

VACCINES

Vaccines are in vogue and practically taunting pharma with the potential of blockbuster price tags. But while big companies reign in the sector—largely due to cost- and resource-related barriers of entry—a handful of smaller players are taking a stab at creating vaccines for a narrowing field of unmet diseases, like RSV and *C. diff*. **Rebecca Mayer Knutsen** reports

The vaccines segment is seeing a jailbreak from the standard prophylactic mold in favor of trendy therapeutic vaccines—and demand for both needleless and generic vaccines is rising. Novel vaccines for new targets and improvements to existing vaccines will fuel growth. Forecast to top \$40 billion this year, the global vaccines business will record growth through at least 2020. US vaccine sales rose 22.2% in the 12 months to May, reaching \$7.5 billion, according to IMS Health.

Expanded applications in new categories include oncology and immunology. “Immunization is moving from an intervention in infancy to one that can help foster health and wellness throughout one’s lifetime,” notes Angela Hwang, regional head, US, Pfizer Vaccines.



Pfizer hopes to expand Prevnar 13, its pneumococcal vaccine, to include both ends of the age spectrum. Above, a still from a recent TV ad

Hardworking vaccines mimic an infection to teach the immune system how to eradicate it from the body. Composed of disabled antigens, or specific parts of the bacteria or virus, traditional vaccines stimulate the immune system’s B cells to produce antibodies. These protective substances are then tasked with killing germs that enter the body. Once activated, B cells stick around for life, continually recognizing and battling any evidence of the disease.

Topping the vaccines leader board are GlaxoSmithKline, Merck, Pfizer and Sanofi Pasteur. Novartis was on the periphery until it swapped away most of its vaccine assets for GSK’s oncology portfolio. CSL completed its purchase of Novartis’s flu business in April.

LifeSci Capital CEO Andrew McDonald recognizes a small uptick in mergers and acquisitions and consolidation strategies. “Early emerging technologies can help develop the next generation of vaccines,” he says. “Companies with innovative technology will be scooped up right away.” MedImmune made a play to acquire Inovio Pharma’s HPV immunotherapy INO-3112, while Takeda signed on the dotted line for access to Nanotherapeutics’ Vero cell technology platform.

McDonald has his eye on growth via sales and label expansion for high-value pediatric and adolescent vaccines. They include Merck’s prophylactic vaccine Gardasil for HPV types 6, 11, 16 and 18; Pfizer’s pneumococcal conjugate vaccine Prevnar 13; and GlaxoSmithKline’s Cervarix vaccine for HPV types 16 and 18.

Pfizer is making a push to expand Prevnar 13 for infants, the foundation of its business, to benefit more geographies and ages. The company’s portfolio is set to conquer new areas with a *Staphylococcus aureus* asset in Phase IIb trial enrollment and a *Clostridium difficile* asset in early development. Sanofi Pasteur is keeping Pfizer company on the *C. diff* development front with its vaccine in Phase III studies.

TOP 25 VACCINES

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales \$ (millions)	Vs. prior 12 mos.	TRx	Vs. prior 12 mos.	US DTC media \$ (000s)	Vs. prior 12 mos.	US journal media \$ (000s)	Vs. prior 12 mos.
1	Prevnar 13	Pfizer	\$1,611.9	92.0%	640,942	8728.4%	\$55,520.8	N/A	\$0.0	N/A
2	Gardasil	Merck	\$781.5	8.9%	38,990	-11.6%	\$380.3	-97.0%	\$0.0	N/A
3	Zostavax	Merck	\$743.3	8.5%	2,251,490	3.6%	\$1,283.8	-87.0%	\$253.0	N/A
4	Varivax	Merck	\$591.5	22.3%	39,954	52.8%	\$0.0	N/A	\$0.0	N/A
5	Pneumovax 23	Merck	\$512.1	7.1%	852,535	9.7%	\$0.0	N/A	\$272.0	220.3%
6	Proquad	Merck	\$391.7	45.9%	612	841.5%	\$0.0	N/A	\$0.0	N/A
7	Adacel TDAP	Sanofi	\$333.7	27.7%	324,395	78.2%	\$0.0	N/A	\$0.0	N/A
8	Menactra	Sanofi	\$305.5	4.7%	38,335	34.5%	\$0.0	N/A	\$0.0	N/A
9	Boostrix TDAP	GlaxoSmithKline	\$256.3	-14.3%	514,488	11.4%	\$0.0	N/A	\$0.0	N/A
10	Rotateq	Merck	\$233.9	6.9%	142	-13.9%	\$0.0	N/A	\$114.0	22.3%
11	M-M-R-II	Merck	\$225.5	20.9%	62,338	116.1%	\$0.0	N/A	\$0.0	N/A
12	Pentacel	Sanofi	\$185.4	17.3%	267	1113.6%	\$0.0	N/A	\$0.0	N/A
13	Engerix-B	GlaxoSmithKline	\$163.0	3.9%	110,406	16.5%	\$0.0	N/A	\$0.0	N/A
14	Pediarix	GlaxoSmithKline	\$149.9	24.5%	207	111.2%	\$0.0	N/A	\$0.0	N/A
15	Havrix	GlaxoSmithKline	\$112.7	2.0%	67,356	-8.0%	\$0.0	N/A	\$0.0	N/A
16	Menveo	GlaxoSmithKline	\$98.9	8.2%	61,329	-7.9%	\$0.0	N/A	\$0.0	N/A
17	Recombivax HB	Merck	\$89.3	27.8%	26,771	124.8%	\$0.0	N/A	\$0.0	N/A
18	Vaqta	Merck	\$85.6	2.0%	10,323	144.7%	\$0.0	N/A	\$0.0	N/A
19	Rotarix	GlaxoSmithKline	\$65.7	-1.5%	56	5.7%	\$0.0	N/A	\$0.0	N/A
20	Twinrix	GlaxoSmithKline	\$60.7	-9.9%	45,973	16.1%	\$0.0	N/A	\$0.0	N/A
21	Ipol	Sanofi	\$52.2	-7.3%	7,067	531.0%	\$0.0	N/A	\$0.0	N/A
22	Typhim VI	Sanofi	\$47.2	16.5%	34,733	111.7%	\$0.0	N/A	\$0.0	N/A
23	ActHIB	Sanofi	\$44.5	-24.5%	1,614	74.7%	\$0.0	N/A	\$0.0	N/A
24	RabAvert	Novartis	\$42.3	25.9%	3,346	35.3%	\$0.0	N/A	\$0.0	N/A
25	Ixiaro	Novartis	\$40.4	242.4%	3,827	47.3%	\$0.0	N/A	\$0.0	N/A

Sources: Sales, IMS Health; DTC media spend, Nielsen; journal media spend, Kantar Media Sales, TRx and journal data run from June 2014-May 2015; Nielsen data run from January-June 2015

Approval of the HPV vaccines duo was a win-win for the industry, says Victor Cohen, associate professor at Arnold & Marie Schwartz College of Pharmacy and Health Sciences. “Their development was the first instance of cancer cross-walking in the vaccines realm.”

Merck and Glaxo raced to win first-to-market bragging rights for HPV. Merck was the clear winner—gaining marketing approval with a superior product three years in advance of Cervarix—and continues to benefit from its first-to-market status, Berkeley Research Group managing director Edward Buthusiem notes. Capturing market share, especially for specialized disease vaccines, permits the company to charge a premium, he says. Gardasil raked in \$1.74 billion in global sales in 2014.

The additional challenge is that most of the easy targets have been satisfied. “These diseases already have effective vaccines on the market,” says Jim Tartaglia, VP at Sanofi Pasteur, the vaccines branch of Sanofi. “There is no low-hanging fruit.”

Explosive growth, says LifeSci Capital’s director of research Jerry Isaacson, will come from the shift to therapeutic vaccines as well as from vaccines for cytomegalovirus (CMV), one of the herpes viruses, and respiratory syncytial virus (RSV). VBI Vaccines’ lead asset is a prophylactic CMV vaccine. Several companies, including Mucosis BV and Novavax, are chipping away at RSV (see Clinical Corner, p. 70).

Hard targets

In the shadow of an Ebola outbreak that ravaged Sierra Leone last year, the race is now on to come up with an Ebola vaccine. A GlaxoSmithKline and NIH vaccine appears to be the front-runner, with Merck Vaccines USA and NewLink Genetics’ VSV-EBOV nipping at its heels. Other contenders include Novavax’s recombinant

protein vaccine and J&J and Bavarian Nordic’s two-dose vaccine.

Despite their potential money-making ability, vaccines for the diseases in need of them will be no walk in the park, development-wise. Developing a vaccine for dengue, for example, involves key scientific challenges, including covering four serotypes in the formulation. Sanofi Pasteur’s dengue vaccine met that challenge, however, and is staring down registration and market launch by year’s end.

“The vaccine targets that remain face increasing scientific, technical and regulatory challenges, all of which add cost and time to the development timeline,” Tartaglia explains.

Sanofi Pasteur’s life-cycle management strategy includes enhancing its current vaccines to address evolving epidemiology and extending population coverage. Its Fluzone high-dose influenza vaccine, for example, addresses the weakened immune systems of those 65 years and older.

A Scripps Research Institute and Janssen Pharmaceutical study points to the possibility of one day eliminating the age-old process of formulating a new flu vaccine year after year. Research of the informally dubbed “universal flu vaccine” has shown success in an animal model in targeting hemagglutinin, a protein on the surface of influenza, which appears across all flu subtypes.

Vaccine delivery methods are due for a modern makeover as well. According to Cohen, the intranasal route is a high service area because it’s not systemic, plus it adds a convenience factor for those with a needle phobia. MedImmune’s quadrivalent nasal spray vaccine FluMist and CSL Behring’s trivalent vaccine Afluria are two needle-free options.

Cohen is most fascinated with the intratumoral vaccines in development. “The vaccines aren’t systemic—but cancer is. So researchers



CLINICAL CORNER

Things are heating up on the RSV vaccine development front. Why the commotion? Two reasons: The virus has stymied research efforts for years and the first-to-market winner will likely have a blockbuster.

The race to bring a respiratory syncytial virus (RSV) vaccine to market is important. As a respiratory virus that infects the lungs and breathing passages, RSV can cause serious problems in infants, older adults and the immunocompromised. RSV has widespread implications; almost all children endure an RSV infection by their second birthday. “Most patients can have a cold and there’s no problem,”



Tom Johnston

says Victor Cohen, associate professor at Arnold & Marie Schwartz College of Pharmacy and Health Sciences. “Infants and the immunosuppressed are the ones at risk for RSV.”

Many challenges have nearly derailed the decades-long fight to create a RSV vaccine, including the need to step outside the standard mouse/rat species used in lab research. “Classically, vaccines have been inactive forms of the virus,” says Jerry Isaacson, director of research for LifeSci Capital. “It’s been difficult to create RSV vaccines in that way. The vaccines in development still have some technological work to be done.”

Novavax and MedImmune both received FDA fast-track designation. In a Phase II trial with 1,600 adults ages 60 and older, a Novavax study showed a 40% to 60% reduction in cases of bronchitis and pneumonia. To put that in context, a 60% efficacy rate has the potential to wipe out those diseases in 18 million children worldwide each year. The Novavax candidate is also being assessed in infants via maternal immunization in a Phase II trial involving pregnant women.

MedImmune, AstraZeneca’s biologics arm, launched Phase I trials for its vaccine candidate MEDI8897 with healthy adults and a Phase Ib/Ia study in healthy preterm infants. The company needs to bring a next-generation RSV treatment to market as Synagis, its blockbuster monoclonal antibody for high-risk infants, loses its patent this year.

Bavarian Nordic recently launched a Phase I trial of its RSV vaccine candidate MVA-BN RSV, and researchers at Georgia State University believe recombinant engineered nanoparticle vaccines could induce long-term protection against RSV. Dutch biotech Mucosis is taking a different approach: Its intranasal RSV candidate SynGEM activates mucosal defenses. According to Tom Johnston, CEO, Mucosis BV, the stabilized recombinant vaccine is suitable for complex multimeric antigens and multiple routes of administration, including intranasal or oral application for children, pregnant women or the elderly population.

The vaccine relies on Mucosis’ Mimopath technology, a needle-free mucosal vaccine platform that converts non-recombinant bacteria into nonliving, nontoxic, bacterium-like particles (BLPs) that can be tethered on its surface with various types of antigens. The BLP technology aims to elicit locally secreted IgA in the mucosal layers along with a balanced Th1/Th2-type of systemic immune responses that are protective. SynGEM will enter human proof-of-concept studies in 2016.



are determining whether they elicit the pro-inflammatory response,” he says. “It’s an exciting area that has real potential.”

Combination vaccines are also gaining momentum and winning the favor of patients, although they come with their share of challenges. “When combining two or more monovalent vaccines, it’s imperative that the final product produce the same antibody level in the blood as monovalent vaccines,” Buthusiem adds.

If Merck and Sanofi Pasteur’s pediatric hexavalent vaccine Hexaxim gets the green light from the FDA, it will be the first pediatric combo vaccine to protect against six diseases. The full list: diphtheria, tetanus, pertussis, polio, invasive disease caused by *Haemophilus influenzae* type b and hepatitis B.

The therapeutic vaccine market is evolving rapidly and garnering lots of interest with its promising application in several therapy areas. With Dendreon’s Provenge, an immunotherapy for prostate cancer presiding over the category as the lone therapeutic vaccine, the field is wide open.

“Companies will need the right partnerships to bring these vaccines to light,” Tartaglia says. “We’re keeping our eyes open and looking at immunotherapy in the context of overall disease management.”

The category is attracting pharma investments in droves because of the inherent flexibility in market prices. Preventative vaccines charge a premium that’s tied to the number of people likely to be vaccinated, Buthusiem explains. “The pricing model for therapeutic vaccines, however, will be similar to drug treatments. The return is much higher.”

Current research might pave the way for a solution to the war on cancer. Instead of using therapeutic vaccines as intended, Cohen proposes their eventual use as prophylactic vaccines against cancer. “Can we use some of the procedures being developed to vaccinate the population against cancer?” he asks. “We’re not at that point, but it would be a home run. Numerous complex immune considerations could prevent the strategy from working.”

Anti-Vaxxer fallout

In recent years the necessity of vaccines has given rise to an emotionally charged debate. Anti-vaccine groups fixated on a study linking vaccination to autism as well as conspiracy theories based around financial gains for doctors and pharma companies advocating vaccines. Although these theories have been debunked, small pockets of anti-vaccinators march on.

“Revitalized public attention hasn’t affected R&D, which has been continuously steady, but it has reinforced the need for safe, effective and accessible vaccines,” Tom Johnston, CEO, mucosal vax maker Mucosis BV, says. He points to the development of intranasal vaccines as an example of the industry addressing adoption and compliance issues.

The question remains whether this type of hot-button awareness can be parlayed into better, more effective marketing messages. “The Internet is the great equalizer,” notes Sean Trapani, VP of creative at Discovery USA. “Not only is content readily available, but it’s also consistently judged, evaluated and shared by the people who impact the consumer’s life most profoundly: friends and family.”

Trapani believes the debate creates an opportunity for pharma to influence those facing a choice. “Vaccine manufacturers must actively contribute to the conversation, through their own channels and advocates, to help balance the scales of information and influence,” he concludes. ■