

# VACCINE TECHNOLOGIES

AT PATH



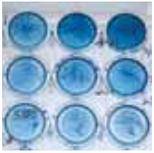


PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps to provide appropriate health technologies and vital strategies that change the way people think and act. PATH currently works in the areas of health technologies, maternal and child health, reproductive health, vaccines and immunization, and emerging and epidemic diseases. Headquartered in Seattle, PATH has offices in 30 cities in 21 countries.



**PHOTO (COVER)** Various vaccine technologies. ©PATH/Patrick McKern. **PHOTO (BACKGROUND)** A health worker on an off-road motorcycle transporting vaccines (in a vaccine carrier) and medical supplies in the countryside of Niger. ©Ümit Kartoglu  
**PHOTO (TOP)** Thermostable vaccine formulations. ©PATH/Scott Areman. **PHOTO (BOTTOM)** Microneedle technology. ©PATH/Scott Areman.

# VACCINE TECHNOLOGIES AT PATH



Every year vaccinations against infectious diseases save the lives of 2.5 million children and protect over 100 million more from illness and disability.<sup>1</sup> New technologies that improve vaccine products and the way they are delivered can further increase vaccine effectiveness and safety worldwide, and ease the logistical burdens of immunization programs in low-resource settings.

PATH and partners have been advancing innovative vaccine technologies for more than 30 years. We strive to design, adapt, and develop technologies—not just stopgaps but lasting, user-centered solutions—that are appropriate and affordable.

Ongoing work in more than 70 countries helps ground us in the realities in which the technologies will be used. Our work in vaccine development projects, including the PATH Malaria Vaccine Initiative, the Meningitis Vaccine Project, and many others, means we understand how technologies must integrate with vaccine research, development, testing, scale-up, and production.

We are mindful of the rapidly changing world and the timeline involved in developing and commercializing technologies. We work to achieve solutions that will meet current needs as well as evolving conditions of use. For every technology, during each stage of development, we critically evaluate its technical and commercial feasibility as well as user acceptability—and proceed or change course accordingly.

Our teams include technical specialists as well as experts who ensure that the public health, business, regulatory, economic, policy, and introduction aspects of each technology are competently managed and monitored. Cross-sector collaboration and external partnerships are essential to our work—ensuring that our efforts are synergistic with those of our stakeholders. While many of the technologies that we advance originate from outside of PATH, we also invent and test technologies in our onsite laboratory and product development shop (see page 8).

In this report, we outline the philosophy and focus of our work. We also describe a number of individual vaccine technologies at various stages of development and market introduction to put our work in perspective and to inspire future collaboration. Please feel free to contact us at any time to learn more about PATH and our work in vaccine technologies.

## HIGHLIGHTS OF OUR WORK

### Formulation and production methods:

- Freeze-protection technology for alum-adjuvanted vaccines.
- Formulation methods to improve vaccine heat stability.
- High-throughput screening assays.
- Lyophilization, spray drying, and supercritical fluid spray drying.

### Packaging technologies:

- Vial adapters and dual-chamber containers to improve reconstitution safety.
- Time-temperature indicators.

### Cold chain technologies:

- Highly efficient solar-powered refrigerators.
- Use of phase-change materials for insulation.
- Passive cooling technologies.

### Delivery technologies:

- Autodisable, prefilled, and reuse-prevention syringes.
- Disposable syringe jet injectors.
- Intradermal devices: adapter for standard needles, microneedles, and syringe-mounted microneedle array.
- Intranasal delivery technologies.
- Dissolvable tablets and wafers for oral delivery.
- Thermoresponsive gels for sublingual delivery.

<sup>1</sup> WHO, UNICEF, World Bank. State of the world's vaccines and immunization. 3rd ed. Geneva: World Health Organization, 2009.

# PHILOSOPHY & APPROACH



To address current global health issues and emerging challenges, PATH draws upon a robust global presence and network for identifying needs, establishing ideal product attributes, and advancing solutions—including original ideation and design.

We have a well-established process for assessing product concepts and identifying those with the best chance of success—ideas that are technologically strong, potentially marketable, and likely to be acceptable to developing-country health systems.

Technologies are screened at each stage of development to ensure that only those that are likely to deliver on their promise are advanced to the next stage.

Whether in our own product development facility or laboratory or in the facilities and laboratories of collaborating universities or companies, we validate our work with scientific rigor.

Most importantly, PATH involves end users at all stages of the process—from assessing the need and designing technologies, to creating policies, guidelines, and systems that integrate with other local interventions and lead to lasting improvement in public health outcomes.

As a nonprofit organization, PATH takes an objective stance on technologies—we work to ensure that the best solutions are advanced and that they are economically and commercially sustainable for the target populations we serve.

Research and development efforts always produce valuable information. The knowledge gained from both success and failure in research is valuable. We therefore strive to share, where permissible, our lessons learned with the wider public health community and other stakeholders. PATH and collaborating partners regularly publish in top, peer-reviewed journals. Concurrently, we seek out external review, analysis, and validation of our data and our product prototypes.



PATH believes that creative collaborations are essential to advancing the availability of appropriate and affordable vaccine technologies.

We work with a variety of partners from both the public and the private sectors to develop and catalyze technology solutions that meet the needs of the public sector and accommodate the requirements of the private sector. Although public-sector support is indispensable for development of technologies for low-resource settings, it may not yield economically sustainable outcomes. Conversely, market forces alone may be insufficient to meet the health needs of resource-constrained populations.

Each of our mutually beneficial, collaborative relationships is unique. Successful partnerships begin with the shared goal of improving global health and build on a respect for each partner's contributions, followed by a skillful assessment of joint interests, capabilities, and opportunity costs.

To ensure the affordability and availability of new technologies, PATH has developed guidelines

for working with the private sector, including approaches to managing intellectual property that serve both private and public interests. PATH recognizes the critical importance of intellectual property and the measures necessary to ensure that novel ideas and designs are protected and their value preserved, when appropriate, so that capital can be raised and reasonable returns on private investment can be achieved.

Altogether, our experience suggests that successful collaborations can accelerate product development and access for resource-constrained populations while preserving commercial goals and building shareholder value.

**PATH is a World Health Organization (WHO) Collaborating Centre for Vaccinology.**

# TOOLS TO ENSURE VACCINE EFFECTIVENESS



The safe and effective distribution, storage, administration, and disposal of vaccine products are vital elements of a successful immunization program, but they can be difficult tasks in low-resource settings.

As more new and increasingly expensive vaccines become available, it will be critical to bolster country storage capacity—to protect temperature-sensitive products from damage and to achieve immunization coverage and impact.

PATH is working with partners to evaluate and improve vaccine distribution and management from a variety of angles. We strive to improve vaccine formulations to protect them from heat and freeze damage (see page 5); improve vaccine presentations and packaging to meet user needs and minimize environmental impact; develop new equipment to store, monitor, and transport vaccines; and assist with strategies, policy development, and training to promote best practices.

For example, to make refrigeration affordable and practical for more health clinics and facilitate

immunization services in remote settings, PATH is working with collaborators to advance both low-cost solar refrigerators that do not require batteries and “smart” refrigerators that keep vaccines cold, yet shield them from freezing.

Both technologies aim to make refrigeration more affordable for health clinics and to facilitate immunization services in remote settings.



2 Matthias DM, et al. *Vaccine*. 2007;25:3980-6.

3 Welte, M. (2007), *USA Today*, 4 December. Available at: [http://www.usatoday.com/news/health/2007-12-04-spoiled-vaccines\\_N.htm](http://www.usatoday.com/news/health/2007-12-04-spoiled-vaccines_N.htm). Accessed January 14, 2010.

4 Five senses, vaccine vial monitors page. World Health Organization website. Available at: [www.who.int/immunization\\_standards/vaccine\\_quality/vvm\\_five\\_senses/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/vvm_five_senses/en/index.html). Accessed January 3, 2010.

5 WHO, UNICEF, World Bank. *State of the world's vaccines and immunization*. 3rd ed. Geneva: World Health Organization, 2009.

**PHOTO (TOP)** Solar panel technology. ©iStockphoto.com.

**PHOTO (INSET)** Community members of the Indaman village located in the Chintabaraden region of Niger help a health worker unload a vaccine carrier and other medical supplies from his motorcycle. ©Ümit Kartoglu.

## IMPROVING VACCINE THERMOSTABILITY

For more than a decade, PATH has conducted research on both the technical and commercial feasibility of improving vaccine thermostability. In addition, we have identified and evaluated novel vaccine formulations and processing technologies as well as investigated the economic, logistical, regulatory, procurement, and policy issues associated with development, licensing, and use of stabilized vaccines.

PATH's expertise and capabilities in vaccine stabilization include:

- Amorphous glass, stable liquid, tablet, and gel formulations.
- Lyophilization and spray-dry processing.
- Protein structural assays and other modern analytical techniques.
- Experience with a range of vaccines, from live-attenuated viral and bacterial vaccines to subunit and conjugate vaccines.

Our work on seven antigen types with more than 33 technical collaborators has yielded some major improvements in the heat stability of vaccines—offering possibilities for improving vaccine effectiveness and facilitating outreach of vaccines beyond the constraints of traditional cold chain storage. PATH has also



worked to address the longstanding but under-recognized problem of vaccine freezing. There is a growing body of evidence that cold storage facilities and transportation methods in both developing and industrialized countries often inadvertently expose vaccines to freezing temperatures; this is especially problematic for vaccines containing aluminum salt adjuvants, which should never be frozen.<sup>2</sup> The US Centers for Disease Control and Prevention (CDC) estimates that the federal Vaccines for Children program alone incurs more than US \$20 million in vaccine waste annually from poor refrigeration and vaccine exposure to freezing temperatures.<sup>3</sup>

**PHOTO** PATH scientists conducting an onsite test with the Karl Fischer Titrator that is used to determine the moisture content in dry vaccines. ©PATH/Scott Areman.

## MONITORING VACCINES IN THE HEAT



In 1979, responding to a need expressed by WHO for indicators to monitor the heat exposure of individual vaccine vials, PATH developed prototype vaccine vial monitors (VVMs) using a licensed technology. These VVMs were tested in collaboration with WHO and the ministries of health of numerous countries. Simultaneously, PATH and WHO worked with and encouraged other companies to develop superior VVM products and, when one such technology became available, PATH worked with its owner, Temptime Corporation, to refine and advance its technology for use with vaccines.

By 1994, Temptime began providing VVMs to vaccine suppliers throughout the world for distribution on vaccines purchased by the United Nations Children's Fund (UNICEF). PATH also assisted WHO with development of VVM training materials—helping health workers decide whether to use or discard vaccines exposed to heat. Thanks to the VVM, WHO revised its policies to allow some vaccine vials to remain open and be used for more than one day, resulting in less vaccine waste and greater cost savings. The VVM is also helping to expand the reach of immunization. PATH estimates that VVMs will allow health workers over the next decade to recognize and replace more than 230 million doses of inactive vaccine and to more effectively deliver an additional 1.5 billion doses<sup>4</sup> in remote settings. To date, more than 3.2 billion VVMs have been used on vaccines in immunization programs throughout the world.<sup>5</sup>

**PHOTO** Vaccine vials with integrated vaccine vial monitors on labels at a vaccine production facility in Indonesia. ©Umit Kartoglu.

# NOVEL VACCINE DELIVERY



Worldwide, nearly 40 percent (in some countries, as high as 70 percent) of injections are given with syringes and needles reused without sterilization.<sup>6</sup>

Many individuals receiving injections to prevent or treat illness are inadvertently placed at risk of infection from use of contaminated devices. An estimated 23.5 million new HIV, hepatitis B, and hepatitis C infections occur every year through needle reuse and accidental needlestick injuries.<sup>7</sup> Disposal of used injection devices is also a challenge, especially in areas with limited resources.

Since the 1980s, in collaboration with many different partners, PATH has developed technologies that make it easier to safely handle and dispose of injection equipment and medical waste. We developed the first commercialized **autodisable** one-time-use syringe as well as the world's most inexpensive **prefilled syringe** with autodisable features. Both syringes deactivate following use, thereby preventing improper reuse. More recent work includes evaluation and advancement of **safety syringes** to prevent needlestick injuries as well as **reconstitution syringes and devices** to safely prepare and deliver lyophilized or spray-dried vaccines.

PATH is also exploring options for **intra-dermal vaccine delivery** because some vaccines when

administered directly under the skin may actually be protective at far lower doses than currently used. The smaller doses could potentially expand the impact of a vaccine in short supply. Currently, PATH is working with partners to refine an **intra-dermal adapter** for standard needles and evaluate **microneedle technologies**.

PATH knows that novel safe injection devices are only part of the puzzle. We also work with health ministries worldwide to assess and prioritize low-cost options for **medical waste disposal technologies, practices, and policies** to protect health workers and the general public from needlestick injuries and other exposures to biohazardous materials.

PATH has a long history of researching and evaluating **needle-free vaccination methods**—including disposable syringe jet injectors, which use a high-pressure liquid stream to penetrate the skin (see page 7). We are also exploring new vaccine formats for mucosal delivery (**fast-dissolving tablets**) and sublingual delivery (**thermo-responsive gels**), which may enhance immunization effectiveness, safety, and efficiency in low-resource settings.

<sup>6</sup> WHO. Injection safety page. WHO website. Available at: <http://www.who.int/mediacentre/factsheets/fs231/en/>. Accessed April 6, 2010.

<sup>7</sup> WHO. Safety of injections: global facts and figures [fact sheet]. WHO/EHT/04.04. Geneva: WHO; 2004. Available at: [http://www.who.int/injection\\_safety/about/resources/en/FactAndFiguresInjectionSafety.pdf](http://www.who.int/injection_safety/about/resources/en/FactAndFiguresInjectionSafety.pdf).

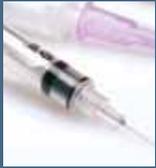
<sup>8</sup> WHO Department of Vaccines and Biologicals. WHO-UNICEF-UNFPA Joint Statement on the Use of Auto-Disable Syringes in Immunization Services. Geneva: WHO; 2003. Available at: <http://www.who.int/vaccines-documents/DocsPDF99/www9948.pdf>.

<sup>9</sup> UNICEF. 2009 AD syringes projections: quantities and pricing [fact sheet]. New York: UNICEF; 2009. Available at: [http://www.unicef.org/supply/index\\_7995.html](http://www.unicef.org/supply/index_7995.html).

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™ SoloShot is a trademark of BD.

## AUTODISABLE SYRINGES



In 1985, more than a decade before the international public health community mobilized around the problem, PATH started assessing technologies that could help to ensure safe injection in low-resource settings. Funding from the US

Agency for International Development enabled the aggressive advancement of a previously patented PATH design which culminated in 1990 with licensing to BD, one of the world's largest syringe manufacturers.

The PATH technology—eventually known as SoloShot™—became the first commercialized autodisable (AD) syringe and catalyzed a global policy<sup>8</sup> shift in safe injection with a joint WHO and UN statement recommending procurement and use of AD syringes by immunization programs worldwide. After launching SoloShot™, PATH began to work with numerous other syringe manufacturers to help them enter the market and developed training materials that represented all available AD syringe designs. Scale-up was achieved, and AD syringes soon replaced standard syringes in all immunization programs supplied by UNICEF and the GAVI Alliance. Since 2007, UNICEF has procured more than 1.3 billion AD syringes each year for use in developing-country immunization programs.<sup>9</sup>

**PHOTO** SoloShot™ Syringe. ©PATH/Patrick McKern.

## PREFILLED UNIJECT® DEVICE



PATH took syringe safety one step further by creating the Uniject® device—a prefilled AD syringe that combines the separate pieces (vial, syringe, and needle) into one. Prefilled with a single dose of

vaccine, it is especially appropriate for use by health workers in low-resource settings because it requires no assembly or preparation. The device also reduces vaccine wastage associated with use of multi-dose vials.

WHO has prequalified both tetanus toxoid and hepatitis B vaccines in Uniject®. The device has been used by UNICEF for tetanus elimination campaigns in Afghanistan and many African countries. It is currently used throughout Indonesia for birth-dose administration of hepatitis B vaccine. Vaccine producers are working to commercialize additional vaccines in Uniject® devices.

**PHOTO** A woman receives tetanus toxoid vaccine in a Uniject® device from a traditional birth attendant in Mali. ©UNICEF/NYHQ2002-0263/Pirozzi.



## SHOTS WITHOUT NEEDLES

Jet injectors were first introduced in the 1940s. Until the 1990s, they were used to deliver hundreds of millions of injections—most notably for the eradication of smallpox. Health officials then determined that the injectors, which administered multiple doses through a reusable nozzle, could be spreading hepatitis.

The “second-generation” jet injectors use disposable syringes, each filled with a single dose of vaccine to prevent transmission of infection from one person to the next. Disposable syringe jet injectors (DSJIs) generate a high-pressure liquid stream that allows the vaccine to penetrate the skin without the need for a needle. DSJIs may improve immunization effectiveness by reliably delivering certain vaccines intradermally, which can reduce the amount of vaccine required by up to 80 percent. PATH is assessing the appropriateness of DSJIs for developing-country use.

Since 2005, PATH has conducted field assessments in five countries using DSJI prototypes developed by technology partners. Feedback from health care workers and immunization program managers has informed developers' design adjustments.

In collaboration with WHO, the US Centers for Disease Control and Prevention, vaccine manufacturers, and device developers, PATH is evaluating the efficacy of DSJIs in clinical trials with inactivated polio; measles, mumps, and rubella; rabies; and influenza vaccines. PATH is also working to clarify the DSJI value proposition for suppliers and purchasers and to plan for international regulatory approval and potential inclusion of DSJIs in global immunization programs.

**PHOTO** Disposable syringe jet injector in use. ©PharmaJet/Michael Royals.

# CAPABILITIES



Our work in vaccine technologies is a team effort—enabled through creative collaborations with partners. We encourage interested parties to contact us about emerging technologies, ideas, or potential collaborations.

## STAFF EXPERTISE

PATH's technical and management capabilities reflect more than 30 years of experience in end-user needs assessment, strategic adaptation and original product design, bench and field testing, market analysis, licensing, technology transfer, manufacturing, scale-up, advocacy, and product introduction of immunization-related technologies. Our team includes:

- Strategic advisors and project managers.
- Scientists and laboratory technicians.
- Policy, regulatory, commercialization, and business development experts.
- Immunization and public health specialists.
- Clinical trial coordinators.
- Health economists.
- Product development engineers.

## ONSITE FACILITIES

PATH's onsite laboratory and product development facilities are valuable resources for testing promising concepts and technologies—often under conditions similar to those of developing country immunization programs.

PATH conducts its vaccine formulation research in a multipurpose Biosafety Level 2 laboratory equipped to produce liquid, lyophilized, and spray-dried vaccine products. Our processing equipment includes a Buchi 290 Mini Spray-Dryer—installed inside an isolator within a low-humidity lab with High Efficiency Particulate Absorbing (HEPA) and Ultra Low Particulate Air (ULPA) ceiling filter controls. Both the isolator and low-humidity lab are designed for powder processing and filling. Our lab also has a pilot-scale lyophilizer to produce freeze-dried vaccines, a Malvern particle sizer, a differential scanning calorimeter, environmental chambers and incubators, a Karl Fischer moisture analyzer, Zeta Sizer, Micro-Osmometer, and many other devices that enable the characterization and testing of vaccines and their delivery systems.

Additional PATH facilities—including a machine and model shop, environmental testing lab, and microscopy—enable sophisticated product design, engineering, development, fabrication, and evaluation. Also onsite are manual machining tools, vacuum and thermoforming equipment, a flat-bed laser cutter, casting and injection molding, electronics testing equipment as well as two Instron instruments for materials testing and 4-axis Computer Numerical Control (CNC) machine tools with parametric 3D solid modeling software.



**PHOTO (BACKGROUND)** PATH scientist using the onsite Buchi 290 Mini Spray-Dryer. ©PATH/Scott Areman.  
**PHOTO (TOP)** Scientist in PATH's onsite laboratory conducting a test to gauge the particle size of a powder vaccine sample. ©PATH/Scott Areman. **PHOTO (BOTTOM)** Thermoresponsive gel technology. ©PATH/Scott Areman.

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MAIL PO Box 900922, Seattle, WA 98109, USA  
STREET 2201 Westlake Avenue, Suite 200, Seattle, WA 98121  
ONLINE [www.path.org](http://www.path.org) EMAIL [vaccinotech@path.org](mailto:vaccinotech@path.org) TEL +1 (206) 285-3500