Human Papilloma Virus Immunization in Adolescent and Young Adults

A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions

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Background: The large-scale implementation of human papilloma virus (HPV) immunization will be followed by cases of autoimmune diseases occurring in temporal association with immunizations. To anticipate events that might be mistakenly assumed to be caused by immunization, their prevalence was monitored before vaccine introduction.

Method: Cohort study carried out within a database of female adolescents (n = 214,896) and young adults (n = 221,472) followed in the pre-HPV vaccine era (2005), computing rates of emergency consultations, hospitalizations and outpatient consultations, and estimation of risks of coincident associations.

Results: Immune-mediated conditions were a frequent cause (10.3%) of emergency room consultation by adolescent girls. Non-allergic immune-mediated conditions affected 86 per 100,000, diabetes ranking first. In 2005, 53 per 100,000 adolescents and 389 per 100,000 women were hospitalized for diseases of presumed autoimmune origin, thyroiditis being the most frequent diagnosis. If HPV immunization had been used with 80% coverage, 3 per 100,000 adolescents would have required emergency care for asthma/allergy within 24 hours and 2 per 100,000 for diabetes within 1 week of an injection. The risks of hospitalization in temporal association with immunization are 4 times higher for thyroiditis than for multiple sclerosis or Guillain-Barré's syndrome, and more than 20 times higher in young women than in adolescents.

Conclusion: The distinction between HPV vaccine-caused adverse reactions and events only observed by chance in temporal association is difficult. The prior use of population-based data allows for identification of issues of potential concern, for monitoring the impact of large-scale interventions and for addressing rapidly vaccine-safety issues that may compromise vaccine programs.

Key Words: vaccine safety, temporal associations, adolescent immunization, autoimmunity, public health

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Concerns about supposed adverse effects of vaccines seem to occur regularly. Usually the evidence for the adverse effect leading to the scare derives from some case reports rather than from trials or carefully conducted comparative studies. Spontaneous reports of suspected adverse drug reactions, including those to vaccines, remain an important source of new information for monitoring the safety of medicines. However, "suspicion" about an event does not demonstrate causality. Many suspected adverse drug reactions are simply coincident in time with administration of the drug or vaccine.

During the next few years, there will be vaccines introduced to groups of people who have not traditionally been vaccinated. Pandemic flu vaccine may be given to age groups who have not been, in large scale, recipients of vaccines. The human papilloma virus (HPV) disease burden and the outstanding efficacy profile of the novel HPV vaccines are such that these vaccines are currently being implemented[1] or considered for implementation in many industrialized countries. Surveys predict that vaccine acceptance will be high, despite significant misunderstanding about HPV infection, cervical cancer screening, and the sequelae of HPV infection.[2–5] The interest of parents, young women, and health care providers in HPV vaccines will doubtless be strongly supported by large-scale promotional events led by 2 competing major pharmaceutical companies. This should result in rapid vaccine uptake by adolescents targeted by national immunization programs. In addition, catch-up immunizations will be implemented in some countries for young women, as prior exposure to HPV does not prevent vaccine-induced efficacy against other HPV genotypes.[6] Altogether, this is expected to lead to a rapid uptake of HPV vaccines by

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adolescent girls and young women in industrialized countries able to afford them.

The rapid large-scale implementation of a vaccine in the young adult population of industrialized countries is not without precedent. In the early 1990s, the recommendation to immunize adolescents with hepatitis B vaccines (HBV) was supported by such vigorous promotional efforts in France that it rapidly led to the immunization of 20 million individuals, mostly adolescents and young adults.[7] A few years later, reports of temporal association between HBV immunization and the onset of multiple sclerosis (MS)[8] were sufficient to fuel major vaccine-safety controversies associating HBV immunization to MS and other autoimmune diseases.[9] Public confidence was lost and national HBV vaccination efforts interrupted. A decade later, the existence of an increased risk of MS after HBV immunization in adults has still not been demonstrated.[10] However, as the best epidemiology studies may never exclude the existence of a risk, the debate continues, especially in France,[11] where HBV vaccine coverage remains below 25%.[12] This vaccine-safety issue spread internationally, including in developing countries, despite worldwide efforts for explanation and reassurance.[13] More recently, the large-scale implementation of a quadrivalent conjugate vaccine against meningococcal disease (Menactra) in adolescents led to 5 cases of Guillain-Barré's syndrome within 6 weeks of immunization. Although this did not exceed the expected baseline incidence, it was sufficient for the U.S. authorities to launch an alert.[14] A year later, an update indicated that because of the ongoing risk for meningococcal disease and the limitations of the data indicating a small risk for Guillain-Barre syndrome after a vaccination with quadrivalent conjugate vaccine against meningococcal disease, current Centers for Disease Control and Prevention recommendations remained unchanged .[15]

The novel HPV vaccines (Gardasil and Cervarix) share similarities with HBV vaccines. Both HPV and HBV vaccines are recommended as a 3-dose schedule given in at least 6 months, and include aluminum salts (Gardasil) or a new potent adjuvant (Cervarix) for which large-scale surveillance data is not yet available. Gardasil is produced by yeast, as was one of the HBV vaccines used in France in the 1990s. Both vaccines protect against sexually transmitted viral infections that may result in cancer (ie, will be implemented on a large scale not only in adolescents but also in the young adult population). Although the safety profile of the 2 HPV vaccines appears to be as excellent[16,17] as that of HBV vaccines,[13] they have formally been tested on less than 50,000 women. Thus, their safety databases are limited and rare (<1 per 10,000), severe adverse events may not yet have been identified. Consequently, reports of immune-mediated diseases issued from the postmarketing surveillance could be considered as possible adverse events, at least initially. These signals will be difficult to address given the limited availability of the incidence of most immune-mediated diseases in the adolescent and young adult population.

We are concerned that the large-scale implementation of HPV vaccines in industrialized countries could reactivate the vaccine-safety debates linking vaccination to autoimmune diseases. This could possibly represent a major issue for the sustainability of HPV immunization programs in industrialized countries, and consequently for their implementation in developing countries where they are most needed.[18] To anticipate the crisis and identify the potential danger signals, we have computed the utilization of health resources by the entire female adolescent and young adult population registered within the Northern California Kaiser Permanente (NCKP) Medical Care Program health maintenance organization (HMO) during 2005 The number of emergency consultations, hospitalizations, and outpatient consultations were used to identify the most frequent immune-mediated conditions, ie, those most likely to be temporally associated with a putative HPV vaccine administration.

METHODS

Databases. NCKP maintains administrative databases to capture all inpatient and outpatient (including emergency department) utilization within the HMO. The utilization databases contain the date of admission or visit, International Classification of Diseases (ICD)-9 coded diagnoses, and a unique identification number.

Data Retrieval. Rates of emergency department, inpatient, and outpatient utilization were collected for females 9–18 years of age, likely to be targeted by adolescent immunization programs, and 19–30 years of age, who will be considered for catch-up immunization. To compute rates of utilization, the denominator was estimated by membership at the midpoint of the evaluation year, on June 30, 2005 (9–18 years of age, n = 214,896, adolescent group; 19–30 years of age, n = 221,472, adult group). The frequencies were computed with the first instance of each diagnosis code for each individual.

Selection of Target Diseases. For this report, we selected ICD-9 codes for immune-mediated diseases, considering that the biologic plausibility of a vaccine-induced trigger would markedly enhance the notification of temporal associations and thus the likelihood of signal generation.

Risks of Temporal Association Between Events and a Hypothetical HPV Immunization. The risk of coincident temporal association between medical conditions and a hypothetical HPV immunization was estimated under various assumptions. The distribution of medical events during the year was assumed as random, without any influence of season or month. We assumed a 0–1–6 months vaccine schedule, as officially recommended, and defined several time windows (from 1 day to 6 weeks after each putative vaccine dose) during which a previous HPV immunization would likely be considered as a triggering or precipitating event. The proportion of subjects with expected temporal associations between a medical event and trigger administered at 0–1–6 months intervals was calculated by dividing the yearly rate of event by the number of corresponding at-risks periods, taking into consideration overlapping periods. It was corrected for vaccine coverage likely to be reached in the adolescent (80%) and the young adult (40%) population.

Statistical Analyses. Rates of specific immune-mediated disease conditions were used to calculate the aggregate rates of immune-mediated events requiring medical attention in the adolescent or young adult population, respectively.

RESULTS

Rates of Emergency Consultations for Immune-Mediated Conditions in Female Adolescents and Young Women. The demand for an emergency room (ER) consultation reflects either a recent onset or a recent exacerbation of a preexisting disease condition, 2 situations that inevitably lead to a search for putative precipitating events. Among 12,443 ER consultations required by 214,896 adolescent girls (aged 9–18) followed during 2005 in the NCKP Medical Care Program HMO, 35% resulted from infections and 30% from psychologic or psychiatric conditions (not shown). Immune-mediated conditions were the third most frequent cause (1277, 10.3%) of ER consultation by adolescent girls (Table 1). Asthma conditions ranked first among atopic/allergic conditions, cumulating to a rate of 325 per 100,000 ER consultations. This included 183 per 100,000 ER consultations for acute IgE-mediated allergic reactions, including a few cases (3.7 per 100,000) of anaphylactic shock. Nonallergic immune-mediated conditions were frequent (86 per 100,000, Table 1). The first cause of ER consultation for nonallergic immune disease was juvenile- or adult-onset diabetes (51.3 per 100,000). In 2005, only 4 girls followed in the NCKP HMO required ER medical care for systemic lupus erythematosus (SLE) and none for MS. Emergency consultations for immune-mediated diseases were also frequent (837 per 100,000) in young women likely to be targeted by HPV catch-up immunization strategies (Table 1). Asthma or other IgE-mediated allergic reactions also ranked first (366 and 302 per 100,000, respectively). Among diseases presumably of an autoimmune nature, diabetes, Bell palsy, and SLE had the highest rate of ER consultation (Table 1).

Rates of Hospitalizations for Autoimmune Diseases in Female Adolescent and Young Adults. The need for hospitalization also reflects either a recent disease onset or a recent exacerbation of a disease condition sufficiently severe to require inpatient medical care. In 2005, the hospitalization rate of adolescent girls for diseases of presumed autoimmune origin reached 53 per 100,000 (Table 2). Thyroiditis, an autoimmune process in adolescents and young adults, was the most frequently encoded diagnosis. In contrast, episodes of MS or optic neuritis were relatively rare (3.7 per 100,000). The same ranking was obtained by the computation of outpatient consultations required by adolescent girls throughout 2005 (Table 2), confirming the relative disease burden of these immune-mediated conditions. Of note, thyroiditis generated a 10-fold higher utilization of medical resources than any other condition in this category.

During the same period, the rate of hospitalization of young women for autoimmune conditions reached 389 per 100,000 (Table 2). Thyroid disorders also ranked as the first cause of hospitalization for autoimmune-mediated diseases. SLE ranked next, whereas MS-like conditions required hospitalization rates of 12 per 100,000. Again, the computation of outpatient consultations provided a similar ranking (Table 2), confirming the relative importance of the burden of these conditions on medical resources and their occurrence at a markedly higher rate in young women than in adolescents.

Temporal Associations Between Specific Disease Conditions and a Hypothetical HPV Immunization Regimen. All the above-mentioned events occurred in the pre-HPV immunization era. Consequently, none may be considered as an HPV vaccine-induced adverse event. The likelihood of an external factor being considered as a potential triggering/precipitating factor essentially results from temporal associations.[19,20] We thus estimated the likelihood of temporal association that would occur in pure coincidences, in the absence of any causal relationship, with the putative administration of 3 doses of a saline placebo administered at 0, 1, and 6 months intervals. Rates of ER consultation or hospitalization were computed by specific time windows to estimate the likelihood that an event

TABLE 1. NCKP Emergency Room Utilization by Female Adolescent and Young Women

ICD-9 Codes	Diagnoses	Adolescents		Adults Rates per 100,000
		Frequency Counts	Rates per 100,000	
49390	Asthma without status asthmaticus	366	170	183
49392	Asthma—acute exacerbation	319	148	176
49391	Asthma—status asthmaticus	14	6.50	7.20
9953	Allergic reaction, unspecified	182	84.7	167
7080–89	Allergic urticaria	128	59.5	97.5
4779	Allergic rhinitis	40	18.6	19.0
37205	Allergic conjunctivitis	25	11.6	9.00
6918	Allergic atopic dermatitis	10	4.70	1.40
9950	Anaphylactic shock	8	3.70	7.70
7291	Myalgia and myositis	39	18.1	40.2
25011	Diabetes—ketoacidosis, juvenile	38	17.7	12.6
25000	Diabetes adult	27	12.6	39.3
25010	Diabetes—ketoacidosis, adult	24	11.2	14.9
25001	Diabetes juvenile	21	9.80	1.13
3510	Bell's palsy	15	7.00	20.3
3643	Iridocyclitis	8	3.70	5.00
7100	Systemic lupus erythematosus	4	1.90	15.4
24290	Thyrotoxicosis	4	1.90	6.80
3709	Keratitis	3	1.40	6.30
5559	Regional enteritis	2	0.9	7.70

TABLE 2. 2005 NCKP Hospital Admissions and Outpatient Consultations for Autoimmune Conditions in Adolescent Girls and Young Women

ICD-9 Codes	Diagnoses	Adolescents		Adults Rates per 100,000
		Frequency Counts	Rates per 100,000	
Hospitalizations				
(. . .)	Thyroid disorders	35	16.3	286.77
556.X	Ulcerative colitis	22	10.2	14.90
7100	Systemic lupus erythematosus	18	8.4	31.16
555.X	Regional enteritis	16	7.4	20.32
71430	Juvenile rheumatoid arthritis	9	4.2	19.87
2794	Autoimmune disorders (NS)	6	2.8	2.26
37730	Optic neuritis	6	2.8	1.81
340	Multiple sclerosis	2	0.9	9.94
3570	Acute polyneuritis	1	0.45	1.81
Outpatient care				
Several	Thyroid disorders	859	396	1412.05
556.X	Ulcerative colitis	76	35.4	117.52
555.X	Regional enteritis	68	31.6	97.18
7100	Systemic lupus erythematosus	63	52.9	120.23
7140	Rheumatoid arthritis	29	13.5	119.33
37730	Optic neuritis	10	4.7	13.56
340	Multiple sclerosis	9	4.2	64.18
71659	Polyarthritis	7	3.3	30.74

NS indicates not significant.

would occur within a given interval after an injection. For psychologic reasons, the likelihood for an association to be considered as causally related is inversely proportional to the time elapsed between exposure to the putative factor and the onset/exacerbation of the disease. Based on biologic plausibility, we considered time windows of 1 day, 1 week, and 6 weeks after any injection putatively administered according to a 0–1–6 months schedule to all adolescents and young women (Table 3).

Correcting the rates obtained in Table 3 for likelihood of exposure to an injection trigger predicts that if 80% of NCKP adolescent girls had been injected with a saline placebo in 2005, 3 per 100,000 would have required ER medical care for asthma or allergy within 24 hours of an injection. Two per 100,000 adolescent girls seen in the ER department for diabetes would have been within 1 week of an injection, and hospitalizations for autoimmune diseases would have occurred within 6 weeks of an injection in 10 per 100,000 adolescents. Of even greater concern,

TABLE 3. Coincident Temporal Associations With Putative Placebo Injections Administered at 0–1–6 Months to All Adolescent and Young Women

Age Group	Condition	Rate per 100,000 by Temporal Association Windows		
		1 d	1 wk	6 wk
Adolescent	ER consultation/asthma	2.7	18.8	81.3
	ER consultation/allergy	1.5	10.6	45.8
	ER consultation/diabetes	0.4	2.9	12.8
	Hospitalization/inflammatory bowel disease	0.2	1.0	4.5
	Hospitalization/thyroid disease	0.1	0.9	4.0
	Hospitalization/SLE	0.1	0.5	2.0
	Hospitalization/MS or optic neuritis	0.0	0.2	1.0
Adults	ER consultation/asthma	3.0	21.2	91.5
	ER consultation/allergy	2.5	17.4	75.3
	ER consultation/diabetes	0.6	3.9	17.0
	Hospitalization/thyroid disease	2.4	16.6	71.8
	Hospitalization/inflammatory bowel disease	0.3	2.0	8.8
	Hospitalization/SLE	0.3	1.8	7.8
	Hospitalization/MS or optic neuritis	0.1	0.7	3.0

MS indicates multiple sclerosis; SLE, systemic lupus erythematosus.

if a catch-up program reaching only 40% of young adult women had been implemented, 28 per 100,000 patients requiring hospitalization for the recent onset or exacerbation of thyroiditis would have been within 6 weeks of an injection. That such figures would not trigger vaccine-safety signals thus appears as most unlikely.

DISCUSSION

Anticipating future vaccine-safety concerns at the time of the enthusiastic implementation of novel vaccines effective against cancer may seem odd. However, history has taught us that the life and death of immunization programs can occur rapidly. As a recent example, the Food and Drug Administration approved in 1998 a new recombinant Lyme vaccine that reduced new infections in vaccinated adults by nearly 80%. Just 3 years later, the manufacturer voluntarily withdrew its product from the market amid media coverage, fears of vaccine adverse events, and declining sales.[21] To date, there is no evidence that this Lyme vaccine would have caused the adverse events that led to its withdrawal. We are concerned that history may repeat itself with any large-scale vaccine introduction in an adult population, HPV vaccines being the closest to this important step.

Immunizations activate the immune system, which may be considered as sufficient to blame vaccines, should the onset or the exacerbation of immune-mediated diseases occur in temporal association with an immunization,[22] despite some evidence to the contrary.[23] The prevalence of autoimmune diseases in the young adult female population is not low. As an example, it is estimated that SLE occurs in 1 of 2000 Americans and in as many as 1 of 250 young African American women (NIAID, Understanding autoimmune diseases, http://www.wrongdiagnosis.com/artic/understanding_autoimmune_disease_niaid.htm), whereas MS affects 1 in 700 persons in the United States and 1 in 1200 in Europe.[24] Unfortunately, baseline disease incidences are not established for most diseases, and country, ethnic, and age-group specific incidences are largely lacking. Consequently, it will be difficult to monitor globally the impact or to demonstrate the lack of impact—of a large-scale immunization program on the incidence of autoimmune conditions. This was unfortunately illustrated by the allegation of a causal relationship between hepatitis B immunization and MS, which a decade of negative or inconclusive studies[25,26] has not yet settled. As autoimmune conditions have already been included in the adverse events section of the Gardasil Summary of Product Characteristics, one can predict that conditions occurring in temporal associations will be reported as potentially associated with HPV immunization.

Temporal association is required for vaccine-safety signals/concerns to be raised. However, additional factors are at play. This is best illustrated here by the fact that diseases that have most frequently been reported in temporal association with immunization, such as MS, SLE, or Guillain-Barré's syndrome are not the most frequent autoimmune conditions in adolescents or young women. This is likely to reflect the influence of additional factors including the severity of the disease and the absence of an alternative cause to the disease conditions. The data presented here suggest that reporting is also largely influenced by a notification bias resulting from the perception by the medical community that certain conditions (such as Guillain-Barré's syndrome for example) are much more likely than others (such as diabetes or thyroiditis) do to be triggered by exposure to infection or immunization. This implies that many new temporal association signals could be generated by effective pharmacovigilance systems.

Certain national health authorities are aware of the fact that the upcoming implementation of large-scale adolescent and adult HPV immunization programs will inevitably lead to the observation of disease conditions occurring in close temporal association with injections (Swiss Federal Office of Public Health, www.cfv.ch). They expect at least some of these cases to be notified to their pharmacovigilance systems, and fear that their interpretation will be made difficult by the lack of data on age-specific baseline incidence of disease, limiting the capacity of performing "observed versus expected cases" analyses. Consequently, clusters of cases or reports, possibly resulting from biased perceptions and notification processes, are likely to result into danger signals requiring the initiation of complex epidemiologic studies. One may unfortunately predict that certain issues may remain without conclusive answers for many years and exert a profound influence on the sustainability of HPV immunization programs.

The simple approach described in this report offers many advantages compared with the collection of individual reports resulting from temporal associations. First, the computation of medical resource utilization provides population-based data, which is particularly powerful for the assessment of infrequent events, as it may be extended to large parts of the population. Second, it may readily be repeated at regular intervals—providing a rapid tool for the monitoring of any disease condition, by the comparison of pre- and postintervention rates. Third, it is not limited by working hypotheses or triggered by a few individual case reports. As an example, we would not have predicted immune-mediated thyroiditis to be as frequent in adolescents and young women as was observed. Should this concern arise because of adverse event notification, rapid answers could be provided by comparing the rate of ER consultation and hospitalizations before and after the implementation of HPV immunization. This approach is not limited to immune-mediated diseases. We observed that gynaecologic conditions resulting into abnormal uterine bleeding or pain are frequent in adolescent and much more so in young women (not shown). Should a first episode of abnormal uterine bleeding in adolescents or fertility issues in HPV-immunized young women be attributed at some point to the recent administration of a "uterine-targeting vaccine," population-based data could provide rapid answers. Lastly, such population-based approaches allow an estimation of the likelihood of disease conditions in various age groups. For example, the much higher risks of coincidental associations with autoimmune diseases that is expected in the young women compared with the adolescent population is worth considering at time of implementation of catch-up strategies in young women.

Predicting the future is difficult, and this study has limitations. The autoimmune conditions that may generate concerns may not be in our list. They could, however, be readily included into similar analyses, now or in the future. The data are from one single year, which does not allow for fluctuations or temporal variations of medical disorders. The utilization of medical resources is notoriously influenced by a number of factors, and may not reflect true disease prevalence. Diseases resulting into more than 1 hospitalization/consultation could have affected the data—which may be corrected by using unique patient identification numbers. The use of identification number would also allow discriminating between new onset of diseases and relapses, defined by the occurrence of a given ICD code before the suspected triggering event. A related potential limitation of our study is that the reason for a patient to seek medical care may not necessarily imply a relapse or exacerbation of an underlying condition. Consequently, rates of outpatient consultations, in particular, are likely to be less reliable than demand for emergency care or hospitalization. Rates of medical resource utilization will also differ from one population to another. Thus, it is important that the rates indicated here be not taken as figures against which to compare a given safety signal. Indeed, the objective of this study is not to provide universally valid baseline incidence rates of diseases in adolescent or young women at a national or international level. Its objective is to issue an alert for similar analyses to be run in as many populations and country settings as possible, before and after the implementation of large-scale interventions.

The apparently unavoidable future vaccine-safety issues, allegations, and debates warrant taking specific actions for HPV immunization programs to be sustained for many years. This includes a better evaluation of adolescent health, and the estimation of population-based incidence/prevalence rates in the pre-HPV vaccine era, to allow a rapid distinction between real vaccine-induced adverse events and alleged concerns. It also includes educational efforts to increase understanding that coincidence is not causality, and thus improve handling of putative vaccine-associated adverse events by the medical community, including by gynecologists who have been less involved with immunization issues than have pediatricians or general practitioners.

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