Stabilizing influenza vaccines

HEALTH NEED

Influenza causes mild to severe respiratory infections, which can lead to death in the very young, the elderly, and those with vulnerable immune systems. It occurs in seasonal patterns worldwide, resulting in 250,000 to 500,000 deaths and approximately 5 million cases of serious illness each year.[1] If a highly virulent pandemic strain were to emerge in today's interconnected world, influenza has the potential to kill more than 60 million people,[2] especially in developing countries with limited to no resources for pandemic planning, preparedness, and outbreak response.

The regional development, production, and distribution of influenza vaccines could potentially save millions of lives during a pandemic, yet current influenza vaccines are difficult to produce quickly and in large quantities. In addition, the vaccines are temperature sensitive and require the use of a cold chain, a distribution network of temperature-controlled equipment and procedures for maintaining vaccine quality (potency) during transport and storage.

Enhancing the ability to store and use influenza vaccines independent of the cold chain would markedly improve global pandemic preparedness by helping to better meet the needs of underserved and hard-to-reach populations. However, the development of thermostable influenza vaccines can be a challenging task.

Not only are live virus vaccines heat sensitive, other types (both traditional split vaccines and newer recombinant vaccines) are irreversibly inactivated when exposed to heat. Currently, the typical stability of split and live attenuated influenza vaccines (LAIV) is less than two weeks at 37°C. New formulation technologies are therefore needed to better address the technical hurdles associated with the development and manufacture of thermostable influenza vaccines.

PATH/Amynah Jannohamed

TECHNOLOGY SOLUTION

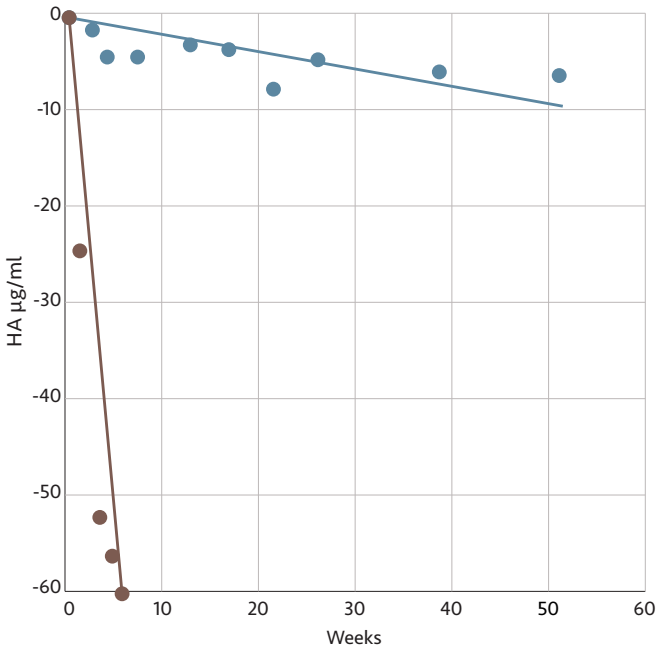
Thermostable influenza vaccines hold promise for extending product shelf life and easing logistics during introduction and rapid deployment. A longer shelf life can decrease the turnover of vaccine stockpiles, helping to reduce immunization costs and better enable the distribution of fully potent vaccines at an outbreak's point of origin—a key strategy for containing the virus and preventing a potential pandemic.

With funding from the United States Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA), PATH recently developed formulations for H1N1 subunit vaccine that are stable at 37°C for over one year. A key project subcontractor, Aridis Pharmaceuticals, also developed LAIV formulations that are stable at 37°C for over five months. The stable formulations were prepared using excipients with a proven safety record and produced using lyophilization (freeze-drying), spray-drying, and foam-drying processing methods. Animal immunogenicity tests confirm that the thermostable formulations are as immunogenic as the original non-thermostable formulations.

1 World Health Organization (WHO). *Influenza (Seasonal) [Fact Sheet No. 211]*. Geneva: WHO; 2009. Available at: www.who.int/mediacentre/factsheets/fs211/en/index.html.

2 Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–1920 pandemic: a quantitative analysis. *The Lancet*. 2006;368(9554):2211–2218.

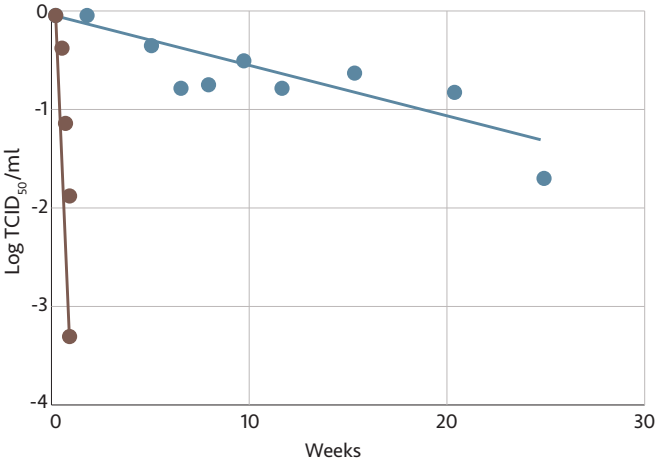
FIGURE 1: **Shelf life of a thermostable subunit/split influenza vaccine at 37°C compared to a control formulation of commercial subunit/split influenza vaccine.**



HA = hemagglutinin, measured in micrograms per milliliter.

Freeze-dried Liquid

FIGURE 2: **Shelf life of a thermostable live attenuated influenza vaccine (LAIV) at 37°C compared to a control formulation of commercial LAIV vaccine.**



$TCID_{50}$ = median tissue culture infective dose per milliliter.

Foam-dried Liquid

PATHWAY FORWARD

PATH and Aridis Pharmaceuticals will continue to monitor the lead thermostable formulations for up to two years. The applicability of the formulation technologies to additional subunit and LAIV strains will also be investigated. At the same time, PATH has worked with Aeras to scale up the production of the leading thermostable H1N1 subunit influenza vaccine formulations by lyophilization, the processing method of choice for heat-sensitive vaccines when a reasonable shelf life cannot be achieved in a liquid product format. With production processes now ready for technology transfer, developing-country vaccine manufacturers are one step closer to producing seasonal and pre-pandemic vaccines with robust stability—helping to ensure vaccine performance and availability under a variety of temperature and pandemic conditions.

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PATH
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