Efforts to improve vaccine stabilization heat up

When researchers tracked the temperature of hepatitis B vaccine being delivered to frigid, remote reaches of western China in 2007, they found vaccine vials spending a median time of more than four days below their freezing point of minus 0.5 degrees Celsius.

The issue isn't trivial: freezing can inactivate hepatitis B vaccine, as it does other vaccines that use alum as an adjuvant to increase the vaccine's effectiveness. (When vaccines freeze, alum forms large clumps and thus loses its vaccine-boosting function.) Compounding the problem, most of the staff at the far-flung centers where the vaccine finally arrived didn't know that they could be damaged by freezing (*Public Health Rep*. **124**, 745–750; 2009).

Now, freeze protection for hepatitis B and potentially other alum-adjuvanted vaccines may be at hand. In June, researchers led by Dexiang Chen at PATH, a Seattle-based nonprofit whose vaccine stabilization work is funded by the Bill & Melinda Gates Foundation, reported that they had developed a formulation for the hepatitis B vaccine that doesn't lose potency after repeated freezing at minus 20 degrees Celsius (*Vaccine* **27**, 4609–4614; 2009). The researchers added to the vaccine a compound called propylene glycol, a viscous alcohol used as a solvent in many pharmaceuticals. It is also used in a host of other substances, from massage oils to toothpaste.

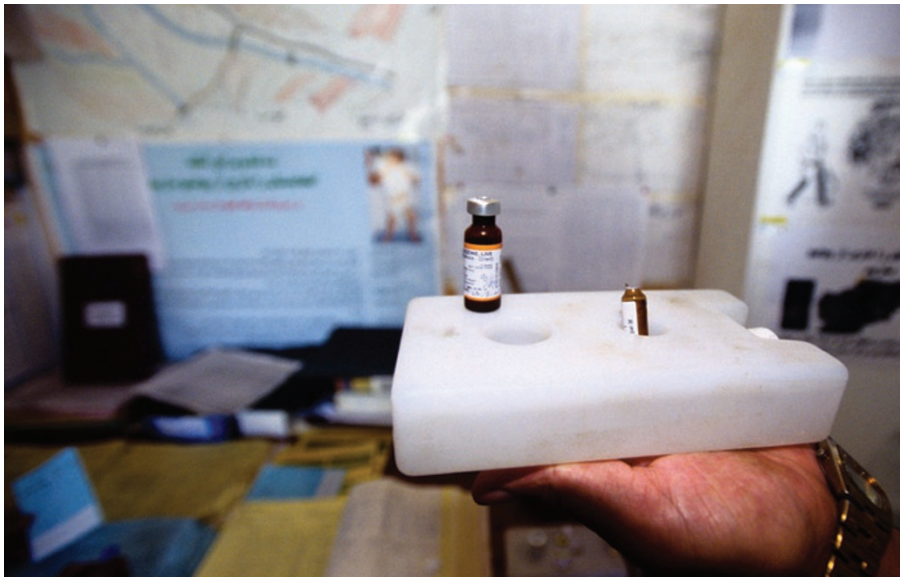
The freeze protection technology "is very, very affordable, and we made it broadly available to all the vaccine programs and manufacturers. We hope it is put into use," says Chen.

In August, Chen's group also announced progress on the more widely recognized problem of heat damage to vaccines, reporting a new hepatitis B vaccine formulation developed with their collaborator Arecor in Sharnbrook, United Kingdom. On the basis of work done *in vitro* and in mice, it remains stable for at least six months at up to 45 degrees Celsius (*Hum. Vaccin.* **5**, 529–535; 2009).

Chen explains that, in the past, research to find compounds that can stabilize vaccines involved a lot of trial and error. These days, scientists have access to sophisticated analytical techniques, instruments and computer software that can shed light on the structure of the antigen proteins used in vaccines.

By stimulating and analyzing how these proteins fold in solution, and therefore having a picture of the unstable groups and the charges on their surfaces, vaccine developers now have more information about which compounds can stabilize the antigens. It was this technique that led PATH scientists and collaborators to select the amino acid histidine in combination with phosphate—which provided heat protection to the hepatitis B antigen.

"The PATH work is tremendously exciting," says Rudi Eggers, a vaccine delivery expert with the World Health Organization (WHO) in Geneva, which collaborates with PATH. In addition to its heat stability, "the freeze protection to us is quite important. A lot of vaccine can be damaged by freezing, and it's happening repeatedly all over the world."



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Freeze forward: Vaccines may become less sensitive to varying temperatures

Chain reaction

The PATH researchers are not alone in tackling vaccine temperature stability, which is a major logistical challenge to achieving widespread vaccination, especially in developing countries. In September, Merck and the Wellcome Trust announced a new collaboration to develop vaccines for poor countries, aimed in part at modifying vaccines to eliminate the need for the so-called 'cold chain'—the temperature-controlled supply chain of storage and delivery facilities that aims to keep vaccines at a widely-agreed 2 to 8 degrees Celsius all the way from the factory floor to remote health clinics.

Smaller companies are also active in this research area. Aktiv-Dry, based in Boulder, Colorado, has created a stable dry powder formulation of the hepatitis B vaccine that can be stored at temperatures from 66 Celsius to minus 20 Celsius without loss of potency (*J. Supercrit. Fluids* **42**, 385–391; 2007). However, reconstituting dry vaccine in the field poses additional logistical and training challenges; part of PATH's accomplishment is having created a stable vaccine that, as a liquid, doesn't require reconstituting.

Still, some experts caution that the devil remains in the details of getting new formulations into widespread use. "Until you actually have produced something at manufacturing scale and conducted formal long-term stability studies, you can't be certain you'll have a thermally stable vaccine," says Russ Middaugh of the University of Kansas in Lawrence, who heads a major lab working on vaccine thermal stability.

Even then, adds Martin Friede, a vaccine development specialist with WHO, "for real impact at the field level, this will require manufacturers to adopt it, countries to purchase it and regulatory pathways in place for [temperature-stable formulations] to be used outside the cold chain."

Undeterred, PATH is pressing ahead, preparing to report that it has extended the stability of *Haemophilus influenzae* B vaccine from the current one or two weeks to 14 weeks at 45 degrees Celsius. It has transferred its freeze-protection technology—which it has also made freely available in the public domain—to vaccine manufacturers for use in two vaccine products. Its heat-and-freeze–stable hepatitis B vaccine formulation, meanwhile, is being validated by a commercial vaccine producer that plans to take the formulation into clinical trials in 2010.

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