

Flu, vaccines and the egg incubator: an unexpected partnership

The hatchery industry is part of a billion dollar food chain that relies on the use of incubating machines to hatch the chicks, ducklings and turkey poults that find their way to the market and our tables as our broiler chickens, ducks and turkeys. The business is specialised and the market is strong.

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But there is also a multi-million dollar tributary of this industry which uses the hatching capacity of an incubator for a much more intimate, and potentially life saving purpose: yearly flu vaccines.

In fact more human vaccines are manufactured in embryonated eggs than in any other biological substrate, with more than 250 million doses of inactivated seasonal influenza vaccine distributed to 100 countries annually. Vaccines for yellow fever and many veterinary vaccines are also routinely made in eggs.

Many in our society rely heavily on the 'jab' to help them get through the treacherous flu season and some, like the elderly and

very young, can find the procedure imperative.

As with many scientific procedures, we tend to benefit from the end product without having any real appreciation for the process necessary to create something as critical as our flu vaccine.

It is a fascinating and somewhat inconspicuous industry that has the modest chicken's egg at the core. And here is where we discover the role played by Jamesway and other incubator companies.

How we outsmart the flu virus every year

Vaccines are made by weakening a virus so that it performs poorly when injected directly into the body. Initially viruses are programmed to reproduce thousands of times when they are able to get inside a body and, consequently produce a disease such as the seasonal flu virus.

Viruses within a vaccine injection, however, reproduce themselves fewer than 20 times, not enough reproduction to cause a disease, but

enough to create an impression which triggers the manufacture of 'memory B cells' which, in turn, protect the body from future infections.

The most common way to make a flu vaccine is using an egg-based manufacturing process that has been in existence for over 70 years.

Egg-based vaccine manufacturing is used to make inactivated or 'killed' vaccine (usually called the 'flu shot') and live attenuated or 'weakened' vaccine (usually called the 'nasal spray'). This is where, the incubator company enters the picture. The egg-based production process begins with an influenza collaborating centre providing private sector manufacturers with vaccine viruses grown in eggs per current regulatory requirements. These vaccine viruses are then



Egg-based vaccine production was originally developed in the 1950s.

injected into fertilised hen's eggs and incubated for several days to allow the viruses to replicate.

The 'virus-containing' fluid is carefully removed from the eggs. In the case of flu shots, the influenza viruses for the vaccine are inactivated (killed), and virus antigen is purified.

The antigen is the substance which induces the formation of antibodies because it is recognised by the immune system as a threat.

The manufacturing process then continues with purification and testing. For the attenuated nasal spray vaccine, the viruses are weakened rather than killed and go through a slightly different production process. Because the process is under strict regulation the manufacturers package the doses into vials, syringes, or nasal sprayers but cannot release the lots until there is government testing and approval and each lot is approved separately (in most countries).

Because vaccine production takes so long, public-health officials must predict problem flu strains nearly a year in advance. In the US particularly, the Center for Disease Control and Prevention (CDC), develop stocks of each virus and distribute them to vaccine makers.

The CDC attempt to predict which strains will be the most prevalent and offer the most poten-

tial for harm. That is why there are sometimes two flu shots in the same year. For example, in 2009 the vaccination production for H1N1 virus did not begin until the virus emerged as a fully sprung pandemic in late spring, once the next season's vaccine development had already been in development and therefore requiring its own injection that fall.

Other countries have their own procedures for predicting which viruses will be a threat and developing vaccines accordingly.

What does this have to do with chickens?

Let us get down to the details. How is the egg incubator used in the process? Tiny needles inject live viruses into fertilised chicken eggs. It takes one egg to make one dose of vaccine, which means somewhere around 100 million eggs are needed to create seasonal flu vaccines. And that is also one of the major limitations of the current process; the volume of eggs needed is massive.

There is a fear that if a strain of avian flu started infecting humans, for example, there might not be enough healthy chickens and healthy eggs to produce vaccines.

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Some governments even pay egg producers to produce a certain volume of eggs every year in case they are needed for vaccine production.

The supply of vaccine is also vulnerable to outside influences. An outbreak of avian flu in particular could reduce the laying capacity and put eggs in short supply, restricting the amount of vaccine that could be produced.

The vaccine production also depends on the creation of a new live virus reference strain (from the CDC) before any production can begin and this process could take several weeks.

Scientists are constantly exploring new approaches that would replace the egg incubation step with something faster and more reliable, such as engineered cells that could churn out virus-like proteins.

Today the egg incubation process is most commonly used for the growth of the influenza virus. The excellent yield of virus from chicken eggs has led to widespread use in research laboratories and for vaccine production. In fact the vast majority of influenza vaccines – both inactivated and infectious – are produced in chicken eggs.

Advanced medicine: saving lives with an egg

Egg-based vaccine production is on occasion wrongly characterised as outdated and old-fashioned. Originally developed in the 1950s, the technology has been used to produce seasonal influenza vaccines for more than 30 years.

However the process has not been static and has evolved to address various challenges, including yield, automation, capacity, quality assurance and production speed. There have also been improvements to the variability of egg supply minimising and often eliminating the periods of time that eggs were, previously, unavailable for use.

In fact, the idea that we are at risk because of low egg supplies is often cited as a problem in the face of pandemic preparedness. Egg-based production comes under duress from the belief that livestock management is an erratic, un-evolved process.

Manufacturers, however, have developed new technologies to improve egg supply and increase availability in advance of vaccine production dates. With the advent of restructured flock management, embryonated eggs previously unavailable for certain periods of time, can now support vaccine production year round.

Newer manufacturing methods such as cell-based production are predicated on improving areas like

speed-to-market, risk of contamination and vaccine potency. But cell-based vaccines undergo many of the same critical processes as the egg-based method such as vaccine isolation, extraction and purification.

Furthermore, in cell-based technologies, the use of animal cells is disadvantageous because of concerns over bio-burden potential and batch variability – two factors which compromise viral yield.

Another shared concern is strain variability. Because of the influenza virus' propensity to change composition, trivalent vaccines that consist of different influenza strains must be formulated annually. While cell-based production is designed for faster response, it is still subject to the physical constraints of strain availability.

Thirty years ago, egg-based production was completely manual and very labour intensive. However, over time, manufacturers have automated multiple steps in the manufacturing process including harvesting and inoculation, reducing the frequency of human error, bio-burden and the risk of contamination.

Egg-based influenza vaccine production is an almost completely automated process where eggs are loaded, inspected, inoculated, decapped, harvested and unloaded with virtually no human interference.

The process

When production begins the fertilised hens eggs are brought from the laying farms to the incubators where they are carefully monitored for the first 10 days. They are placed in massive incubators and temperature and humidity levels are precisely controlled and adjusted when necessary.

Once the initial 10 day period is over the eggs undergo candling where they are held to the light in order to remove any eggs that are not viable. Then they are moved into a special incubator that has been customised for the vaccine industry often called a 'hot room'.

The eggs are held here in these rooms with the correct climate until time for transport to the vaccine making facility. Unlike conventional incubators, these machines do not 'turn' the eggs and consequently the racks holding the eggs take up less room. Often the ceilings have been lowered to perfect the air flow once the room has been re-dimensioned in this way.

The recent use of single-stage machines has allowed for more

accurate profiling of the precise environment the embryos need during any period of development, whereas multi-stage machines are often redesigned to emulate the profiling of a single-stage. Since the eggs will not fulfill an entire hatch cycle the multi-stage machines remain at one set point.

Normally the different stages of embryos within a multi-stage machine maintain the temperatures for all the eggs with older embryos supplying increased temperatures and CO₂ for the younger eggs. In the vaccine industry all the eggs are held at the same temperature.

The machines

Machines such as Jamesway's P120 single-stage incubator have had some influence on the productivity of the industry. Initially selected for its ability to handle a massive 120,000 count of eggs at a time the fact that it was a single stage machine was less important.

It was only after continued use that the vaccine producers realised that these incubators were actually producing more viable embryos for production than the multi-stage machines of the past.

The single-stage machine was also perfect for an industry where cleanliness and biosecurity are paramount.

The Jamesway single-stage machine became very popular in the vaccine industry since it could be thoroughly washed and disinfected in a very short period.

Sealed motors, waterproof wiring conduit and thermistor temperature probes were just a few of the design features of single-stage that made it uniquely suitable for the industry.

Jamesway also customised the vaccine producing incubators by replacing many internal components with stainless steel. It now became possible for one machine

to be emptied, cleaned, sanitised, dried and put back into production in one day.

Jamesway machines offered additional biosecurity with their tightly sealed Platinum Incubators. Because of the removable ECU/fan unit that is unique to Jamesway, the machines had no belts from large paddle fans to create openings in the ceiling, which, when combined with the best door seals in the industry created a completely sealed box, perfect for maintaining biosecurity.

The Jamesway machine also required less additional artificial air because of the tightness of the seal, avoiding another biosecurity risk.

Jamesway machines had the additional design advantage of having their water controls within the front panel, instead of on the roof. This allowed the environment inside to be very closely monitored and controlled without opening any doors, making it easier to meet the demands of health and safety regulations.

The vaccine industry is obviously tightly controlled and regulated. Any production so closely linked to the welfare of the population is necessarily subject to extremely tight regulations and procedures. It is a credit to the advances of modern medicine that the production of vaccines is so structured, monitored and systematic.

Hopefully, with continued research and advancements in science, we can look to the practice of inoculation to combat even more threatening diseases.

In the meantime, the industry producing the machines that the pharmaceutical industry relies on will also be working to ensure even more control over the process.

Not just hatching eggs; also saving lives. ■

References are available from the author on request

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