Vaccines

The anti-vaccination movement continues to make noise, but the Ebola scare has highlighted the role vaccines play in controlling diseases—and saving lives. **Joe Dysart** looks at the implications of the quest for an anti-Ebola vaccine, as well as the corporate shakeup in the vaccine sector.

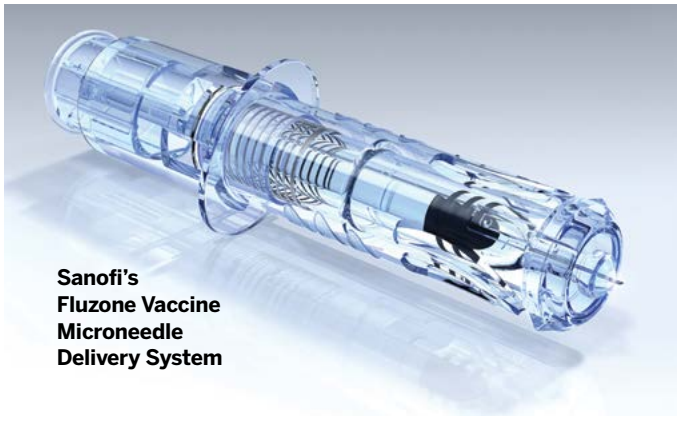
Despite the enduring controversy surrounding the anti-vaccination movement, the vaccines sector is gearing to roll out some world-changing treatments in the next year, most notably in the campaigns against Ebola and malaria.

Amid the ongoing Ebola scare, probably the most surprising global player has been Canada. During the summer, the country donated several hundred doses of an experimental Ebola vaccine, VSV-EBOV, to West Africa as part of an effort to beat back the disease.

A product of Canada's bioterrorism defense program, the experimental vaccine became a must-share after the country watched more than 1,400 people die of Ebola this summer, according to government officials. "Our government is committed to doing everything we can to support our international partners, including providing staff to assist with the outbreak response, funding and access to our experimental vaccine," says Rona Ambrose, Canada's Minister of Health.

Long-term, the vaccines industry—and the rest of a very concerned world—has its anti-Ebola hopes pinned on fast-tracked clinical trials co-developed by GlaxoSmithKline and the National Institutes of Health. The lightning-quick reaction "shows how private and public partners can pull together to respond to this critical public health emergency," says Dr. Moncef Slaoui, GSK's chairman of global R&D and vaccines. "Developing a new vaccine is complex, with no guarantees of success, and we're still in the early days for our Ebola vaccine candidate. But we are encouraged by the progress so far"

Funded by an international consortium, GSK has already begun ramping up a run of up to 10,000 doses, which it says will be deployed if clinical trials prove successful. "The tragic events unfolding in Africa demand an urgent response," says Adrian Hill, director of the Jenner Institute at the University of Oxford, another player in the worldwide effort to thwart what the US Centers for Disease Control has dubbed an international health emergency.



Sanofi's Fluzone Vaccine Microneedle Delivery System

GSK is also hoping to roll out an experimental malaria vaccine next year: RTS,S, the first vaccine of its kind and the product of nearly 30 years of research, according to Bruce Carlson, publisher, Kalorama Information. (See sidebar, p. 66.) GSK hopes to use the candidate treatment in a mass vaccination program across sub-Saharan Africa.

All told, it's been a historic year for the vaccine industry. Most notably, the sector saw one of its big players, Novartis, diminished this past spring via the $7.1-billion sale of most of its vaccine business to GSK. "The deal enables Novartis to shed its books of the flailing vaccines unit, which had operating losses in 2013," says Dr. Brian Whalen, vice president of science and medicine at Evoke Health. "GSK, on the other hand, is able to further bolster a strong current portfolio, as well as streamline its manufacturing and delivery systems."

With Novartis virtually gone from the vaccine space, that leaves only four major players—Merck, Sanofi, GSK and Pfizer—to divvy up the lion's share of the profits. Together, those companies command

between 77% and 82% of the global market, which generates $26 to $28 billion annually, according to Salim Shaikh, market research head, Transparency Market Research. Pfizer pulled a similar play earlier this year, gobbling up Baxter's portfolio of vaccines for $635 million—a move viewed as "strategically positive" by Credit Suisse.

"I believe that these players will continue to lead the market in a consolidated manner at least for another decade, either individually or through integration," Shaikh says. All four companies can look forward to the vaccines industry growing at a nice clip in 2015, likely at a compounded annual growth rate of 7% to 9%. That's somewhat better than the pharma industry's overall predicted growth rate for 2015 of 4% to 5%, Shaikh says.

Helping spur that growth will be the CDC's recommendation that Pfizer's Prevnar 13 vaccine be expanded for use by adults over the age of 65, according to Carlson. "Prevnar currently generates about $4.5 billion per year," Carlson says. "This indication expansion could generate an additional $2 billion. It could also spur other developers to examine indication expansions."

Meanwhile, Shaikh also predicts potential new revenues from in-development immuno-oncology vaccines. If successful, ongoing research could prompt a collaboration between Inovio, Roche and Immatics for the release of a DNA-based candidate vaccine (INO-5150, for the treatment of a number of cancers).

Other growth is expected in the wake of the FDA's decision this summer to license Novartis's manufacture of the first US cell-culture influenza vaccines in North Carolina. It's the first US facility of its kind to produce influenza vaccine—Flucelvax—without chicken eggs. "Cell-culture technology is the first major advancement in influenza vaccine production in the US in more than 40 years," says Andrin Oswald, division head, Novartis Vaccines.

A key advantage of the new manufacturing process is the ability to quickly ramp up production of Flucelvax during a pandemic. The US relied on the process last year to quickly stockpile H7N9, a vaccine that fights the avian influenza virus. That virus first surfaced in China in Spring 2013.

Vaccines are being bolstered by new delivery technologies as well. PharmaJet won FDA approval in August for its needle-free injection technology for vaccines and other treatments. The one-time-use injector delivers the vaccine via a narrow, precise, fluid stream that penetrates the skin in about one-tenth of a second. "This is a significant step forward in the effort to improve public health through broader immunization coverage," says Ron Lowy, PharmaJet's CEO.

Meanwhile, market researcher Lux Research predicts that a proliferation of patch delivery technologies should similarly boost vaccines. Currently, 81 clinical trials of patch delivery systems are underway. That should result in a sales jump for all patch-delivered treatments—including vaccines—of $6 billion by 2024, according to Lux. "A unique strength of transdermal patch delivery is the ability to deliver constant regulated levels of API (active pharmaceutical ingredient) for the treatment of chronic conditions," says Lux research director Kevin Pang.

Overall, the vaccine industry has evolved into something of a cozy sector, with "few instances of direct competition between two major vaccines with the same indication," says Whalen. Even so, the anti-vaccine movement, informally led by TV host Jenny McCarthy, is still impacting profits—not to mention the world of public health.

Despite the thorough repudiation of the fraudulent report published in *The Lancet* in 1998 that triggered the latest resurgence in anti-vaccine fervor, too many parents still place children at needless risk by turning their backs on scientifically proven treatments. Consequently, for too many diseases, the current rates of vaccination "are truly abysmal," says Jeffrey Levi, PhD, executive director

CLINICAL CORNER

After 30 years of research, GlaxoSmithKline is waiting for approval on what it says is the world's first vaccine that can prevent malaria, RTS,S. "This is a key moment in GSK's 30-year journey to develop RTS,S and brings us a step closer to making available the world's first vaccine that can help protect children in Africa from malaria," says Dr. Sophie Biernaux, head of GSK's malaria vaccine franchise.

Under evaluation by the European Medicines Agency and World Health Organization, RTS,S could be approved in 2015, Biernaux adds. "RTS,S has the potential to protect hundreds of thousands of children," says Robert Stein, chief scientific officer at Agenus, which contributed its QS-21 Stimulon adjuvant to GSK's vaccine.

Sophie Biernaux

GSK has the jump on Sanaria, which has been developing its own vaccine against the same parasite GSK's vaccine fights: Plasmodium falciparum, commonly found in sub-Saharan Africa. Last year, a Phase-I clinical trial of Sanaria's vaccine, PfSPZ, revealed that the treatment provided complete protection against malaria in 40 people.

"Scientists have struggled to produce an effective malaria vaccine for more than three decades," says Sanaria CEO Stephen Hoffman. "These results show that we have a safe, successful, injectable vaccine that has the potential to save millions of lives." Adds Dr. Adel Mahmoud, a Sanaria board member, Princeton professor and former president of Merck Vaccines: "This whole parasite vaccine, produced in a form that can be easily administered, is now shown to stimulate immunity with a clear-dose response, leading to full protection."

GSK is seeking approval of its vaccine for use in sub-Saharan Africa, where 90% of malaria deaths occur. Seventy-seven percent of those deaths are children under the age of five, according to Biernaux. All told, malaria claims more than 600,000 lives each year.

Biernaux says most sub-Saharan countries require approval of GSK's candidate vaccine by the EMA prior to its deployment. Supporting GSK's filing are results from a Phase-III vaccine trial, conducted at 13 African research centers in eight countries: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, Nigeria and Tanzania. More than 16,000 infants and young children participated in the study.

RTS,S works by attempting to trigger the body's immune system to defend against P. falciparum malaria. The reaction activates when the parasite enters the bloodstream and/or when the parasite infects liver cells. Essentially, the vaccine is designed to prevent the parasite from infecting, maturing and multiplying in the liver. In the Phase-III trial, RTS,S was administered in three doses, each a month apart.

GSK has led the overall development of RTS,S, investing more than $350 million so far and expecting to invest $260 million more during its development. Another $200 million-plus in funding has come from the Bill & Melinda Gates Foundation, and the PATH Malaria Vaccine Initiative has provided financial, scientific, managerial and field expertise.

of Trust for America's Health, a Washington, DC lobbying group.

Indeed, a 2014 report on vaccine rates for 2011-2012 released by the CDC revealed:

- Only 14% of adults aged 19 and older received the Tdap vaccination, which protects against tetanus, diphtheria and whooping cough
- Only 20% of adults aged 60 and older received the shingles vaccination
- Only 34.5% of women aged 19 to 26 received the human papillomavirus (HPV) vaccine.

One major battleground in the vaccine wars has been California, where a substantial segment of parents have rejected vaccines. As a result, more than 9,000 cases of whooping cough were reported in California in 2010—the highest number in more than 60 years, according to the California Department of Public Health. The disease, once thought to be all but eradicated in the United States, has continued to balloon in the state. Alarmed, California health officials have declared whooping cough an epidemic for 2014.

Spurring the rise of these preventable diseases are Washington, DC lobbying groups like the National Vaccine Information Center (NVIC), which has attempted to position vaccine requirements as a civil rights issue. Currently, the group has 58 bills pending in 24 states. It hopes to rid those states of laws that penalize individuals who refuse to comply with state-mandated vaccine programs.

"The right to exercise voluntary informed consent to medical risk-taking is a human and civil right," says Barbara Loe Fisher, NVIC co-founder and president. "We will speak out against all attempts to subject Americans to vaccine laws that allow doctors and government officials to bully and sanction citizens for making independent vaccination and other health choices for themselves and their children."

Taking the biggest hit from such efforts have been the makers of pediatric vaccines sold in developed nations. "It's products like MMR and polio," says Carlson. "But vaccines that are not required and still considered optional, such as HPV products, are also suffering."

Exasperated, many doctors are putting their feet down. According to "Pediatricians' Experience with and Response to Parental Vaccine Safety Concerns and Vaccine Refusals: A Survey of Connecticut Pediatricians," a 2011 study, more than 30% of Connecticut pediatricians told families who refused to vaccinate their children that they wouldn't take care of them.

Meanwhile, an August survey conducted by Sermo, a social network with more than 270,000 doctors, found that 79% of doctors thought unvaccinated children should be banned from public schools. "Few topics in modern medicine produce such impassioned arguments as vaccinations," says Sermo CEO Peter Kirk. Too, a July 2014 report released by Agency for Healthcare Research and Quality concluded what pharma companies and physicians have been telling vaccine-averse parents for years: adverse incidents associated with vaccine use in the US are extremely rare. "Vaccines are some of the safest medical products available, and our recommendations and use of them is based on an assessment of the benefits and the risks," says Bruce Gellin, MD, National Vaccine Program Office Director, US Department of Health and Human Services.

While the mainstream media has largely dismissed the anti-vaccine movement—*The Daily Show with Jon Stewart* titled its piece on the movement "An Outbreak of Liberal Idiocy"—some damage has been done. Industry insiders like Whalen concede it may be "impossible to un-ring" the vaccine scare-mongering bell. But the industry has to continue to try, he says. ■