturers are likely to await the declaration of a pandemic by the World Health Organisation.

Regulatory Issues

Before a vaccine can be used in the UK, the vaccine and the process and premises of its manufacture need to be approved by the Medicines and Healthcare products Regulatory Agency (MHRA), or the European Medicines Agency (EMEA). EMEA approval means that the vaccine can also be marketed in other European countries, so most companies seek EMEA rather than MHRA approval.

Approval by the EMEA or MHRA is specific both to the product and the production method. To gain approval, a company must provide detailed information about the safety of the vaccine and the consistency of the manufacturing process. As the vaccine will be against a new flu strain, limited data can be provided on how effective the vaccine will be.

As assessing these data prior to approval takes some time (typically 110-200 days), the EMEA has a system of 'mock-up' dossier approval, in which a company can submit the details of manufacture of a product to the EMEA before that product has been developed. This allows the company to gain approval for the production of a vaccine without knowing the strain of virus which will be involved. Once the strain is known, the company applies to EMEA for a 'variation' to the licence, which takes 2-3 days. It then has to supply the EMEA with data on safety and efficacy of the vaccine as it emerges. Baxter and GSK both have EMEA licences, so can supply pandemic vaccine once a variation has been granted.

Advances in Vaccine Science

Many novel types of vaccine, or methods of vaccine manufacture, are currently under development (Box 2). These are either alternative ways of producing the viral material (such as the use of baculovirus), or alternative ways of eliciting an immune response (such as live attenuated viruses, DNA vaccines). However, none of these have been licensed by the MHRA or EMEA. Given the time needed to gather the data to gain regulatory approval these do not present a faster route to obtaining the required doses of pandemic vaccine for UK citizens.

Box 2. Alternative Vaccine Production Techniques

- Rather than using isolated proteins or killed viruses, some newer vaccines contain a **'live attenuated' virus**, which can replicate within the body without causing the disease. In some cases, these produce a stronger immune response, so less viral material is needed per dose. A vaccine of this type for seasonal flu is currently awaiting EMEA approval, but there are no pandemic flu vaccines of this type with an EMEA licence.
- It is possible to use the genetic machinery of insect cells to rapidly produce virus proteins which can be used in a vaccine. A virus called **baculovirus** can be used to transfer the gene for the desired protein to the insect cells. This is used by GSK to produce other vaccines for UK use, but no company has a licence to produce pandemic flu vaccine for the UK in this way.
- **DNA vaccines** do not contain viruses or virus proteins, but just virus genes, which elicit the production of virus proteins within the body's own cells. DNA vaccines are still very much at the experimental stage, so could not be used to tackle the current H1N1 outbreak.
- There is ongoing research into novel **adjuvants**, which reduce the amount of viral material needed per dose of vaccine. For example, GSK uses a recently developed adjuvant, ASO3, in its pandemic vaccine.
- Ultimately researchers hope to develop vaccines based on the parts of the flu virus that do not rapidly mutate. However, such research is still at an early stage.

Endnotes

[1] David Salisbury, Department of Health, personal communication

POST is an office of both Houses of Parliament, charged with providing independent and balanced analysis of public policy issues that have a basis in science and technology. POST is grateful to Dr Zillah Boraston for researching this briefing, and to the Department of Health, MHRA and NIBSC for providing information. For further information, please contact Dr Pete Border at POST.

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