FACT SHEET

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New Vaccines to Address Bacterial Causes of Diarrhea

Diarrhea is the second leading cause of death in children under the age of five. Each year, approximately 1.3 million children worldwide die from severe, dehydrating diarrhea and dysentery, and millions more are hospitalized, mostly in low-resource countries. The leading bacterial causes of diarrhea are enterotoxigenic *Escherichia coli* (ETEC) and *Shigella*, and, together they account for about one billion cases of diarrhea annually. Insufficient data exist, but conservative estimates suggest that ETEC and *Shigella* are responsible for the deaths of approximately 500,000 children under the age of five each year. In addition, many more children suffer from diarrheal disease-associated malnutrition and its adverse consequences on physical and cognitive development. Enteric diseases like these often perpetuate the cycle of poverty in low-resource countries.

ETEC may be the first enteric illness encountered by many infants, and *Shigella*, along with rotavirus, is the most frequent cause for hospitalization of infants and young children experiencing severe diarrhea and dysentery in low-resource settings. Access to appropriate medical care for severe diarrhea and dehydration is limited in these areas, and *Shigella* is becoming increasingly more resistant to the antibiotics most commonly used to manage febrile diarrhea and dysentery. In addition, bacterial causes of diarrhea are spread more easily in areas with poor sanitation and limited access to clean water, which is a frequent concern in the developing world. For all of these reasons, prevention through vaccination is a critical part of the strategy to reduce the incidence and severity of diarrheal disease.

PATH is collaborating with private- and public-sector partners to accelerate the development of safe, effective, and affordable vaccines against ETEC and *Shigella* for children in endemic areas. By pursuing a wide range of promising vaccine approaches and related research, PATH aims to identify at least one vaccine candidate for each pathogen to prioritize for late-stage development. A scientific advisory board provides strategic guidance to this project, with experts in the enteric vaccine field playing a key role in shaping PATH's portfolio and providing strategic recommendations. PATH is also assessing manufacturing partners, mostly in emerging countries, to participate in the late development and eventual manufacture and distribution of these vaccines.

PATH/Deborah Phillips

In addition, PATH aims to increase awareness of diarrheal disease and the need for new enteric vaccines by pursuing an advocacy and policy strategy that integrates information about enteric diseases within broader public-health priorities. This framework connects the problem of diarrheal disease with solutions that include new and forthcoming vaccines as well as existing prevention and treatment interventions. Additionally, in collaboration with BIO Ventures for Global Health, PATH conducted an assessment of the market opportunity for ETEC vaccines to provide product developers and donors with a business case for investment (report available at www.path.org). PATH is currently preparing a similar market assessment for *Shigella* vaccines, with a report expected in 2012.

Enteric vaccines in development

PATH is pursuing a spectrum of activities to advance enteric vaccine research and development, with a target product profile focused on infants and children in low-resource countries. Based on a comprehensive landscape analysis of the various approaches and candidates being developed for ETEC and *Shigella* vaccines, PATH is accelerating the development of those it identified as the most promising.

Killed whole-cell vaccines offer a superior safety profile, a relatively simple and cost-effective manufacturing process, and stability at room temperature. However, these vaccines may elicit poor immune responses from people in endemic countries. PATH is working with the University of Gothenburg

in Sweden to evaluate an inactivated whole-cell ETEC vaccine candidate, supporting proof-of-concept studies to test for improved immunogenicity compared to an earlier version of the candidate. PATH is also collaborating with the Walter Reed Army Institute of Research to conduct early clinical research on an inactivated *Shigella* whole-cell vaccine candidate.

Subunit vaccines also offer potentially greater safety profiles, but they frequently lack the immunogenicity needed to be protective in animal models or human trials. PATH is working with several partners to evaluate promising subunit antigens, which may confer broader protective coverage to vaccines.

Two of PATH's partners are conducting preclinical research on vaccine concepts against ETEC. One is targeting the heat-stable enterotoxin (ST) that is expressed by approximately 66 percent of the ETEC strains associated with diarrheal disease in travelers and in children living in endemic areas. An ST toxoid vaccine is being developed by the International Enteric Vaccine Consortium, a group of universities anchored by the University of Maryland School of Medicine. The other vaccine concept targets the conserved fimbrial tip adhesin proteins of ETEC and is being developed by the US Naval Medical Research Center. PATH is also collaborating with two groups to evaluate *Shigella* subunit vaccine approaches, supporting the International Vaccine Institute in South Korea to evaluate a prototype vaccine based on a novel antigen (Pan-*Shigella* Surface Protein 1) in preclinical and early clinical studies and Oklahoma State University to research a vaccine comprising conserved proteins as a novel means of inducing broad immune coverage.

Live attenuated strains have shown promise with ETEC and *Shigella*, as they can more closely mimic natural infection and may induce more protective immune responses. Some vaccines of this type have shown unacceptable levels of reactogencity in clinical trials performed in the United States and other developed-world sites or have shown reduced immunogenicity in developing countries, particularly in infants and young children.

PATH has supported early clinical research on ACE527, an ETEC vaccine candidate developed by TD Vaccines, a Danish biotechnology company. ACE527 is an oral, whole-cell vaccine comprised of three attenuated ETEC strains. Results from these studies were promising, and PATH is planning to conduct further testing of ACE527 in a descending-age study in an ETEC-endemic country, expected to launch in 2012. For *Shigella*, PATH is supporting optimization and early-stage clinical trials of the CVD1208S vaccine candidate by the University of Maryland, Baltimore. This oral vaccine is ultimately envisioned to be a multivalent vaccine designed to prevent illness resulting from common disease-causing strains of the *Shigella* bacteria.

Research to support vaccine development

PATH is working with several partners on supporting research that may also benefit the broader enteric-vaccine community. Adjuvants, ingredients that may enhance the effectiveness of some vaccines, are one important area. PATH in-licensed the double mutant heat-labile toxin (dmLT) vaccine/adjuvant, LTR192G/L211A, from Tulane University. This highly promising vaccine/adjuvant is an ETEC antigen that may offer protection against both diarrhea and intestinal infection. LT is also one of the most effective mucosal adjuvants known. Due to its improved attenuation, the dmLT could provide a breakthrough in mucosal adjuvants and may be tested in conjunction with a number of candidates in PATH's vaccine portfolio. PATH is currently working with the Division of Microbiology and Infectious Diseases, National Institutes of Allergy and Infectious Diseases, part of the US National Institutes of Health, on early clinical studies of the dmLT and will begin testing it in combination with other candidates soon.

In recognition that new vaccines must be practical for use with infants and children in low-resource countries, PATH is optimizing vaccine stabilization and investigating new formulations that may make the vaccines more immunogenic and easier to administer in these populations. For instance, PATH is partnering with Mucosis, B.V., in the Netherlands to explore the use of their Mimopath™ technology to facilitate oral delivery of subunit vaccines against ETEC and *Shigella*. In addition, PATH is conducting research on novel vaccine-formulation options, such as a fast-dissolving tablet technology platform and intradermal- and sublingual-delivery options.

Finally, PATH partnered with Johns Hopkins University to refine an ETEC challenge model for assessing the protective efficacy of candidate vaccines. Results from the studies found that the standard human challenge model has been utilizing a higher dose than is necessary to determine effectiveness. Using a challenge dose that is too high may result in premature elimination of promising vaccines that could work in developing-country populations. Going forward, the use of lower-dose challenge models can be used by researchers to better assess ETEC vaccine candidates in human challenge studies.

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