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Conjugated Typhoid Vaccine: New Hope for an 'Urgent Problem'?

And why has it taken so long?

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For one terrible night in March 2010, in a field clinic outside Port-au-Prince, Haiti, I watched a child die of typhoid fever. She had arrived earlier in the day from a tent city, one of many wretched encampments that had sprung up in the wake of the earthquake 2 months earlier. By the time she arrived at the hospital, she'd had abdominal pain and a high fever for several days. Despite treatment with antibiotics and intravenous fluids, her pain and fever intensified over the course of the afternoon, and by midnight her blood pressure plummeted. She died in the early morning in the hospital's tiny pediatric intensive care unit—her lungs filled with fluid and her mother wailing at the bedside.

Typhoid Fever Is an 'Urgent Problem'

Typhoid fever causes an estimated 21.5 million illnesses[1] and 222,000 deaths[2] worldwide each year, concentrated among people in low-resource settings with unreliable access to safe water and sanitation facilities. Vaccines against the infection have existed in various forms for over a century. In fact, several weeks before traveling to Haiti, I was vaccinated with one of the orally administered forms of typhoid vaccine.

My patient, however, had almost certainly not been vaccinated. Because typhoid vaccines have historically not been useable in infants, they are rarely used in the regions where typhoid is concentrated. Instead, typhoid epidemics—such as the one that killed my young patient—are treated reactively with antibiotics.

But growing antibiotic resistance worldwide is "making what was for many years a treatable disease an untreatable disease again," says Kathy Neuzil, MD, MPH, director of the University of Maryland's Center of Vaccine Development, which recently partnered with the Oxford Vaccine Group at the University of Oxford and the nonprofit organization PATH to create the Typhoid Vaccine Acceleration Consortium (TyVAC). And as treatment has become more difficult, preventing infection to begin with has become an urgent problem.

A new, better typhoid vaccine could be the solution—and many expect that soon it will be. A conjugate typhoid vaccine,[2,3] different from its predecessors in its ability to elicit a strong immune response in infants and children, is now commercially available in early-adopting countries and will soon be used in studies that hope to set the stage for its inclusion in immunization programs for children in developing countries.

Typhoid and Early Vaccination Efforts

Typhoid disease is caused by infection with a group of *Salmonella enterica* serovars collectively called Typhi and, less commonly, Paratyphi. The infection is transmitted by the fecal-oral route, often causing explosive epidemics in areas of poor sanitation and unreliable access to clean water. Although typhoid infection can often result in mild symptoms —especially among people who are frequently exposed to it—it can also cause prolonged febrile illnesses that can be complicated by bleeding and perforation in the gastrointestinal tract.[1] Children, especially infants and toddlers, bear a significant burden of disease, especially in resource-poor areas of Southeast Asia and Africa.[4]

"There have been efforts to vaccinate people against typhoid since the turn of the 20th century," says Peter Hotez, MD, PhD, director of the Texas Children's Hospital Center for Vaccine Development. An early version of the vaccine was successfully used in the late 19th century to protect British troops fighting in the Boer War in South Africa.[5] For years, typhoid vaccine technology changed very little, using either killed whole typhoid cells or purified molecules from the cells as the main ingredient.

Typhoid Vaccines: 'Far From Perfect'

But these vaccines remain far from perfect. Because they rely on the humoral immune system, which is immature in infants, they are ineffective in children younger than 2 years. Even in older populations, the vaccines offer uneven levels

of protection, as low as 53% in some studies, and a relatively short duration of protection—only 3-7 years.[6,7]

"We can do a lot better in terms of making a vaccine that has a better safety profile and induces higher levels of protection," says Dr Hotez. And in the late 1990s, the National Institutes of Health, in partnership with scientists in Vietnam, did just that.[8] Their prototype was a conjugate vaccine—a polysaccharide molecule from the *S typhi* capsule tethered to a powerfully immunogenic portion of a bacterial toxin.

That toxin component is key to the conjugate vaccine's ability to create immunity in infants because the toxin component stimulates the immune system's T cells, which are relatively robust in infants. The result is a strong and long-lasting immune response that can be achieved in patients as young as 6 months—a substantial improvement over older polysaccharide-only vaccines.

Conjugate Typhoid Vaccine: New Hope for the Youngest Victims?

The new vaccine's potential for use in infants means that it is a better candidate for integration into the Expanded Programme on Immunization of the World Health Organization (WHO), which administers infant vaccination programs in low-resource countries. In those settings, infancy is the time when children come in for immunization, and that's when vaccine coverage rates are highest, says Dr Neuzil. "You may be able to reach 90% of 14-week-olds, but you're not going to reach that many 6-year-olds."

The vaccine is already being produced by at least one Indian company, Bharat Biotech, and is commercially available in India. In late 2017, TyVAC will begin a multidisciplinary effort to determine the public health impact of the vaccine in a variety of settings. TyVAC's goal is to eventually get the vaccine approved for use globally by the WHO, which could happen in as few as 5 years. The WHO's Strategic Advisory Group of Experts on Immunization is expected to provide recommendations for use of the new vaccine in late 2017.

Why Is Vaccine Development Taking So Long?

Why did it take so long for this vaccine technology to get from the bench to the bedside? "It might be more market forces and political will than anything else," says Dr Neuzil. "If you think about it from the manufacturing perspective, if I don't have a huge market and my only market is a poor country, that's not a good business decision," she says.

The Gates Foundation, whose 2016 grant of nearly $37 million will fund TyVAC's work, "de-risks" manufacturers' investments in these projects. Similar investments by Gates and other funders under the umbrella of Gavi, the Global Alliance for Vaccines and Immunization, have dramatically increased coverage with other vaccines in resource-poor countries since the fund's inception in 2000.

Another factor may be the difficulty of measuring the burden of typhoid worldwide, which complicates predictions of a vaccine's public health impact. "It's quite challenging for a country to measure the magnitude of its typhoid problem, let alone figure out where the high-risk areas or groups are," says John Crump, MB ChB, co-director of the Centre for International Health at the University of Otago in New Zealand. Diagnosing typhoid accurately in the developing world requires a blood culture, which is often unavailable or unreliable in low-resource settings and has a relatively low sensitivity of 80% even when it can be performed.[9]

Although estimates have improved as new sources of epidemiologic data are identified, high-risk groups are often only identified well after outbreaks begin, says Dr Crump. Consequently, infected patients often go untreated or are mistreated with antimicrobials directed at more commonly diagnosed diseases, such as malaria. This results in an increased risk for severe illness or death and also has resulted in the emergence of resistance to antimicrobial drugs, including beta-lactams, sulfonamides, fluoroquinolones, and other drug classes.

Multidrug-resistant typhoid is now considered endemic in many developing countries, especially in South and Southeast Asia, with extended-spectrum beta-lactamase resistance reported in several cases.[10]

Treatment and Prevention Strategies: 'We Need Both'

With such pervasive potential for treatment failure, the focus has shifted to preventing typhoid infection to begin with. And although efforts to improve sanitation and access to clean drinking water are important components of reducing typhoid and other enteric diseases, they should happen in parallel with vaccine development—not in opposition to it, says Dr Crump.

In some circles, "there has been an unhelpful dichotomization of vaccine and nonvaccine prevention strategies," he says, "whereas in fact, what we really need is both."

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