Developing the 2009 H1N1 Vaccine

Delays That Were Faced and Improvements That Can Be Made

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The H1N1 outbreak was identified in April 2009, and the WHO declared a state of global pandemic in June 2009. The forecasted risk of H1N1 spreading through the American population was high. The President's Council of Advisors on Science and Technology (PCAST), in August 2009, predicted that up to 30% of the US population could contract H1N1, meaning that 90 million Americans could get sick, 1.8 million Americans would need hospitalization, and 30,000 Americans could die. They predicted that the number of cases would start to rapidly increase in September and peak in October, but a vaccine would not be available till at least late October. In fact, a vaccine was not approved by the FDA till September 2009, only after which bulk production could start.

The development of a vaccine is typically a long process involving an intensive research and development stage, animal testing, clinical trials and regulation, and mass production. Given this long timeline, how is a country able to respond to a national pandemic such as the 2009 H1N1 influenza outbreak?.

Vaccine Development is a Lengthy Process

Because the influenza virus mutates so quickly, each year the strain characteristics must be identified and a new vaccine produced. In 2009, scientists followed the same process to produce a vaccine for H1N1 in addition to the normal flu virus.

The first step of vaccine production is the development of a seed strain. Cheek-swabs were taken of patients predicted to have H1N1 to obtain the strain. Seed strains are made by various government agencies. Influenza viruses are typically amplified in chicken eggs, but the originally isolated H1N1 strain grew poorly in eggs. So, the government agencies reassorted the strain, meaning that the genetic material of the original H1N1 strain and fast growing strains were mixed to obtain fast growing properties while still maintaining all of the antigenic characteristics of the H1N1 strain.

The process of generating seed strains can take up to 2 months. The strains are then distributed to the vaccine producers who assess the ability of the strain to produce a high yield and maintain stability across the production processes. The strain and production process is then reviewed by the FDA and regulation agencies in other countries, a process that usually takes another month. After this lengthy process of seed strain generation and approval, the seed is finally ready for bulk production.

For decades, influenza vaccines have been mass-produced in embryonated chicken eggs. Egg supply is key in this process, and it often takes months to raise the eggs needed to meet the needs of a pandemic. All of the steps of egg-based production are automated. One company, CSL Biotherapies, produced their H1N1 vaccine using egg-based methods and was able to process up to 300,000 eggs a day with about 7 doses per egg.

The US Response to the 2009 H1N1 Outbreak Faced Multiple Delays

The US government contracted five companies to produce the H1N1 vaccine to ensure adequate supply. The FDA approved H1N1 vaccines from CSL Biotherapies, MedImmune, Novartis, and Sanofi Pasteur in September of 2009, and a vaccine by GlaxoSmithKline in November. All of the vaccines were inactivated injectables except MedImmune's, which was a live attenuated vaccine delivered by nasal spray. These five companies produce seasonal flu vaccines every year, and were well-equipped to respond to the government contracts.

The vaccines were all grown in chicken eggs as described above. It was also difficult for some companies to obtain eggs. Generally, eggs are supplied in the autumn for seasonal flu vaccine production, but the H1N1 pandemic required eggs in late spring and summer. This led to delays in vaccine production.

The companies producing inactivated injectable vaccines faced significant delays in production due to issues with the seed strain that was provided by government agencies. The first seed strain, received in June 2009, grew at a third of the speed of typical flu strains. The companies all investigated ways to optimize the growth of the virus, but were unable to obtain better yields. A better seed strain was available in August 2009 after which sufficient growth rates in eggs were achieved.

MedImmune developed a nasal-spray vaccine that was approved for use in the US. This strain is delivered "live" and can grow in the cool temperatures of the human nose, where an immune response is generated. The attenuated vaccine is killed in the warmer temperatures of the lungs, such that it cannot cause influenza in the host. Over 10 times as many doses of vaccine can be produced per egg of the live vaccine than the inactivated vaccine produced by the other companies. While not limited by production, MedImmune was limited by the supply of specialized nasal sprayers and the ability to fill the sprayers with vaccine.

The whole process of vaccine production, testing, approval, and filling took the companies 4-6 months.

Room for Pandemic Response Improvement

The biggest problem in the national response to the H1N1 pandemic was the slow production of vaccine. There are many ways to improve the bulk vaccine production process. Initially, a larger assortment of seed strains should be made. As seed strains often do not have optimal growth properties, having more seeds strains increases the probability of having strains that can achieve high yields.

Second, new adjuvants, or vaccine "add-ins", may enhance the immune response to the vaccine, which will lower the dosage and essentially lead to an increased number of doses. Novartis has a proprietary adjuvant, MF59, that is approved for use in Europe but not in the US. Novartis claims to have demonstrated that the adjuvant can produce a higher immune response than unadjuvanted vaccines in young children and the elderly, that it can lower the required dose yielding a 2-4 fold increase in vaccine supplies, and that it can increase the likelihood of the vaccine protecting mutated influenza strains. The adjuvanted vaccine has a similar safety profile to the unadjuvanted vaccines. Still, the FDA never approved the use of the adjuvant for the 2009 H1N1 pandemic claiming it to be unnecessary.

Also, cell culture vaccine production instead of egg-based production may reduce vaccine production time and dependency on egg supplies. In this case, the vaccine would be grown up in cells, generally mammalian kidney cells. While egg-based production is long established and cost-effective, it requires a large supply of eggs which requires careful planning and a long development time. Cell culture based methods have the advantage of being able to be scaled up more easily and quickly. Egg-based methods also risk contamination by antibiotics or other viruses in the eggs, risks that are much lower in cell culture. The virus grown in eggs are mixtures of antigenically distinct variants, while the strains grown in culture are the same as the seed. Also, as many strains do not grow well in eggs, seeds may be easier to develop for cell culture. Further, egg-produced vaccines cannot be used on patients with egg allergies, while cell-produced vaccines can. Novartis has also developed a cell culture based production system for the production of H1N1 vaccine that was approved and used in Germany. However, the cell culture produced H1N1 vaccine was not approved in time by the US.

While later than originally sought, the US was eventually able to produce a national supply

of the H1N1 vaccine. Unfortunately, what was originally thought of as a response "too little too late," became a case of "too much too soon." The spread of H1N1 ended up being much milder than originally predicted by the PCAST, and as the media coverage of the pandemic waned, people weighed the safety risks of the vaccine over its benefits and opted out of vaccination. This has resulted in a national surplus of vaccine and the government grossly overspending for vaccine production.

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