Vaccines, in general, help protect people from harmful infections before they come in contact with the disease. Vaccines may also help alleviate the symptoms of the infection caused by the virus.

**How a Vaccine Works**

The function of the vaccine is to enable our body’s natural defences, i.e. our immune system, to fight and defend our body against a disease.

When the vaccine is injected into our body, it will trigger an immune response in the same way our body would respond after an exposure to the virus, but without the person suffering symptoms of the disease. Our body’s immune system will detect and recognise the pieces of virus or the killed/weakened virus (also known as the antigen) in the vaccine as a foreign invader. Our immune system will then start an immune response by producing proteins called antibodies. The antibody proteins produced by our body during an immune response will then identify and neutralise these foreign viruses or viral particles.

If our body comes in contact with the same virus in the future, our immune system should be able to respond fast enough to prevent the development of the disease. The immune system will be able to recognise the virus and make the antibodies fight against the virus faster, leading to a much more rapid immune response. This faster immune response will protect our body from the potential viral infection or ease the symptoms of the infection.

A lag time will be required for the body to build up its immunity against the virus. Hence, a vaccine is best given to the individual two weeks before the individual is exposed to the virus or infection.

**Types of Vaccine**

There are two types of vaccines available in the market:

- **Non-adjuvanted** vaccine, which has only the antigen as its main component.
- **Adjuvanted** vaccine, which has two main components, the antigen (pieces of virus or killed/weakened virus) and the adjuvant.

**Antigen and Adjuvant**

An antigen is the substance that will trigger an immune response in the human body and this will cause the body to produce antibodies. Usually virus proteins or a weakened virus are used as vaccine antigens. There are different manufacturing methods, as described below, to produce antigens for vaccines.
An *adjuvant* is a chemical substance that is added to a vaccine to help enhance the immune response of the vaccine.

The key advantage of adding an *adjuvant* in a vaccine is that it will reduce the amount of *antigen* required in the vaccine to create an immune response.

- By enhancing the vaccine’s ability to create an immune response with fewer antigens, a smaller dose of *adjuvanted vaccine* will be required to trigger an immune response similar to that of a *non-adjuvanted* vaccine. The dose of vaccine *antigens* needed in an *adjuvanted* vaccine for triggering an immune response to result in the same effectiveness as a *non-adjuvanted* vaccine, can be reduced by two to four times (from 15 microgram/dose in regular seasonal flu vaccine to 3.75 to 7.5 microgram/dose in an adjuvanted formulation).

- As such for the same vaccine production capacity, the addition of an *adjuvant* will allow the number of people to be vaccinated be increased by two to four times. This would be an advantage in pandemic situations, where vaccine manufacturers have both a limited production capacity and time to manufacture the vast quantities of vaccines needed.

It is worthy to note that historically, adverse events to vaccines have been associated with the *antigen* (pieces of virus or killed/weakened virus) as well as the *adjuvant*. Like drugs, no vaccine, whether *non-adjuvanted* or *adjuvanted*, is 100 percent safe.

### Types of Vaccine Manufacturing Methods

Seasonal influenza vaccines have been in the market for over 60 years. There are different methods which vaccine manufacturers use to produce vaccines, and they are:

- Traditional method using eggs
- New method using mammalian cells
- Investigational methods using plant, insect cells or bacteria cultures, and these are still being actively investigated in research laboratories.

### Egg-Based Vaccines

Over the last 60 years, seasonal flu vaccines have been manufactured using fertilized embryonic eggs. Using this method, it takes about four months to produce a batch of vaccines for a new strain of influenza virus; from the moment the new influenza virus’ culture becomes available for vaccine manufacturing.

The advantages of using embryonic eggs to manufacture seasonal flu vaccines are that the safety and effectiveness of the vaccines produced have been well established.
Cell-Based Vaccines
Since the mid 1990’s, newer vaccine manufacturing methods were developed. The cell-based vaccine manufacturing process is one of such methods.

The cell-based vaccine manufacturing process uses cells from mammals to culture the influenza virus for vaccine production. Various pharmaceutical companies use different sources of mammalian cell cultures for the vaccine manufacturing process. Baxter Healthcare uses cells extracted from the kidney of the African Green Monkey while companies such as Solvay Biologicals and Novartis Vaccines use kidney cells from canines to produce seasonal flu vaccines.

Among the advantages of using cell culture based manufacturing processes to produce vaccines include:

- The capability for manufacturers to increase vaccine production with ease. This enables vaccine production to be amplified to easily meet any sudden increase in demand for vaccine such as in the event of a pandemic.

- The ability to produce vaccines faster. The production time of vaccines using cell culture based production process reduces vaccine production time by half in relation to the embryonic egg process.

- The reduced possibility of the virus culture mutating during the manufacturing process. Virus mutation can result in culturing vaccine failure and this may be possible if using embryonic eggs.

- Cell-based vaccines are cultured in a biosafety level 3 (BSL3) conditions. This level of biosafety provides an isolated environment to ensure pathogenic viruses can be produced safely without escaping into the environment. Egg-based process is run at lower biosafety level and it cannot handle the pathogenic viruses safely.

- People who are allergic to vaccines made from chicken eggs may not suffer similar allergies to vaccines made from cell cultures. However, the cell-based manufacturing process has its disadvantages, which include:

- The relatively higher manufacturing costs. This may translate to more expensive vaccines

- This process produces fewer viruses for vaccine manufacturing. The volumetric yield of the cell-based flu virus is about four-fold lower than the egg-based process. This means much a larger volume bioreactor is needed and the capital investment is much higher for the production plant. This will further add to the cost of the vaccine.
• This production method is relatively new in comparison to the process using embryonic eggs. As such, there is a lack of long-term safety or rare adverse event data.

Investigational Vaccine Manufacturing Methods
Investigational vaccine manufacturing methods use plant, insect cell or bacteria culture and manufacture the viral genetic material (needed for vaccine production) is currently being actively investigated in research laboratories.

Each of these investigational-manufacturing systems has its advantages and disadvantages. The advantage of these novel systems includes faster production times and a potentially higher yield of the antigen. However, their disadvantages include the potential contamination of a vaccine by plant or bacterial viruses that may be present in the plant or bacterial material used to manufacture these vaccines. Such contamination may have an impact on the vaccine’s effectiveness.

At present, these investigational methods are still in their early developmental stages. It is not anticipated that any of these new methods will be commercialized for the purpose of vaccine manufacturing within the next eight to ten years.

Clinical Development of Vaccines
Pharmaceutical companies must demonstrate the safety and efficacy of a medicinal product or vaccine through the use of clinical trials, before a regulatory authority registers the product.

Phase 1 and 2 of a clinical trial are preliminary trials involving small number of patients (about 100-300 subjects) that seek to determine limited safety parameters and the appropriate dose for clinical use. Phase 3 trials are efficacy trials that are intended to gather additional information to evaluate the overall benefit-risk relationship of the product in question. In this phase, the drug is given to large groups of people (minimum 1,000-5,000 subjects) to confirm its efficacy and collect information that will allow the drug to be used safely. These studies typically take about three to five years to complete and are intended to provide an adequate basis for marketing approval.
In the process of vaccine development, clinical trials are needed to:

- **Identify the appropriate dose of the vaccine that will trigger a protective immune response.**

- **Identify the appropriate vaccination schedule.**
  A vaccination schedule is a series of times for administrating vaccine. For some vaccines, there will be a need for booster doses after the initial vaccination and the schedule of such doses will also be established.

- **Determine the effectiveness of the vaccine in the intended recipients, e.g. adults, elderly, children.**

- **Determine the safety of the vaccine.**

- **Determine the consistency of the vaccine study.**
  Such studies are conducted to determine that there is no variability within the final vaccine formulation that may have an effect on the patient.

- **Determine whether this vaccine interacts with other vaccines or medicines.**

- **Determine if the vaccine is able to provide cross protection against other types of antigens (or strains of viruses).**

Clinical Development of Pandemic Vaccines

In a pandemic situation, due to the urgent need to produce vaccines to protect the public against the next wave of the pandemic, vaccine manufacturers would not have enough time to complete all clinical testing on the pandemic vaccines. Time constraints would mean that the clinical data at the time of administration of the vaccines to the patients would be limited.

Drug regulatory authorities around the world have developed mechanisms for expediting the review of pandemic vaccines. In Singapore, the Health Sciences Authority (HSA) employs a similar approach of a 'rolling review' submission of pandemic vaccines. This allows vaccine manufacturers to submit data sets for regulatory review as and when they become available, without having to wait until all the data is ready before submission to the authority, as is the case for products reviewed under normal circumstances. Based on available scientific data, the HSA will advise the Ministry of Health on the safety and efficacy of the vaccine.