



HPV Vaccination Compliance

Global Review of HPV Compliance Programs

Jean Steckler, Senior Vice President

February 2010

Table of Contents

I	Executive Summary.....	4
II	Background	5
	Pricing.....	6
III	Markets.....	7
	A. GARDASIL Footprint	7
	B. CERVARIX Footprint	7
IV	The HPV Vaccine Pipeline	8
	A. HPV-L2.....	8
	B. Inovio Biomedical’s VGX	8
V	Opportunities.....	8
	A. Improve Compliance Rates	9
	1. Baseline Compliance Rates	9
	2. HPV Compliance Research	9
	3. Ethnicity Differences in HPV Vaccine Compliance	9
	4. Socio-economic Differences.....	10
	5. Geographic Differences.....	11
	B. Expand Coverage.....	11
	C. Formulary Adoption.....	11
VI	Current Compliance Programs.....	13
	A. United Kingdom	13
	B. Scotland.....	13
	C. Australia / CSL Biotherapies.....	13
	D. Switzerland - Hôpitaux Universitaires de Genève	14
	E. Finland.....	14
	F. Germany.....	14
	G. United States.....	15
	1. State and Federal Immunization Information Systems	15
	2. School-based health centers (SBHC).....	15

3.	University of Pennsylvania, Philadelphia, Pennsylvania	15
4.	Parkland Health & Hospital System, Dallas, Texas.....	16
5.	Columbia University Research on Parental Readiness for Text Message Reminders.....	16
6.	Merck’s US-based GARDASIL Compliance Programs.....	16
7.	CERVARIX US-based Adherence Programs	19
VII	Best Practices & Recommendations	19
	Comprehensive Adherence Program	19
1.	Automated and Tracked Vaccination Reminders and Confirmations.....	19
2.	Support for Varied Stakeholders.....	20
3.	Multiple Methods of Communication.....	20
4.	Ethnic-centric Programs.....	20
5.	Socio-economic Programs.....	21
6.	Program Evaluation.....	21
VIII	Sources.....	22

HPV Vaccination Compliance

I Executive Summary

In the four years that the three-dose HPV vaccines have been available, rates of compliance have varied widely across the world. Rates have been as high as 92% for the first dose and 87.8% for the second dose (Scotland) and as low as 15.8% (Mississippi, USA). There is a public health imperative to close this gap.

While many compliance programs exist, it is clear that they are not equally successful. In this white paper, we review the research that has been conducted on U.S. and international HPV vaccine compliance programs. We also discuss the recommendations of the American Immunization Registry Association. Based on this review, we provide a list of best practices and recommendations for HPV vaccine compliance programs.

The most effective HPV vaccine compliance programs share the following qualifications:

- **Automated and Tracked Vaccination Reminders and Confirmations**

Automated reminder and follow-up messages are effective in increasing compliance levels by 5% to 20%. Reminder notifications for the second and third doses are scheduled from two to four weeks before the recommended due date for each dose. The best systems make multiple attempts to reach patients until they report that they have received the vaccination and that any specific issues around the treatment have been resolved.

- **Use of Multiple Enrollment Methods**

A simple, single technology that supports multiple enrollment methods is highly efficient and produces more accurate data. Patients can enroll themselves or be enrolled at their physician's office. The latter enables physicians to track patient progress. Successful national health reminder services, available in Europe, demonstrate the benefits that can be realized when payers (managed care) enroll members and track vaccine compliance. Public health initiatives also are effective.

- **Privacy**

To protect privacy, successful vaccine compliance programs request minimal patient information, such as name, at least one contact method to send reminders, and the date of the first dose. Phone call authentication is used to ensure that only the patient receives the reminder message.

- **Multiple Delivery Methods**

The best of breed systems provide seamless, integrated SMS/Phone/Email/Mail reminders and follow-ups. Patients identify the best place(s) to reach them, and if they are not reached at the first location, these systems automatically escalate to the patient's next preferred method of contact.

- **Ethnic-centric Programs**

Programs that specifically address ethnic issues improve patients' three-dose completion rates. Notifications produced in the language preferred by the patient are highly effective. Similarly, campaigns that include celebrities popular in a given age bracket and culture are successful means for reaching adolescents in diverse ethnic groups and are strong motivators.

- **Socio-economic Programs**

Compliance programs targeted to adolescents above the poverty level in the U.S. need to focus on getting the patients to their first HPV vaccination. For those below the poverty level, programs need to focus on compliance with the second and third doses. Better compliance and follow-up programs, such as those described above, improve completion rates.

- **Program Evaluation**

There are two types of program evaluations that are critical to the success of compliance programs. The first is tracking patient progress in real-time, enabling physicians to reach out when patients are not coming in for their next dose.

The second is how successful the program is at improving compliance rates. To track each program's impact, de-identified, automated monthly reports are shared with pharmaceutical companies, payers, public health officials and other interested organizations, such as state immunization programs. Feedback from Health Care Providers (HCPs) and patient exit interviews also provide insight into continuous improvement opportunities.

II Background

The first human papillomavirus (HPV) vaccine was launched in the US in June 2006 to prevent specific strains of the HPV virus, the primary cause of cervical cancer. Worldwide, cervical cancer is the fifth most deadly cancer in women¹ reason enough for rapid global adoption. Since HPV vaccines do not treat the HPV infection or cervical cancer, the vaccines are recommended for girls and young women who are 9 to 26 years old and have not been exposed to HPV. Only one of the HPV vaccines is US FDA approved

for boys ages 9 to 26 for prevention of genital warts (GARDASIL®). The other marketed HPV vaccine is approved in the UK for boys ages 9-15 (CERVARIX®), to prevent the spread of HPV.

Despite worldwide private and governmental support for HPV vaccines, patient compliance can be challenging. The age demographic includes children who often do not have regular physical exams. According to the CDC, by the end of 2008, 37% of the U.S. teen population (13-17 year olds) had at least one vaccine, but less than half of those (18%) had completed all three.²

GARDASIL

GARDASIL launched in June 2006 in the U.S. for girls and women 9 -26 years old. The vaccine is indicated for the prevention of HPV types 16- and 18-related cervical cancer, cervical vulvar and vaginal pre-cancers and for the prevention of genital warts and low-grade cervical lesions caused by HPV types 6, 11, 16, and 18. Three doses are recommended according to the following schedule: 0, 2, and 6 months.

GARDASIL does not protect patients against diseases caused by all types of HPV or against HPV types to which a patient has already been exposed. Girls and young women ideally need to get the vaccine prior to sexual activity.

GARDASIL is patented by CSL Biotherapies and marketed in the U.S. by Merck. It is marketed in 19 European countries by Sanofi Pasteur MSD, a joint venture between Sanofi Pasteur, the vaccine division of Sanofi-Aventis, and Merck & Co., Inc. In other Central and Eastern European countries, GARDASIL is marketed by Merck Sharp & Dohme as either GARDASIL or SILGARD.

CERVARIX

The CERVARIX vaccine is indicated for the prevention of HPV types 16- and 18-related cervical cancer and pre-cancers. CERVARIX is approved for use in the U.S. for females 10 - 25 years of age. Three doses are recommended according to the following schedule: 0, 1, and 6 months. CERVARIX was approved for a booster (4th) dose in the US in August 2009.

Although GlaxoSmithKline's (GSK) CERVARIX was approved in the US and Japan in October 2009, it had already been approved in 100 countries around the world, including the 27 member states of the European Union (EU), Australia, Brazil, South Korea, Mexico and Taiwan (See Table I).

Pricing

GSK's CERVARIX wholesale cost of US\$386 for a three-course dose is slightly less expensive than GARDASIL's wholesale cost of US\$399, making the GSK vaccine more attractive for payers. The price strategy already has helped GSK win its vaccine contract in the UK.

III Markets

HPV vaccination is recommended and funded in the U.S., Australia, New Zealand and Canada. HPV vaccination is now recommended in 18 of the 19 European countries and is funded or due to be funded soon in 16 of them.³

Tim Anderson, an analyst with Sanford C. Bernstein, predicts that in 2015, GARDASIL will have 65% of an estimated \$3.7 billion worldwide market for HPV vaccines, with CERVARIX accounting for the rest (35%).

A. GARDASIL Footprint

GARDASIL® is now approved in 112 countries and 44 million doses have been distributed worldwide since its launch in June 2006 through the end of March 2009.⁴ GARDASIL's 2008 worldwide sales rose from \$234.8 million in 2006 to \$1.5 billion in 2007 and dipped to \$1.4 billion in 2008. According to the Merck 2008 Annual Report, the 18% year-on-year fall in US sales was due to a strong launch uptake; that is, a significant portion of the 11-18 year old eligible population had already been vaccinated. The number of total vaccinations in girls ages 19-26 also declined as compared with 2007.

B. CERVARIX Footprint

CERVARIX sales are forecasted to grow from USD\$231 million in 2008 to USD\$1.35 billion by 2014, and it is predicted to be GSK's biggest individual sales growth driver over the next six years.⁵ GSK has been much more successful at winning government tenders: about three-quarters of global contracts have gone to CERVARIX.³

Table I: HPV Vaccine Annual Sales WW (\$m)

Product	Company	2008	2010	2012	2014	Launch WW	Launch US
GARDASIL	Sanofi Pasteur MSD	865	1,222	1,686	1,984	10/17/2006	—
GARDASIL	Merck	1,403	1,227	1,399	1,372	06/08/2006	06/08/2006
CERVARIX	GSK	231	797	1,246	1,353	06/30/2007	12/21/2009
	Total HPV Vaccine Market	2,449	3,246	4,331	4,709		

USA Sales (\$m)

Product	Company	2008	2010	2012	2014
GARDASIL	Merck	1,041	824	928	877
CERVARIX	GSK	--	62	145	172

IV The HPV Vaccine Pipeline

A. HPV-L2

One new HPV vaccine is currently in development. Sanofi Aventis acquired Indian vaccines maker Shantha Biotechnics, which is developing a vaccine against minor capsid antigen L2 to prevent HPV infection L2. The company has completed development of a new molecule, HPV-L2, and clinical trials are anticipated to start soon. The L2 vaccine can be produced inexpensively and has the promise of providing broader cross-type virus immunity than GARDASIL and CERVARIX.

The Hyderabad, India-based company (Shantha) originally planned on pricing its HPV-L2 vaccine at less than USD\$15 a dose — a considerable discount from Merck's GARDASIL and GSK's CERVARIX. If passed successfully, the L2 vaccine is expected to give tough competition to Merck's and GSK's existing HPV-L1 vaccines.⁶

The company expects to complete all the phases of trials with the goal of launching the product in the next five years.

B. Inovio Biomedical's VGX

Unlike other HPV vaccines, VGX, manufactured by Inovio Biomedical Corporation (NYSE Amex: INO) is the first vaccine to treat patients who have already contracted HPV. The company announced on Oct. 6, 2009 interim safety and immunogenicity data from the trial of its therapeutic cervical cancer vaccine, VGX-3100. VGX-3100 is a DNA vaccine targeting the E6 and E7 proteins of human papillomavirus (HPV) types 16 and 18 and is delivered via in vivo electroporation.* VGX-3100 Phase I clinical trial is now enrolling the second cohort of patients. Inovio expects full enrollment of all three cohorts in the first half of 2010 and full analysis of immunogenicity and safety data by 3Q 2010.

V Opportunities

Value-added vaccination compliance tools provide a competitive edge, as either a defensive strategy for protecting market share or an offensive strategy for growing market share. According to Ken Frazier, EVP and President of Global Human Health at Merck, his company has a commitment to further increase the compliance levels for GARDASIL,⁷ -- an achievable goal with good adherence tools.

* Insertion of DNA and other molecules into cells

A. Improve Compliance Rates

1. Baseline Compliance Rates

According to the CDC, 37% of girls, ages 13 to 17, in the U.S. had received one or more doses of Merck's GARDASIL in 2008.⁸ However, only 18% of the girls received the full three-dose series of the vaccine.⁹

An October 2009 study by the University of Illinois at Chicago and the University of Chicago found that 30% of 13- to 17-year-olds and 9% of 18- to 26-year-olds reported receiving at least one HPV injection.¹⁰

Another study conducted at the University of Texas Southwestern Medical Center shows below average vaccination compliance in low-income populations, where the vaccine is readily available, and poor uptake of the three-dose HPV vaccine series. Overall 30% of patients received the first dose of the vaccine and a meager 6.5 % completed all three doses required.¹¹ The conclusion of the study was that physicians should be alerted to recommend HPV vaccinations for patients within the appropriate age range, and that patient reminders for the second and third doses are urgently needed.¹²

2. HPV Compliance Research

Research demonstrates the efficacy of HPV Vaccine reminders. One study conducted by The Children's Hospital, Aurora, CO and the University of Colorado found a 9% increase in HPV vaccinations when a series of email and phone reminders were sent to families ($p < .001$). In this study, families received up to 2 mailings and 2 phone calls. Telephone and letter reminders were effective in increasing adolescent immunization rates in both pediatric and family medicine practices.¹³

Vaccine recall and reminder systems—in which clinics contact patients by phone or mail to remind them to make or keep vaccine appointments—are known to be effective in increasing vaccination rates in both children and adults.¹⁴

3. Ethnicity Differences in HPV Vaccine Compliance

When Merck first launched GARDASIL, they needed to sell both a new category and a new product. Merck could not leverage its product launch on existing awareness of health issues regarding HPV, and needed to create its own buzz in multiple markets regarding the disease itself. The company's initial demographic outreach was to mothers with the message of safeguarding their daughters and to Tweens and young women with the message of empowerment and taking control of their own destiny.

Research shows HPV awareness is not consistent across all demographics:

- Nearly 20% more Caucasian caregivers are aware of HPV vaccines than are African-Americans in the U.S.¹⁵
- Hispanic females were more likely than African-Americans and Caucasians to start the HPV vaccination series (44.4%), but less likely to complete the recommended three-dose series (14.7%).[†]
- While fewer Caucasian females than Hispanics started the HPV vaccination series (35.0%), more completed the three-dose series (19.5%).

“It's great to report that we're doing better at reaching Hispanic females and those living below the poverty level about the threat of the human papillomavirus, but we need to do more to increase the rate of those actually completing the three-dose schedule,” said Lance E. Rodewald, MD, Director, Immunization Services Division, National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC).¹⁶

4. Socio-economic Differences

Even for vaccinations that are routinely recommended, rates have not yet reached the target set forth in 2000 by the year 2010. “Adolescents are less likely to have regular wellness visits,” according to Amy B. Middleman, M.D., M.P.H, MEd, Director of Adolescent and Young Adult Immunization at Texas Children's Hospital Center for Vaccine Awareness and Research and Liaison Representative to the ACIP for the Society for Adolescent Medicine. “They're a challenging group to reach, with increasingly busy lives; their health needs are uniquely different from those of infants and adults. We need to address this challenge and develop immunization delivery strategies that make sense for this specific age group.”¹⁷

Another obstacle to vaccinations is that parents and providers don't make them a priority during adolescence. While infants and toddlers regularly have wellness visits where they are weighed, measured and inoculated, adolescents are more likely to see a health care provider only when they're ill, and vaccinations are not likely to be offered during sick visits. Sports and camp physicals are good opportunities to capture this age group, but that still leaves out a large contingent of teens.

According to the CDC's National Immunization Survey (NIS) Teen survey, vaccine coverage rates for the nation's preteens and teens are increasing, but they remain low. The survey of teens ages 13-17 years reveals socioeconomic disparities. In this survey, teens living below poverty level are *more* likely to start the HPV vaccination series (46.4%) than those living at or above the poverty level (35.8%).

[†] In July 2008, The U.S. Citizenship and Immigration Services (USCIS) required female immigrants between the ages of 11 and 26 who seek to adjust their citizenship status to receive the HPV vaccine. The I-693 "Report of Medical Examination and Vaccination Record" required that immigrant females receive only the first dose "to be medically cleared for adjustment of status." This mandate was reversed on Dec. 14, 2009.

5. Geographic Differences

The CDC Survey also documents that vaccination rates vary significantly among states in the U.S. Six states (Arizona, New Hampshire, New York, Massachusetts, Rhode Island and Vermont) had coverage exceeding 50% for one or more doses, while rates failed to reach 20% in Georgia, Mississippi and South Carolina. New Hampshire reported the highest vaccination rate at 54.4%, and Mississippi reporting the lowest at 15.8%.¹⁸ Heather Brandt, a public health researcher at the University of South Carolina, said, “It’s disturbing to see those states at the lower end of participation because those are states with some of the highest rates of cervical cancer.”¹⁹

B. Expand Coverage

In addition to better compliance, vaccination growth can be achieved by increasing the number of lives covered by expanding indications and age ranges and extending it to males.

Merck has adopted this strategy for GARDASIL. For example, Merck applied to the FDA for the following.

- Expanded indications:
The FDA expanded the use of GARDASIL to prevent vaginal and vulvar cancer caused by HPV types 16 and 18, in girls and women ages 9 to 26 (9/12/2008). The FDA originally approved GARDASIL in 2006 for girls and women in this same age group to prevent of cervical cancer caused by HPV types 16 and 18, precancerous genital lesions caused by HPV types 6, 11, 16, and 18 and genital warts caused by HPV types 6 and 11.
- Expanded age range:
Merck has applied for FDA approval for women, ages 27 to 45. However, the FDA has so far declined approval for this age group.
- Gender:
The FDA approved the use of GARDASIL to prevent genital warts in boys and men ages 9-26 years (FDA approved on 10/16/2009).

The impact on sales for the expanded gender use is not expected to generate additional robust sales. Leerwink Swan forecasts GARDASIL sales in men will peak at \$200m-\$300m in the US.²⁰ Tim Anderson, an analyst with Sanford C. Bernstein, predicts Merck will find it harder to persuade parents and health insurers to pay for GARDASIL shots to reduce the chance of developing a nonfatal condition like genital warts in males than to market the vaccine to reduce a potentially deadly disease like cervical cancer.²¹

C. Formulary Adoption

Vaccines in the U.S. market need a second recommendation before widespread adoption can occur. Once a vaccine has gotten FDA approval, it needs the CDC's Advisory Committee on Immunization Practices (ACIP) to recommend “routine” use of the vaccine. If the CDC also approves the vaccine for its Vaccines for Children (VFC) program, the CDC provides the vaccine free of charge for qualified

patients and approved doctors.[‡] Note that without ACIP's recommendation for "routine use", private insurers are reluctant to include the vaccine on their formularies.

The ACIP recommendations are:

- "Routine use" of GARDASIL and CERVARIX in adolescent girls (11-12 years of age). Both vaccines are recommended for CDC funding through the agency's Vaccines for Children (VFC) program
- "Routine use" of a 3-dose 'catch-up' series for females ages 13-26
- "Permissive use", but not "routine use", for males ages 9-26, leaving the decision with their HCP on whether to immunize those who request the vaccine. However, the committee did recommend that the CDC provide funding for administration of the vaccine through the agency's VFC program for males who want to receive it. (10/2009)

Merck also supports GARDASIL with two reimbursement programs. A patient assistance program covers uninsured males and females ages 9 to 26. The dose replacement program reimburses doctors[§] whose claims are denied by replacing the dose. This assures the doctor that he/she is not left with an economic outlay.

Although 99% of privately insured 19 to 26 olds have some level of coverage, there is a lack of consistency of vaccination coverage in many benefit plans. Merck proactively tracks MCOs' co-payments, coinsurance, and deductibles and provides this information to HCPs through Merck's Reimbursement Support services:

https://www.merckvaccines.com/vaccines/gardasil/compliance_one.html.

In Europe, coverage for HPV vaccines is provided by many of the national health services. In the U.S., some states fund programs for all resident children, such as New Hampshire's Universal Vaccine Distribution Program.²²

[‡] Providers must obtain the vaccine through the VFC Program for Medicaid-eligible, uninsured, underinsured, or American Indian or Alaska native girls ages 9-18, and are reimbursed for the administration of the vaccine by managed care, if the patient has adequate coverage. Eligibility requirements are posted at <http://www.cdc.gov/vaccines/programs/vfc/providers/elig-scrn-rec-doc-req.htm>. Only VFC-approved doctors receive the vaccine reimbursement. Doctors, including many OB-GYNs who are not VFC-approved, need to apply to their state VFC Program to become participating providers.

[§] The dose replacement program is intended to support doctors who do not routinely vaccinate patients, such as OB/GYNs and may have concerns about managed care reimbursements.

VI Current Compliance Programs

Manufacturers and public health organizations can reduce cervical cancer by improving HPV vaccination compliance. For this reason, many national health services have adopted compliance programs, as described below.

A. United Kingdom

Patients are encouraged to enroll in a free vaccination reminder program through the GSK website, <http://www.vaccinesreminder.co.uk> and through patient leaflets distributed in HCPs' waiting rooms.

This compliance program sends SMS and optional email reminders to prompt patients to schedule their next immunization. Patients receive up to four SMS messages. They can register either online or by sending an SMS message (charged at their carrier's normal rate). Patients enter the date of their first immunization, select which HPV regimen they are on (e.g. 1 & 6 months, or 2 & 6 months), and confirm that they have read and accepted GSK's privacy policy and legal statement.

Note that neither the patient nor the HCP name is required to register for the program. Upon registration, a confirmation text message is sent to the patient explaining the scope of the service. SMS and optional email reminders are sent for the second dose three weeks after the date of the first injection. Just short of 6 months after the first dose (10 days before the 6-month mark), a reminder is sent for the third and final dose. A final 'thank you' message is sent to the patient. All incoming SMS reminders are free of charge.

GSK makes this program available in other European countries, including Germany, Denmark and Greece. GSK offers the compliance program as a patient value-added service to promote HCP loyalty to the brand.

B. Scotland

The National Health Service (NHS) in Scotland provides free, automated SMS reminders. Instructions for enrolling for the reminders are provided on the NHS website:

<http://www.fightcervicalcancer.org.uk/more-information/hpv-sms-reminder.aspx>. Patients are instructed to text the date of their first HPV "jab" to 64746, enter the key code: HPVJAB and the date of their first immunization. By March 2009, Scotland achieved 92.2% vaccination rates for the first dose, and 87.8% vaccination rates for the second dose.²³ The first dose has been completed nationwide at time of this publication, and the second and third doses were still being delivered.

C. Australia / CSL Biotherapies

Patients in Australia can enroll for free SMS or email reminders for GARDASIL through the CSL Biotherapies website: <http://www.cervicalcancer.com.au/>.^{**} Patients schedule the automated

^{**} Merck licenses GARDASIL from CSL Biotherapies.

reminders by completing a web form that asks for their email address or mobile phone number. It also asks whether they have already started their vaccination program, which of the three doses they have already received, the date of their last dose, their postcode, year of birth, gender, and the reason why the patient is motivated to get the vaccine. For patients younger than 16, instructions state that a legal guardian must complete the form. The form also requests the patient's doctor's phone number, however this field is optional. Patients must confirm that they have read and understood the site's legal and privacy policies. The website's enrollment form emphasizes that patients should continue with regular Pap smears.

D. Switzerland - Hôpitaux Universitaires de Genève

This email and SMS reminder service is sponsored by the healthcare provider Hôpitaux Universitaires de Genève. The registration site <https://www.hpv-hug.ch/> includes a registration form that captures the patient's name, date of birth, email address (required), mobile phone number (optional), username, password, language (French or English) and date and time requested for the first appointment. Patients are told that all of their personal information will be deleted at the end of the vaccination series (3 doses).

E. Finland

Sanofi Pasteur sponsors free SMS reminders for Finnish GARDASIL patients. Doctors provide the patients with a vaccination card when they get their first dose. The card instructs patients to register for the reminder service by sending an SMS message from their mobile phone with the word GARDASIL to a toll-free SMS short code. An enrollment confirmation message is texted back to the patient. The patient receives a reminder seven days before the second vaccination date and another reminder is sent on the day of the second vaccination. The same routine is used for the third vaccination. The day after the third vaccination the patient receives an SMS text message indicating they have completed the GARDASIL program.

F. Germany

Free, automated email and SMS reminders are offered in Germany for HPV vaccine patients by Monks - Ärzte im Netz GmbH, a health portal company, with the endorsement of Germany's Professional Association of Gynecologists and German Society of Gynecology and Obstetrics. Patients enroll in the reminder service by completing a web form, which requests: email address, date of birth, date of their first HPV vaccine, the vaccine brand name (GARDASIL or CERVARIX), and mobile phone number. Patients must also accept the conditions of use and privacy policy. The registration form is posted at: http://www.frauenaerzte-im-netz.de/de_hpv-bzw-gebaermutterhals-erinnerungsdienst-hpv-impfung_1019.html

G. United States

1. State and Federal Immunization Information Systems

In the early 1990's the CDC established a national goal to implement statewide immunization registries that would allow physician access to patient vaccine histories regardless of where the immunization had been received. The CDC provides annual funding grants to 56 Immunization programs (at least one in each state and in Washington DC. Today, several states provide Immunization Information Systems or Registries to help providers and families consolidate immunization records and information,^{††} and to provide physician support for vaccination reminder/recall programs.

The North Carolina South Central Partnership for Public Health offers an "HPV Vaccine Project" (<http://www.hpvvaccineproject.org/>) as part of its North Carolina Immunization Registry (NCIR). The program generates patient reminders by mail, and includes patient vaccination histories and recommendations.^{††}

2. School-based Health Centers (SBHC)

It is estimated that there are approximately 2,000 school-based health centers (SPHC) in the U.S. providing comprehensive health care to students and staffed by physicians, nurse practitioners and physicians assistants. A recent study²⁴ found that 84% of the 815 SBHCs surveyed reported that they administer vaccines. Eighty percent (80%) administer HPV vaccines. The SBHCs use a variety of reminder/recall methods to reach their student population:

- Contacted adolescents directly at school (60%)
- Telephoned adolescents' home (54%)
- Sent mail home (54%)
- Emailed parents (3%)
- Emailed adolescents (2%)

3. University of Pennsylvania, Philadelphia, Pennsylvania

The University of Pennsylvania is using SMS reminders to drive HPV vaccine adherence. A medical provider supplies the young women with information about the HPV vaccine and gives them the opportunity to opt-into an SMS reminder.

Patients provide the date of their appointment to receive the first dose of the HPV vaccine. The automated reminder system reminds the patient when to go to their next appointment. It also

^{††} A list of state Immunization Information Systems and their contact information can be found on the CDC website at <http://www.cdc.gov/vaccines/programs/iis/default.htm>.

^{††} The American Immunization Registry Association (AIRA) has partnered with the CDC to develop a Best Practices guidebook for immunization information systems, which can be found at: http://www.immregistries.org/pdf/AIRA_MIROW_RR_041009.pdf.

allows them to schedule an appointment. Once they have completed the three doses, they are congratulated with an SMS message.

4. Parkland Health & Hospital System, Dallas, Texas

To address the low completion rates of the HPV vaccination series in low-income populations, the Parkland Health and Hospital system in Dallas, TX incorporated automated telephone reminders as part of their standard procedures. Their electronic medical record system alerts the healthcare professional if a patient is eligible for the HPV vaccine. Automated calls are scheduled to remind the patient to keep clinic appointments and receive their second and third vaccine doses.²⁵

5. Columbia University Research on Parental Readiness for Text Message Reminders

Researchers at Columbia University conducted focus groups and individual interviews in a diverse population of parents to qualitatively explore preferences and readiness for text message immunization reminders. Text message reminders were well-accepted by parents; many thought they would be more effective than standard phone or mail reminders. Parents preferred text message reminders to be brief and personalized. Most were able to retrieve sample text messages but many had difficulty texting a reply.²⁶

6. Merck's US-based GARDASIL Compliance Programs

Merck's 2006 launch of GARDASIL was aggressive, and included a well-supported compliance program called "3 is Key".

- **"3 IS KEY" Compliance Campaign for Girls and Their Mothers**

The campaign targeted two main groups, girls ages 18 to 26-year and moms of girls ages 10- to 26. They found Moms are more interested in email and snail mail reminders, but young adult females were more apt to be reached by text messaging.

To encourage physician support, Merck provided an online e-detailer (https://www.merckvaccines.com/vaccines/gardasil/compliance_one.html) explaining the compliance program. They also sent kits to doctors to get patients to sign up in the office immediately after receiving their first dose. Patients enrolled in the reminder service by completing a postage-paid business reply card, which was mailed by the office staff to Merck (for mail and email reminders). Alternatively, patients could text "REMIND" to GARSIL from a cellular phone. Patients could also opt in for mail and email reminders through the GARDASIL web site.

Patient reminder message examples include: "IT'S TIME to get your second dose of Gardasil" and "3 IS KEY, did you get your third dose?"

- **“3 IS KEY” partnership with MCOs²⁷**

Although 99% of privately insured women ages 19 to 26 have some level of coverage, there is a lack of consistency of vaccination coverage in many benefit plans. Merck worked proactively with MCOs to track co-pays and patient out-of-pocket expenses, and provided the data to HCPs.

Merck supported their compliance campaign with several awareness campaigns including, disease awareness and education, viral marketing, and Direct to Consumer (DTC) advertising:

- **"Make the Connection"** multilingual, disease awareness campaign
Merck distributed "Charm4life" beaded bracelet kits. Girls would string together their own bracelets with beads. Accompanying educational packets explained the connection: "stringing together the beads, stringing together the facts about HPV and cervical cancer." Celebrities^{§§} sported their own beaded bracelets at various events. Merck also pledged to donate \$1 (up to \$100,000) to the Cancer Research and Prevention Foundation for each kit ordered. The response was so great that the program ran out of kits. The campaign was run by the nonprofit groups Cancer Research and Prevention Foundation and the Step Up Women's Network.
- **"Tell Someone"** Direct-to-Consumer (DTC) campaign
Actresses⁺⁺ in these television ads spoke directly to the camera, as if speaking directly to a friend, family member, or simply another girl who needed to know. Girls were encouraged to send out personalized "Tell Someone" e-cards — imprinted with photos of girls lining up to use the phone or gossiping together at a beauty salon — and stamped with the question: "Did you know that cervical cancer is caused by certain types of a common virus?" DTC advertising was also shown in movie theaters and placed in print publications.
- **"One Less"** disease education campaign
This campaign targeted young women with the message of empowerment to take control of their own destiny: "We chose to protect ourselves against cervical cancer and other HPV diseases. Now the Choice is Yours."
- **Hpv.com** disease education website
This unbranded website provides HPV facts, and encourages viral information sharing (e.g. Send to a Friend).

^{§§} Beverley Mitchell of the series "7th Heaven" and Elisabeth Rohm from "Law and Order"

- *GARDASIL.COM* branded viral campaign
This product-branded website includes patient stories, buddy icons and downloads for holding events at sororities.
- “*Health Talker Ambassador*” viral campaign
The campaign encourages women to become Cervical Cancer and HPV awareness ambassadors. Members of the program are mailed educational materials for 20 friends. Girls and young women can sign up to join the campaign through the website:
<http://www.healthtalker.com/ambsplash/src1>
- “*Take a step against cervical cancer*” Facebook Fan Page
As of Feb, 2010, the GARDASIL Facebook page has acquired 108,614 fans. The Facebook site includes links to the “3 is Key” compliance program as well as other programs. The site includes a “Make Your Mark” Facebook application, which allows people to create a personal or group logo (with frames, icons, expressions and Greek letters) and post it on the Make Your Mark board. Participants can commit to getting vaccinated, ask a doctor about cervical cancer, set up an event to raise awareness, tell at least one friend about cervical cancer, and tell a friend about the application. The site also posts the winner of a “Lead Out Loud” Contest, offers a “Talk to Your Doctor” checklist, a “Plan an Event” event guide and tips, a “Get the Facts” slideshow that includes information on the “3 is Key” compliance program, a “What You Should Know” Tear sheet, case studies, buddy icons and wallpaper downloads.
- *Patient Assistance*
Merck introduced a new patient-assistance program for vaccines. This patient assistance program is made available to patients at private physicians’ offices and private clinics. Merck makes available, free of charge, GARDASIL and other Merck vaccines indicated for use in women ages 19 and up who are uninsured and who are unable to afford vaccines.
- *Lobbying* campaign for state mandates
In 2006 Merck launched a campaign lobbying State legislators to mandate that middle school age girls be vaccinated with GARDASIL. Many vaccines are mandated in the US,^{***} and Merck’s goals were consistent with other vaccination programs. By August 2007, 41 states and the District of Columbia had introduced legislation to require, fund, or educate the public about the HPV vaccine, and 17 states enacted this legislation.⁺⁺⁺
However Merck announced in February 2007 that it would no longer lobby to pass laws

^{***} See <http://www.immunize.org/laws/> for a list of vaccine mandates by state.

⁺⁺⁺ When several new vaccines became available in the 1950s and '60s in the U.S., including vaccines for polio, measles, mumps and rubella, disease rates did not decline significantly until states started requiring vaccination for school enrollment.

mandating HPV vaccinations in the face of concern regarding the speed of GARDASIL adoption.⁺⁺⁺ Abstinence organizations such as the Family Research Council also opposed efforts to make this vaccination mandatory.

- 2009 “Back to School” campaign
Nearly two thirds of well visits for females ages 9 to 18 occur during the second and third quarters of the year, with the third quarter – the back-to-school season – being the highest. The brand launched the “Back to School” campaign to encourage students and physicians to include HPV vaccines in their well visits. The campaign encouraged and supported vaccine-day events with doctors' offices and clinics, and provided posters, direct-mail pieces and pocket cards.

7. CERVARIX US-based Adherence Programs

CERVARIX has the advantage of being able to leverage off of Merck’s disease awareness and educational programs, and the disadvantage of coming to the U.S. market three years after GARDASIL. GSK continues to commit to CERVARIX compliance; however, current U.S.-based compliance programs could not be identified to date. In the past disease education efforts included a cervical cancer awareness site; however, that site was removed in July 2008.

VII Best Practices & Recommendations

Comprehensive Adherence Program

We propose a list of best practices and recommendations for HPV vaccine compliance programs based on published research, international compliance programs, pharmaceutical branded programs and recommendations from the American Immunization Registry Association.

1. Automated and Tracked Vaccination Reminders and Confirmations

The best of breed vaccination compliance programs provide automated systems that generate multiple contacts with patients at appropriate times in their care (e.g. females who reach the age of 11, prior to the first dose and after the scheduled dates of second and third doses). These systems track all contacts made to the parent and patient and the responses that were provided.

The information tracked includes patient or parent responses regarding their immunization status and issues, such as:

⁺⁺⁺ Some health experts were concerned that mandating Gardasil was premature and the American Academy of Pediatrics advocated at “go-slow approach” that focused on raising awareness of HPV and monitoring the safety of the vaccine.

- Agreed to make appointment
- Cannot get access to care
- Refused
- Appointment already scheduled
- Child no longer lives in home
- Parent concerned with vaccine safety

This information can be provided on an individual basis to the HCP, and in the aggregate to pharmaceutical manufacturers for program monitoring.

A single Reminder Notification should be considered 2 to 4 weeks before the recommended due date/date range for each dose of the vaccine. Up to three follow-up confirmations (“recall”) notifications are scheduled, until the patient or her parent reports that she has completed the vaccination and any addressable issues, such as those in the bulleted list above, have been resolved.

2. Support for Varied Stakeholders

Multiple areas of responsibility exist for compliance and follow-up programs, so automated programs need to be flexible enough to provide account access for each stakeholder:

- Patient and parent accounts
- HCP accounts
- Managed Care accounts
- Public Health accounts

The same software and telecommunications system can be used for programs by any stakeholder. To be successful, it needs to be simple to enroll patients, asking only for the minimum amount of information required.

3. Multiple Methods of Communication

The best of breed systems provide seamless, integrated SMS/Phone/Email/Mail reminders and follow-ups. Multiple notification attempts are made before the process is ended.^{§§§} Patients and parents are allowed to select multiple notification methods that best conform to their lifestyle. If not reached, the system automatically escalates to the patient’s next preferred method of contact.

4. Ethnic-centric Programs

Given the ethnic variations in compliance, campaigns specifically targeting ethnic groups improve their completion rates. Minimally, notifications are produced in the language preferred

^{§§§} The American Immunization Registry Association recommends three (3) notification attempts before ending the process.

by the patient or caregiver. Campaigns that include celebrities popular in a given age bracket and culture are motivators and work effectively to reach adolescents in specific demographics.

5. Socio-economic Programs

Much work has been done to provide adequate coverage for adolescent girls who are under-insured or not insured in the U.S. (e.g. CDC's Vaccines for Children, Merck's Patient Assistance Program). We know these funding programs work because teens living below poverty level are more likely to start the HPV vaccination series (46.4%) than those living at or above the poverty level (35.8%).

Compliance programs for adolescents above the poverty level need to focus on starting the HPV vaccine series and, for those below, complying with the second and third doses. Better compliance and follow-up programs, such as those described above will increase vaccination rates.

6. Program Evaluation

There are two types of program evaluations that are critical to the success of compliance programs. The first is tracking patient progress in real-time, enabling physicians to reach out when patients are not coming in for their next dose.

The second is how successful the program is at improving compliance rates. To track each program's impact, de-identified, automated monthly reports are shared with pharmaceutical companies, payers, public health officials and other interested organizations, such as state immunization departments. Feedback from Health Care Providers (HCPs) and patient exit interviews also provide insight into continuous improvement opportunities.

VIII Sources

¹ World Health Organization (February 2006). "Fact sheet No. 297: Cancer".

<http://www.who.int/mediacentre/factsheets/fs297/en/index.html>. Retrieved 02/01/2010.

² http://www2a.cdc.gov/nip/coverage/nisteen/nis_iap.asp?fmt=v&rpt=tab01_iap&qtr=Q1/2008-Q4/2008.

Retrieved 02/01/2010.

³ "New study results further support the evidence that the HPV vaccine GARDASIL® will provide long-lasting protection," Sanofi pasteur MSD News Release, 5/10/2009

<http://www.spmsd.com/press/CO00435%20PR%20New%20results%20GARDASIL%C2%AE%20will%20provide%20long-lasting%20protection.pdf>

⁴ "New study results further support the evidence that the HPV vaccine GARDASIL® will provide long-lasting protection," Sanofi pasteur MSD News Release, 5/10/2009

<http://www.spmsd.com/press/CO00435%20PR%20New%20results%20GARDASIL%C2%AE%20will%20provide%20long-lasting%20protection.pdf>

⁵ "Glaxo's U.S. CERVARIX Approval More Important for Company's Pride than for Sales," Sept. 10, 2009, EP

Advantage. <http://seekingalpha.com/article/160957-glaxo-s-u-s-CERVARIX-approval-more-important-for-company-s-pride-than-for-sales> Retrieved 02/01/2010.

⁶ BV Mahalakshmi, "Shantha Bio working on novel vaccines," Feb 02, 2009, The Financial Express,

<http://www.financialexpress.com/news/shantha-bio-working-on-novel-vaccines/417822/>

⁷ Merck & Co., Inc. Q3 2009 Earnings Call Transcript, Oct. 22, 2009 <http://seekingalpha.com/article/168289-merck-amp-co-inc-q3-2009-earnings-call-transcript>

⁸ "CDC: 1 in 3 teen girls got cervical cancer vaccine." MIKE STOBBE, AP, 9/17/2009 <http://www.ajc.com/health/cdc-1-in-3-140524.html>

⁹ Centers for Disease Control and Prevention 9/17/2009 data.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5836a2.htm>

¹⁰ "Knowledge and Early Adoption of the HPV Vaccine Among Girls and Young Women: Results of a National Survey," Rachel Caskey, Stacy Tessler Lindau, G. Caleb Alexander, Journal of Adolescent Health, Volume 45, Issue 5, Pages 453-462, November 2009. <http://www.jahonline.org/article/S1054-139X%2809%2900184-0/abstract>

¹¹ "Factors associated with adolescent HPV vaccine uptake in safety-net clinics," Jasmin A. Tiro, Corinne Bruce, Wendy P. Bishop, Katharine Goodell, Celette Sugg Skinner. University of Texas Southwestern Medical Center, Dallas, TX, Proceedings of American Association for Cancer Research, Dec. 6-9, 2009

http://cancerpreventionresearch.aacrjournals.org/cgi/content/short/3/1_MeetingAbstracts/B14?rss=1

¹² "Factors associated with adolescent HPV vaccine uptake in safety-net clinics," Jasmin A. Tiro, Corinne Bruce, Wendy P. Bishop, Katharine Goodell, Celette Sugg Skinner. University of Texas Southwestern Medical Center, Dallas, TX, Proceedings of American Association for Cancer Research, Dec. 6-9, 2009

http://cancerpreventionresearch.aacrjournals.org/cgi/content/short/3/1_MeetingAbstracts/B14?rss=1

- ¹³ "How Successful is Reminder/Recall at Improving Immunization Rates for Adolescents?" Christina A. Suh MD, Instructor of Pediatrics, University of Colorado Denver, March 31, 2009, Centers for Disease Control and Prevention 43rd National Immunization Conference
<http://cdc.confex.com/cdc/nic2009/recordingredirect.cgi/id/4738>
- ¹⁴ Jacobson VJ, Szilagyi P. Patient reminder and patient recall systems to improve immunization rates. *Cochrane Database Syst Rev* 2005:CD003941. <http://www.ncbi.nlm.nih.gov/pubmed/16034918>
Retrieved 02/04/2010.
- ¹⁵ "Disparities in How Parents Are Learning about the Human Papillomavirus Vaccine," Jessica Hughes, Joan R. Cates, Nicole Liddon, Jennifer S. Smith¹, Sami L. Gottlieb³ and Noel T. Brewer, *Cancer Epidemiology, Biomarkers & Prevention* February 2009 18; 363
<http://cebp.aacrjournals.org/content/18/2/363.abstract> Retrieved 02/02/2010.
- ¹⁶ "Teenagers Difficult To 'Capture' For Vaccinations; Rates On Rise Overall, But Still Low," Oct. 27 2009
<http://www.medicalnewstoday.com/articles/168766.php>
- ¹⁷ "Vaccination rates among teens increase but remain low," *Pediatric SuperSite*, Oct. 27, 2009
<http://www.pediatricssupersite.com/view.aspx?rid=44994> Retrieved 02/02/2010
- ¹⁸ "National, State, and Local Area Vaccination Coverage Among Adolescents Aged 13--17 Years --- United States, 2008," *CDC MMWR Weekly*, Sept. 18, 2009, 58(36); 997-100
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5836a2.htm> Retrieved 02/02/2010
- ¹⁹ "CDC: 1 in 3 teen girls got cervical cancer vaccine," Mike Stobbe, *Associated Press*, Sept. 17, 2009
<http://www.ajc.com/health/cdc-1-in-3-140524.html> Retrieved 02/02/2010
- ²⁰ "Boys Prove to be of little value to Merck," *Evaluate Pharma*, Sept. 10, 2009,
<http://www.epvantage.com/Universal/View.aspx?type=Story&id=195004&isEPVantage=yes>
Retrieved: 02/01/2010
- ²¹ "Two Giants Vie for Billions in S.T.D. Vaccine Market," *Natasha Singer*, Sept. 9, 2009, *NY Times*
<http://query.nytimes.com/gst/fullpage.html?res=9403E5DD1630F933A2575AC0A96F9C8B63&scp=2&sq=Two%20Giants%20Vie%20for%20Billions%20In%20S.T.D.%20Vaccine%20Market&st=cse>
- ²² "Human Papillomavirus Vaccine Uptake in Adolescent Female Medicaid Enrollees – New Hampshire, 2007," Sherry L. Burrer, DVM, MPH, Ludmila Anderson, MD, MPH, Jason Stull, VDM, MPVM
<http://www.dhhs.state.nh.us/NR/rdonlyres/ek5tgwyqygwbkqiy4ijyptte5rgtlozpqfilyq5wxjujgwsn5g6kiffakhky4g3qmnngheamokewd3zbrk2boxis7lg/hpvinnh.pdf> Accessed 2/9/2010.
- ²³ *ISD Scotland*. <http://www.scotland.gov.uk/News/Releases/2009/03/26094529>
- ²⁴ "Adolescent Immunization Delivery in School-based Health Centers: a National Survey," Matthew F. Daley, MD, Associate Professor, Pediatrics University of Colorado Denver, presented at the 43rd National Immunization Conference, March 30, 2009
<http://cdc.confex.com/cdc/nic2009/recordingredirect.cgi/id/4740>
- ²⁵ "Researchers identify barriers to HPV vaccination uptake in low-income populations," *American Association for Cancer Research Frontiers in Cancer Research Conference*, Houston, Dec. 8, 2009.
<https://www.aacr.org/home/public--media/aacr-press-releases/press-releases-2009.aspx?d=1678>
Retrieved 02/03/2010.

²⁶ “Text4Health: A Qualitative Evaluation of Parental Readiness for Text Message Immunization Reminders,” Elyse Olshen Kharbanda, MD, MPH, Melissa S. Stockwell, MD, MPH, Harrison W. Fox, MPH and Vaughn I. Rickert, PsyD , December 2009, Vol 99, No. 12 | American Journal of Public Health 2176-2178
<http://ajph.aphapublications.org/cgi/content/abstract/99/12/2176>

²⁷ Merck & Co., Inc. Q1 2008 Earnings Call Transcript
<http://seekingalpha.com/article/73171-merck-co-inc-q1-2008-earnings-call-transcript> Retrieved 02-04-2010.