

when a child swallows a foreign object.¹ Pharyngeal trauma can be associated with trivial injuries that are often

unwitnessed, and the patients often present with incomplete histories. A tragic, but important, cause of pharyn-

geal trauma is child abuse.² Inconsistencies in the patient's history may alert clinicians to this serious problem. A delay in the recognition and management of pharyngeal trauma can lead to avoidable complications such as retropharyngeal abscess, mediastinitis and airway compromise.

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REFERENCES:

1. Luqman Z, Khan MA, Nazir Z. Penetrating pharyngeal injuries in children: trivial trauma leading to devastating complications. *Pediatr Surg Int* 2005;21:432-5.
2. Ramnarayan P, Qayyum A, Tolley N, et al. Subcutaneous emphysema of the neck in infancy: under-recognized presentation of child abuse. *J Laryngol Otol* 2004;118:468-70.



Figure 3: Computed tomography scan showing extensive emphysematous collections surrounding the carotids (arrow).

PUBLIC HEALTH

Autoimmune diseases after adolescent or adult immunization: What should we expect?

In October 2006, the Israeli minister of health temporarily suspended the national influenza immunization program after 4 elderly patients with underlying cardiovascular disease suddenly died only days after receiving the influenza vaccine. There is compelling evidence that subunit and protein-based vaccines do not trigger sudden death even in the most vulnerable infants¹ and that influenza vaccines are safe for elderly patients.² Despite this evidence and the absence of a biological hypothesis that connects injection of a subunit vaccine with sudden death, the psychologic impact of the close timing between in-

jection and death was so strong that vaccination was considered as a potential death trigger. Although this was later proven not to be the case,³ this example illustrates how the rational approach of distinguishing a coincidence from a cause⁴ fades when a severe unexpected event occurs soon after what one might instinctively believe to be a putative cause.

Both human instinct and the art of medicine include the search for causes and triggers of adverse events. The intensity of the search increases when the outcome is unexpected, severe or disabling; when it is poorly understood;

and when it affects a previously healthy person whom we love or care for. Accordingly, decades of experience and multiple large-scale epidemiologic studies have not yet convinced all people that vaccination does not cause sudden infant death, autism or asthma. The likelihood of an event being considered a trigger or a cause of disease apparently increases if the event is perceived to be aggressive (needle, compulsory immunization) or complex (immune stimulation), if it has long-lasting effects (induction of immunity) or if the disease is only partly characterized. New vaccines meet all of these criteria; thus, the likelihood of a new vaccine being incriminated as a trigger for a severe outcome is extremely high.

The likelihood of a temporal association between vaccination and a given disease is proportional to vaccine coverage.

This likelihood increases rapidly during the implementation of a large-scale immunization program and is proportional to the prevalence of the disease in the target population. In contrast to programs for immunization of children, programs to immunize adolescents and young adults are still in the early stages, and little is known about the baseline incidence of many diseases in these populations. For example, a national alert was rapidly issued by public health authorities in the United States following reports of 5 cases of Guillain-Barré syndrome (GBS) among college students who had been immunized with Menactra. One year later, the US Food and Drug Administration (FDA) and the US Centers for Disease Control and Prevention (CDC) issued the following statement: "At this time, CDC and FDA cannot determine with certainty whether Menactra does increase the risk of GBS in persons who receive the vaccine and, if so, to what degree."⁵ They also comment that "additional, larger studies are being planned to provide a more definitive assessment."⁵ This conclusion is politically and scientifically sound. However, it is of little help to those who advise parents or the public about whether vaccination increases the risk for Guillain-Barré syndrome. We have learned from recent history that large-scale epidemiologic studies take many years to perform, and that uncertainty prevails during this time. We have also learned that even the most powerful epidemiologic studies that find absolutely no statistical association between vaccination and adverse outcomes can, by definition, never conclude that there is zero risk. Thus, concerns about vaccine safety may irreversibly affect the public's confidence and the success of immunization programs, even if these concerns are eventually found to be unsubstantiated. This is illustrated by the very low vaccine coverage against hepatitis B in France more than 10 years after the initial reports of cases of multiple sclerosis that occurred after hepatitis B vaccination.⁶

It does not take much foresight to predict that after the large-scale implementation of a new vaccine (e.g, vaccination of adolescent and adult women against human papillomavirus [HPV]), physicians will be faced with patients

Key messages

- It is tempting to consider that 2 events that occur in close temporal association are causally related. This temptation is greatest for outcomes that are unexpected, severe or disabling; for outcomes whose pathophysiology is poorly understood; and for outcomes that affect previously healthy people whom we love or care for.
- The temptation to consider a temporal association as causal increases if the event is perceived to be aggressive or complex, if it has long-lasting effects or if the disease is only partly characterized.
- The likelihood of a temporal association between vaccination and an adverse event is proportional to vaccine coverage and to disease prevalence in the target population.
- Autoimmune diseases occur in adolescents and young women, and they are more frequent in young women.
- The large-scale implementation of a new vaccination program in a population of adolescent and young women inevitably will markedly increase the number of apparent cases of autoimmune diseases occurring after immunization.
- Coincidences are not indicative of a causal link.
- Determining local health-resource use before and after initiation of a new vaccination program may be a useful method to provide the rapid answers that vaccine safety concerns deserve to protect public health.

presenting with diseases that occurred within days, weeks or months of injection. Because HPV immunization requires injection of 3 vaccine doses over a 6-month period, virtually anything that occurs during 1 year in the adolescent's life will be temporally associated with an injection of the vaccine. Adolescent and young women are often considered to be healthy people who have outgrown the vulnerability of childhood and who are not yet affected by senescence. Thus, the baseline incidences of many diseases have not been studied in these populations. This prevents us from predicting which adverse events are more likely than others to occur after vaccination because of coincidence.

We have proposed a novel approach to estimate disease prevalence among adolescent and young women. This approach makes use of the rate of emergency department consultations, admissions to hospital and outpatient consultations recorded within a health maintenance organization (HMO).⁷ Using this approach, we determined emergency department use by women registered with Northern California Kaiser Permanente Medical Care Program HMO in 2005 (i.e., before introduction of the HPV vaccine). We identified a total of 12 443 consultations by 214 896 adolescent girls aged 9–18 years. Most consultations were because of infections (35%) and psychosomatic or psychiatric

conditions (30%). Gynecological issues (excluding pregnancy-related issues) were frequent (6%). Less than 1% (127 per 100 000 girls) of consultations were because of uterine pain or bleeding.⁷ If 80% of these girls had received a saline injection on a schedule similar to that for HPV vaccination (i.e., 0, 1 and 6 months), about 10 per 100 000 girls who presented with uterine bleeding or pain that required emergency care or admission to hospital would have presented within 1 week of receiving a injection. Such a temporal association may not be considered coincidental when the preceding event was receipt of a vaccine against cervical cancer.

A substantial proportion (6%) of emergency medical care was required because of immune-mediated diseases. Allergy-related diseases were most common and affected more than 350 per 100 000 girls. If 80% of these girls had received a saline injection, 5 per 100 000 girls would have presented with an allergy-related disease within 24 h of injection.

In addition, autoimmune-mediated conditions were not rare in this population. The most frequent diagnosis was type 1 diabetes mellitus (50 per 100 000 emergency consultations), followed by Bell's palsy, ocular diseases and autoimmune thyroiditis.⁷ We found that, compared with Guillain-Barré syndrome and multiple sclerosis, the rate of admission

to hospital because of thyroiditis, inflammatory bowel diseases and lupus was much higher. The incidence of each of these diseases was in the range that is easily picked up by passive surveillance systems (1–10 per 100 000); thus, it is likely that these diseases would be observed and reported in temporal association with injection during any large-scale intervention. Immunization has repeatedly been evoked as a potential cause or trigger of autoimmune disease, an assumption that is supported by biological plausibility and by some experimental animal models. Although the evidence supporting this hypothesis in humans remains extremely limited,⁸ the onset or relapse of a severe autoimmune disease within a few weeks of an injection would surely be considered as being potentially induced by the vaccine.

When we performed a similar analysis of medical-resource use by young women (aged 19–28 years), we found a much higher rate of consultations and admissions to hospital because of autoimmune diseases compared with adolescent girls.⁷ Thyroiditis was the most common diagnosis (more than 280 admissions to hospital per 100 000 women). Diagnoses of thyroiditis and multiple sclerosis were more than 10 times more frequent among young woman compared with adolescent girls. Lupus and rheumatoid arthritis were also much more prevalent diagnoses among young women. Thus, the likelihood of an occurrence or a relapse of an autoimmune-mediated disease occurring within a few weeks of any intervention in a population of young women is very high. This issue, along with the age distribution of new HPV infections in adolescent and young women, was taken into account by health authorities in Switzerland who have recommended that catch-up vaccination programs for HPV be limited to women aged 20 years or less.⁹

Consequently, the large-scale implementation of a new vaccination program in adolescents and young women inevitably will markedly increase the number of reports of apparent autoimmune diseases occurring within a few days, weeks or months of injection. However, although frequent, these co-incidences will not be indicative of a causal link. In order to demonstrate a causal link between vaccination and diseases, it must be shown that the risk of disease is increased among women who were vaccinated compared with those who were not.

We also suggest that analysis of health-resource usage in pre-intervention periods can provide initial estimations of whether an intervention is associated with a specific adverse event. Assessing the baseline incidence of each autoimmune disease in adolescents and young adults, through large-scale epidemiologic studies performed in both pre- and post-intervention periods, is not feasible and would be of limited usefulness because of heterogeneity of populations in different areas, which would necessitate monitoring at the local level.

Furthermore, it remains difficult to predict which temporal associations will be of sufficient concern to become a vaccine safety issue or scare. For example, Guillain-Barré syndrome is much more rare in adolescents and young adults compared with other autoimmune-mediated diseases. Thus, the frequent consideration that it may be triggered by vaccine injection reflects the influence of factors other than temporal association. It is tempting to postulate that the perceived likelihood of the contribution of a vaccine trigger to an adverse event is one of these factors, as it affects physicians' concerns, reporting rates and, eventually, the public at large. Determining local health resource use both before and after an immunization program is initi-

ated appears to be a useful approach to provide the rapid answers that vaccine safety concerns deserve and to thus protect the population and the immunization program (i.e., public health).

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REFERENCES

1. Stratton K, Almarino DA, Wizemann TM, et al., editors. *Immunization safety review: vaccinations and sudden unexpected death in infancy*. Washington: The National Academies Press; 2003.
2. Rivetti D, Jefferson T, Thomas R, et al. Vaccines for preventing influenza in the elderly [review]. *Cochrane Database Syst Rev* 2006;(3):CD004876.
3. Influenza team, European Centre for Disease Prevention and Control. No link established between deaths in elderly patients in Israel and influenza vaccination. *Euro Surveill* 2006;11:E061026.1. Available: www.eurosurveillance.org/ew/2006/j061026.asp#1 (accessed 2007 Oct 18).
4. Global Advisory Committee on Vaccine Safety. Causality assessment of adverse events following immunization. *Wkly Epidemiol Rec* 2001;76:85-9.
5. US Food and Drug Administration (FDA) and Centers for Disease Control (CDC). FDA and CDC update information on Menactra meningococcal vaccine and Guillain-Barré syndrome, 2006. Available: www.fda.gov/cber/safety/gbs102006.htm (accessed 2007 Oct 2).
6. Denis F, Levy-Bruhl D. Mass vaccination against hepatitis B: the French example. *Curr Top Microbiol Immunol* 2006;304:115-29.
7. Siegrist CA, Lewis EM, Eskola J, et al. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. *PIDJ* 2007; 26:979-84.
8. Wraith DC, Goldman M, Lambert PH. Vaccination and autoimmune disease: What is the evidence? *Lancet* 2003;362:1659-66.
9. Federal Committee on Vaccination. Recommandations pour la vaccination contre les papillomavirus (HPV), 2007. Available: www.cfv.ch (accessed 2007 Oct 2).