

Vaccines

While public health agencies see eye-to-eye with industry on the need to inoculate, vaccination rates among some patient groups remain stubbornly low. **Noah Pines** on what this means for drug makers, and other areas where industry is rolling up its collective sleeves in an effort to get patients to roll up theirs

Unlike babies, you just can't hold teens or adults down and vaccinate them. As a result, vaccinations for many preventable illnesses remain stubbornly low, despite a massive effort by drug makers and public-health officials to educate the community.

For example, Merck and GlaxoSmithKline have fought an uphill, politically charged battle to persuade the parents of teenage girls and boys to get them vaccinated against human papillomavirus (HPV), which is the most common sexually transmitted infection and is associated with several types of cancer, especially cervical.

While progress is being made in getting more boys vaccinated—CDC data published in July show that 21% received Merck's Gardasil in 2012, up from 7% in 2011—the rate among girls is leveling off. “We're dropping the ball,” the CDC's director, Thomas Frieden, MD, said in July. As to possible reasons why, data from a survey of parents, which appeared in *Pediatrics* in 2011, indicated that over half of US girls ages 13 to 17 had not gotten even one dose of

HPV vaccine due to poor awareness (19.4%) and the failure of doctors to recommend vaccination (13.1%).

These conversations parents are expected to have with their teens can be uncomfortable, and a

strong doctor recommendation could help, says Krista Geller, MD, a pediatrician and VP, medical director at IPG's ICC Lowe. “The physician-caregiver dialogue regarding the rationale and importance of HPV vaccination is a platform for pediatricians to model a responsible approach to difficult conversations.”

Still, “people view Merck's Gardasil as an innovative product, and it's back on a growth trajectory,” Bernstein Research analyst Tim Anderson, MD, tells *MM&M*. “The challenges have been political issues, and then compliance in terms of getting all three shots. A lot of that is in the rearview mirror, though.”

Gardasil, he wrote in a July investor note, benefits from uptake in males in the US but “Japan's recent decision to suspend recommending immunization of girls with Gardasil will have a clear, negative impact in 2013 (Gardasil sales in [Japan] were \$140M in 2012).”

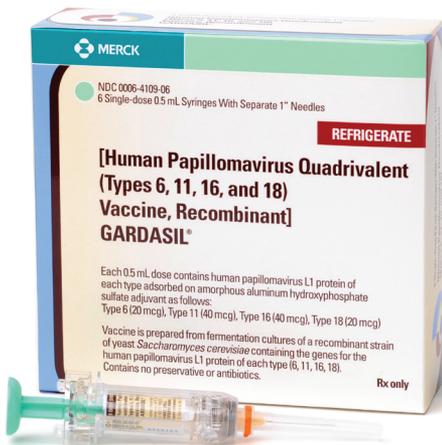
Pfizer's Prevnar 13—its follow-up to Prevnar 7 launched in 2009 and now the most widely used pneumococcal conjugate vaccine (PCV) in the world—may also have an opportunity to expand.

Having helped reduced rates of everything from meningitis to ear infections in children, Prevnar 13, hopes Pfizer, might prevent community-acquired pneumonia in adults. It's conducting an 84,000-patient study, dubbed CAPiTA, with a read-out expected in early 2014.

“A lot is riding on CAPiTA,” says Anderson. “Every analyst has adult usage built in over time. There's not a whole lot else available, [and] the adult population is not insignificant.”

Marketers of seasonal influenza vaccine face a different hurdle—differentiation. Martin Mannion, EVP, director of strategy and branding at ICC Lowe, whose clients have included Sanofi Pasteur, adds, “One of the most common challenges vaccines specifically struggle with during their marketing lifecycles is commoditization (whether real or perceived) in the minds of healthcare professionals.”

Manufacturers are rolling out new options for 2013-2014, especially



TOP 50 VACCINES, 2012

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

Rank	Product	Manufacturer	US sales \$ (000s)	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	Pprevnar 13	Pfizer	\$810,134.5	-0.1%	2,198.0	>100.0%	\$0.0	-100.0%	\$599.0	-29.6%
2	Zostavax	Merck	\$477,815.5	>100.0%	2,236,063.0	>100.0%	\$46,037.1	>100.0%	\$11.0	N/A
3	Pneumovax 23	Merck	\$307,471.4	23.3%	472,772.0	50.84%	\$0.0	N/A	\$1,123.0	N/A
4	Engerix-B	GlaxoSmithKline	\$212,333.8	-7.3%	53,253.0	8.21%	\$0.0	N/A	\$0.0	N/A
5	Fluvirin 2012-2013	Novartis	\$208,715.4	N/A	6,878,150.0	N/A	\$0.0	N/A	\$0.0	N/A
6	Havrix	GlaxoSmithKline	\$159,545.5	-24.1%	33,048.0	20.79%	\$0.0	N/A	\$0.0	N/A
7	Gardasil	Merck	\$137,436.9	32.5%	38,707.0	9.14%	\$43,659.7	-1.0%	\$0.0	N/A
8	Twinrix	GlaxoSmithKline	\$101,964.9	-4.0%	26,055.0	33.87%	\$0.0	N/A	\$0.0	N/A
9	Fluarix 2012-2013	GlaxoSmithKline	\$96,514.9	N/A	31,539.0	N/A	\$0.0	N/A	\$0.0	N/A
10	Menactra	Sanofi Pasteur	\$93,200.4	8.5%	40,644.0	>100.0%	\$0.0	N/A	\$0.0	N/A
11	Fluzone 2012-2013	Sanofi Pasteur	\$82,817.0	N/A	3,239,155.0	N/A	\$19,340.1	100.0%	\$0.0	N/A
12	FluLaval 2012-2013	ID Biomedical	\$81,050.4	N/A	92,644.0	N/A	\$0.0	N/A	\$0.0	N/A
13	M-M-R II	Merck	\$75,903.0	19.7%	18,498.0	68.59%	\$0.0	N/A	\$0.0	N/A
14	Varivax	Merck	\$73,588.0	20.1%	15,649.0	94.83%	\$0.0	N/A	\$0.0	N/A
15	Rotarix	GlaxoSmithKline	\$71,255.7	-40.4%	33.0	>100.0%	\$0.0	N/A	\$0.0	-100.0%
16	FluMist	MedImmune	\$55,224.5	2.8%	14,550.0	25.16%	\$3,153.7	-28.0%	\$147.0	N/A
17	Recombivax HB	Merck	\$51,198.5	11.3%	6,740.0	52.83%	\$0.0	N/A	\$0.0	N/A
18	Afluria	CSL Ltd.	\$44,942.3	N/A	1,956,954.0	N/A	\$0.0	N/A	\$0.0	-100.0%
19	RotaTeq	Merck	\$41,606.4	5.2%	257.0	-25.07%	\$0.0	N/A	\$239.0	-5.8%
20	Fluzone High-Dose 2012-2013	Sanofi Pasteur	\$41,376.4	N/A	1,378,844.0	N/A	\$0.0	N/A	\$40.0	-61.9%
21	Rabavert	Novartis	\$38,475.6	12.3%	1,939.0	15.97%	\$0.0	N/A	\$0.0	-100.0%
22	Typhim VI	Sanofi Pasteur MSD	\$34,903.6	-5.6%	19,856.0	45.64%	\$0.0	N/A	\$0.0	N/A
23	Menveo A-C-Y-W-135-Dip	Novartis	\$21,491.2	176.9%	106,243.0	>100.0%	\$0.0	N/A	\$0.0	N/A
24	Ipol	Sanofi Pasteur	\$18,875.5	2.4%	4,471.0	41.89%	\$0.0	N/A	\$0.0	N/A
25	Imovax Rabies Vaccine	Sanofi Pasteur	\$15,157.1	-11.0%	1,651.0	20.78%	\$0.0	N/A	\$0.0	N/A
26	Pentacel	Sanofi Pasteur	\$14,839.3	-49.6%	192.0	-12.73%	\$0.0	N/A	\$119.0	-74.7%
27	Act-HIB	Sanofi Pasteur	\$10,397.3	21.4%	792.0	74.45%	\$0.0	N/A	\$0.0	N/A
28	Vivotif Berna	CruceCell	\$10,305.8	17.2%	142,352.0	7.44%	\$0.0	N/A	\$0.0	N/A
29	Vaqta	Merck	\$8,561.7	62.1%	757.0	57.05%	\$0.0	N/A	\$0.0	N/A
30	ProQuad	Merck	\$7,259.4	60.5%	11.0	>100.0%	\$0.0	N/A	\$28.0	N/A
31	PedvaxHIB	Merck	\$5,664.1	45.5%	95.0	5.56%	\$0.0	N/A	\$0.0	N/A
32	Fluvirin 2011-2012	Novartis	\$4,982.5	-97.3%	225,882.0	-96.47%	\$0.0	N/A	\$0.0	N/A
33	Fluzone 2011-2012	Sanofi Pasteur	\$3,547.3	-95.2%	155,379.0	-94.48%	\$0.0	N/A	\$0.0	N/A
34	Menomune A-C-Y-W-135	Sanofi Pasteur	\$3,469.7	22.8%	5,498.0	74.60%	\$0.0	N/A	\$0.0	N/A
35	Cervarix	GlaxoSmithKline	\$3,389.0	>100.0%	131.0	-41.78%	\$0.0	N/A	\$0.0	-100.0%
36	Fluzone Intraderm. '12-'13	Sanofi Pasteur	\$2,951.4	N/A	100,722.0	N/A	\$0.0	N/A	\$0.0	N/A
37	Fluzone Pedi 2012-2013	Sanofi Pasteur	\$1,527.9	N/A	333.0	N/A	\$0.0	N/A	\$0.0	N/A
38	Ixiaro	Novartis	\$1,238.1	-74.1%	1,228.0	>100.0%	\$0.0	N/A	\$0.0	N/A
39	YF-VAX	Sanofi Pasteur	\$1,168.8	75.7%	12,476.0	61.48%	\$0.0	N/A	\$0.0	N/A
40	Fluarix 2011-2012	GlaxoSmithKline	\$572.5	-99.4%	1,273.0	-96.57%	\$0.0	N/A	\$0.0	N/A
41	Fluzone 2011-2012 (PF)	Sanofi Pasteur	\$350.6	-98.9%	47,030.0	-96.85%	\$0.0	N/A	\$0.0	N/A
42	Afluria 2011-2012 (PF)	Merck	\$247.8	-97.4%	21,084.0	-96.97%	\$0.0	N/A	\$0.0	N/A
43	Fluvirin	Novartis	\$246.0	-97.1%	466.0	-99.87%	\$0.0	N/A	\$0.0	N/A
44	BCG (TICE strain)	Merck	\$160.2	-98.0%	1,825.0	-3.18%	\$0.0	N/A	\$0.0	N/A
45	Fluzone High-Dose '11-12 (PF)	Sanofi Pasteur	\$91.5	-99.5%	4,823.0	-99.31%	\$0.0	N/A	\$0.0	N/A
46	COMVAX	Merck	\$88.7	-32.8%	5.0	N/A	\$0.0	N/A	\$0.0	N/A
47	Afluria 2011-2012	Merck	\$82.7	-98.1%	3,665.0	-95.95%	\$0.0	N/A	\$0.0	N/A
48	Afluria	Merck	\$59.1	-91.1%	189.0	-99.58%	\$0.0	N/A	\$0.0	N/A
49	Fluzone Intradermal	Sanofi Pasteur	\$25.4	-68.0%	808.0	-77.43%	\$0.0	N/A	\$1,160.0	N/A
50	Fluzone	Sanofi Pasteur	\$23.9	-99.0%	258.0	-99.74%	\$0.0	N/A	\$0.0	N/A

*Integrated manufacturer benchmark sales (MBS); sales data reflect a subset of total market for each product (audit includes retail, non-retail and institutional but not government and some private distribution channels), and should be used for ranking purposes only

Sources: Sales/TRx: Symphony Health Solutions; DTC media spend, Nielsen; journals, Kantar Media



CLINICAL CORNER

In 1984, Margaret Heckler, HHS head under Ronald Reagan, said that there would be an HIV vaccine available within two years. Almost 30 years and 35 million or so infections later, it hasn't happened yet.

But there have been green shoots. In September, Dr. Louis Picker at the Oregon Health & Science University published a study in *Nature* demonstrating how a novel experimental vaccine tested in 16 monkeys infected with the simian version of HIV not only protected nine of them, but also actually may have cured them.



Ian Frank

"The thing about Picker's strategy which may have been effective is that it did not result in general immune activation the way other vaccines do," notes Dr. Ian Frank, director of the Clinical-Therapeutics Program of the University of Pennsylvania Center for AIDS Research, and director of Penn's clinical trial unit of the HIV Vaccine Trials Network.

Why has developing an HIV vaccine been so elusive? Frank enumerates three main barriers.

"First, the infection is incredibly diverse," he says. Second, HIV has a latency period that, once established, precludes any vaccine from doing its job. And third, since HIV replicates in activated lymphocytes, activating the immune system may produce the opposite effect.

There have been encouraging signs, including two documented cases where HIV appears to have been cured. In the first, a man with HIV received a stem-cell transplant after developing leukemia. The donor had a rare gene mutation that confers resistance to HIV, and the patient has not needed antiretroviral (ARV) medication since 2007.

"So do we treat all people with HIV with chemotherapy?" posits Frank. "The problem with that is that some people die from getting the kinds of cancer chemotherapy that wipes out your immune system."

In the second case of functional cure, a baby born with HIV was treated with ARV drugs within hours of birth. Despite detectable virus initially, the baby was essentially HIV-negative after five months.

Among a number of anomalies, Frank says, "The most unusual thing is that in general, when kids are infected in utero they end up having very high viral loads and being pretty sick at the time of their birth. This baby's mother had a low viral load," due possibly to genetics.

Also, because HIV replicates in activated memory lymphocytes, "and newborns do not have a lot of memory cells," says Frank, the baby may "never [have] had a latent reservoir of cells that were infected."

More recently, a vaccine called RV 144 displayed modest benefit, including a specific immune response, that is leading to some optimism. Still, another vaccine study, the ACTG 505 study, failed in humans after showing some benefit in animals.

"A bottom line is that humans are not monkeys," says Frank, who adds "and a vaccine that works in non-human primate models does not mean it will work in humans."



quadrivalent (i.e., four-strain coverage) vaccines. These new options—being developed by GSK, Sanofi, and AstraZeneca—are expected to provide better protection but may face supply headwinds. Trivalent influenza vaccines have been the mainstay since the 1980s but build protection against only two influenza A strains and one influenza B strain. In addition to those options, Novartis and Protein Sciences are preparing egg-free varieties for adults with egg allergies. Earlier in the year, FDA approved Flublok, Protein Sciences' "outside of the [egg] shell" flu jab.

Sanofi is another firm striving to differentiate. A recent study demonstrated that its high-dose formulation of Fluzone offered superior protection in a set of patients 65+. The company plans to submit the data to the FDA by early next year.

Notwithstanding the challenges inherent here—vaccination rates remain below 40%, says Marco DiBonaventura, PhD, VP at Kantar Health. "There is belief that influenza vaccines are not effective," he says—the vaccine "represents a unique entity in the 'dreaded' vaccine arena," adds ICC Lowe's Geller. "Many have experienced the illness...and so they understand the benefits of prevention." Still, physicians will have to ensure that patients understand their level of risk, help manage expectations and minimize confusion, she says.

In pipeline news, Novartis is developing a meningitis B vaccine, Bexsero, considered to be a substantial advance. However, Anderson notes, "the commercial potential for this product is less clear given the low overall incidence of meningitis B. In the US the product has been delayed because of a more complicated regulatory pathway."

And Sanofi is gunning for an inoculator against dengue, a mosquito-borne illness which represents the fastest-growing tropical disease threat in the world, according to WHO figures. Analysts, however, are less sanguine that it will succeed after it produced mixed results in a Phase IIb where the vaccine did not work against one of the major serotypes in infected patients. And it could have trouble commercially. ("It's hard to see how you sell that at a premium to the countries who need it most," says Anderson.)

And then there are the so-called cancer vaccines. Despite a great deal of hype going into 2013, GSK's novel melanoma-associated antigen 3, or MAGE-A3, vaccine recently hit a snag—it failed to help melanoma patients.

While MAGE-A3 has been trumpeted as a promising area of research designed to encourage a patient's own body to recognize and eliminate cancer cells, the trial missed its first co-primary endpoint after failing to outperform a placebo in a Phase III trial of 1,345 melanoma patients. GSK plans to continue the study to determine whether the medication helped patients with a specific genetic profile.

Following lung-cancer data next year, the gene-specific biomarkers piece won't come out until 2015 but is more crucial to MAGE-3's future, says Anderson. "Even if [it works] in that gene-signature subset, it would be meaningful. A grand total of zero products have worked in terms of cancer vaccines (despite lots of attempts). If you work in melanoma, you start to wonder in other tumor types."

Indeed, "Despite the GSK setback and the fact that [Dendreon prostate cancer drug] Provenge has not really lived up to expectations, there is a lot of hope and excitement around cancer vaccines," says Marc Engelsjerd, MD, from *inThought*, a part of Symphony Health Solutions.

He likes Amgen's melanoma program, T-VEC, which he says has shown "an impressive increase in the response rate as compared to the control group. What we have not seen is the overall survival data." ■