



## Review

## A summary of the post-licensure surveillance initiatives for GARDASIL/SILGARD®

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## ABSTRACT

GARDASIL® has been shown to reduce the incidence of pre-cancerous cervical, vulvar, and vaginal lesions, and external genital warts causally related to HPV6/11/16/18. Because of its expected public health benefit on reduction of cervical cancer and other HPV-related diseases, this vaccine has been rapidly implemented in the routine vaccination programs of several countries. It is therefore essential to assess its impact and safety through post-licensure surveillance programs. Here, we present a summary of 16 post-licensure safety and impact studies across 20 countries. These studies address general safety, including autoimmune disorders, long-term effectiveness, and type replacement. A summary of the surveillance efforts of the United States Centers for Disease Control and Prevention can be found in the accompanying article by Markowitz et al.

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## 1. Introduction

A prophylactic quadrivalent HPV6/11/16/18 vaccine (GARDASIL/SILGARD, Merck & Co., Inc., Whitehouse Station, NJ), received US Food and Drug Administration (FDA) approval in June 2006 for use in girls and women aged 9–26 years. Licensure was based on international studies of the safety, immunogenicity, and efficacy of GARDASIL in over 21,000 girls and women. The vaccine has since been approved in over 100 countries including Australia, Canada, and several European, African, and Asian countries. In the United States, it has been recommended by the Advisory Committee on Immunization Practice and incorporated into the Vaccines for Children Program [1]. Likewise nearly all countries worldwide have issued recommendations. In May 2009, GARDASIL became the first cervical cancer vaccine to receive World Health Organization (WHO) pre-qualification, which means that GARDASIL is now eligible for procurement by the United Nations Children's Fund and other United Nations agencies (including the Pan American Health Organization) for use in national immunization programs.

Due to the potentially widespread use of GARDASIL (over 55 million doses distributed globally as of December 2009), it is important to monitor its safety and impact, including its effectiveness, in vaccinated populations. Across 5 phase 3 clinical trials involving 21,480 females aged 9–26 years and boys aged 9–16 years, vaccination was associated with more injection-site pain than placebo but similar incidences of systemic and serious AEs and new medical conditions potentially consistent with autoimmune phenomena. However, rare and potentially serious adverse experiences to vaccination may not emerge during clinical trials. Therefore accurate post-licensure safety assessment relies on the continued collection, management, and assessment of safety data by both the vaccine's manufacturer and regulatory authorities such as the FDA and the European Medicines Agency (EMA).

The long-term impact of GARDASIL and the potential need for a booster dose is as yet unknown, as is the case for most new vaccines. Thus it is necessary to monitor the incidence of pre-cancers and cancers in vaccinated populations to determine if breakthrough disease occurs. The overall reductions in HPV-related disease must also be estimated to determine the health economic benefits of vaccination. Other outcomes of interest include the ability of HPV vaccination to efficiently complement cervical cancer screening and to determine if vaccination modifies attitudes toward cervical cancer screening or sexual behavior practices.

In recognition of the need for continued post-licensure surveillance, the WHO's Strategic Advisory Group of Experts on vaccines and immunization recommended in November 2008 that "countries should consider establishing sentinel surveillance to monitor the impact of vaccination on the prevalence of HPV types, the incidence of abnormalities and pre-cancerous lesions, the incidence and mortality of invasive cancer, and the incidence of anogenital warts (if using the quadrivalent vaccine)" [2]. In addition, many

authorities in Western European countries have recommended setting up local post-licensure surveillance studies. In the US, the Centers for Disease Control (CDC) is monitoring the safety and effectiveness of GARDASIL through several initiatives [3].

Here we present a summary of the post-licensure safety and effectiveness studies being conducted in collaboration with the vaccine's manufacturers and marketers (Merck and Co., Inc., Sanofi Pasteur MSD) as well as other known independent initiatives in Europe, Canada, and Australia (Table 1). This summary includes known efforts as of February 2010 and is not intended to be comprehensive. Surveillance efforts of the CDC are summarized in the accompanying manuscript by Markowitz et al. (in press).

## 2. Post-licensure commitments and initiatives in collaboration with Merck and Co., Inc.

*2.1. Protocol V501-015: a registry-based study in countries with centralized cervical cancer screening infrastructures to evaluate the long-term effectiveness, immunogenicity, and safety of GARDASIL*

*Objectives:* To evaluate the safety and immunogenicity of GARDASIL, and its long-term effectiveness in preventing cervical, vulvar, and vaginal cancers and related pre-cancers caused by HPV6/11/16/18, and those caused by non-vaccine types, in Nordic women.

*Population:* 5496 women aged 16–23 who participated in FUTURE II [4].

*Summary:* This long-term follow-up (LTFU) study is a Nordic extension of the phase 3 trial Protocol V501-015 (FUTURE II, NCT00092534), which is a randomized, worldwide, placebo-controlled, double-blind, four-year study designed to investigate the impact of GARDASIL on the incidence of HPV16/18-related CIN2/3 or worse in 16–23-year-old women. The original protocol and the primary results have been described [4]. Vaccine efficacy for the prevention of the primary composite end point (HPV16/18-related CIN2/3 or worse) was 98% (95.89% confidence interval [CI], 86–100) in the per-protocol susceptible population.

The primary hypothesis for the extension is that GARDASIL will remain effective for at least 14 years after the start of vaccination. The monitoring of disease cases will indicate when the reduction in the incidence of HPV16/18-related CIN2, CIN3, AIS and cervical cancer is less than 90%, relative to the estimated incidence in unvaccinated subjects. Due to the absence of a control group, the hypothesis is not formally controlled by statistical power and significance levels.

Protocol V501-015 included 5496 women from Denmark, Iceland, Norway, and Sweden, randomized in a 1:1 ratio to receive either GARDASIL or placebo between the years 2002 and 2003. Upon completion of the original four-year study, women signed an informed consent allowing for participation in the LTFU study.

Subject-level data will be collected from two cohorts in this LTFU study. Cohort 1 consists of approximately 2750 subjects who received GARDASIL at the start of Protocol V501-015. These subjects will contribute approximately 14 years of follow-up after vaccination (four years within Protocol 015 plus an additional 10 years within the LTFU study). Cohort 2 is made up of approximately 2750 subjects who received placebo at the start of Protocol V501-015 and will have been vaccinated with GARDASIL at the completion of the randomized controlled trial follow-up period and prior to entry into the LTFU. These subjects will contribute 10 years of post-vaccination follow-up. No additional HPV vaccinations will occur within the context of the LTFU study. GARDASIL was licensed in Europe in 2006, therefore earliest vaccine recipients (cohort 1) are a sentinel cohort that will provide three to four years lead time for identifying potential breakthrough disease and to determine if there is a need for a booster dose.

Protocol V501-015 had ~95% subject retention, which will continue in the LTFU study through the highly efficient screening and surveillance systems that exist in the Nordic countries. In the Nordic countries every citizen has a unique Personal Identification Number (PIN), which is registered in a national computerized database. These identification numbers are used universally in the society of the respective country, and make it possible to do reliable linkages with different registries. The national centralized cervical cancer screening programs in Denmark, Iceland, Norway, and Sweden recommend that women have Pap tests every 2–3 years. LTFU study investigators in each of the four participating countries will lead the National Registry Study Centers (NRSCs) which will obtain Pap tests and histopathology results from biopsies and definitive therapy specimens that are collected and linked to the subject's PIN through the national registries.

The NRSCs will: 1) search the relevant registries on an annual basis to identify Pap testing, genital tract biopsy, or definitive therapy results; 2) obtain biopsy and definitive therapy slides and blocks from the local pathology laboratories and send them to the central laboratory; 3) search health-related registries to find safety events of interest; and 4) coordinate serum collection for HPV serological testing at years 5 and 10 using a competitive Luminex immunoassay as described [4,5]. When NRSCs provide slides and blocks, the central laboratory will cut tissue for Thin-section Polymerase Chain Reaction (PCR) testing for 14 HPV types (6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) as described [4,6,7] and will also create new slides for diagnosis by an expert Nordic Pathology Panel. Long-term effectiveness will be assessed by determining the incidence of HPV6, 11, 16, and 18-related pre-malignant and malignant genital tract disease in the vaccine recipients. As an aid to interpretation, the expected incidence of disease in an unvaccinated (placebo) cohort will be carefully estimated. Information from the Nordic registries prior to introduction of the vaccine accurately measures the incidence of disease prior to the vaccine's introduction. For the purposes of the LTFU study, it was estimated that the rate of CIN 2 or worse in the LTFU cohort, had they remained unvaccinated, would be 5.62/1000 person-years. Over the course of the LTFU, the subjects will get older and their risk profile will change. Thus as an approximation, the background rate will be assumed constant at 5.62/1000 person-years. It will also be assumed that 55% of the CIN 2, CIN 3, or AIS lesions in the population data are related to HPV 16/18 (i.e., absolute incidence rate of 3.09/1000 person-years). A threshold for breakthrough disease incidence will be used to guide decision-making within the LTFU study. The threshold is designed to indicate when vaccine effectiveness is decreasing to less than 90%.

The registries such as the National Hospital Register and the Cancer Registry in each country which are being utilized for the LTFU study in the respective countries have the capacity to search for adverse events, and therefore, will search for deaths, cancers,

hospitalizations and other safety outcomes to measure the long-term safety in the vaccinated group and descriptively compare adverse event rates to those in the age and sex-matched general population.

## 2.2. Protocol V501-033-00: Vaccine Impact in Population (VIP) Study

**Objectives:** To monitor the impact of the vaccine on any vulvar, vaginal, and cervical cancers and their respective precursor lesions and HPV6/11/16/18-related infection and disease in the general female population. To evaluate and describe congenital anomalies in women who were inadvertently exposed to HPV vaccination during pregnancy.

**Population:** General female population in participating Nordic countries.

**Summary:** The study is being conducted in Denmark, Norway, Iceland and Sweden. As described in Section 2.1 above, in the Nordic countries every citizen has a unique PIN which is registered in a national computerized database. An important part of this study is to establish a baseline measurement of HPV infection as well as HPV-related diseases before the introduction of vaccination. This will serve as the starting point for future follow-up. By taking advantage of the nationwide registries and the corresponding biological sample repositories in the four participating Nordic countries, the overall and age-stratified incidence of disease will be assessed from 1 to 3 years before the introduction of GARDASIL in the Nordic region, until 5 years after the introduction of GARDASIL (first follow-up). This includes: 1) the incidence of cervical cancer and high-grade cervical intraepithelial neoplasia (CIN2/3); and 2) the incidence of other HPV-related female genital diseases including vaginal and vulvar cancer as well as high-grade vulvar and vaginal intraepithelial neoplasia. During the follow-up the overall and age-stratified incidence of the diseases will also be assessed among women who have been vaccinated and in those who have not, by linkage to the vaccination register in each country.

The incidence of HPV6/11/16/18-related cervical cancer and CIN2/3, and cervical cancer and CIN2/3 related to HPV types other than 6/11/16/18 will also be assessed before and after the implementation of HPV vaccination. This will be done by randomly selecting and retrieving the relevant tissue blocks from 200 women with cervical cancer and 300 women with CIN2/3 from each of the participating Nordic countries. These tissue blocks will be cut in a central laboratory (Histolab, Gothenburg, Sweden) and will be tested for HPV in a central laboratory (Dept. of Clinical Microbiology Malmö University Hospital, Sweden).

The HPV type distribution in the general female population (18–45 years of age) in each of the participating countries will be assessed for the years preceding the introduction of vaccination (2006–2007) and around 5 years after (2011–2012). This has/will be done by selecting liquid-based cytology samples from 2000 randomly selecting women in each country. These samples will be tested for HPV in the central laboratory.

The study also has a safety component. Using the Medical Birth Registry in the respective country, babies born with congenital anomalies after the implementation of HPV vaccination will be identified. Subsequently, the mothers' records will be linked to the Vaccine Registry to identify those who have received GARDASIL during pregnancy. An expert panel on teratology, consisting of one expert from each participating country will review all the available material and search for any pattern indicative of an association between GARDASIL exposure in the mother and the subsequent congenital anomaly in the baby. Finally, the incidence of congenital anomalies in babies born to women with pregnancy exposure to HPV vaccine will be compared to the incidence in the general population.

The study will also characterize the 18–45-year-old women from the general population in the participating Nordic countries. This will be done by conducting two questionnaire surveys which will collect information such as history of genital warts and other sexually transmitted diseases, sexual behavior, life style habits such as smoking, alcohol consumption, contraceptive habits, and pregnancy history. The first survey has been completed and enrolled nearly 70,000 women from the general female population of the four countries [8]. The second survey will be conducted in 2011–2012 on a new random sample to collect similar data as at baseline. It will also be possible to link all these women with different types of registries to obtain information on previous and current cervical cancer screening history. The data from the survey part of the study can be used to get an indication of whether changes have occurred in sexual habits or screening habits after the introduction of HPV vaccination.

### 2.3. Protocol V501-018: a long-term immunogenicity, safety, and effectiveness study of GARDASIL among adolescents who received GARDASIL at 9–18 years of age

**Objectives:** To evaluate the safety, immunogenicity, and long-term effectiveness in preventing HPV6/11/16/18-related infection or disease.

**Population:** 1078 adolescents that were vaccinated between the ages of 9 and 18 years in the context of Protocol 018 [9].

**Summary:** This study will evaluate the long-term immunogenicity and safety of GARDASIL in adolescents that were vaccinated between the ages of 9 and 18 years. In addition, the study will evaluate the effectiveness of GARDASIL in preventing disease caused by HPV6/11/16/18. This 10-year immunogenicity, safety, and effectiveness study will provide the first long-term data among adolescents.

This study is an extension of Protocol V501-018 (NCT00092547) which was originally designed to assess the safety and immunogenicity of GARDASIL in 9–15-year-old girls and boys. The original protocol and the primary results have been described [9]. In the original study, 1781 sexually-naïve children were assigned (2:1) to vaccine or saline placebo at day 1, months 2 and 6. Between months 30–36, all placebo recipients were offered vaccine following the same regimen. All subjects who received 3 doses of vaccine were eligible to participate in the extension. In total, 1078 subjects (501 boys and 577 girls) from 10 countries in North America, Latin America, Europe, and Asia were enrolled in the extension. The total of the vaccination phases and follow-up period will be 126 months. Thus, the original vaccine arm will be followed up for 10 years post-dose 3, and original placebo arm will be followed up for 7.5 years post-dose 3.

An interim analysis will be conducted at 5.5 years post-dose 3. Serum samples will be collected and a physical exam will be performed annually until the age of 16 [5]. Starting at age 16, twice yearly visits will include the collection of sexual history and genital clinical specimens.

Immunogenicity data will be described by age and gender. The incidence of HPV6/11/16/18-related persistent infection and cervical, vaginal, and vulvar disease in females will be estimated and observationally compared to the incidence of the same outcomes among placebo subjects in previous Phase II/III trials [4,10]. The incidence of HPV6/11/16/18-related persistent infection and penile, perineal, and perianal disease in males will be estimated and observationally compared to the incidence of the same outcomes among placebo subjects in an ongoing adult male study [11]. If observed, the risk factors for vaccine failure will be examined. Serious adverse experiences (vaccine or procedure-related) and pregnancy outcomes will be monitored.

There is no formal hypothesis being tested in the extension, thus the concept of power is not completely relevant. However, it is important to consider the potential of the study to address the effectiveness objectives. At each analysis time point, the cumulative (from the start of this extension) and current (incremental for current period) incidence rate for effectiveness endpoints will be computed, along with the associated 95% confidence intervals. The assumed vaccine efficacy, attack rate in unvaccinated subjects, and predicted person-years-at-risk that will accrue by the end of the 10-year follow-up period will be used to predict the number of cases likely to be observed and will inform the decision to continue the study. Consideration will be given to discontinuing the effectiveness component of the study when the estimates of endpoint incidence in the current follow-up period will be too wide to provide meaningful information, i.e., when the width of the confidence interval for a current incidence rate exceeds half of the assumed rate in unvaccinated subjects.

### 2.4. Protocol V501-031-00: a post-licensure surveillance program for the safety of GARDASIL in a managed care organization setting

**Objectives:** To detect potential safety signals in females.

**Population:** 44,000 females aged 9–26 in managed care organization databases.

**Summary:** This observational surveillance program is designed to serve as a preliminary tool for detecting potential safety signals in females who received GARDASIL. There will be 3 components in this surveillance program, including the monitoring of general safety, the surveillance of safety regarding inadvertent exposure during pregnancy, and safety regarding selected autoimmune disorders.

This program is being conducted in collaboration with two large U.S. managed care organizations (MCOs), Kaiser Permanente Southern California and Kaiser Permanente Northern California and overseen by an independent Safety Review Committee consisting of five experts in vaccine safety and disease areas of interest. Both MCOs have participated in the CDC-funded Vaccine Safety Datalink (VSD) project (see accompanying manuscript by Markowitz et al. (in press) for a description of the VSD), and have had extensive experience in both CDC-funded and industry-funded studies of post-licensure vaccine safety surveillance. This surveillance will take advantage of existing MCO computerized databases and infrastructure. At the MCOs, vaccination and healthcare records are routinely entered into the computerized databases and can be linked by a unique identifier. Therefore, the data are collected prospectively and can be analyzed at a later time point retrospectively. The MCO setting allows for the efficient accrual of a large population and to generate safety data in a timely fashion.

This post-licensure safety surveillance program will consist of a primary study population of 44,000 females between ages 9–26 at receipt of first dose of GARDASIL (current indicated age range in the U.S.) who are members of the participating MCOs and have completed the 3-dose regimen within 12 months with an interval of at least 28 days between dose 1 and dose 2 and 12 weeks between dose 2 and dose 3. In addition, a secondary study population will consist of females of any age who received at least one dose of GARDASIL at the MCOs during the time period of accrual of the primary study population.

The sample size was requested by the FDA. As this post-licensure study is designed to describe the incidence of adverse events subsequent to vaccination with GARDASIL, no formal hypothesis will be tested. The study is powered to detect an increased risk for a specific adverse event with an  $\alpha = 0.05$  (one-sided). The study will have more than 90% power to detect a relative risk of 3 for an adverse event for which incidence is known to be 1 per 10,000 unvaccinated girls (followed for 180 days each), and nearly 100% power to detect a relative risk of 5 for such an adverse event.

Within these 44,000 females, there will be a sub-analysis of approximately 25,000 girls aged 9–15 years at receipt of the first dose of GARDASIL. This sub-population, with similar assumptions as mentioned above, will have an 80% power to detect a relative risk of 3 for such an adverse event (with incidence known to be 1 per 10,000 girls).

For the evaluation of general safety in the primary study population, an evaluation of potential safety signals associated with diagnoses from hospitalizations and emergency room visits occurring within 60 days post-vaccination for each dose in the 3-dose regimen. The recipients of GARDASIL will serve as their own controls twice, namely the pre-vaccination and the post-vaccination periods. The pre-vaccination own control is a 6-month period prior to vaccination with GARDASIL. The post-vaccination control is a 6-month period after completion of the 3-dose series.

In addition, the study will monitor miscarriages and congenital anomalies among women inadvertently exposed to GARDASIL during pregnancy. Pregnancy outcomes will be examined up to 6-months subsequent to the resolution of pregnancy for congenital anomalies. Ascertainment of a miscarriage or congenital anomaly in the women exposed to GARDASIL during pregnancy will be made via independent review of the medical records by a pregnancy case review committee of experts masked to vaccination status of the mothers. All medical records will then be reviewed by a safety review committee for detecting any emerging patterns or evidence suggesting an association between use of GARDASIL and miscarriage/congenital anomalies.

Although there was no indication of safety signals in the clinical program of GARDASIL [12], FDA requested that new onset of select conditions be monitored. The pre-specified autoimmune conditions for this surveillance study are:

- *Autoimmune/Rheumatologic*: immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AHA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and juvenile rheumatoid arthritis (JRA);
- *Endocrine*: type 1 diabetes, Hashimoto's disease, Graves' disease;
- *Neurology/Ophthalmology*: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), other demyelinating diseases of the CNS, vaccine-associated demyelination, Guillain-Barre syndrome (GBS), neuromyelitis optica, optic neuritis, and uveitis.

For monitoring these conditions in the recipients of GARDASIL, outpatient records, in addition to the emergency room visits and hospitalization records, will be used, as these conditions are almost exclusively diagnosed at outpatient visits.

### 2.5. GARDASIL pregnancy registry

**Objectives:** To collect further data regarding the safety of GARDASIL in pregnancy.

**Population:** General population of women in the United States, Canada, and France.

**Summary:** Because GARDASIL is recommended for women of child-bearing age, it is acknowledged that inadvertent pregnancy exposures are likely to occur in the post-licensure setting. To collect further data regarding the safety of GARDASIL in pregnancy, Merck and Co., Inc. has established a pregnancy registry [13].

The registry is based on post-licensure reports of pregnancy exposures that are spontaneously reported to the company. The pregnancy registry is conducted in the United States, Canada, and France; however, regardless of the country of origin, all reports of exposure during pregnancy that are received by Merck and Co., Inc. or Sanofi Pasteur MSD, are entered into the Merck safety database termed the New Worldwide Adverse Experience Systems (NWAES) and are reviewed by registry personnel [14]. The NWAES database

serves as a repository for the reporting of all serious adverse events and adverse events of special interest that are reported to Merck & Co., Inc. Reports are generally submitted to Merck by health care providers, consumers, and regulatory agencies. Reporting is spontaneous and voluntary and reports are included in the database regardless of the reporter's, or Merck's, assessment of causality. External experts are consulted as needed.

The pregnancy registry enrollment criteria include: 1) an identifiable woman (presence of a unique patient identifier); 2) exposure within one month prior to the date of onset of the last menstrual period or at any time during pregnancy; 3) identification of a health care provider; and 4) residency in a country where the registry is active. Reports are classified by the timing of registry notification in relation to pregnancy outcome. Prospective reports are those received before the outcome of the pregnancy is known. Retrospective reports are those received after the outcome of the pregnancy is known and include reports made after prenatal testing has identified an abnormality, even if the pregnancy outcome has not yet occurred.

The primary outcomes of interest include live births, fetal deaths, elective terminations, spontaneous abortions, and birth defects. Birth defects are defined according to the Center for Disease Control's Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [15,16]. Rates for birth defects are calculated on prospective reports using MACDP methodology: prevalence at birth, expressed as the number of affected cases (liveborn, fetal deaths, and terminations at 20 weeks or later) per 100 liveborn neonates. The overall rate of spontaneous abortion is calculated as the number of spontaneous abortions per the total number of natural pregnancy outcomes. Because the natural outcome of a pregnancy that was terminated is unknown, elective abortions are not included in rate calculations. The rates of fetal death are calculated as the number of fetal deaths per the number of live births plus fetal deaths. Confidence intervals (CIs) for the rates are calculated following the procedures of Lilienfeld and Stolley [17].

Annual reports including cumulative data are prepared and then reviewed by a consultant teratologist. The annual reports are distributed to health care providers who report cases of exposure to the registry [18]. Because of the variability of rates of anomalies there is no definitive definition of a signal; however, the evaluation of pregnancy outcomes that were reported in the first two years the registry has been active have generated no safety concerns [18]. The rates of spontaneous abortions and major birth defects were not greater than the unexposed population rates. Although no adverse signals have been identified to date, the HPV6/11/16/18 vaccine is not recommended for use in pregnant women. Health care professionals are encouraged to enroll patients who inadvertently receive the vaccine into the pregnancy registry. Information on reporting to the registry can be found in the prescribing information in countries where the registry is active.

### 2.6. Other

In addition, there are two ongoing clinical trials in women aged 24–45 [19] and in males aged 16–26 [11], which may be extended into long-term follow-up studies to follow these populations.

## 3. Post-licensure commitment studies in collaboration with Sanofi Pasteur MSD in Europe

### 3.1. Surveillance of HPV type distribution in women attending organized cervical cancer screening in Italy

**Objectives:** To evaluate non-vaccine type replacement following the introduction of HPV vaccination.

**Population:** Women aged 18–64 years followed up within regional organized cervical screening programs.

**Summary:** There are more than 100 known HPV types and biologic history of the virus does not suggest any competition between HPV types. Nevertheless it has been hypothesized that the elimination of HPV vaccine types through vaccination could lead to an increase in the prevalence of oncogenic HPV types other than HPV16/18. This mechanism would be called type replacement [20].

In Europe, studies on HPV type replacement are being conducted in Nordic countries (see Section 2), but such studies are lacking in subjects from non-Nordic regions. Following the licensure of GARDASIL, the EMA requested that HPV type prevalence and potential non-vaccine type replacement in the post-vaccine era be examined in non-Nordic European countries. Therefore, a project is being initiated in Italy based on the existence of regionally organized vaccination and cervical cancer screening programs managed by the public health system.

At present, little is known about the prevalence and distribution of HPV types in Italy and only a few studies, mainly based in northern Italy, have investigated the prevalence of cervical HPV infection in healthy women [21]. The goal of this project is to obtain baseline HPV prevalence data in Italy prior to the introduction of HPV vaccination, and to use these data to evaluate non-vaccine HPV type replacement following the introduction of HPV vaccination. Several studies providing data on HPV type specific prevalence and distribution have been conducted or are ongoing in Italy. In order to complement these data, the primary objective of the study is to estimate the overall and age-stratified prevalence of HPV6/11/16/18 and high-risk types other than HPV16/18 in women aged 18–64 years. Secondary objectives include the estimation of the overall and age-stratified prevalence of HPV6/11/16/18, high-risk types other than HPV16/18, and low-risk types other than HPV6/11, stratified by cytological results and/or vaccination status (sample size permitting). Samples will be analyzed in a single reference laboratory. Basilicata is the only Italian region that has active, free of charge vaccination programs for four cohorts of young women, and has a high rate of compliance of organized screening. Women aged 25–64 years attending organized cervical cancer screening will be included during the routine screening visit, whereas younger women aged 18–24 years will be invited by letter.

It is also envisaged, in regions where both vaccination and cervical screening are organized, to implement an electronic data collection system that will link screening data with vaccination data, using a unique identifier, to support the evaluation of type replacement in future cross-sectional studies which will include stratification by vaccination status. Multicentre population-based cross-sectional studies could be repeated every 3–5 years, with similar designs in order to allow comparability of data over time.

### 3.2. HPV surveillance study in Belgium

**Objectives:** To evaluate HPV prevalence and distribution in cervical disease.

**Population:** General female population  $\leq 64$  years, attending cervical cancer screening.

**Summary:** In 2003, the overall age-standardized incidence rate of cervical cancer in Belgium was 9.8 per 100,000 [22]. A recent study has shown the age-standardized high-risk HPV prevalence in Belgium women aged 30–64 years is one of the highest among the 14 European countries that were considered, ranging from 2% in Spain to 12.5% in Belgium [23]. In the framework of the EMEA commitment to assess HPV type prevalence and non-vaccine type replacement, a long-term project is being implemented in Belgium, based on cross-sectional studies in the general female population attending cervical cancer screening, to be repeated every 3 years. The study will evaluate HPV prevalence and distribution in cervical

disease in screened women up to 64 years of age. Cytology and histology samples will be sent to a central laboratory (Laboratory for Clinical Pathology, RIATOL, Antwerp, Belgium) and HPV genotyping will be performed using a multiplex real-time PCR assay targeting E6/E7 genes of 14 high-risk HPV types. Stratification by HPV vaccination status is also planned (with vaccination status collected through self-administered questionnaires and validated by chart review, as there is no vaccination registration currently in place in Belgium). The first study (baseline study) will include 3000 women <27 years and 3000 women aged 27–64 years and will be conducted in 2009–2011 across the whole Belgian territory.

## 4. Post-licensure commitments in collaboration with Sanofi Pasteur MSD in France

GARDASIL vaccination has been funded in France since July 2007 and recommended for 14-year-old girls and 15–23-year-old virgin women (or no later than one year after the onset of sexual activity). Following the introduction of HPV vaccination in France, official bodies within the French Ministry of Health requested that a series of public health impact studies be conducted. To address this broad commitment, the following studies were implemented via collaboration between Sanofi Pasteur MSD (founded in 1994 as a joint venture between Sanofi Pasteur and Merck and Co., Inc.) and independent experts.

### 4.1. Study of GARDASIL and auto immune diseases using the PGRx<sup>®</sup> Information System

**Objectives:** To assess whether the use of GARDASIL is associated with a modified risk of nine autoimmune diseases.

**Population:** General population of women aged 14–26.

**Summary:** There has been a lot of concern regarding a potential link between hepatitis B vaccination and the occurrence of multiple sclerosis or other demyelinating diseases of the central nervous system in France. With this historical background in mind, French health authorities requested that a surveillance study for several autoimmune and other inflammatory diseases among girls and young women exposed to HPV vaccination was set up [24]. The PGRx<sup>®</sup> (Pharmacoepidemiological General Research) Program was developed in 2006 for conducting pharmacoepidemiological studies using prospective case-control designs. A particular focus of PGRx is to provide the opportunity to study the relationship between exposure to various drugs and vaccines and the risk of occurrence of rare autoimmune/inflammatory diseases. Case-control studies are commonly regarded as the most appropriate design to investigate risk determinants of rare diseases because of the very large population sizes that would be required for the identification of uncommon events in longitudinal cohort studies.

Using a network of more than 200 French referral centres, the PGRx program collects medical information prospectively from incident cases with a variety of selected diseases on a routine basis. In addition, the program includes a large population-based cohort of potential control subjects who are recruited by general practitioners. For both cases and controls, exposures to about 300 drugs/vaccines are documented through guided telephone interviews and review of their medical records and data on lifestyle and medical and familial risk factors are gathered.

The objective of the study is to assess the potential association between the use of GARDASIL and the occurrence of the following groups of autoimmune/inflammatory diseases: Guillain-Barré syndrome, multiple sclerosis/other demyelinating diseases of the central nervous system, systemic lupus erythematosus, polymyositis/dermatomyositis, inflammatory arthritis, autoimmune thyroiditis, type 1 diabetes and idiopathic thrombocytopenic

**Table 1**  
Ongoing post-licensure surveillance studies of GARDASIL.

Ongoing studies	Objectives	Study population	Questions addressed										
			Duration of protection	Impact on genital warts	Safety <sup>†</sup>	Long-term Immunogenicity	Impact on any HPV infection/disease	Impact on screening and sexual behavior	Vaccine coverage and compliance	Potential for HPV type replacement	Attitudes towards HPV vaccination	Burden of HPV infection/disease	
<b>2.1. Protocol V501-015: Long-term Follow-up study (LTFU)</b> (Denmark, Iceland, Norway, Sweden)	To evaluate the safety, immunogenicity, and long-term effectiveness.	5496 women aged 16–23 who participated in FUTURE II [4]	✓		✓	✓					✓		✓
<b>2.2. Protocol V501-033: Vaccine Impact in Population study (VIP)</b> (Denmark, Norway, Iceland and Sweden)*	To describe the impact on any HPV disease (excluding genital warts) and HPV6/11/16/18-related infection and disease in the general population. To evaluate pregnancy outcomes.	General female population in participating countries	✓		✓			✓	✓		✓		✓
<b>2.3. Protocol V501-018: Adolescent Study</b> (10 countries)	To evaluate the safety, immunogenicity, and long-term effectiveness	1078 adolescents that were vaccinated between the ages of 9 and 18 years [9]	✓	✓	✓	✓							
<b>2.4. Protocol V501-031: Safety Study</b> (United States)	To detect potential safety signals in females.	44,000 females aged 9–26 in managed care organization databases			✓								
<b>2.5. GARDASIL pregnancy registry</b> (Canada, France, US)	To collect further data regarding the safety of GARDASIL in pregnancy.	General population of women in the United States, Canada, and France			✓								
<b>3.1. Surveillance of HPV type distribution</b> (Italy)	To evaluate non-vaccine type replacement following the introduction of HPV vaccination.	Women aged 18–64 years followed up within regional organized cervical screening programs						✓			✓		✓
<b>3.2. HPV surveillance</b> (Belgium)	To evaluate HPV prevalence and distribution in cervical disease.	General female population ≤64 years, attending cervical cancer screening						✓			✓		✓
<b>4.1. PGRx autoimmune disease study</b> (France)	To assess if GARDASIL is associated with a modified risk of autoimmune diseases.	General population of women aged 14–26			✓								
<b>4.2. HPV-EST study</b> (France)	To assess the impact on abnormal Pap smears, CIN, and invasive cancers and to document the impact of vaccination on screening coverage.	Women born <1992 living in Alsace and followed within the EVE organized screening program						✓	✓				✓



purpura. The study targets women aged 14–26 years, living in France, with no prior reported history of the diseases under investigation, who are able to read the interview guide and answer a telephone interview questionnaire, and who accept to participate in the study. Cases and controls will be matched on age, gender, date of the telephone interview, region of residence and other relevant parameters.

Prior to the study launch in 2007, scientific committees convened for each disease group and decided on the target sample sizes that are both feasible in terms of recruitment and provide sufficient statistical power. Accordingly, the retained target numbers for case recruitment over a 3-year period were 75 cases of multiple sclerosis/other demyelinating diseases of the central nervous system, 90 cases of connective tissue disorders (i.e., systemic lupus erythematosus, inflammatory arthritis and polymyositis/dermatomyositis), 90 cases of endocrine autoimmune diseases (i.e., type 1 diabetes, Grave's disease and other autoimmune thyroiditis), 45 cases of idiopathic thrombocytopenic purpura and 9 cases of Guillain-Barré syndrome. These sample sizes are powered to allow detection of risk increases, i.e., odds ratios, ranging from 2 to 4 except for Guillain-Barré syndrome for which, owing to its rarity, the minimum detectable odds ratio at the given level of statistical significance is 12. The main analyses are planned 36 months after recruitment of the first index case.

#### 4.2. The Eastern France (EST) survey: impact of vaccination against human papillomavirus types 6, 11, 16, and 18 on cervical morbidity (with a focus on CIN2/3 lesions)

**Objectives:** To assess the impact on abnormal Pap smears, CIN, and invasive cancers and to document the impact of vaccination on screening coverage.

**Population:** Women born <1992 living in Alsace and followed within the EVE organized screening program.

**Summary:** There is no organized cervical cancer screening program in France but pilot initiatives have been set up in several regions. For example, the EVE program was created in 1990 to promote and organize cervical cancer screening in the Alsace region [25–27]. This program offers cervical screening, including both cytological and histological analyses, for a population of approximately 480,000 women aged 25–64 years-old among whom 45,000 are aged 25–29 years-old. It is estimated that approximately 70–75% of the overall female population living in this region attend cervical cancer screening. Taking advantage of the EVE program, the EST study was designed to assess the incidence of HPV-related CIN2/3 disease before and after the introduction of GARDASIL. Secondary objectives are to investigate the impact of vaccination on the combined group of cervical morbidities (i.e., abnormal Pap smears, CIN and invasive cancers), and on the coverage of cervical cancer screening.

The EST survey will include a baseline analysis for 2001–2007, i.e., the period prior to the introduction of HPV vaccines, and a prospective follow-up component after 2007. For the primary objective, the incidences of CIN 2/3 will be compared across two triennial periods 2004–2007 and 2013–2016 and within the sub-population of 25–29-year-old women. In light of the HPV vaccination policy in France and particularly the extensive catch-up vaccination program for 15–23-year-old women, the vaccine coverage rate among women aged 25–29 years-old during the period 2013–2016 is anticipated to be 85%. Under the assumptions of an expected 3-year cumulative incidence of CIN 2/3 lesions of 0.09% (at baseline in 2004–2007), the study will allow a 50%–reduction in the incidence of CIN 2/3 lesions to be detected in 2013–2016. However, under the assumption of a lower vaccine coverage, e.g., 50%, the study will likely lack statistical power to demonstrate a significant decrease in the incidence of CIN 2/3 lesions as early as this.

Therefore, additional follow-up analyses are planned on a regular basis with a final analysis in 2024.

#### 4.3. Impact of HPV vaccination on acceptability and behavior (REMPAR)

**Objectives:** To assess the determinants of HPV vaccination acceptability.

**Population:** Physicians and patients.

**Summary:** The aim of the REMPAR (Recherche – Evaluation des Moyens de Prévention anti-HPV en Rhône-Alpes) project is to assess the determinants of HPV vaccination acceptability, from both the physician's and patient's perspective. It will also assess the impact on the prevention of sexually transmitted infections (STI), as well as the ability of HPV vaccination to efficiently complement cervical cancer screening in France in terms of compliance, efficacy, and access to the hard-to-reach. In particular, the project will evaluate whether the combination of screening and vaccination is well understood by the target population for vaccination, if HPV vaccination is effective in populations not well screened, and if vaccination modifies attitudes towards screening and STIs.

The REMPAR project consists of a series of four sub-studies: 1) HPV-MED—a study of the acceptability of HPV vaccination by physicians, based on a self-administered questionnaire that collects information on overall practices to prevent cervical cancer (including both cervical screening and vaccination), perception of, and compliance to HPV vaccination by physicians; 2) HPV-FEM—a study of the acceptability of HPV vaccination by women considering vaccination either for themselves or for their daughters, based on a self-administered questionnaire that evaluates the understanding of cervical cancer prevention and the perception of HPV vaccination; 3) HPV-VAC—a study of the perceived role of HPV vaccination in the prevention of cervical cancer and STIs in 14–23-year-old women, using a self-administered questionnaire provided by the physician; and 4) HPV-COL—a prospective collection by physicians of cervical screening data and vaccination data in the general female population aged 18–65 years.

These studies have some overlapping objectives: 1) to estimate the acceptability of HPV vaccination by physicians who may be administering GARDASIL (HPV-MED study) and by the female population targeted by HPV vaccination (HPV-FEM and HPV-VAC studies); 2) to evaluate the impact of HPV vaccination on the perception of STI risk in teenagers and young women (HPV-VAC study); 3) to characterize the target population aged 14–23 years (HPV-VAC study); and 4) to evaluate the impact of HPV vaccination on screening compliance and practices in the female population aged 14–65 years who would benefit from cervical cancer prevention, including HPV vaccination and Pap testing (HPV-COL study).

The REMPAR studies involve a representative sample of physicians (stratified by medical specialty, administrative area, geographical area, and gender). The project will be conducted over three time periods of 1–4 weeks each: 1) introduction of HPV vaccination; 2) introduction of vaccination plus one year; and 3) introduction of vaccination plus three years. Questionnaires are standardized and have been validated by focus groups. Both quantitative and qualitative analyses will be performed and will also estimate the impact on hard-to-reach populations.

#### 4.4. Impact of HPV vaccination on cervical cancer screening using the CRISAP-RA database

**Objectives:** To evaluate possible behavioral changes in vaccinated women with respect to screening attendance.

**Population:** Women undergoing screening in the Rhône-Alpes region.

**Summary:** CRISAP (*Centre de Regroupement Informatique et Statistique en Anatomie et cytologie Pathologiques*) is an established database in France that anonymously collects histological and cytopathological data in order to utilize the information on a regional or national level. The aim of this project is to evaluate possible behavioral changes in vaccinated women with respect to screening attendance in the years following vaccination, in the Rhône-Alpes (RA) region of France. Two hypotheses have been postulated: 1) vaccination provides women with a false sense of security, so that they refrain from attending the regular screening program when reaching adult age; or 2) vaccination sensitizes young women to the importance of attending regular screening, thereby improving overall screening attendance. Using the CRISAP-RA database, the impact of vaccination on screening attendance will be evaluated based on the number of Pap smears performed between 2004 and 2015, stratified by age and also taking into account low income categories. The impact of HPV vaccination information campaigns on cervical cancer screening, regardless of whether women were vaccinated or not, will also be explored.

## 5. Other European initiatives in collaboration with Sanofi Pasteur MSD

### 5.1. Impact of HPV vaccination on the incidence of genital warts: EFFICAE study

**Objectives:** To evaluate the impact of vaccination on genital warts among females, and the indirect impact on the incidence of genital warts among males.

**Population:** 39,000 randomly selected women aged 15–26 and ~93,000 randomly selected men aged 20–30.

**Summary:** The EFFICAE study (*EFFicacité de la vaccination HPV sur l'Incidence des Condylomes Acuminés Externes*) consists of two parallel observational cross-sectional studies to evaluate the direct impact of vaccination on the incidence of genital warts among females, as well as the indirect impact on the incidence of genital warts among males.

The studies will include approximately 39,000 randomly selected women aged 15–26 years recruited by 150 gynecologists and 93,000 randomly selected men aged 20–30 years recruited by 420 dermatologists. Proportions of women or men presenting to their gynecologist or dermatologist with a first episode of genital warts will be analyzed. Four-month periods of observation are planned two years apart (2008 and 2010) in the female population and four years apart (2009 and 2013) in the male population. In parallel, a comparative analysis of the number of cases of genital herpes as a reference disease (sexually transmitted disease with a similar epidemiology, easily diagnosed, and not targeted by HPV vaccination) will be performed.

### 5.2. HPV surveillance in Sweden

**Objectives:** To evaluate the burden of genital warts, disease awareness, and vaccine acceptability.

**Population:** 1) Male and female patients with a documented diagnosis of genital warts; 2) parents of girls and boys randomly selected from the Swedish population.

**Summary (CODIS):** Like in other Nordic European countries, cancer registries are in place in Sweden to evaluate morbidity and mortality. With the introduction of a nationwide vaccination program, Sweden is planning to create a register which will link already established cancer and vaccination registries. However, there is currently no registry for genital warts. Thus, a retrospective study to generate baseline data for future evaluation of the impact of HPV vaccination on genital warts is being initiated in Stockholm, namely

the CODIS study (COndyloma burden of disease in Stockholm). The aim is to evaluate the burden of genital warts defined as the prevalence of genital warts in patients visiting 10–12 selected youth clinics in Stockholm. The prevalence of genital warts will be calculated by database extractions from the 2004–2008 time periods. At least 1500 male and female patients with a documented diagnosis of genital warts and/or registered prescription of podophyllotoxin or imiquimod for genital warts will be included.

**Summary (Disease awareness and vaccine acceptability):** Sweden has also engaged in studies evaluating disease awareness and vaccine acceptability and its correlates. The aim is to study the awareness of HPV vaccination and the attitude towards HPV vaccination among the parents of children aged 12–15 years and among young adults. Approximately 16,000 parents of girls and 4000 parents of boys, randomly selected from the Swedish population, have been invited to participate in the survey for evaluating the parents' awareness and attitudes, while 16,000 women and 4000 men aged 18–30 years have been randomly invited to participate in the survey for the young adult cohort.

Dahlström et al. have recently published the survey undertaken in parents concluding that the willingness to vaccinate their children was reasonably high and information about vaccine safety and efficacy was important to parents as well as information about HPV and the vaccine [28].

### 5.3. Other

Initiatives are currently being implemented in Germany and other European countries to establish baseline prevalence data prior to vaccination implementation to be able to estimate the impact of HPV vaccination on HPV infection and HPV-related disease incidence (genital warts and cervical dysplasia).

## 6. Other surveillance efforts

### 6.1. EudraVigilance

EudraVigilance is a data processing network and management system that was launched in December 2001 for reporting and evaluating suspected adverse reactions during the development, and following the marketing authorization, of medicinal products in the European Economic Area (EEA). It supports the electronic exchange of suspected adverse reaction reports between the EMA, national Regulatory and Public Health Authorities, marketing authorization holders, and sponsors of clinical trials in the EEA. It constitutes a powerful tool for the EMA and national authorities in monitoring the safety of medicinal products and is also one of the main pillars of the European risk management strategy. EudraVigilance facilitates the risk management process at several levels including risk detection, assessment, minimization, and communication.

### 6.2. HPV surveillance in Australia

**Objectives:** To support the HPV vaccination program and monitoring and to evaluate the impact of HPV vaccination of genital warts.

**Population:** General population.

**Summary:** In 2007, Australia introduced a national HPV vaccination program. Through the program, the Australian government provides GARDASIL free to girls aged 12–13 years on an ongoing basis. There is also a two-year period where the vaccine is provided free for girls and young women aged 14–26 years.

A national HPV register was implemented by the Australian government to support the HPV vaccination program and for ongoing monitoring and evaluation. The register, hosted by the Victorian Cytology Service, receives data from all states and territories in

Australia and from all types of vaccination providers. The HPV register records data about the doses administered, select demographic data, and details about the healthcare professional administering the vaccine. The register will send completion of vaccination statements to vaccinees, reminders to those who are overdue for vaccination, notify vaccinees of the need for a booster dose, if required, and provide reports on vaccination status to vaccination providers. De-identified data from the register will be used to inform policy making and for approved research. The HPV register will also facilitate cross-referencing of vaccination data with information from cervical cytology or cervical cancer registries for evaluation purposes.

In 2008, CSL Biotherapies sponsored a national Genital Warts Surveillance Study. This study involves the collection, analysis, and reporting of routinely collected clinical data from 10 to 12 large sexual health services across Australia. Information on demographics, recent travel history, sexual behavior, HPV vaccination status, and past or current diagnosis of genital warts are collected from all clients attending the participating services.

It is estimated that 10,000 patients younger than 25 years attend the 10 participating sexual health services. Assuming a genital warts diagnosis rate of 10% among clinic attendees and power of 80%, the surveillance system will be able to detect, as statistically significant at the 0.05 level, a change between two years in the diagnosis rate of genital warts of 0.9% or greater (i.e., from 5.0% to 4.1%). Initial data from the genital warts surveillance study from the Melbourne Sexual Health Centre has shown a rapid and marked reduction in the incidence of genital warts following the introduction of GARDASIL [29]. The proportion of both men and women diagnosed with genital warts was significantly lower in 2008, compared with 2004–2007.

### 6.3. HPV surveillance in Canada

**Objectives:** To collect reports on adverse events following immunization.

**Population:** General population and 12 pediatric hospitals.

**Summary:** In January 2007, the Public Health Agency of Canada's National Advisory Committee on Immunization (NACI), which advises on recommendations for the use of new vaccines, recommended that all Canadian girls and women aged 9–13 be vaccinated against HPV, as well as older girls and women who might already be sexually active but not infected with the virus [30]. Subsequent to this recommendation, the Canadian federal government allocated \$300 million (Cnd) per capita over three years for provinces and territories to support the launch of a national human papillomavirus vaccine [31]. All of the ten provinces and three territories have responded by introducing GARDASIL through school-based programs [32].

From the perspective of vaccine safety, as with all licensed vaccines in Canada, Health Canada and the Public Health Agency of Canada conduct ongoing monitoring to ensure its continued safety and efficacy. The Public Health Agency of Canada coordinates and supports the Canadian Adverse Events Following Immunization Surveillance System, which collects reports from health care providers on adverse events following immunization. Moreover, there is an active surveillance system that is based out of 12 pediatric hospitals across Canada, called IMPACT (Immunization Monitoring Program ACTIVE).

The ability to evaluate the effectiveness and the impact on HPV disease burden of the vaccine through linked databases and registries is recognized as an important element to the ongoing surveillance of the provincial HPV vaccination programs. Most notably, two studies have evaluated the incidence and prevalence of genital warts in Canada, as anogenital warts are associated with a significant burden of illness and costs to the Canadian health-

care system [33,34]. These results provide a baseline to assess the future impact of GARDASIL with respect to effectiveness and duration of protection at a population level, representing an important indicator of the success of the Canadian HPV vaccination program.

Several provinces are in the process of establishing specific HPV vaccination surveillance programs towards assessing the impact of the vaccine on several different aspects such as health care provider and public education and awareness of HPV, vaccination uptake, circulating HPV strains, impact on anogenital warts, pre-cancerous lesions, other related HPV-related cancers, and sexual behavior. Such future surveillance and evaluation strategies would provide information to decision makers around optimal HPV prevention strategies involving the integration of primary and secondary prevention [35].

### 6.4. CDC sponsored initiatives for monitoring the safety and effectiveness of GARDASIL

Since licensure, the CDC and the FDA have been monitoring the safety of GARDASIL. As for all vaccines licensed in the United States, there are three systems used to monitor the safety of vaccines: 1) the Vaccine Adverse Event Reporting System (VAERS); 2) the Vaccine Safety Datalink (VSD) Project; and 3) the Clinical Immunization Safety Assessment (CISA) Network. The CDC will also monitor disease impact, including cancer, cancer precursors, and genital warts, and HPV type specific prevalence. Vaccine coverage and implementation will also be assessed through several initiatives. These efforts are summarized in the accompanying manuscript by Markowitz et al. (in press).

## 7. Summary

Vaccines are introduced via population-based vaccination programs as soon as their efficacy is shown to be higher than any potential risk. The long-term effectiveness and full safety profile of any new healthcare intervention or technology is frequently not fully known until it can be monitored through long-term post-licensure surveillance programs. The surveillance efforts for GARDASIL represent one of the most comprehensive vaccine surveillance programs to date. While public health authorities have enabled widespread access to GARDASIL vaccination based on positive clinical trial data, the overall GARDASIL surveillance program is critical in order to validate its long-term safety and effectiveness in the vaccinated population.

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employees of Sanofi–Pasteur MSD. Richard M Haupt is an employee of Merck and Company, Inc., and holds stock/stock options.

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