Technological Innovation for Global Health: Vaxess' Long Road to Heat-Stable Vaccines

It was only April, but 2015 was shaping up to be a busy one for Livio Valenti. The Harvard Kennedy School graduate was named to Forbes' prestigious "30 under 30" list of the brightest entrepreneurs in science and healthcare, just as Vaxess Technologies, the biotech start-up he co-founded in 2012, was starting to attract attention. Indeed, the company was awarded a research grant from the U.S. National Science Foundation and the U.S. National Institute of Health to put toward the development of heat-stable vaccines—a major honor and accomplishment, though the grants themselves were modest.

Most vaccines had to be refrigerated (or frozen) to preserve their efficacy. However, keeping vaccines at the appropriate temperature from manufacturer to recipient posed significant costs and logistical challenges, especially in many low- and middle-income countries where the majority of the world's children lived. Valenti believed Vaxess' technology could provide a potentially simpler, safer approach to heat-stabilizing vaccines from both a scientific and regulatory standpoint—formulating them to withstand a lack of refrigeration—compared to other preservation techniques. In the vaccine field however, the risks and costs of research and development, and lengthy regulatory approval processes were major challenges to advancing products to market. Furthermore, with the greatest need for heat-stable vaccines in developing countries, market incentives for companies to invest in heat-stabilization research and development (R&D) were weak. Still, the U.S. Food and Drug Administration (FDA) had approved silk fibroin—the key ingredient for Vaxess' platform to heat-stabilize vaccines—for use in medical devices such as surgical sutures and implantable surgical mesh, giving the Vaxess team confidence that their innovation would eventually gain FDA approval.

Valenti was hopeful this new technology could deliver significant benefits for public health in developing countries, but how could he get from this early-stage technology to impact? Vaxess planned to work with vaccine manufacturers to conduct preclinical, clinical and bridging studies to include silk fibroin in new heat-stabilized formulations of vaccines but Vaxess had to navigate a very complex ecosystem to help achieve its mission. Valenti and his team knew they faced a long and complicated journey; many organizations played a role in helping determine if a vaccine would ultimately be available and accessible to the children worldwide who could benefit from them.

This case was written by Laura Winig, Senior Case Writer in collaboration with Suerie Moon, Research Director and Co-Chair of the Forum on Global Governance for Health, Harvard Global Health Institute and Harvard School of Public Health, for use at the John F. Kennedy School of Government (HKS), Harvard University. Support for this case was provided by the Harvard Kennedy School's Sustainability Science Program. HKS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

Decade of Vaccines

More than three million people die each year from vaccine-preventable diseases; half are children younger than five years old.[1] In 2011, the World Health Organization (WHO) declared the start of the "Decade of Vaccines," announcing a $50 billion plan to avert nearly 26 million deaths by increasing vaccinations in the developing world.

WHO's Global Vaccine Action Plan (GVAP), endorsed by the health representatives of 194 countries as well as stakeholders in academia, the private sector, non-governmental agencies and manufacturers, aimed to expand routine immunization and accelerate control of vaccine-preventable diseases by introducing new and improved vaccines.

To meet GVAP's goals, frontline vaccine providers needed to reach unvaccinated people—especially those living in remote or difficult-to-access areas—as well as the under-vaccinated (those who had received some vaccine doses but were not fully immunized); only then could WHO hope to achieve its ultimate goal of eradicating deadly viral and bacterial diseases. "There is no mystery to it—once vaccination coverage is raised to a high enough level, these viruses and bacteria will have nobody to infect," a WHO report stated.[2]

In 2014, WHO published a progress report but the news was grim: of WHO's six key immunization targets only one was on track to meet 2015 goals. The report noted the failure was systemic: "The targets are disease-specific, but the improvements needed to achieve them are largely shared."[3] Recommended improvements included improving training of healthcare workers, building additional facilities for vaccination and establishing or maintaining a cold chain for vaccine distribution.

The cold chain issue was a particularly vexing challenge. To maintain their potency, nearly all vaccines—97%—had to be kept cold, between 2 and 8 degrees Celsius.[a] An effective cold chain required an uninterrupted path of refrigerated storage and distribution facilities from the time of manufacture to administration of the vaccine. Therefore, vaccine distribution was largely dependent upon players along the distribution route to maintain the vaccines within that narrow temperature range, using methods ranging from refrigerated trucks to camel-top ice chests. Consequently, a reliable electricity supply was often required.

Approximately 80% of the total cost of vaccination programs went toward supporting vaccines which traveled via cold chain.[4] Nevertheless, cold chains were routinely broken in developing countries, leading to ruined batches of vaccines; indeed, by one estimate nearly half of all vaccines were rendered ineffective before they could be administered to patients due to cold chain breaks.[5]

Some in the vaccine industry pressed for an alternative: heat-stable vaccines that might safely be transported and stored at elevated or fluctuating temperatures. But given the complexity of the global immunization system with its large number of stakeholders—pharmaceutical manufacturers, health care workers, private philanthropic funders, public health agencies and governments of vaccine-producing and vaccine-using countries—with competing priorities, how could it be done?

[a] 35 to 46 degrees Fahrenheit.

The History of Vaccines

Vaccines dated back to the 10th century and variolation, a technique used to immunize healthy people against smallpox by exposing them to the scabbing pustules of those infected with the disease.[6] The technique worked but caused side effects and was set aside when British physician Edward Jenner successfully created a smallpox vaccine[b] in the 1790s.[7]

By the 1800s, governments had begun to mandate smallpox vaccination to protect public health.[8] In the meantime, the scientific community worked to develop new vaccines and by the end of the 1920s, vaccines were available for diphtheria, tetanus, whooping cough and tuberculosis.

Over the next 40 years, governments in wealthier countries began to introduce vaccination programs against these diseases, systematically ensuring their citizens were inoculated.[c] Indeed, in the twentieth century, as a standard battery of childhood immunizations was developed (to include diphtheria, measles, mumps, and rubella), vaccination was frequently managed or adjudicated by governmental entities (from the municipal to the federal level).

The successful worldwide eradication of smallpox by 1980, one of the world's most notable public health achievements, was made possible by the widespread dissemination of the smallpox vaccine. Many in the vaccine stakeholder community kept this example in mind as they worked to put an end to polio, measles and other contemporary diseases.[9]

Vaccines in the Developing World

By the 2010s, children in high-income countries were routinely vaccinated against a myriad of diseases ranging from chicken pox to rubella. While the WHO recommended a similar vaccination schedule for those in low- and middle-income countries (LMICs), many governments faced significant challenges to making vaccines accessible to their countries' children, relying on initiatives sponsored by the United Nations (UN), private foundations and foreign governments for assistance.

Besides price, many LMICs faced significant challenges to widespread distribution of vaccines, including a shortage of trained healthcare workers to administer vaccines, scarcity in logistical infrastructure to support vaccine storage and distribution and, crucially, breaks in the cold chain.

Quest for a Heat-Stable Vaccine

Creating heat-stable vaccines emerged as a strategic priority for stakeholders because of the many benefits of eliminating the cold chain: decreased distribution costs, reduced vaccine spoilage, improved immunization coverage and increased compliance with vaccination schedules, to name a few.

[b] A vaccine was a suspension of weakened live or inactivated bacteria or viruses administered to induce immunity to an infectious disease.

[c] In 1962, the U.S. enacted the Vaccination Assistance Act which offered significant government support for childhood immunization through the funding of mass immunization efforts.

Through 2015, vaccine manufacturers relied on a freeze-drying process, lyophilization, to improve vaccine stability, but the process did not eliminate the need for refrigeration, nor was it effective for all vaccines; it could not, for example, be used for those containing aluminum adjuvants, such as hepatitis A, tetanus or diphtheria or inactivated polio. Vaccine manufacturers, who also bore costs from cold-chain requirements, as well as an interest in increasing the distribution of their products, were therefore motivated to explore heat-stabilization options.

Vaxess Technologies and Silk-Stabilized Vaccines

In July 2012, Fiorenzo Omenetto and David Kaplan, professors of biomedical engineering at Tufts University in Boston who were researching innovative applications for silk biomaterials, uncovered the potentials of silk as a vaccine stabilizer. Since 2004, the Kaplan lab at Tufts University investigated the properties of silk proteins as an advanced biomaterial. Long used largely for textiles, silk had unique biological, medical and mechanical properties: namely, when implanted or injected into the human body, silk protein—fibroin—was absorbed like any other protein.

To develop the silk-stabilized vaccine, Omenetto had created a silk fibroin matrix that enveloped the vaccine molecules, preventing them from degrading over time at elevated temperatures. This enabled the vaccine to be stored at ambient conditions yet remain protected against temperature extremes. Silk fibroin, in combination with other pharmaceutical excipients provided stabilization without altering the vaccine itself, as there was no chemical bonding between the vaccine and the silk fibroin matrix.

After introducing the attenuated virus, the heat-stabilized vaccine could be packaged in a traditional vial. The healthcare provider could then follow the same process used for traditional lyophilized vaccines: reconstitute the vaccine by dissolving it in water and administering it to the patient via injection.

Omenetto's and Kaplan's research revealed that silk fibroin could be used to stabilize a wide range of biological products, including various enzymes, proteins, antibiotics, and small molecules. Silk, then, could potentially serve as the basis of a platform technology to create heat-stable formulations of many–if not all–vaccines.

Vaxess Technologies Launches

In 2010, while serving as a junior officer at the UN, Livio Valenti was assigned to a project to help rural silk farmers in Cambodia preserve the country's traditional fabric weaving culture. The products the farmers created from the silk they harvested were handicrafts sold to tourists in the local markets and the farmers were unable to earn enough to sustain themselves and their families. The farmers needed to find new ways to increase their income.

While researching alternative uses for silk, Valenti learned of Omenetto's work and in 2011, Valenti and Omenetto began to discuss the idea of using rurally-produced silk to stabilize vaccines. By then, Valenti had been admitted to the Harvard Kennedy School of Government (HKS) and in September, enrolled in a Harvard Business School (HBS) course, "Commercializing Science." He invited Omenetto to present the silk stabilization technology to his classmates. It was through this course that Valenti, Michael Schrader, an HBS student, Kathryn Kosuda, a postdoctoral fellow in Harvard's chemistry department, and Patrick Ho, a Harvard Law School student, teamed up

to develop a business plan for Vaxess Technologies, a yet-to-be-formed company that would use silk to heat stabilize vaccines.

The team developed the business plan as a final project for the course, then refined it for HBS's annual Business Plan competition in spring of 2012. It won the grand prize: $25,000 in seed financing. A few weeks later, Vaxess was also awarded the first prize in the inaugural Harvard President's challenge for Social Entrepreneurship, securing an additional $70,000. The Sustainability Science Program at HKS's Center for Business and Government and the Harvard Global Health Institute also supported studies aimed at understanding the potential impact of the silk-stabilization technology on global health.

By early 2013 Vaxess had finalized an agreement with Omenetto's and Kaplan's labs and Tufts University for the exclusive license to use the vaccine stabilization technology and in May, the company secured $3.75 million in equity financing from Norwich Ventures, a Boston-based venture capital firm. The funds were to be used to help Vaxess to advance its silk-stabilization process through pre-clinical development. Shortly after, the four students graduated from their respective programs and took on full-time roles within Vaxess: Schrader as Chief Executive Officer, Kosuda as Vice President of Research and Development, Ho as Vice President of Licensing and Regulatory and Valenti as Vice President of Policy and Strategy. The company expanded rapidly, hiring a scientific team and establishing laboratory facilities in the Boston area to advance R&D as it prepared to bring its technology to market.

Major Stakeholders in the Global Vaccine Community

Vaxess had the potential to develop a key new technology to facilitate immunization efforts in some of the poorest, most remote parts of the world. But what had initially seemed like a straightforward scientific challenge to address a widely-shared goal, quickly revealed itself to be much more complex as Valenti began to navigate the complex global health ecosystem: vaccine industry stakeholders included pharmaceutical companies, charitable foundations, global health organizations and the governments of LMIC countries. What kind of relationship did Vaxess need with each of these stakeholders in order to move toward its goal?

The World Health Organization

WHO was a global health organization established in 1948 by the UN to act as its international health agency. Headquartered in Geneva, Switzerland with offices in 150 countries, WHO influenced the international research agenda on health matters, set norms and standards, advocated for ethical and evidence-based policy, provided technical support and monitored global health and evaluated trends. Supported by contributions from outside donors and member-states (primarily countries that were member-states of the UN), in 2014/2015, the agency had a US$4 billion, 24-month program budget of which US$347 million was allocated to addressing vaccine-preventable diseases.[d]

[d] Programme Budget 2014-2015, World Health Organization, http://www.who.int/about/resources_planning/PB14-15_en.pdf?ua=1, accessed March 10, 2016.

Reducing outbreaks of vaccine-preventable diseases was a top priority for WHO's Expanded Programme on Immunization (EPI), which played an advisory role within the immunization community. EPI provided guidance to manufacturers on the vaccine types and attributes that were best suited to developing countries and advised them on what to keep in mind when they designed vaccines. Through the vaccine prequalification program, WHO provided countries with a vetted seal of approval on vaccines, assuring their quality and suitability for use. The EPI Team in the WHO Department for Immunization, Vaccines, and Biologicals, together with the Prequalification Team in the WHO Department of Essential Medicines and Health Products, collaborated with UNICEF's Programme Division, to serve as conveners, including on vaccine innovations such as formulations and packaging that might make a vaccine more suitable to the market. "We hosted the vaccine packaging and presentation advisory group which is a forum for dialog between the public and private sectors," said Anna-Lea Kahn, technical officer. WHO played an important role in facilitating the dialog and ensuring opportunity for programmatic priorities to be conveyed, however, WHO did not directly fund vaccine development. "WHO isn't really an organization that gives out a lot of money," said Simona Zipursky, a WHO consultant.[e]

WHO's Role in the Introduction of Heat-Stable Vaccines

Recognizing that maintaining the cold chain was a constraint and challenge within developing countries, the introduction of heat-stable vaccines was a priority for WHO. "Countries tend to do two types of immunization work—bring kids to clinics to be vaccinated and mass campaigns where the goal might be to go out into the field and vaccinate 10 million people in 2 weeks," explained Zipursky. "For those mass campaigns, services are really constrained by the cold chain."

WHO helped to facilitate the introduction of controlled temperature chain (CTC) vaccines—the first step toward a true heat-stable vaccine. CTC vaccines could be stored outside the cold chain for short periods of time while still maintaining their potency. For example, the meningitis A vaccine, MenAfriVac, was the first vaccine licensed and relabeled for a heat-stable CTC. WHO developed the guidelines for field implementation and also coordinated a pilot distribution effort, facilitating the use of the vaccine in a campaign setting. "We're trying to boost that practice so any other vaccines that are in the pipeline for licensure and prequalification would receive similar treatment for dedicated guidelines and technical support with implementation," said Zipursky. WHO was also working to negotiate the complex regulatory process. "This is quite new to regulators. WHO is working on guidelines for a regulatory pathway, highlighting what regulatory authorities need to look at," said Kahn.

Kahn added that stability studies have revealed that many vaccines have a higher tolerance for heat exposure than the traditional cold chain range of 2-8 degrees Celsius—more so than previously believed and more so than the labeling of those vaccines would suggest. "We are interested in seeing more of such heat-stable vaccines developed and to have the labels reflect the true stability of existing vaccines," said Kahn, noting that some of them could potentially be taken out of the cold chain, in which case health workers would rely on vaccine vial monitors (VVMs)[f] to demonstrate accumulated heat exposure and peak threshold temperature indicators to signal when the

[e] Anna-Lea Kahn and Simona Zipursky were interviewed by the case writer on November 11, 2014.

[f] Introduced in the early 1980s, VVMs were small, circular indicators that adhered to the tops of vaccine vials or were printed directly on vial labels. A small square on the indicator was chemically active and changed color from light to dark with exposure

vaccine had been exposed to high temperatures. These tools served as proxy indicators of potency after heat exposure. WHO maintained that a VVM "clearly indicated to health workers whether a vaccine [could] be used."[10]

Supporting Emerging Technologies

Many companies were working to develop heat-stable technology. "We have already been contacted by at least three with claims and interest in this area of work who are asking for guidance and support," said Zipursky. "We have to be fair and mindful of not offering any one company any competitive advantage over another."

WHO's Vaccine Presentation and Packaging Advisory Group (VPPAG) provided a forum for public sector and vaccine manufacturers to discuss and reach consensus on vaccine presentation and packaging issues for products being developed for LMICs. VPPAG was established in 2007 by Gavi; in 2008, WHO took over the role of convening VPPAG, and by 2009, VPPAG had developed a draft generic preferred product profile for the range of potential new vaccines in the development pipeline. VPPAG provided a forum for companies to present their technology and get guidance and feedback.

Nevertheless, Kahn felt a manufacturer would have to have already made a significant financial investment before approaching WHO. "It depends on what point the technology is at. If a manufacturer came to us and said, 'I have a vaccine that is heat stable and how can we work together?' then we do have specific guidance to help us assess whether we could be supportive of the vaccine. But it would depend on what the vaccine is for. It would have to be a disease we see in LMICs. We would need multiple heat-stable products addressing all of the broad range of vaccine-preventable diseases in the routine immunization schedule before we can get rid of the cold chain," said Zipursky. Kahn agreed, adding, "If it is a process itself that the start-up is presenting, then they have to partner with a vaccine manufacturer."

To introduce a new vaccine technology, a manufacturer would first need to seek regulatory clearance in the country of manufacture. "A lot of regulators are reluctant to do this," explained Zipursky. "They are comfortable with 2 to 8 degrees and beyond that is a risk and they don't see why heat stability is important," she said.

Gavi, the Vaccine Alliance

Gavi, the Vaccine Alliance[g] was a public-private partnership established in 2000 by the major organizations[h] involved in global immunization (with initial funding from the Bill & Melinda Gates Foundation[i]) to improve immunization rates by pooling demand and then subsidizing the costs of the vaccines. Gavi sought to increase use of vaccines in lower-income countries through innovative finance mechanisms, including co-financing by recipient countries, to secure sustainable funding for an adequate supply of quality vaccines.

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to heat over time. By comparing the color of the inner square to the color of an outer reference ring, a health worker could determine whether the vaccine had been exposed to an unacceptable amount of heat. VVMs could be used throughout the distribution process—from manufacturing through the time of administration.

[g] Formerly the Global Alliance for Vaccine and Immunization (GAVI).

[h] Gavi brought together developing country and donor governments, the World Health Organization, UNICEF, the World Bank, the vaccine industry, technical agencies, civil society, the Bill & Melinda Gates Foundation and other private sector partners.

[i] The Bill & Melinda Gates Foundation committed $750 million (increased to $1.3 billion by 2013) to Gavi.

The organization's mandate was to serve the poorest countries, defined each year by gross national income per capita (a maximum of $1500 in 2015). "We focus our interventions on the countries with the most challenging environment," said Lauren Franzel, senior specialist on the market shaping team.[j] As a result, when Gavi considered vaccine characteristics and programmatic suitability, they did so with these countries in mind.

The countries themselves specified their vaccine requirements, applied to Gavi for funding and took responsibility for oversight over the implementation of their immunization programs. Gavi's co-financing policy meant that countries contributed to the cost of their vaccines. By aggregating demand and providing grants, Gavi enabled countries to increase their immunization rates and contributed to lower vaccine prices. For example, as a result of Gavi's efforts, the price for a dose of human papillomavirus (HPV)[k] vaccine, dropped from US$100 to US$4.50 between 2000 and 2013 for Gavi beneficiary countries.[11]

Gavi's Role in the Introduction of Heat-Stable Vaccines

Gavi did not develop vaccines: "We look to our Alliance partners, the vaccine industry, to do that," said Franzel. Instead, Gavi provided funding and helped to set industry priorities. "As we gradually come to better understand the value proposition of a particular vaccine or innovation, we send a clearer message to industry partners that it is an innovation that could potentially be of interest for Gavi supported countries," said Franzel, noting that heat-stable vaccines would be welcomed because of the difficulty of maintaining an adequate cold chain in countries Gavi serves. "In many Gavi countries, as you go from the capital to remote villages and communities, the ability to access refrigeration—and therefore the ability to keep vaccines in the correct storage conditions—is called into question. That's really the value proposition behind heat-stable vaccines," said Franzel.

Indeed, the need for heat stability was most acute in the "last mile" that vaccines traveled: the point from a regional health facility that might have a refrigerator to an "outreach setting" (remote village) that did not. Gavi countries used vaccine carriers that typically kept vaccines cool only for short periods of time. "Outreach can take several days or even a week or more. If you have to continuously go back to the fridges between trips, it is very constraining. It can also mean lower coverage and higher waste," said Franzel. The implications were significant: because the vaccines were considered life-saving interventions, ensuring their potency could contribute to reducing mortality rates. "Even if there is limited access to a health care facility, vaccines can reduce the likelihood that remote populations will suffer from a vaccine-preventable disease," said Franzel.

By increasing the number of available heat-stable vaccines, more space for other vaccines could be freed up within the cold chain. "If you have a heat-stable vaccine, it even allows you to go further without being constrained by the cold chain," explained Franzel. In a big country such as Ethiopia that had rural populations that were hard to reach because of the geographic diversity, "heat-stable vaccines can also help us reach marginalized populations that live in remote areas and remove barriers to access," said Franzel.

[j] Lauren Franzel was interviewed by the case writer on November 6, 2014.

[k] Human papillomavirus is a cause of cervical cancer.

Shaping Markets

One of Gavi's strategic goals was to shape vaccine markets. "We ensure that there is adequate supply of appropriate, safe and quality vaccines at a low and sustainable price," said Franzel who explained that heat stability contributed to a vaccine's appropriateness. Moreover, Gavi required data when making decisions about which vaccines to support. "As we consider heat-stable vaccines, we want to understand the value, the benefits for the countries," explained Franzel. "We need evidence that those vaccines will have an impact."

As one of the biggest purchasers of vaccines in the world, Gavi had significant market influence. "Vaccine manufacturers know that if their competitor is developing a heat-stable vaccine, they could lose some market share if they don't move quickly with a similar innovation," said Franzel. However as of 2015, country demand was low. "It is about demand generation. Trying to create heat-stable vaccines is all for naught if there is no demand from countries, however, countries don't necessarily come to us and ask for it explicitly," said Franzel.

Supporting Emerging Technologies

Franzel said Gavi was very interested in being kept abreast of the relevant technologies being pursued by biotech firms. Though Gavi did not provide financial support to biotechnology or pharmaceutical companies directly, some of its Alliance partners did, such as the Gates Foundation. "They have traditionally been in the role of providing financial backing," said Franzel who stressed that technology with market value and relevance would gain interest from the vaccine industry.

Vaccine price was also a hurdle, and Franzel noted that the final price of a vaccine would have to be competitive. If the technology that makes the vaccine heat-stable was too expensive, then Gavi might not buy it. "We fund nearly $1 billion per year of vaccines, but we don't buy any and every vaccine. We have a defined approach and there must be country demand for the vaccine," she said.

As pharmaceutical companies invested in research and development, they took Gavi's actions into account. "We create product strategies – or roadmaps – for each vaccine to inform stakeholders like vaccine manufacturers so they are aware of our market objectives," explained Franzel. "They can use this knowledge when making their own decisions about production, types and presentation."

The meningitis A vaccine was a prime example. The Bill and Melinda Gates Foundation had provided funding to support the research and development of the vaccine by the Serum Institute of India through the WHO/PATH Meningitis Vaccine Project. "It is now available in the market at a very affordable price," said Franzel. Gavi funded its 2011 introduction in the countries most affected by the disease. It was widely lauded as a significant public health success story—one that Gavi touted as a model for future development efforts. "There was a clear public health need, a gap was identified and global health partners including donors, came together to address it through science and with a successful approach to deliver it to the most at risk," said Franzel.

Afterwards the manufacturer worked to have the vaccine pre-qualified by WHO for use in a CTC system. The Meningitis A vaccine was deemed stable up to 40°C for 4 days prior to reconstitution and then had to be used

within 6 hours.[12] "It was a game changer," said Franzel. "The vaccine can move around the countries with greater facility." Nevertheless, the new approach had its challenges, noted Franzel:

> Countries have been inundated for so long with the message: "never below 2°, never above 8°" that now we have difficulty getting some countries to move away from that approach. Health care workers in these countries are not as well trained as workers in other parts of the world. We have therefore seen a lack of understanding or uneasiness with this change.

The vaccine was piloted in 2012 in Benin and the early findings were encouraging. "There was a lot of positive feedback from the healthcare workers that *were* taking advantage of the concept," said Franzel, who noted that other vaccines could use similar strategies. "Oral cholera and HPV, for instance, are potential candidates for CTC."

Having data from the manufacturers that showed that a vaccine was heat-stable, was critical. "The onus is on the manufacturers to have the data and then engage with the regulatory authority where the vaccine is licensed. Then WHO looks at the data and pre-qualifies the product and its use," she explained. This meant that manufacturers would be required to invest in additional research to obtain the required data, however, if companies tested for a vaccine's heat stability early in the R&D process, it might save the company both time and money later when it filed for regulatory approval. "These data are necessary for the vaccine community to know how vaccines can be managed in the field," said Franzel.

Merck Vaccines

Merck & Co., Inc. was an American pharmaceutical company, the world's fourth largest. Merck was well-known for its innovations in pharmaceutical and vaccine development; the company developed many vaccine "firsts"—including vaccines for mumps, rubella, MMR trivalent, Hepatitis B, varicella (chicken pox) and HPV.

In the 1980s and 1990s, a series of factors eroded profitability and increased business risk and, as a result, many pharmaceutical companies left the vaccine industry. Around the same time, emerging market vaccine manufacturers began to introduce vaccines and the increased competition drove the prices of many older vaccines down, particularly in emerging markets. By 2015, only five multinational companies conducting R&D, manufacturing and selling vaccines remained: GSK, Johnson & Johnson, Merck, Pfizer, and Sanofi Pasteur. At the same time, global disease elimination efforts, including those for polio and measles, heightened awareness of the importance and value of routine childhood vaccination, and growing economies in middle-income countries resulted in increased demand for vaccines appropriate for LMICs. "There was pressure to make vaccines available at low prices," explained Dr. Mark Feinberg, Chief Public Health and Science Officer for Merck Vaccines.[l] "At the same time, the level of regulation on vaccines was increasing significantly which led to increased manufacturing quality requirements and other investments needed to meet those increasingly complex and stringent regulations."

With the creation of Gavi, demand for low-cost vaccines further increased. Pricing tiers evolved to reflect the new markets created by Gavi: in higher-income countries, pharmaceutical companies could sell their vaccines for a

[l] Mark Feinberg was interviewed by the case writer on December 5, 2014. After his interview, Feinberg left Merck and joined the International AIDS Vaccine Initiative.

price that offered them a "meaningful" return on their investment; in lower-income countries, Gavi subsidized vaccine purchases giving the pharmaceutical companies a more stable and predictable market—albeit at much lower or even no profit prices.

Merck's Role in the Introduction of Heat-Stable Vaccines

It was unclear if the introduction of heat-stable vaccines would emerge as a priority for Merck. "If you're a vaccine developer who is thinking about how to prioritize, you really want to invest in products that have a high probability of meeting end-user needs as defined by the target product profile, because if you invest in something that doesn't meet people's expectations or address their needs, then you have wasted a lot of time and resources and missed opportunities," said Feinberg.

He noted that Merck had already made significant investments in vaccines for use in low-income countries, but within the vaccine market, there was not sufficient clarity of direction when it came to demand for heat stability. "When we asked them what they want and how they would value it, the answer wasn't clear," said Feinberg. "There was not the kind of clarity that would be necessary to stimulate the development of vaccines that would be optimized for use in low-income countries." There were so many vaccines in the cold chain in Gavi-financed countries that space for new vaccines was very limited, making the idea of taking vaccines out of the cold chain attractive. But stakeholders were uncertain how to proceed. "Some say, 'We wouldn't know what to do with just one vaccine outside of the cold chain.' But you have to take them out one by one," said Feinberg.

Developing innovations like making vaccines heat stable were likely to cause a vaccine to cost more per dose than the traditional version. There were research and development investment costs and costs associated with new manufacturing facilities to produce and package a new vaccine. Even if the innovator did not intend to profit from sales in low-income countries, they would still need to recoup their additional investments, which would increase vaccine prices. "Pharmaceutical companies cannot invest in products that are going to face uncertain markets or lose a significant amount of money," said Feinberg. As a result, it was unclear if stakeholders would fund innovations such as heat-stable vaccines. "Would buyers be willing to spend another quarter on a heat-stable vaccine? The system and overall program costs could be much more favorable but the people who are buying the vaccine aren't the ones looking at the overall system cost, because that's not how the global health community looks now," said Feinberg. Some pharmaceutical industry leaders felt that their efforts could be accelerated if they could discern what buyers wanted and clarify how much they were willing to invest to get it.

Engineering existing vaccines to incorporate heat-stable technologies was both expensive and time consuming, as Merck discovered with the launch of its rotavirus oral vaccine, RotaTeq, in 2006. The Merck R&D program which led to the licensure of Rotateq was initiated in 1991–well in advance of the creation of Gavi when a clear path to enable accelerated and more predictable vaccine access in low-income countries became available. As a result, the vaccine was originally designed to meet the needs of higher-income countries where cold-chain issues were not a major consideration. Consequently, the need for heat stability was not prioritized during the vaccine's creation. With the new countries now accessible because of Gavi, it became clear that it would be useful for the vaccine to be heat stable. However, Rotateq did not have the characteristics that would allow it to have a VVM. "Our vaccine has 5 strains in it and each has a different thermal decay rate. So there wasn't a single vial monitor

that could be placed on it," said Feinberg. Gavi wanted the vaccine to have a VVM on it (customary practice for vaccines in these markets), so Merck developed a new formulation of the vaccine with a different chemical composition that would accommodate vial monitoring. To meet these needs, Merck had to re-formulate the product and then conduct clinical trials to show that it was equivalent in terms of safety and efficacy. Merck invested in developing the formulation and conducting the clinical trials, and worked with national regulatory authorities to get the new formulation licensed and with WHO to get it pre-qualified—at Merck's expense. "We did this because we wanted to have a vaccine formulation that would be relevant to low-income countries," said Feinberg. By 2015, the vaccine came closer to meeting Gavi's targets for the size of the vaccine package but even with the significant investments, the vaccine still needed to remain in cold chain.

Supporting Emerging Technologies

There were many challenges when applying technological advances to new or existing vaccines. "There are lots of examples of small biotech companies that have had very good ideas about how to improve vaccine heat stability or vaccine delivery—intradermal delivery, vaccines delivered on patches, vaccines that are inhaled rather than injected—and with a few exceptions, those companies have struggled or died," said Feinberg.

While these new ideas had the potential to increase uptake of vaccines, it was difficult to displace an established product that was in routine practice where healthcare workers were familiar with how to deliver the vaccine and for which the regulatory foundation was in place. "In 10 to 20 years, we will have much better ways of delivering vaccines, but it's not up to a single company—we are part of a broader ecosystem. Success depends upon different stakeholders aligning around what's most beneficial and collaborating on removing the barriers to developing those products. There's a world of technological possibility, but you need an enabling environment. It is a function of how well different stakeholders see things similarly and work together to deliver the results," said Feinberg.

MSD-Wellcome Trust Hilleman Laboratories

MSD-Wellcome Trust Hilleman Laboratories (Hilleman), based in New Delhi, India, was a not-for-profit joint-venture partnership between Wellcome Trust, a global charitable foundation focused on investing in health-related research and Merck Sharp & Dohme Corporation, a subsidiary of Merck & Co. Recognizing that the lack of commercial profit discouraged traditional pharmaceutical companies from investing in new vaccines for diseases that primarily affected low-income countries, Hilleman's R&D staff conducted medical research toward creating new vaccines as well as adapting existing vaccines for use in low-income countries. The organization's goal was to devise a "novel immunization platform" by focusing on developing less costly vaccines that were heat stable, easier to administer and had less bulky packaging.[13] Hilleman focused on vaccines to combat strains of diseases most prevalent in low-income countries, noting that they bore 90% of the global burden of disease.[14]

Hilleman CEO Dr. Davinder Gill said the joint venture between Merck and Wellcome offered the organization unique benefits.[m] "Aside from funding and support, we have access to the expertise of a large pharma company

[m] Davinder Gill was interviewed by the case writer on November 19, 2014.

[Merck] and can draw on Wellcome's public health and public policy experience," said Gill, adding that the partnership model enabled Hilleman to pursue contract research and manufacturing and also helped with clinical trials.

Hilleman's Role in the Introduction of Heat-Stable Vaccines

Hilleman's mandate was to develop affordable vaccines for global health, mostly for children and infants. The introduction of heat-stable vaccines was a priority for Hilleman. "We are looking toward optimizing current vaccines that have been developed in high-income countries and adapting them for the needs of low-income countries," said Gill. "We believe that in poor countries where storage, distribution and access are not available, [heat instability] is a huge problem. If you can take existing vaccines and engineer them to have higher heat stability it would have high impact on accessibility and also lower cost because they will be more potent."

Hilleman was already working on heat-stable vaccines including a heat-stable version of Merck's RotaTeq. "It will have higher stability than in current vaccines—much higher than exists," said Gill, noting that the underlying platform technology could be applicable to many vaccines. "The impact is much broader than one single program."

Hilleman's approach was to create a dry powder which they formulated to remain stable at temperatures as high as 45 degrees Celsius for up to ten months. The organization also developed simple, easy to use, low-cost packaging for the powders, which were designed to be reconstituted prior to administration. Traditionally, countries transported vaccines in two vials: one with powder and one with liquid and then combined them (reconstituted) just before vaccination. Hilleman, however, designed a simple plastic container with two chambers—one containing the powder and the other the liquid. The healthcare worker used mechanical pressure (their thumb) to break the field between the chambers and reconstitute the vaccine. "No problem with confusion, mismatch, errors, or the packaging being too big. This way the powder stays dry and stable," said Gill.

Supporting Emerging Technologies

Gill imagined that if Hilleman Labs were to decide to work with a start-up to jointly advance the uptake of heat-stable vaccines, the price of the innovation would be a significant hurdle. "In the developing world, affordability trumps innovation. Heat stability itself does not guarantee that the product would be successful or used if it makes it unaffordable." Gill also pointed out that if, by engineering heat stability, other attributes were compromised—the ease of handling, delivery, disposal of waste items—then the impact of the heat stability would be mitigated. "It depends on whether the heat stability is incremental or transformational. There are some vaccines on the market that are heat stable up to 30 days at 37 degrees Celsius. If there is a technology that extends to 35 to 60 days, that is incremental and not as impactful. If it goes for a year or two years, that's transformational," said Gill.

He had a final thought about the stakeholders that participated in global health. "It is important that they take a broader perspective on vaccine innovation because you can envision a technological innovation that may increase the procurement cost of the vaccine but that incremental cost gives you a feature that really significantly minimizes your systems cost. But it requires confidence and vision. Only then will we begin to see the real impact of these types of products," said Gill.

The Bill & Melinda Gates Foundation

The Gates Learning Foundation was established in 1997 by Bill Gates, the billionaire founder of Microsoft, and his wife Melinda with $200 million to enable every library in the United States to offer free Internet access to patrons. The next year, the Gates' made a gift of $100 million to a Seattle-based program to provide vaccines for children. In 2000, the Foundation—by then named the Bill & Melinda Gates Foundation (BMGF)—became a founding member of Gavi, pledging $750 million over 5 years. A 2006 gift of $30 billion, offered by investor and philanthropist Warren Buffett, effectively doubled BMGF's annual payouts.[15]

In 2015, BMGF funded $4.2 billion in grants for initiatives ranging from reducing homelessness to promoting communications technologies to support micro financing. BMGF had pledged $1.5 billion to Gavi for childhood immunization; $456 million for a malaria vaccine initiative, and $355 million to Rotary International to combat polio, among other health-related projects.[16]

Vaccine development was fundamental to BMGF's global health strategy. The organization was dedicated to ensuring that vaccines were available, affordable and accessible in low-income countries. BMGF also funded efforts to find new vaccines for diseases such as HIV, TB, and malaria. "This is fundamental to why the foundation was established and constitutes two-thirds of the resources that we spend in the global health program," said Hannah Kettler, Senior Program Officer with the Life Sciences Partnership team at BMGF.[n]

Tina Lorenson, program officer on the Vaccine Delivery Team's Market Dynamics Group at BMGF said they worked with partner organizations to make sure vaccines were not just efficacious, but appropriate for the settings in which they were to be used. "Heat stability is one factor, but so is presentation and delivery device," she explained. For example, auto-disabled syringes to prevent needle re-use and small containers and packaging, or "presentations" to reduce the vaccine product footprint in the cold chain. "Vaccine presentations should maximize ease of use and minimize safety risk without requiring a lot of training or re-training of health care staff. Use of visual cues and intuitive design should help to mitigate the potential for errors, such as using the wrong diluent to reconstitute a lyophilized vaccine," said Lorenson.

As a funding agency, BMGF prioritized developing tools for disease prevention and then looked for partners with the best science and research capabilities and made grants and investments to develop new vaccines for those diseases. "We set a goal of eliminating malaria, for instance, and within this broader disease strategy, vaccines, along with drugs and vector control products play a critical role," said Kettler.

For those diseases where vaccines were already available, such as pneumococcal disease and rotavirus, BMGF focused on innovative approaches to improve low-income country access to these products. "Gavi is one of our primary investments; they play a critical role procuring and supporting the uptake of life-saving vaccines. They are one stakeholder in the continuum of partners that work on vaccines from discovery through to delivery," said Kettler. Indeed, since 1999, BMGF had awarded $2.5 billion to Gavi to enable that organization to purchase vaccines for low-income countries. Even so, BMGF did not dictate how Gavi would use the funding. "We sit on their board

[n] Hannah Kettler and Tina Lorenson were interviewed by the case writer on February 29, 2016.

but we work as an alliance—Gavi, Unicef, Gates and other partners—to help make decisions about where that money gets spent. Gavi is autonomous," said Lorenson.

Providing Vaccines

GAVI's vaccine procurement system was designed to allow qualifying LMICs to request the vaccines and presentations that they preferred. "Countries cannot specify a specific vaccine brand, although, assuming adequate supply, countries are able to request, for example, a 2-dose versus a 3-dose regimen rotavirus vaccine," said Lorenson.

Lorenson explained that when Gavi provided vaccines, the country's out-of-pocket cost for a vaccine was the same regardless of the brand and of the price that was secured from the company in the tender process. Gavi paid the difference between the vaccine tender price and the country co-pay. "The co-pay is specific to a country's socio-economic status and should not vary based on the brand of the vaccine," said Lorenson.

BMGF was trying to encourage countries to be more aware of the properties of the vaccines they were procuring, to understand the implications certain vaccine presentations, schedules and formulations might have on cold chain and other immunization systems costs. "But because Gavi subsidizes the cost of vaccines as well as health systems costs, countries typically do not reflect on the most cost-effective presentation for their context until they begin to face graduation from Gavi funding," said Lorenson.

BMGF preferred vaccines that were heat stable or qualified for CTC environments because if there was a cold chain breach, healthcare workers could be more confident that the vaccine would still be effective. But unless all priority vaccines in the EPI schedule were heat stable, the country would still be dependent on the cold chain. CTC could be useful in a vaccine-specific campaign, for instance meningitis A or polio, so health workers could execute the entire outreach without ice, for example. "But all other things being equal, we do not see countries prioritizing CTC for vaccines used in routine immunization over other factors," said Lorenson.

Though the pharmaceutical companies could invest in improving the heat stability of their existing products, transitioning all products to be heat stable might necessitate adopting new spray drying or foam drying techniques.[o] "The compromise would be more heat-stability but potentially less useful products because to use the drying techniques, the vaccine will no longer be 'ready to go' in liquid form but will transition into a lyophilized format or foam dried format that needs to be reconstituted before use," explained Lorenson. The new formulation would likely not be compatible with a preservative and therefore multi-dose presentations would need to be discarded within 6 hours after reconstitution to avoid bacterial growth. In addition, this format might "increase the cold chain footprint" by having a diluent that would need to be stored at 2-8C with the lyophilized vial. Finally, to transition from a liquid vaccine to a foam dried or spray dried vaccine would mean investments in new equipment, and new technology that a pharmaceutical company may not have experience using.

[o] Most live virus vaccines (about one-quarter of vaccine doses) were lyophilized (freeze dried) because they were unstable. These needed to be reconstituted to be administered. The remaining vaccines were provided in liquid form. Lyophilizing carried risks; for example, if the health care worker used a diluent other than saline to reconstitute the vaccine.

The McKinsey Study

Around 2011, there were so many new vaccines being introduced that the supply chain was being threatened and BMGF knew they could not get vaccines to the last mile without appropriate transport and storage in place. However, many countries did not have a working grid infrastructure and in many places, lacked access to roads. BMGF staff asked: how can we improve that infrastructure to ensure vaccines get to people? They realized they could approach the problem from one of three angles: improve the logistics/supply chain infrastructure, improve the vaccines to reduce dependence on a strong cold chain infrastructure—or both.

BMGF funded McKinsey & Company, a global management consulting firm, to conduct an assessment of heat-stable vaccines (the findings were later published in the journal *Vaccine*[p] in 2015). "At the time, there were lots of technologies being developed that professed to create more heat-stable vaccines. The Foundation needed to decide whether to make a big bet," said Lorenson. McKinsey conducted a qualitative and quantitative assessment to help BMGF answer a fundamental question: which approach—systems or product—would be the most cost effective?

McKinsey concluded that heat stability would not completely eradicate the need for a cold chain so it would not justify the investment; BMGF could spend just as much money improving the cold chain to achieve an equivalent or better result which would service more than just one vaccine. Therefore, McKinsey recommended against reformulating existing vaccines to make them more heat stable. "They concluded it wasn't worth the time, the investment, or the new regulatory approval that would be needed," said Lorenson. For existing vaccines, McKinsey encouraged BMGF try to push their heat-stability profile and get them labeled for CTC if they were otherwise very stable vaccines. In addition, the firm recommended that BMGF try to strengthen the country supply chain to accommodate 2 to 8 degree vaccines. McKinsey did, however, recommend that pharmaceutical companies try to make new vaccines as heat stable as possible. As a result, BMGF decided to invest in cold chain development instead of making a "big bet" with product-specific heat stability.

After the study, BMGF discontinued the investments it had been making in new heat-stable technologies. "We are not investing directly into any type of platform technology that would improve the heat-stability of vaccines, but we are encouraging companies to push the envelope in heat-stability when they are involved in vaccine development," said Lorenson "We don't want manufacturers to slow down the timeline to formulate a vaccine to the optimal heat stability but we're encouraging development and stability testing and labeling for higher temperature storage situation," she said.

Supporting Emerging Technologies

Though BMGF planned to heed McKinsey's advice not to invest in heat-stabilizing platforms, the foundation did have an interest in seeing technology companies work with vaccine developers to "tackle the issues themselves, in collaboration with one another," said Lorenson. She admitted this approach might represent a challenge; vaccine manufacturers had an integrated product development plan and a specific timeline for development and if

[p] Christopher Karp, Deborah Lans, et.al., "Evaluating the Value Proposition for Improving Vaccine Thermostability to Increase Vaccine Impact in Low and Middle Income Countries," *Vaccine*, Volume 33, Issue 30, July 9, 2015, pp. 3471-3479.

incorporating a novel technology and formulation offset that timeline, then they might not be interested in incorporating it because it wouldn't differentiate their product significantly. Lorenson elaborated:

> The Gates Foundation can make investments in research and development and suggest a company produce a more heat-stable vaccine, but we're not on the procurement side. We're not defining differentiation for a preferred product over any others. And buyers like Gavi and Unicef—they cannot prefer one product over another either. They put forth a tender and each of the manufacturers comes back with a price for that tender but there's no differentiation in price based on whether a product is more or less heat stable. It begs the question of why would you differentiate and place your development timeline at risk if there is no way to recoup that additional investment?

BMGF was working with Unicef and Gavi to better define the overall cost of a vaccine, with a goal of encouraging those organizations to shift from focusing on price and volume to thinking about total system cost and total system effectiveness. "The Foundation was encouraging vaccine suppliers and technology developers to think more creatively about how to improve the manufacturing, distribution, storage and administration of a vaccine, and look beyond price only," said Lorenson. Kettler agreed. "There are few market incentives or demand for the [manufacturing] companies to investigate either cheaper ways of making a vaccine or improving a vaccine. It points to broader dysfunction within the vaccine market for lower- and middle-income countries," she said.

Vaxess' Challenge and the Dilemma Facing the Global Health System

The main challenges for a young company developing an early stage technology were very practical: how could Vaxess best commercialize an early stage technology? How should it allocate its very limited resources? "How do you get a novel technology from a lab to actually impacting lives–not just in wealthier countries like the US and Europe, but in places where the need for that technology might be greatest? It's certainly not the usual market mechanisms at work," said Valenti.

At the same time, as a private company, Vaxess had to consider the financial implications of its decisions. "We don't produce our own vaccine, so we are going to have to partner with a pharmaceutical company that makes those products," said Valenti. He knew it would be challenging, though, because he wanted a partner that would allow Vaxess to keep control over its technology; indeed, Vaxess wanted to potentially license its technology to multiple pharmaceutical companies. "But pharmaceutical companies tend to want exclusivity and then, they want exclusivity on multiple products," said Valenti. "It makes sense for them from a business point of view—to lock away a number of targets and reduce competition in the future, but from a public health and scientific point of view, it is against the public interest," he said. If there was a valuable heat-stable technology, it would make sense to make it available for use in all vaccines, not just in the vaccines produced by one large company.

But Vaxess had little leverage for negotiation. Its technology was promising, but at an early stage and not yet proven. It could not develop a heat-stable vaccine alone, without a large pharmaceutical company partner, and it did not have its own financing stream to invest in R&D, but rather needed to find investors. With little interest from the Gates Foundation, and no other non-profit R&D investor in the game, investment would likely need to

come from a private for-profit source. Given the constraints posed by the constellation of existing players in the vaccine ecosystem, what could Vaxess and Valenti do to move towards their vision of developing a technology to benefit populations in developing countries?

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