

Enhancing influenza vaccine development in low-resource countries

Pandemic preparedness through seasonal sustainability



Introduction

Globally, seasonal influenza results in three to five million cases of severe illness and up to 650,000 deaths each year.¹ It spreads from person-to-person through coughing and sneezing, and poses particular risk to the elderly, chronically ill, pregnant women, infants, and children—all of whom are more likely to suffer complications as a result of infection. People in low-resource countries are also more likely to feel the effects of influenza due to underlying nutritional deficiency, untreated medical issues, and limited access to health care. Moreover, the virus has the potential to cause millions of deaths worldwide if a highly virulent pandemic strain were to emerge, an event called a pandemic outbreak. Models estimate that 96 percent of these deaths would happen in the developing world, where vaccine access is hindered by high costs, supply shortages, and implementation challenges.²

Vaccines are the best way to control the spread of influenza. To adequately address the global population's seasonal and pandemic needs, however, increasing vaccine production is essential. The world is facing a global vaccine shortage of billions of doses in the event of an influenza pandemic. Global health leaders recognize that the participation of many vaccine suppliers is vital to meeting needs for annual and pandemic influenza control worldwide. Supporting the availability of additional manufacturers to enter the market and produce high-quality, lifesaving vaccines at a lower cost is critical to ensuring preparedness against both seasonal and pandemic influenza.

Through a cooperative agreement with the Biomedical Advanced Research and Development Authority (BARDA), within the US Department of Health and Human Services, PATH, in collaboration with the World Health Organization (WHO), helped to improve sustainable influenza vaccine production capacity by supporting vaccine manufacturers in Brazil, China, India, Serbia, Thailand, and Vietnam. This project was an important step toward increasing local and regional seasonal influenza vaccine supplies and improving real-time response in pandemics.

Project overview

From 2009 to 2019, PATH worked with BARDA and WHO to foster quality influenza vaccine production in low-resource nations to mitigate the overall global shortage of influenza vaccines and ensure adequate manufacturing capacity in the event of an influenza pandemic. To achieve this goal, PATH identified the following objectives:

- Enhance technical competence and quality management systems and implement best practices.
- Provide technical support for the development of seasonal and pandemic influenza vaccines.
- Develop a platform for providing local, technical trainings to vaccine manufacturers.

Specific support was tailored to the individual needs of the participating countries and included working with ministries of health to develop guidelines for developing and using influenza vaccines; establishing manufacturing processes and operationalizing facilities; supporting clinical development by coordinating, conducting, and evaluating clinical trials; supporting licensure applications; and implementing pharmacovigilance systems for post-introduction surveillance.

This report summarizes the project's history, its role in global health security, and the achievements made in the ten years PATH and its partners worked to increase global influenza vaccine supply.

¹ World Health Organization. Influenza (Seasonal)[fact sheet no. 211]. WHO; January 2018. Available at [www.who.int/en/news-room/fact-sheets/detail/influenza-\(seasonal\)](http://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)). Accessed July 16, 2018.

² Murray CJ, Lopez AD, Chin B, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a qualitative analysis. *The Lancet*. 2006;368(9554):2211-2218.



Vaccination is the best way to prevent influenza. Influenza vaccines, however, are difficult to produce in large quantities and at low costs, which means they are often inaccessible for low-resource countries. Photo: PATH/Nguyen Phu Cuong.

Influenza virus

Influenza is a virus that causes mild to severe respiratory illness, and sometimes even death. Infection is marked by high fever, headache, cough, muscle and joint pain, and sore throat. Influenza is highly contagious and spreads easily in saliva droplets generated by coughing or sneezing. Given the similar symptoms and mode of transmission, influenza infection is often associated with the common cold, but it is very important to distinguish between the two. A cold is generally a nuisance while influenza is a serious disease with serious consequences.

In temperate climates, influenza occurs in seasonal epidemics that tend to peak during winter months; in tropical climates, it may occur year-round. Globally, 5 to 10 percent of adults and 20 to 30 percent of children are infected by influenza every year, whether symptomatic or not.³

Influenza can be controlled through vaccination but is complicated by the fact that influenza viruses are constantly changing over time into different strains—which means that infection or vaccination one year does not guarantee complete immunity the next.

Further, influenza pandemics can occur when new, highly virulent strains emerge. These viruses have the potential to cause widespread illness and death since most people will have little to no immunity to the virus, allowing it to spread unchecked across the globe. When this happens, a pandemic outbreak is declared.

Current influenza vaccines

Vaccination is the best way to protect against influenza. Safe and effective vaccines have been available on the global market for more than 70 years. Seasonal influenza vaccines are generally trivalent or quadrivalent

³ World Health Organization. Influenza. WHO; November 2017. Available at www.who.int/biologicals/vaccines/influenza/en/. Accessed July 9, 2018.

formulations, which means they include either three or four virus strains respectively. Pandemic influenza vaccines are designed to react to a pandemic outbreak and include a single virus strain. Current influenza vaccines need to be updated on an annual basis to keep up with circulating strains.

Most vaccines on the market are inactivated influenza vaccines (IIVs), which are made of killed (or, “inactivated”) viruses. IIVs are generally delivered via intramuscular injection. Live-attenuated influenza vaccines (LAIVs), which are made from weakened influenza viruses, are also sometimes used to combat influenza. LAIVs are delivered as a nasal spray. An injectable recombinant influenza vaccine is also on the market and approved for use in adults.

Most influenza vaccines are made from viruses grown in chicken eggs; however, newer vaccine technologies include cell-based influenza vaccines for which influenza viruses are grown in cultured cells of mammalian-origin. These vaccines have been approved in low-resource countries but developing country vaccine manufacturers do not yet have the technology to make them. Such vaccines could be promising options in a pandemic situation given their potential to be produced efficiently, at large-scale, and without the need for secure, year-round egg supplies.

Despite the long history of influenza vaccine use and the frequency with which new influenza vaccines must be formulated, these lifesaving vaccines remain difficult to produce in large quantities and at low costs. Furthermore, influenza vaccine production is mostly concentrated in high-resource countries—meaning low- and middle-income countries are often the last to receive the vaccines, if they can afford them at all.

A strategy for global health security

Influenza is a global problem. It does not care where borders begin and end. Our modern, highly-connected world easily facilitates its spread through global air travel, mass migration, urbanization, and overcrowding. Influenza is also an equal-opportunity disease; it affects people of all ages, races, social classes, and economic statuses. This does not, however, mean all nations are affected equally. Like with many other diseases, low-resource countries are more likely to feel the effects of influenza and be less able to mitigate its damage.^{4, 5} The only way to effectively combat influenza is through collaborative, coordinated global efforts.

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Nothing exemplifies influenza’s global reach more than the 1918 influenza A/H1N1 pandemic. Known colloquially as “Spanish flu,” the deadly pandemic started as a localized outbreak in a Kansas army camp that eventually spread around the globe, infecting more than a third of the world’s population and killing at least 50 million people—in fewer than two years.⁶ Unlike seasonal influenza, it primarily affected the young and healthy, and many victims died within just days of showing symptoms—crippling essential services and economies around the world. When all was said and done, the Spanish flu pandemic had killed more people than World War I.⁷ Such pandemics have repeated through the years, though on significantly smaller scale, including:

⁴ Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Madhi SA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*. 2011;378:1979-30.

⁵ Murray CJL, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. *Lancet*. 2006;368:2211-8.

⁶ Tauenberger JK, Morens DM. 1918 influenza: the mother of all pandemics. *Emerging Infectious Diseases*. 2006;12(1):15-22.

⁷ World Health Organization. Pandemic influenza: an evolving challenge. WHO; May 2018. Available at www.who.int/influenza/pandemic-influenza-an-evolving-challenge/en/. Accessed July 26, 2018.

- Influenza A/H2N2 pandemic in 1957; two million deaths worldwide.
- Influenza A/H3N2 pandemic in 1968; one million deaths worldwide.
- Influenza A/H1N1 pandemic in 2009; 284,000 deaths worldwide.⁸

In recent years influenza A/H5N1, an avian virus that circulates among birds and has occasionally been transmitted to people, has particularly concerned public health experts. This strain, which has a 60 percent fatality rate among people, possesses strong pandemic potential.⁹ Influenza strains that could cause pandemics are those that are unfamiliar to human immune systems. They primarily affect animal hosts but can occasionally be transmitted to people. The risk of pandemic occurs if the virus mutates in a way that makes it spread easily among humans. In the cases of influenza A/H5N1, the virus infects birds and people can be infected if they have close contact with a sick animal. Currently, influenza A/H5N1 does not infect humans easily and person-to-person spread is unusual. Southeast Asian countries—including Vietnam, one of the countries in which PATH supported vaccine development efforts—have been disproportionately affected by avian strains such as influenza A/H5N1.

The next influenza pandemic is not a question of “if,” but “when.” The question is, will the world be prepared?

The strongest defense against an influenza pandemic is a well-developed capability to produce seasonal influenza vaccine.

A strong seasonal supply strengthens pandemic preparedness

If an influenza pandemic were to break out, it could be a struggle to keep up with vaccine need. Pandemic vaccines are not produced on an annual basis like seasonal vaccines. Though some high-resource countries maintain limited stockpiles of pre-pandemic influenza vaccines for various strains, those vaccines could be a poor match for the newly emerged strain and would likely be unavailable during the early stages of the pandemic—particularly to low- and middle-income countries that rely on foreign vaccine suppliers.

The strongest defense against an influenza pandemic is a well-developed capability to produce seasonal influenza vaccine, which helps maintain manufacturing capacity on an ongoing basis. Vaccine manufacturers from low- and middle-income countries will play an important role to this end and are expanding their efforts to produce high-quality, lifesaving vaccines.

The WHO Global Action Plan for Influenza Vaccines

WHO launched the Global Action Plan for Influenza Vaccines (GAP) in 2006 to address the expected global vaccine supply shortage in the event of a pandemic. The program aimed to build enough manufacturing capacity to immunize 70 percent of the global population with two doses of pandemic influenza vaccine (approximately 10 billion doses of vaccine).¹⁰ The program identified three major objectives to achieving this:

- Increase evidence-based use of seasonal vaccines;
- Increase vaccine production capacity;
- Promote research and development of improved vaccines and vaccine production technologies.

⁸ Center for Infectious Disease Research and Policy. CDC estimate of global H1N1 pandemic deaths: 284,000. CIDRAP; June 2012. Available at www.cidrap.umn.edu/news-perspective/2012/06/cdc-estimate-global-h1n1-pandemic-deaths-284000. Accessed July 16, 2018.

⁹ World Health Organization. Influenza. WHO. April 2011. Available at www.who.int/influenza/human_animal_interface/avian_influenza/h5n1_research/faqs/en/. Accessed August 18, 2018.

¹⁰ World Health Organization. Global Action Plan for Influenza Vaccines (GAP). WHO. April 2017. Available at www.who.int/influenza_vaccines_plan/en/. Accessed June 20, 2018.



Most influenza viruses for vaccines are grown in chicken eggs. Inside two henhouses maintained by IVAC, about 7,000 hens lay up to 6,000 eggs per day. With collaborator support (from WHO, BARDA, and other funders and later PATH), IVAC was able to procure and manage enough chickens to ensure a sustainable egg supply for vaccine development. IVAC now breeds its own chickens on a lush, 270-acre farm in southeastern Vietnam. Photo: PATH/Matthew Dakin.

The program focused on building capacity for both seasonal and pandemic vaccine production and increasing access to influenza vaccines in low- and middle-income countries. Fourteen different regional vaccine manufacturers from low-resource countries around the world participated in the program.

When the GAP program concluded in 2016 progress had been made toward all three objectives. WHO now estimates global pandemic vaccine production is up from 1.46 billion doses in 2006 to 6.37 billion doses at project's end—not the 10 billion doses the program hoped for, but still a more than four-times increase in capacity.⁷ Moreover, GAP manufacturers committed to providing 10 percent of their vaccine production capacity to WHO in the event of a pandemic, further boosting the world's defenses against influenza. This model was adopted by the Pandemic Influenza Preparedness (PIP) Framework.¹¹

PATH, through a cooperative agreement with the Biomedical Advanced Research and Development Authority (BARDA), within the US Department of Health and Human Services, provided technical assistance to seven developing-country vaccine manufacturers.

The PATH/WHO/BARDA project

Since 2007, BARDA and WHO have collaborated to build independent and sustainable influenza production capacity in underserved nations. Vaccines directed against avian influenza A/H5N1 are a particular focus given the high mortality associated with human cases of the disease and the virus's potential to cause a global pandemic.

PATH is part of those efforts. With funding from BARDA, we provided support to local vaccine manufacturers based in Brazil, China, India, Serbia, Thailand, and Vietnam. Our work fostered new vaccine development and

¹¹ Pandemic Influenza Preparedness (PIP) Framework. WHO;2018. Available at <http://www.who.int/influenza/pip/en/>. Accessed September 5, 2018.

clinical evaluation of seasonal and pandemic influenza vaccines, and we provided technical support for manufacturing, preclinical testing, regulatory obligations, clinical development, and support to licensure. These efforts led to demonstrated manufacturing capacity of safe and effective seasonal and pandemic influenza vaccines. Several of these vaccines are poised to be submitted for licensure.

From technical assistance to independence

PATH's work began in 2010 in Vietnam. We supported state-owned vaccine developer the Institute of Vaccines and Medical Biologicals (IVAC) as it worked to develop influenza A/H1N1 and A/H5N1 pre-pandemic vaccine candidates as well as a low-cost, seasonal influenza vaccine candidate. This work built on previous efforts in which PATH and WHO helped IVAC ready its vaccine production facility for influenza vaccine manufacture and clinical development. PATH also worked closely with Vietnam's Ministry of Health to build a supportive environment for influenza vaccine development and use. IVAC, with PATH support, eventually developed and put through clinical development vaccine candidates against influenza A/H5N1 and seasonal influenza. Licensure of both the seasonal and pre-pandemic influenza A/H5N1 vaccines is expected by 2019. Additionally, with PATH support, IVAC advanced an influenza A/H1N1 vaccine candidate into the clinic and demonstrated IVAC's value in responding quickly to the emergence of influenza A/H7H9 in humans by producing a small number of doses against the strain.

In Vietnam, we also supported the production of cell-based inactivated influenza vaccines at state-owned vaccine and biological production company the Company for Vaccine and Biological Production No. 1 (VABIOTECH). PATH helped VABIOTECH obtain a commercial manufacturing license for a cell line suitable for influenza virus vaccine production, conducted technical trainings, and purchased equipment and supplies to support development of the cell based Good Manufacturing Practice (GMP) process.

In 2014 and 2015, PATH began working with vaccine manufacturers in Brazil, China, India, and Serbia in different capacities. In Brazil, we assisted Instituto Butantan's efforts to achieve WHO prequalification (PQ) of its seasonal, trivalent inactivated influenza vaccine, which is already licensed for use in Brazil. PQ enables a vaccine to be available for procurement by United Nations agencies and Gavi, the Vaccine Alliance for use in low-resource countries and is key for reaching global markets. PQ submission is underway. In addition, PATH provided Butantan guidance on improving its quality management system and developing a pharmacovigilance system, and also provided support for the development of a pre-pandemic inactivated influenza A/H7N9 vaccine candidate.

In China, we helped Changchun BCBT Biotechnology Co. advance a seasonal, trivalent, LAIV candidate. PATH provided clinical, quality management, and project management assistance. BCBT completed all vaccine clinical development and testing by 2018.

In India, PATH provided technical assistance to the Serum Institute of India Pvt. Ltd. (SIPL) for the preclinical development of the world's first seasonal, cell-based LAIV candidate. PATH helped SIPL acquire a license for a cell line that can be used for commercial manufacture of the vaccine. We also supported SIPL with designing and conducting preclinical studies at laboratories in Europe.

In Serbia, PATH provided technical assistance to the Institute of Virology, Vaccines, and Sera "Torlak" to advance a seasonal trivalent inactivated influenza vaccine candidate through clinical development. PATH provided project management, manufacturing process development, and clinical assistance to help Torlak manufacture the vaccine and plan and execute Phase 1 and 3 clinical trials. (Phase 2 trials, which help establish appropriate dosage, are not generally needed for seasonal influenza vaccine because the dose is already well established.) These trials marked the first time that vaccine clinical trials had ever been conducted in Serbia. Licensure preparations are underway, and submission is expected in 2019.

In Thailand, PATH provided technical assistance to the Government Pharmaceutical Organization (GPO) of Thailand in Bangkok, for seasonal trivalent inactivated influenza vaccine production and process development. PATH also provided assistance toward licensure dossier preparation.

Specific support has varied greatly over the years but, ultimately, it has all been geared toward the same end: enabling development and manufacturing expertise. This was made possible by leveraging the beginning-to-end product development expertise of PATH's Center for Vaccines Innovation and Access (CVIA). The achievements made in these different countries are a strong step forward in protecting the world from influenza.

Looking to the future

By helping vaccine manufacturers in low- and middle-income countries strengthen their influenza vaccine production capacities, this project, made possible by BARDA and WHO, took an important step toward increasing local and regional vaccine supplies and improving real-time response in an influenza pandemic. It can also serve as a model for future efforts to build local manufacturing capacity.

The work is not done, though. The world is still vulnerable to influenza pandemics and, despite progress achieved, global vaccine production capacity is still not at the level it needs to be. Regional vaccine manufacturers must maintain the momentum gained during this project to bring their vaccines across the finish line. Moreover, many countries struggle with issues that vaccine availability alone may not solve: many people—including health care workers—are misinformed about the realities of influenza and vaccination and are hesitant to accept the vaccine.¹² Influenza education campaigns are necessary to help people understand the importance of vaccination.

But the world is stronger than it was. This project shows that pandemic preparedness can be greatly strengthened through strong, committed partnerships and focused efforts to build capacity—of both technology and human resources. The successful collaborations that grew out of this multi-year project are representative of the global approach we must take to strengthen our defenses against disease: influenza does not limit itself to borders, and neither should our strategies for preparedness.

The participation of more influenza vaccine suppliers worldwide—like IVAC, VABIOTECH, Butantan, BCHT, SIIPL, Torlak, and GPO—is a vital step forward in sustainably addressing global influenza vaccine coverage gaps. Their contribution can help enhance vaccine supplies in countries that have historically lacked access and faced the highest levels of suffering during influenza outbreaks.

It will also help establish these manufacturers as trusted, essential producers capable of operating at the global level. Not only will production of influenza vaccines from low- and middle-income manufacturers help strengthen regional defenses—it will help equip the world against influenza.

With support from WHO, BARDA, and PATH, these manufacturers are poised to stand up during the next influenza pandemic and help save millions of lives around the world.

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¹² Paterson P, Meurice F, Stanberry LR, et al. Vaccine hesitancy and healthcare providers. *Vaccine*. 2016;52(34):6700-6706.