

DIRECTIONS

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IN GLOBAL HEALTH



New source of key drug for malaria treatments

Innovative approach to producing artemisinin promises better care for women, children, and other vulnerable groups

A public-private partnership led by OneWorld Health, PATH's drug development program, has pioneered an innovative method to manufacture artemisinin, a key ingredient for recommended malaria treatments. The recent launch of industrial-scale production will help to extend effective therapy to millions more people—including pregnant women and young children, who are most vulnerable.

Up to now, the leaves of the sweet wormwood plant have been the world's only source of artemisinin. The new approach uses genetically engineered yeast to produce artemisinic acid and then novel chemistry techniques to convert this into semisynthetic artemisinin.

The unpredictable cost and volatile supply of plant-based artemisinin has put artemisinin-based combination therapies (ACTs) out of reach for many people most at risk. By

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work with global
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PERSPECTIVE

Cross-sector collaboration to expand the availability of malaria treatments

While teaching and providing care at Mulago Hospital in Kampala, Uganda, I saw many patients with malaria. My experience in Uganda helped me appreciate the importance of ensuring that malaria treatments reach the most vulnerable patients, including pregnant women and young children.

Artemisinin-based combination therapies (ACTs) have proved to be a safe and effective cure for malaria and have been recommended by the World Health Organization as a first-line treatment for uncomplicated cases in Africa and Asia caused by the *Plasmodium falciparum* parasite. Global demand for ACTs has skyrocketed. The number of courses of treatment requested worldwide by the public sector rose from 11 million in 2005 to 181 million in 2010.

The world's supply of the key ingredient of ACTs, artemisinin, which is derived from the sweet wormwood plant, has not always kept pace. Rapid market growth and price and demand fluctuations have complicated supply planning, and weather conditions, long lead times for growing sweet wormwood, competing crops, financial concerns, and political instability have all affected production and pricing.

Nine years ago, OneWorld Health (now PATH's drug development program) and other organizations created an innovative public-private partnership to stabilize the artemisinin supply chain and alleviate shortages in malaria treatment. The partnership included a diverse group of experts in research, pharmaceutical product development, and public health and represented the nonprofit, academic, biotech, and pharmaceutical sectors. Recognizing our diversity, we collaborated to establish shared

objectives that kept us focused on our common mission—to use the latest technology and innovation to work toward malaria eradication.

From the technology that provided the foundation for the project—genetically engineered yeast to produce artemisinic acid—to the novel photochemistry process to convert artemisinic acid to semisynthetic artemisinin, the scientific innovation and visionary efforts of our partners have brought us to where we are today. It is extremely exciting to see cutting-edge technology used to expand the market for much-needed drugs and open up new opportunities for global health impact. Over nine years, we went from an idea developed in a lab to industrial-scale deployment of synthetic biology techniques for drug production.

Production of semisynthetic artemisinin at industrial scale was launched last month at a Sanofi factory in Italy, providing the market with an additional, independent source of high-quality artemisinin at stable prices. This product will supplement the current plant-derived supply, enabling a more steady flow of artemisinin and greater availability of ACTs to vulnerable populations across the globe.

The success of the partnership demonstrates that with a shared humanitarian goal—and the flexibility and perseverance of a dedicated team—collaboration across sectors can advance science and improve global health.



Ponni Subbiah, MD, MPH,
directs PATH's drug
development program

NEW ON PATH.ORG

Solving the mystery of missing vaccines

www.path.org/blog/2013/03/missing-vaccines/

Every year, millions of doses of vaccines are lost between manufacture and delivery. PATH President and CEO Steve Davis, who recently cohosted a TED Challenge to find solutions, reveals some of the best ideas to reduce vaccine wastage.

Envision a world without malaria

www.path.org/media/world-without-malaria.php

Malaria sickens millions every year, but we have tools to stop it. See our new video.

HPV vaccine for more families

www.path.org/blog/2013/02/hpv-vaccine-for-more-families/

The GAVI Alliance has announced it will subsidize vaccine against HPV, the virus that is linked to cervical cancer, in eight countries. Dr. Jacqueline Sherris, our vice president for public health impact, writes about the importance of protection.

The truth about diarrhea

www.path.org/stories/jane-wamalwa.php

Her children's deaths drive Jane Wamalwa to reach other parents with lifesaving information. Read her story.

New cervical cancer screening test hits the market

Innovative DNA test promises to revolutionize screening and reduce death rates in low-resource settings

China's Food and Drug Administration recently approved commercial use of a new rapid, low-cost cervical cancer screening test. Approval and sales in China, where the test is manufactured, will open the door for entering the market in India in 2013 and then in other countries.

PATH and QIAGEN, the manufacturer, jointly developed the test, which is designed especially for use in clinics without reliable sources of clean water or electricity. Called *careHPV™*, the test detects the DNA of 14 types of human papillomavirus (HPV) that can cause cervical cancer. Early detection and treatment of precancers is essential for reducing deaths from cervical cancer in low-resource settings.

Tailoring tests to local needs

About 275,000 women die each year from cervical cancer. Nearly 90 percent of these deaths occur in resource-constrained settings—mainly in Africa, Asia, and Latin America—where only a small proportion of women are routinely screened.

Although wealthy countries have for many years used Pap tests for effective precancer screening, these tests have not been widely used in low-resource settings because they require a network of high-quality laboratories and highly trained staff. Also, because Pap tests miss many precancer cases, this method works best when women are screened every couple of years, something many countries cannot afford.

To reduce the burden of cervical cancer in developing countries,

PATH has advanced simple, low-cost screening strategies, such as visual inspection of the cervix with acetic acid, also known as VIA. This technique is now being introduced or ramped up in many countries, but it is less sensitive and more prone to clinician error than newer methods of testing for HPV DNA.

Although most HPV tests are expensive and require sophisticated laboratory equipment, refrigerators, and other resources that may be lacking in developing-country settings, *careHPV* is different. The equipment fits on a desktop and does not require refrigeration of reagents. Also, results are available in less than three hours and are easy for health workers to interpret.

Using field studies to advance product use

PATH conducted field assessments of *careHPV* in China, India, Nicaragua, and Uganda. This work included exploring the potential for using vaginal, rather than cervical, samples for *careHPV* testing to eliminate the need for a pelvic exam, which can be difficult to arrange, costly, and uncomfortable for women.



The *careHPV* test will increase women's access to cervical cancer screening.


We found that *careHPV* was used effectively even in very basic clinics and demonstrated better clinical performance than either VIA or Pap tests. We also found that using *careHPV* with vaginal samples, self-collected by women, gave accurate results. Although some health professionals were initially skeptical of vaginal sampling, they quickly saw its potential for dramatically increasing a clinic's ability to screen many women.

The commercial introduction of *careHPV* is creating new opportunities for countries to establish or expand their cervical cancer screening and treatment programs. Widespread adoption of the new test promises to help spare millions of women from cervical cancer over the next decade. ■

FOR MORE INFORMATION

Contact Dr. Jose Jeronimo, project director, at jjeronimo@path.org.

This work has been supported by a grant from the Bill & Melinda Gates Foundation.

 Read more about PATH's work on cervical cancer at <http://sites.path.org/rh/recent-reproductive-health-projects/cervical-cancer/>.

careHPV is a trademark of QIAGEN.



The *careHPV™* device.

QIAGEN

New source of key drug for malaria treatments

» CONTINUED FROM PAGE 1

supplementing botanical sources, production and distribution of semisynthetic artemisinin will lead to more reliable supplies of lifesaving ACTs.

Malaria as a major threat to maternal and child health

Caused by parasites transmitted to people through the bites of infected mosquitoes, malaria sickens more than 200 million people and kills about 650,000 each year. Among those at highest risk are the 50 million women in malaria-endemic regions who become pregnant each year. Malaria during pregnancy can cause life-threatening anemia and leads to an estimated 10,000 annual deaths. Maternal malaria also increases the risk of spontaneous abortion, stillbirth, premature delivery, and low birth weight, contributing to as many as 200,000 infant deaths each year.

Since 2001, when the World Health Organization identified ACTs as the preferred treatment for most cases of malaria, governments and other stakeholders have encouraged farmers in China, Vietnam, and elsewhere to grow the sweet wormwood plant to meet rising demand for artemisinin. But bad weather conditions, competing crops, and other concerns have made it difficult to manage the supply, resulting in price volatility and periodic shortages.

Solving technical challenges

OneWorld Health launched the Artemisinin Project in 2004 to create a second source of artemisinin using a no-profit, no-loss production model. The aim was to supplement the current plant-derived supply.

Several organizations provided critical expertise and intellectual property for this groundbreaking public-private partnership:

- The University of California, Berkeley, invented the technology on which the project was based: a process that genetically altered yeast to produce artemisinic acid.
- Amyris, Inc., a biotechnology firm in California, refined this process to enable large-scale production, identified chemistry techniques to convert artemisinic acid to artemisinin, and developed a scalable manufacturing process for transfer to an industrial partner.
- Sanofi, a global pharmaceutical company based in France, provided critical improvements and scale-up for the required fermentation process and developed an innovative, high-yield photochemistry method to convert artemesinic acid to artemisinin.
- The National Research Council Canada Plant Biotechnology Institute provided a royalty-free license for needed intellectual property.

Addressing market issues

A critical project objective was keeping manufacturing costs as low as possible. This was achieved by refining the biological and chemical processes for maximum efficiency. For example, the project team researched several methods to maximize the yields of artemisinic acid that could be produced by genetically modified microorganisms and investigated the most efficient chemical process to convert artemisinic acid to artemisinin.

Project partners also developed a strategy for the product launch. One concern was ensuring regulatory approval,

A DECADE OF COLLABORATION TO BRING SEMISYNTHETIC ARTEMISININ TO MARKET

2004

Received a US\$42.6 million grant from the Bill & Melinda Gates Foundation to launch the project.

2004

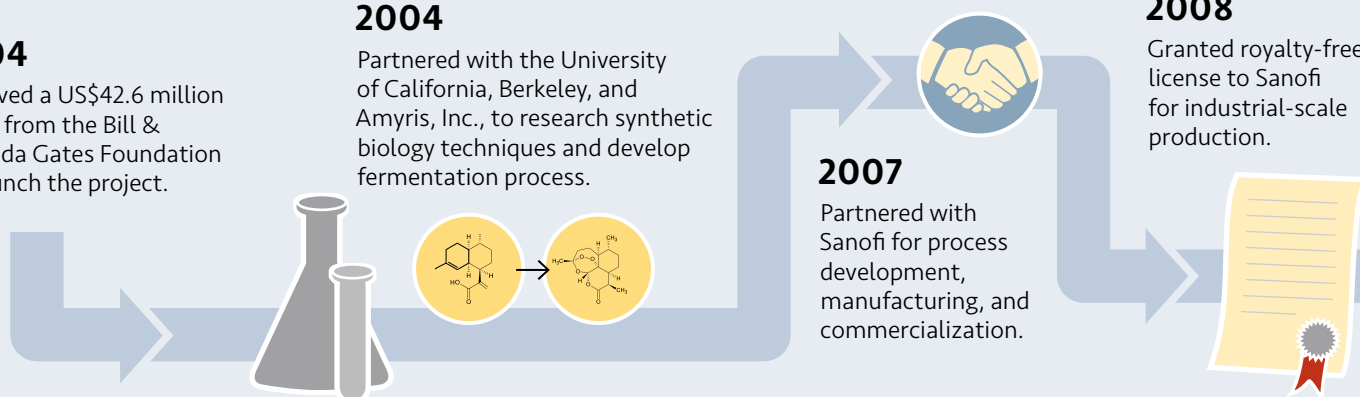
Partnered with the University of California, Berkeley, and Amyris, Inc., to research synthetic biology techniques and develop fermentation process.

2007

Partnered with Sanofi for process development, manufacturing, and commercialization.

2008

Granted royalty-free license to Sanofi for industrial-scale production.



which required demonstrating the equivalency of ACTs based on semisynthetic artemisinin and those based on plant-derived artemisinin. Also, the project team analyzed artemisinin economics and market dynamics to determine how to introduce the product in a way that would alleviate the global ACT shortage and stabilize the market.

Status and outlook

Industrial-scale production of semisynthetic artemisinin was formally launched in April at a Sanofi factory in northern Italy. With regulatory approval in early May, the product is now ready for integration into the supply chain for ACTs.

By providing an additional source of high-quality product at stable prices, the Artemisinin Project will enable a more steady flow of artemisinin and greater availability of ACTs. Approximately 35 metric tons of semisynthetic artemisinin will be produced in 2013, which means approximately 70 million malaria treatments will be available to women, young children, and other patients who need them.

The project illustrates how new, highly innovative technologies can be developed through cross-sector collaboration to simultaneously advance the goals of global health and individual partners. It provides a model

More PATH work to address malaria

PATH is tackling malaria from all sides, with an ultimate goal of eliminating the disease. A new PATH-led project called MalariaCare, funded by the US Agency for International Development, is scaling up high-quality diagnosis and case management services for malaria in high-priority countries in Africa and the Mekong Region of Asia. Meanwhile, the PATH Malaria Vaccine Initiative is working to develop the world's first malaria vaccine. Results of phase 3 clinical trials to date have shown that an advanced vaccine candidate called RTS,S, being developed with GlaxoSmithKline, cuts cases of malaria in infants and young children by one-third and one-half, respectively. PATH is also working to provide useful information and resources to the global malaria community. One example is PATH's recent launch of a new website on malaria control (www.makingmalariahistory.org) and a related e-newsletter.




PATH/Eric Becker

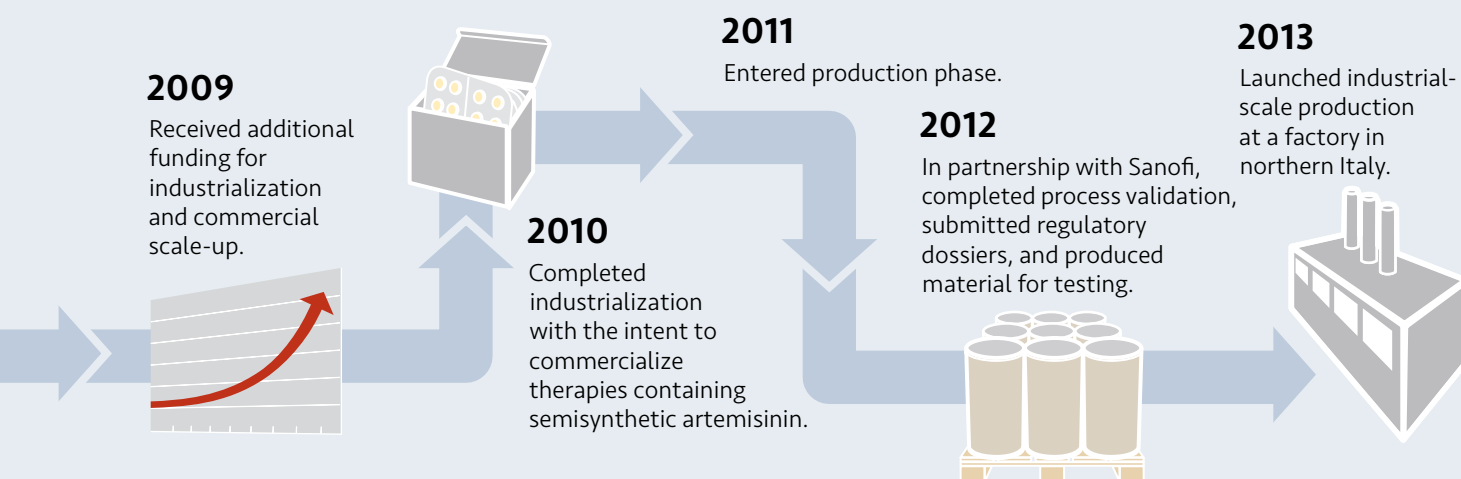
that may be useful for overcoming other major global health challenges. ■

FOR MORE INFORMATION

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This work has been supported by a grant from the Bill & Melinda Gates Foundation.

 Read more about this work at <http://sites.path.org/drugdevelopment/>.



Protecting infants from respiratory syncytial virus

PATH explores immunization of pregnant women to prevent severe disease during the baby's first few months

Severe disease caused by respiratory syncytial virus (RSV) is a major cause of hospitalization and death among infants and young children in low-income countries. A vaccine to prevent infection does not yet exist.

PATH is exploring development of a vaccine that can be given to pregnant women so antibodies against RSV will be transferred through the placenta to their unborn children. This maternal immunization strategy aims to protect infants in the first few months of life, when a newborn's immune system is too immature for direct vaccination.

Collaborating across sectors

Globally, RSV causes more than 30 million new episodes of acute lower respiratory infection each year and up to nearly 200,000 deaths among children under five years old. Ninety-nine percent of these deaths occur in low-resource countries. Peak hospitalization rates occur among children from birth to five months of age.

Previous studies have shown that giving certain vaccines to pregnant women can enhance mother-to-child transmission of antibodies. To advance the development of low-cost RSV vaccines for maternal immunization, PATH is partnering with vaccine developers and researchers from industry, academia, and other groups. Our work includes:

- Partnering with Novavax, Inc., on a phase 2 clinical trial evaluating the company's RSV fusion (F) protein vaccine candidate in women of childbearing age in the United States. Results will inform efforts to develop a vaccine suitable for use in low-resource countries.

- Collaborating with both Novartis Vaccines and Diagnostics and GlaxoSmithKline Vaccines to develop preclinical models for evaluating RSV vaccine candidates for pregnant women. This work includes both in vivo and in vitro models.
- Working with the US National Institute of Allergy and Infectious Diseases to optimize a robust new assay format to enable scientists to uniformly and objectively assess the amount of RSV neutralizing antibody present. This will give the scientific community a better means to compare RSV vaccines.

Assessing feasibility in low-resource settings

Other work streams are evaluating the feasibility of RSV maternal immunization strategies in the developing world. For example, PATH is working with researchers at Johns Hopkins University, Case Western Reserve University, and the Papua New Guinea Institute of Medical Research to assess how malaria may affect the transfer of RSV-specific neutralizing antibody from mothers to infants. With Seattle


Children's Research Institute, we are studying RSV disease burden and the protective effect of maternal-derived RSV antibody in infants in Bangladesh and Nepal. And with the University of Warwick and the Kenya Medical Research Institute, we are evaluating the relationship between maternal RSV-specific antibody titers and protection in infants, as well as the rate at which antibody protection declines after birth.

Work by PATH, our partners, and other vaccine researchers suggests that maternal immunization may be a promising strategy to protect newborns against life-threatening RSV infection. This strategy has already been shown to be useful for prevention of other illnesses among infants, such as influenza and pertussis. ■

FOR MORE INFORMATION


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This work has been supported by a grant from the Bill & Melinda Gates Foundation.

 Read more about PATH's work www.path.org/projects/rsv.php.

Tracking vaccine candidates

PATH maintains an RSV vaccine snapshot to track the development of specific vaccine candidates and provide an overview of vaccine approaches being developed worldwide. PATH regularly updates this snapshot and welcomes input from others working in the RSV vaccine field.

 Download the snapshot at www.path.org/vaccineresources/details.php?i=1562.



Sayana® Press pilot: Increasing access to family planning

Worldwide, more than 200 million women lack access to family planning, often because they cannot reach services. Sayana® Press, a new formulation and presentation of an already popular injectable contraceptive, has the potential to complement existing forms of this safe, reliable, and discreet method by providing an option that is easy to administer, even outside the clinic.

Pfizer's Sayana Press uses the Uniject™ injection system, which PATH developed and licensed to make injections simpler and safer. Uniject is essentially a small bubble of plastic prefilled with one dose of medicine and attached to a single-use needle. Packaging the contraceptive this way allows workers from all levels of the health system to safely provide

injections in community locations and clients' homes.

Between 2013 and 2016, PATH and our partners will introduce up to 12 million doses of Sayana Press to women in sub-Saharan Africa and South Asia and evaluate the product's impact on contraceptive use, access, and service delivery costs. The data will help decision-makers worldwide determine whether and how Sayana Press can support their family planning programs.

The pilot project represents a collaborative commitment made during the 2012 London Summit on Family Planning. Partners include the Bill & Melinda Gates Foundation, the US Agency for International Development (USAID), the United Kingdom's Department for International Development, the United Nations Population Fund, Pfizer Inc., and PATH. Country-level partners will also collaborate on implementation. ■




PATH/Patrick McKem

FOR MORE INFORMATION

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This work has been supported in part by the Bill & Melinda Gates Foundation, USAID, the Frankel Family Foundation, The William and Flora Hewlett Foundation, and individual donors.

 Read more about PATH's work with Sayana Press at www.path.org/projects/uniject-dmpa.php

Sayana Press is a registered trademark of Pfizer, Inc. Uniject is a trademark of BD.

Enabling human milk banks to reach more babies

Breast milk is the perfect food for babies. It provides the energy, nutrients, and fluids they need, as well as antibodies that help keep them free from illness. When a mother's milk is unavailable, donated breast milk can be a lifesaving alternative—especially for babies who are premature, malnourished, or otherwise vulnerable.

PATH is working to identify and implement simple, low-cost approaches that enable human milk banks (HMBs) to provide safe, nourishing milk to as many babies as possible.

We have assessed HMB systems worldwide to learn more about

successful methods and common challenges, particularly in low-resource settings. For example, the process that HMBs use to pasteurize milk can be expensive and difficult to monitor. To address this challenge, PATH, the University of Washington, and the Human Milk Banking Association of South Africa are piloting a simple, mobile phone-based system that guides staff through pasteurization and records key information.

Last year, PATH also convened HMB practitioners to leverage insights and build a global technical advisory group. The group discussed promising technologies and future priorities and helped to draft universal best practices for safe, effective, and sustainable banking. It is now developing a framework to guide implementation of new


programs. The guidelines will be shared widely, providing a road map to strengthen and expand programs.

Together, these efforts are helping to transform HMB systems, allowing them to provide safe, lifesaving breast milk to more vulnerable infants worldwide. ■

FOR MORE INFORMATION

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This work has been supported by the University of Washington Computer Science & Engineering Department, donations to PATH's Health Innovation Portfolio, a grant from the Bill & Melinda Gates Foundation through the Grand Challenges Explorations initiative, and the US National Science Foundation.


 Read more about PATH's support for human milk banking at www.path.org/projects/milk-banks.php.

NEWS AND NOTES

PATH NEWS


Global health leader named chief strategy officer

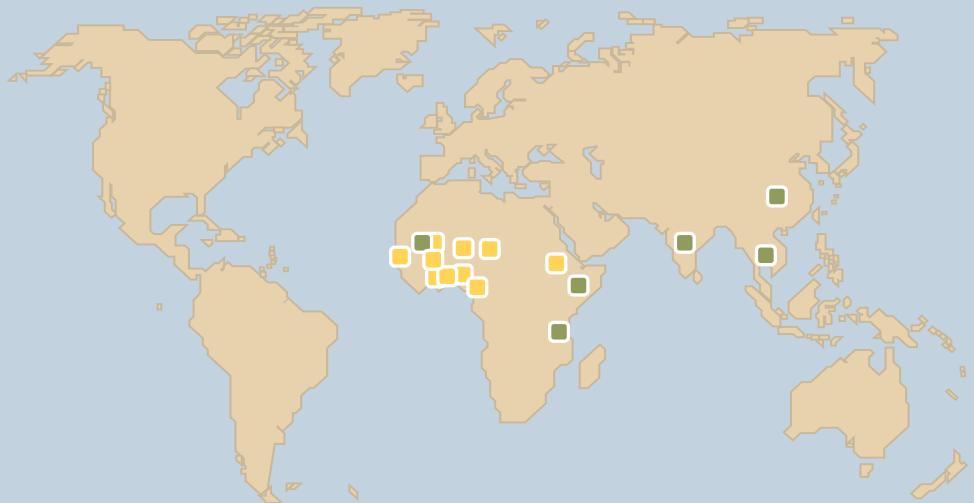
Amie Batson, the former senior deputy assistant administrator for global health with the US Agency for International Development, joined PATH in April as our chief strategy officer. Under the newly created position, Batson helps guide PATH's strategy, strengthens our partnerships and business relationships in the global health community, and contributes to PATH's advocacy and policy priorities. Batson's 20-year global health career includes positions with the World Bank, the World Health Organization (WHO), and UNICEF. Her expertise and experience "will help to strengthen PATH's role as a critical player in this field," said PATH President and CEO Steve Davis.

 Read more about Amie Batson's appointment at www.path.org/news/pr121128-batson.php.

Mercury treaty protects vaccine access

Government delegates have agreed to safeguard access to vaccines containing the preservative thimerosal under a new global treaty on mercury. PATH coordinated a months-long advocacy effort with WHO, UNICEF, the GAVI Alliance, and other global health and civil-society groups to educate United Nations Environment Programme delegates on the importance and safety of thimerosal. These efforts help protect poor countries' access to the many common lifesaving vaccines that contain thimerosal.

 Read more at www.path.org/news/an130118-mercury-treaty.php.




PROGRAM NOTES

MULTICOUNTRY: Meningitis vaccine reaches 100 millionth person, breaks cold chain barrier

Health workers in Nigeria administered the 100 millionth dose of the MenAfriVac® vaccine in December, just two years after it was introduced. PATH and WHO led the creation of the vaccine and worked with Serum Institute of India Ltd. to develop and manufacture it. MenAfriVac® has now reached ten countries.


The vaccine has also reached another milestone—regulatory approval for transport and storage outside of the cold chain. MenAfriVac® can be kept unrefrigerated for up to four days, making it easier to reach rural communities with potent vaccine.

 Read more about the Meningitis Vaccine Project at www.path.org/menafrivac/index.php.

MenAfriVac is a registered trademark of Serum Institute of India Ltd.

MULTICOUNTRY: Design guidelines lead to new family of water filters

Three Chinese manufacturers are selling new, low-cost water filters based on design guidelines developed by PATH. With input from low-income families in five countries in Africa and Asia, our researchers designed an affordable water filter that consumers are likely to buy and use to protect themselves from bacteria that cause diarrhea and other life-threatening illnesses. The guidelines are freely available and may help to increase choices for consumers, encourage competitive pricing, and improve access to safe water.

 Read more at www.path.org/news/pr121212-water-filters.php.

PATH is an international nonprofit organization that transforms global health through innovation. We take an entrepreneurial approach to developing and delivering high-impact, low-cost solutions, from lifesaving vaccines and devices to collaborative programs with communities. Through our work in more than 70 countries, PATH and our partners empower people to achieve their full potential.

Directions in Global Health shares information about PATH's programmatic work with colleagues around the world. To subscribe to this newsletter, please send your contact information to publications@path.org. To subscribe to other PATH publications—including *News From PATH*, our organizational e-newsletter—go to www.path.org/sign-up.php#news.



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