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Side Effects of Vaccination: A Consumer's Guide to Cause and Effect

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Credit — *This lesson is good for 0.2 CE units, with a passing grade of 70%.*

Objectives

1. *To describe historical examples of adverse events truly and spuriously associated with vaccination.*
2. *To describe a rational basis for deciding whether adverse events are causally or coincidentally linked to a medication.*
3. *To demonstrate how to apply this rational basis to a variety of exposure—outcome associations.*

Key Words — *adverse events, causality, immunization, side effects, vaccines*

I got vaccinated four weeks ago. I got sick two weeks ago. Are the two events related? The two events are related in time, certainly. But do the vaccination and the illness have a cause-and-effect relationship? Investigating relationships between vaccines and adverse events is important, to keep people healthy. If a vaccine does cause an adverse reaction, we need to find out as soon as possible and respond appropriately.

But jumping to the conclusion that two events are causally related is scientifically improper. Jumping to a conclusion can also delay finding the true cause of an illness. For example, assuming that egg allergy was linked to anaphylaxis after measles–mumps–rubella (MMR) vaccination may have delayed recognition of the role of gelatin allergy.[1–2]

Vaccination programs provide great public benefit, both to individuals and to communities. By several measures, vaccines provide more benefits than any other medical intervention.[3–4] Vaccination programs are complicated, intricate social endeavors that require vast amounts of energy (eg, time, labor, money) to set in motion and sustain.

Making an ill-founded claim about vaccine safety is like pulling the stop cord on a moving train. It is certainly possible to bring a vaccination train to a complete halt, if needed. But such a drastic measure should follow objective analysis, not unsubstantiated criticism. The energy required to get the train rolling again leads us to want solid evidence, rather than false alarms.

SIDE-EFFECT DETECTIVES

As we investigate the relationship between a vaccine and an adverse event, we collect clues, sift evidence, and consider conflicting lines of argument. What caused the adverse effect? Did the vaccine precipitate the event, or was it an innocent bystander? To render a verdict, what evidence does the court of science need?

A good example of the objective, analytical approach is the prompt assessment in 1999 of rotavirus vaccine as a cause of intussusception.[5–6] Clinical trials detected intussusception in both the vaccine and placebo groups, enough to warrant mention in the package insert, but not a risk sufficient to withhold licensing. The sentinel surveillance program within the Vaccine Adverse Event Reporting System (VAERS) identified more cases of intussusception than expected,

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TABLE 1

Steps in Assessing Cause-and-Effect Relationships

Step 0. Gather Information.
If considering an individual case, gather objective information about the person and the condition of interest, to use in later steps. Confirm the diagnosis. Confirm exposure to the medication of interest.

Step 1. Already Acknowledged?
Find out whether recognized experts already concede that the vaccine (medication) causes the effect (see also Table 2).

Step 2. Novel Event?
Is the condition novel, unique, never reported before? New syndromes are rare.

Step 3. Determine Baseline.
If not novel, determine how often the symptom or condition or disease affects the general population (preferably a corresponding population of the same age).

Step 4. Compare Vaccinated to Unvaccinated.
Leveling the playing field as much as possible, compare the occurrence of the symptom or condition among vaccinated people to its occurrence among unvaccinated people.

Step 5. Full Analysis.
If the baseline rate of occurrence is not known, then use criteria for cause-and-effect relationship proposed by Robert Koch and further refined by Sir Austin Bradford Hill and others[38] (see also Table 3).

enough to warrant a public warning and to commission controlled studies. Those controlled studies revealed an attributable risk of one case of intussusception per 5,000 to 12,000 vaccine recipients.

An objective approach is not the only one available. Holding rigidly to a "vaccines can do no harm" philosophy is one approach, but an inappropriate one. Similarly, assuming that a vaccine causes harm before the facts support this conclusion is also inappropriate. Examples of recent, well-publicized, unsubstantiated claims appear below.

This article focuses specifically on vaccines, but this approach to reasoning applies to all medications and many environmental exposures. Does fluoxetine lead to suicide? Does sildenafil cause heart attacks? Do cellular telephones cause brain cancer? Do power lines cause leukemia? These and analogous questions of this sort can be addressed in a similar manner.

So, how should we evaluate concerns about adverse events? This article suggests a five-step method applicable to vaccines and other medications (Table 1).

STEP 0: GATHER INFORMATION

Begin with Step 0 if you are investigating the health of a particular person. If not, and you are considering adverse events in a broader perspective, proceed directly to Step 1. Ultimately, that broader perspective relies on the validity and veracity of the individual clinical cases that populate it. So, the reliability of the individual cases is key.

For Step 0, gather objective information about this individual who interests you. Confirm the diagnosis. Distinguish objective signs or values from subjective symptoms. Ask about pre-existing conditions. Collect appropriate laboratory data. See if signs or symptoms appeared before vaccination. Ask what specialists or subspecialists had been consulted, and so on.

I know several people who reached erroneous conclusions about their health after being told their blood work yielded a positive antinuclear antibody (ANA) test. An ANA value can be used to assess systemic lupus erythematosus (SLE), an autoimmune disease. These people assumed that they had an autoimmune disease solely on the basis of one ANA test. It takes less time to reach that conclusion than to learn the intricacies of the ANA test, including its propensity for false-negative and false-positive results. Indeed, the main use of ANA tests may be to exclude SLE as a diagnosis. With the disease, the test is positive 95% of the time. Without the disease, the test is positive 50% of the time. In other words, a negative test has more meaning than a positive test.[7]

Similarly, one should confirm exposure to the vaccine by checking dates of vaccination and lot numbers, for example. I have talked with several military personnel and their families concerned about the adverse effects of anthrax vaccine they received during military basic training. The irony here is that anthrax vaccine is not administered during basic training, so any adverse events in that setting certainly would be misattributed if blamed on anthrax vaccine.

After individual exposure and clinical data are collected and considered, proceed to Step 1.

STEP 1: ALREADY ACKNOWLEDGED?

Step 1 applies information that science has already accumulated, and for which there is consensus. Do recognized experts already concede that the vaccine causes the adverse effect in question?

Vaccines have been administered since Edward Jenner gave smallpox vaccination in 1796. With over 200 years of experience, medicine has

TABLE 2

Summarized Version of the Vaccine Injury Table

Vaccine contents	*Illness, disability, injury, or condition covered (acute complications refer to complications of conditions listed in this column)*	*Time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration*	
		Limit for Compensation[a]	**Limit for Reporting[b]**
Tetanus toxoid (eg, DTaP, DTP, DT; Td, TT)	Anaphylaxis and anaphylactic shock Brachial neuritis Any acute complication (including death)	4 hours 2–28 days Within period specified	7 days 28 days
Whole-cell pertussis bacteria or specific pertussis antigen(s) (eg, DTaP, DTP, P, DTP-Hib)	Anaphylaxis and anaphylactic shock Encephalopathy (or encephalitis) Any acute complication (including death)	4 hours 72 hours Within period specified	7 days 7 days
Measles, mumps, or rubella viruses (eg, MMR, MR, M, R)	Anaphylaxis and anaphylactic shock. Encephalopathy (or encephalitis) Any acute complication (including death)	4 hours 5 to 15 days Within period specified	7 days 7 days
Measles virus (eg, MMR, MR, M)	Thrombocytopenic purpura Vaccine-strain measles viral infection in an immunodeficient recipient Any acute complication (including death)	7–30 days 6 months Within period specified	30 days 6 months
Rubella virus (eg, MMR, MR, R)	Chronic Arthritis Any acute complication (including death)	7-42 days Within period specified	42 days
Live poliovirus (OPV)	Paralytic Polio —in a non-immunodeficient recipient —in an immunodeficient recipient —in a vaccine-associated community case Vaccine-strain polio viral infection —in a non-immunodeficient recipient —in an immunodeficient recipient —in a vaccine-associated community case Any acute complication (including death)	 30 days 6 months No limit 30 days 6 months No limit Within period specified	 30 days 6 months No limit 6 months No limit No limit
Inactivated poliovirus (eg, IPV)	Anaphylaxis and anaphylactic shock Any acute complication (including death)	4 hours Within period specified	7 days
Hepatitis B vaccines	Anaphylaxis and anaphylactic shock Any acute complication (including death)	4 hours Within period specified	7 days
Haemophilus influenzae type b polysaccharides (unconjugated, PRP vaccines)	Early-onset Hib disease Any acute complication (including death)	7 days Within period specified	7 days
Haemophilus influenzae type b polysaccharide conjugates	No condition specified	Not applicable	
Varicella virus	No condition specified	Not applicable	
Rotavirus	No condition specified	Not applicable	

[a]Claims may also be filed for a condition with onset outside the time intervals or a condition not included in this table. Information on filing a claim may be obtained by calling 800-338-2382 or at www.hrsa.gov/bhpr/vicp.

[b]From the Reportable Events Table, 42 USC 300aa-25, which lists conditions reportable by law. Events described in the manufacturers' package insert as contraindications to additional doses of a vaccine must also be reported. Individuals are encouraged to report any clinically significant or unexpected events (even if not certain the vaccine caused the event) for any vaccine, whether or not listed here. To report call 800-822-7967 or go to www.fda.gov/cber/vaers/report.htm.

Source: Vaccine Injury Compensation Program, version of October 1998, www.hrsa.dhhs.gov/bhpr/vicp/table.htm

TABLE 3

Intricate Criteria for Assessing Cause-and-Effect Relationships

1. How strong is the association between the exposure and the outcome?
2. What is the quality of the evidence for an association?
3. Is there a dose-response relationship?
4. Is there consistency among several studies?
5. Is there a specific cause for the effect observed?
6. Did the cause exist before the effect occurred?
7. Is the outcome plausible, given what we know about biology?

Source: Adapted from Rothman & Greenland[38]

assembled considerable understanding of adverse events to consider after vaccination.

We understand quite well that injection of any vaccine can result in swelling, redness, and soreness at the injection site.[8] We should acknowledge that people also report swelling, redness, and soreness after injection of isotonic sodium chloride. This suggests that at least some injection-site symptoms are related to the mechanical process of depositing a volume of fluid within a muscle or subcutaneous space.

More rarely, vaccine recipients can have a severe allergic reaction to vaccination, such as anaphylaxis or anaphylactic shock.[9] Anaphylaxis can also be caused by peanuts, penicillin, and other agents, of course. But existing data, plus the rapid time course between exposure and reaction, leave little doubt that anaphylaxis shortly after vaccination is associated in a causal way. When anaphylaxis happens within minutes of a vaccination there are few alternate explanations.

Some other adverse events are presumed to be caused by a vaccine after a vaccination. The more serious of these events are included in the Vaccine Injury Table, the list used in the Vaccine Injury Compensation Program.[10] Adverse events currently listed on the Vaccine Injury Table appear in Table 2.

In some cases, patient advocacy groups may make a point of disavowing a purported link between vaccination and an adverse event. For example, the National Multiple Sclerosis Society and the World Health Organization agree that there is no reliable evidence for a link between hepatitis B vaccination and multiple sclerosis.[11–13]

An adverse-event controversy rarely involves a case where vaccine advocates acknowledge causality. Accepted warnings form the basis for the indications and contraindications of vaccine product inserts. To consider the matter further, proceed to Step 2.

STEP 2: NOVEL EVENT?

Is the adverse event in question novel? Has it ever been reported before? Step 3 asks if the symptom or disease is unique, one-of-a-kind.

New adverse events are rare. None of the recent allegations of harm after vaccination is a novel event. The allegations regard the linkage between the adverse event and the vaccination, not the novelty of the adverse event itself.

Anaphylaxis was "new" in 1902 when Portier and Richet coined the term to describe a syndrome they observed in dogs given repeated injections of a toxin derived from the sea anemone.[9] The death of an Egyptian pharaoh from a wasp sting, recorded in hieroglyphics around 2640 BC, is the oldest known report of anaphylaxis. Anaphylaxis, also called "serum shock," was increasingly recognized in the early 1900s as equine antitoxins and sera became common modes of treating infectious diseases.[14]

"Serum sickness" (*Serumkrankheit*) was a novel diagnosis when it was associated with injections of animal sera in 1905 by von Pirquet and Schick.[14] The symptoms that comprise serum sickness (eg, edema, fever, urticaria, maculopapular rash, myalgia) had certainly been recognized in the 1890s with repeated injections, but the convergence of these individual symptoms into a consistent syndrome, even with the first injection, became widely acknowledged in the early 1900s.[2,14]

Scientists recognized in the 1960s that 20% to 30% of the women who took the sedative thalidomide during pregnancy delivered children with limb and organ deformities. Aside from the increased rate of birth defects, it was the pattern of birth defects of the limbs (phocomely) that was unusual, almost unprecedented.[15]

When veterans of the Persian Gulf War returned home, some reported symptoms and illnesses that raised questions about the health consequences of their service. After considerable inquiry, illnesses among Gulf War veterans are generally acknowledged by scientists as not being qualitatively unique. No unique syndrome or set of syndromes has been found. In other words, these veterans develop the same symptoms and diseases as people who did not deploy to the Persian Gulf. It also does not appear that these veterans die or develop disease more often

than people who did not serve in the Persian Gulf,[16–19] but that is a question more properly considered by the methods described at Step 3 and Step 4.

If the condition or disease was unrecognized before people started being immunized with a particular vaccine, then the likelihood of a cause-and-effect relationship rises. This situation is very rare. In such a rare case, we would consider other criteria, as discussed in Step 5.

The more common situation, however, is that unvaccinated people get a given illness too. Which leads us to Step 3.

STEP 3: DETERMINE BASELINE

The more common situation will be that the adverse event in question is not novel, not unique. In that case, Step 3 asks how often the symptom or the disease affects people unexposed to the medication of interest. For vaccines, Step 3 asks how often unvaccinated people contract or develop the symptom or disease.

To illustrate, we will consider Guillain-Barré syndrome (GBS). GBS is a demyelinating disease that damages nerves, causing temporary weakness. From 80% to 85% recover fully from GBS. About two-thirds of all GBS cases are provoked by an acute infection, at a rate of about once per 62,000 people per year. GBS clearly occurs in the absence of vaccination. Indeed, the Centers for Disease Control and Prevention (CDC) reports that more than 99% of people who contract GBS were not vaccinated during the weeks before vaccination.[20]

If the background rate of GBS is one among 62,000 unvaccinated people per year, then we begin by expecting GBS to occur once per 62,000 vaccinated people per year also. If the rate was much less common than once per 62,000, then we might wonder whether the vaccine offered some protection against GBS. Conversely, if the GBS rate among vaccinated people was much more common than once per 62,000, we should wonder whether vaccination increases the risk of contracting GBS.

The same logic applies to other adverse events. Between 6% to 10% of unvaccinated pregnant women will spontaneously miscarry their fetuses.[21] With this rate as a starting point, we then expect that 6% to 10% of vaccinated pregnant women would miscarry. Similarly, we need to know how often heart attacks, leukemia, thyroid disease, diabetes, or any other event happens among unvaccinated people.

The ideal situation is to know how often the adverse event happens among people who share every other risk factor except vaccination. In other words, the comparison group should have the same age distribution, gender mix, health status, and other personal characteristics as people who get the vaccine. Returning to the GBS example, it might help to know the specific incidence rates of GBS among adolescents, 20- to 45-year-old adults, or people 65 and older, depending on the specific comparison being made. This helps compare apples to apples.

If reliable data do not exist, then scientists and health officials have a responsibility to determine the baseline. Only from the baseline can elevations above baseline be recognized.

Whenever the symptom or condition happens in people who have not been vaccinated, then the burden of proof in our "court" is to show that the condition happens more often in vaccinated people than unvaccinated people. Step 3 establishes the essential baseline that permits the critical comparison step, Step 4.

STEP 4: COMPARE VACCINATED TO UNVACCINATED

For Step 4, leveling the playing field as much as possible, compare the rates of adverse events among vaccinated people and unvaccinated people. For example, we would find evidence for an association between vaccination and Guillain-Barré syndrome only if the rate among vaccinated people was substantially higher than once per 62,000 people per year.

A slightly elevated rate of GBS has been associated with influenza vaccine in some years (eg, 1976, 1992, 1993), but not in most years. The risk of GBS was 2 to 8 cases per million influenza vaccine recipients higher in those three years than the background incidence rate. In other years, the GBS rate was essentially the same among people vaccinated or unvaccinated against influenza. GBS does occur in people recently immunized with other vaccines. In isolated individuals, GBS recurred with revaccination.[22] But other vaccines have not been found to induce a rate of GBS higher than baseline.

Step 4 is the critical step where many purported links between adverse event and vaccine fail to meet objective, scientific standards. For example, brain damage (ie, chronic encephalopathy) after whole-cell pertussis vaccination does not substantially differ among vaccinated and unvaccinated children.[22–25] This alleged side effect, which launched much of the current antivaccine movement, has no substantiated basis in scientific fact.

Similarly, sudden infant death syndrome (SIDS) occurs no more often in the interval shortly after infant vaccination than in comparable intervals before or after vaccination. Indeed, the rate of SIDS fell in the US as infant vaccination rates

increased, but without a cause-and-effect relationship. The fall in SIDS cases is more properly attributed to the recommendations to put infants "back to sleep," rather than on their stomachs.[2,24]

On the other hand, people exposed to oral poliovirus vaccine (OPV) are certainly subject to a higher risk of paralytic poliomyelitis than people not exposed to OPV. The association is very rare, about once per 2.4 million doses, but it is a true cause-and-effect relationship.[22,26]

Leveling the playing field to assess side effects is easier said than done. A proper comparison involves two groups of similar age, gender mix, state of health, employment, likeliness to report symptoms, and many other factors. Information about self-selected groups of people is substantially less reliable and generalizable than information derived from a random sample of a large population. Epidemiologists invest whole careers in the pursuit of valid comparisons. An apples-to-apples comparison requires rigorous planning and often relies on hard-to-find or expensive-to-assemble data sets.

Some people used a set of inappropriate comparisons to conclude that childhood vaccination increases the risk of diabetes. The issue starts with some ecological comparisons, analyses that look at broad populations in which multiple factors can exert effects simultaneously. Epidemiologists interpret ecological data with caution, because this design provides only weak evidence upon which to gain cause-and-effect understanding.

These diabetes claims are based on analyzing nations with different rates of diabetes and different policies for timing of childhood vaccinations.[27–28] No adjustments were made for varying degrees of scrutiny in diagnosing diabetes, varying case definitions of diabetes, or other biases or confounding effects that imperil simple comparisons. Workshops at Johns Hopkins University and the National Institute for Allergy and Infectious Diseases found no basis for a cause-and-effect link between diabetes and vaccination.[29–30] In addition, the investigators of a study upon which the assertions are based recently published results showing there is no association between vaccination and diabetes.[31] Similarly, other researchers have not found an increased risk of diabetes associated with vaccination.[32–36]

If there is no increased rate of illness among vaccinated people, relative to a proper comparison with unvaccinated people, there is no evidence of a cause-and-effect relationship. It cannot and should not be ruled out entirely, however. The studies may not have been large enough to rule out rare effects or effects of small magnitude. Scientists must keep an open mind, of course, striving to avoid the words "never" or "always."

And what if an increased rate of illness in a proper comparison is found? Is the vaccine doomed or damned? Not necessarily. The steps above are the first steps in epidemiologic analysis, but there is much more to consider. Thus, we next apply Step 5.

STEP 5: FULL ANALYSIS

Step 5 involves a broader set of criteria than those considered above. Criteria for cause-and-effect relationships started with the infectious-disease work of Jacob Henle in 1840 and Robert Koch in 1882.[37]

Henle's and Koch's postulates consist of three criteria for causation: (1) the parasite occurs in every case of the disease and under circumstances that account for pathologic changes and clinical course; (2) it occurs in no other disease as nonpathogenic parasite; and (3) after being fully isolated from the body and repeatedly grown in pure culture, it can induce the disease anew.[37]

Henle and Koch did not consider the world beyond microbiology, so their list was short. Their postulates have been augmented and refined over the years, perhaps most notably by Sir Austin Bradford Hill, leader of the team that advanced our understanding of the link between tobacco and lung cancer and cardiovascular disease. Hill suggested nine aspects of an exposure-outcome association to help distinguish causal from noncausal associations: (1) strength of association, (2) consistency of studies, (3) specificity of effect, (4) temporality, (5) biologic gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy. The modern variants of these criteria are described by Rothman and Greenland (Table 3).[38]

The CDC publication, *Epidemiology and Prevention of Vaccine-Preventable Disease* discusses the most reliable and conclusive ways to establish causal relationships for vaccine adverse events,[39] and they are relatively few. Causal links between a vaccine and an adverse event may be established if they produce a unique laboratory result, a unique clinical syndrome, or an epidemiologic study shows vaccinated persons are more likely than unvaccinated persons to experience the adverse event.

Beyond the narrow confines of medicine, other scientists propose ways of distinguishing true science from pseudoscience. James Lett suggests six rules for evidential reasoning: falsifiability, logic, comprehensiveness, honesty, replicability, and sufficiency (Table 4).[40]

USING THE STEPS

Wakefield and colleagues raised concerns about MMR vaccine leading to inflammatory bowel disease (IBD, eg, ulcerative colitis, Crohn's dis-

TABLE 4

Lett's Rules for Evidential Reasoning

Falsifiability: It must be possible to conceive of evidence that would prove the claim false.
Logic: Any argument offered as evidence in support of a claim must be sound.
Comprehensiveness: All of the available evidence must be considered.
Honesty: Evidence must be evaluated without self-deception.
Replicability: Evidence from experimental results or evidence that might be coincidental must be repeated.
Sufficiency: Evidence must be adequate to establish the truth, where (a) the burden of proof rests on the claimant, (b) extraordinary claims demand extraordinary evidence, and (c) evidence based upon authority or testimony is always inadequate for a biologically implausible claim.

Source: Adapted from Lett[40]

ease).[41] Wakefield's theory is based on 12 people referred to a specialty service, even though no vaccine viruses were isolated from these patients. Other laboratories using more sensitive and specific tests failed to detect any findings to support an association.[42–45] Epidemiologic studies failed to confirm an association between measles virus and IBD.[46–51] A purported association between MMR vaccine and IBD fails at Steps 0 and Step 4: The individual clinical information is unpersuasive and there is no evidence for an increased risk, compared with unvaccinated people.[52–54]

Several alleged associations share the common feature that the diseases are diagnosed at the typical age of vaccination. Two current naïve examples of this confusion are MMR vaccine with autism and hepatitis B vaccine with multiple sclerosis. Each will be discussed in turn.

Autism is typically diagnosed after the first birthday, as a child's vocal skills begin to manifest. This is the time when MMR vaccine is administered. The other "evidence" offered for an association between MMR and autism is Wakefield's inference that bowel problems could lead to decreased absorption of nutrients, permitting developmental disorders like autism.[41] This case against MMR is based on speculation and events coinciding in time, no more.[51,55–56] Again, this alleged association fails on the basis of Steps 0 and 4. Moreover, scientifically valid evidence runs contrary to the speculation.[57–59]

Multiple sclerosis (MS) is typically diagnosed in the third and fourth decade of life, coincidentally a time when health care providers are vaccinated against hepatitis B. Isolated case reports of MS in adults vaccinated against hepatitis B received widespread attention in France. At least six controlled studies are currently underway, which will objectively address Step 4. But the hundreds of millions of people around the world vaccinated against hepatitis B who did not contract MS already suggest that an association is at worst very rare.[11–12] Other evidence shows that influenza vaccination of people who already have MS does not affect attack rate or disease progression.[60]

Can vaccination cause cancer? Soon after simian virus 40 (SV40) was discovered in 1960, SV40 was found to be a contaminant of monkey kidney cells used to manufacture inactivated (and to a lesser extent oral) poliovirus vaccines. In 1961, the government required all polio vaccine to be free of SV40, but more than a million people had already received vaccines containing this virus.[61] SV40 can cause some cancers in rodents. Recently, researchers found SV40 in people with rare cancers (eg, ependymomas, osteosarcomas, mesotheliomas), but many of these people were too young to have received poliovirus vaccine containing SV40. So if unvaccinated people have SV40 virus in their tumors, Step 4 calls on us to ask if vaccinated people with these rare cancers are more likely to involve SV40 than unvaccinated people. The evidence shows that the risk is the same, not elevated. There is no indication that any increased risk due to SV40 exists.[62]

Space does not allow an exhaustive consideration of every side effect ever blamed on a vaccine. But the discussion above provides a uniform framework within which to address the role of any vaccine (indeed, any medication) on the incidence of allergic diseases, arthritis, thyroid disease, or any other medical condition.

IMPLICATIONS FOR PHARMACISTS

After the diagnosis of a serious disease, it is rational to search for the disease's precipitating cause. Vaccinations, however, are memorable, painful, well-documented events that have become convenient foci for blame.[11,55,63–65]

Vaccinations are intentional stimuli of the immune system. But the human immune system gets unintentional stimuli all the time. Every trip to a church, school, shopping center, or other place where humans congregate leads to viral and bacterial exchange. We ingest microbes daily in our food and water. Breaches of the skin or mucosa introduce more microbes. Families with children in

daycare know well that they get more infections than other people, because their kids bring other kids' germs home with them.

Despite humanity's daily encounters with microbial antigens, vaccines still seem unnatural and frightening to some people. We can expect additional alarms over vaccine side effects in coming years. How will we know if it is a true alarm (like intussusception) or a false alarm (like diabetes, IBD, autism, multiple sclerosis)? Good science — with intellectually honest inquiry — is the answer.

An oft-quoted book on adverse events after vaccination is Sir Graham Wilson's *The Hazards of Immunization*.[66] Wilson concludes his book by saying: "Vaccines, of one sort or another, have conferred immense benefit on mankind but, like aeroplanes and motor-cars, they have their dangers. . . ." It is for us, and for those who come after us, to see that the sword which vaccines and antisera have put into our hands is never allowed to tarnish through over-confidence, negligence, carelessness, or want of foresight on our part."

Reliable information about vaccine safety is available from a variety of sources, including the CDC at www.cdc.gov/nip/vacsafe/concerns/default.htm.

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Continuing Education Quiz

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1. **Which of the following is an example of a vaccine-adverse event association later found to be unrelated to vaccination?**
   A. anthrax vaccine and injection-site symptoms
   B. diphtheria-tetanus-pertussis vaccine and sudden infant death syndrome
   C. influenza vaccine and egg allergy
   D. tetanus toxoid and anaphylaxis

2. **An example of an adverse event that led to the cessation of a national vaccination program was:**
   A. rotavirus vaccine and intussusception
   B. influenza vaccine and brachial neuritis
   C. tetanus toxoid and Guillain-Barré syndrome
   D. measles vaccine and chronic arthritis

3. **An objective rationale for assessing causal links between vaccines and adverse events can also be applied to other medications, as well as environmental exposures.**
   A. True
   B. False

4. **The first signal of an association between rotavirus vaccine and intussusception came from:**
   A. the VICP program
   B. a toll-free hotline
   C. the VAERS program
   D. clinical trials

5. **Step 0 in the scheme proposed in this article involves:**
   A. verifying an individual's exposure to the vaccine
   B. verifying that an adverse event actually occurred
   C. both A and B
   D. neither A nor B

6. **Which of the following is an adverse event acknowledged to be caused by vaccination?**
   A. Systemic lupus erythematosus after diphtheria vaccination
   B. Heart attacks after hepatitis A vaccination
   C. Serum sickness after yellow-fever vaccination
   D. Anaphylaxis after any vaccination

7. **Name a relatively novel medication-adverse event combination:**
   A. diphtheria antitoxin and anaphylaxis in 1902
   B. influenza vaccine and Guillain-Barré syndrome in 1976
   C. varicella vaccine and headache in 1995
   D. hepatitis B vaccine and multiple sclerosis in 1998

8. **If an adverse event after vaccination is not novel, it means that the event also occurs among unvaccinated people.**
   A. True
   B. False

9. **If an adverse event occurs among unvaccinated people, the key question in Step 3 is:**
   A. Does it really occur among vaccinated people?
   B. Does it really occur among unvaccinated people?
   C. How often does it occur among vaccinated people?
   D. How often does it occur among unvaccinated people?

10. **Roughly what fraction of cases of Guillain-Barré syndrome occur in the absence of vaccination?**
    A. from 6% to 10%
    B. 50%
    C. Two-thirds
    M. More than 99%

11. **If 6% to 10% of unvaccinated women who are pregnant spontaneously miscarry their fetuses, what proportion of vaccinated women are expected to do so?**
    A. 3% to 5%
    B. 6% to 10%
    C. 12% to 20%
    D. 24% to 40%

12. **In some years, but not others, people vaccinated against influenza have a substantially higher rate of Guillain-Barré syndrome than unvaccinated people.**
    A. True
    B. False

13. **Infants vaccinated against diphtheria, tetanus, and pertussis have a substantially higher rate of chronic encephalopathy than unvaccinated infants.**
    A. True
    B. False

14. **Which of the following factors weakens the hypothesis that vaccination leads to diabetes?**
    A. reliance on ecological comparisons
    B. failure to adjust for diagnostic scrutiny
    C. Failure to use common case definitions
    D. all of the above

15. **Which of the following alternative explanations could explain a temporal relationship between hepatitis B vaccine and multiple sclerosis?**

A. hepatitis A vaccine is known to cause multiple sclerosis
B. multiple sclerosis is known to follow hepatitis B viral infection
C. adults vaccinated against hepatitis B virus because of occupational risks are often of the same age as people newly diagnosed with multiple sclerosis
D. not enough reports of multiple sclerosis in hepatitis B vaccine recipient have been mailed in

16. The Vaccine Injury Table includes which of the following events after tetanus toxoid administration?
A. inflammatory bowel disease
B. Guillain-Barré syndrome
C. brachial neuritis
D. intussusception

17. The Vaccine Injury Table includes which of the following events after rubella vaccination?
A. chronic arthritis
B. acute arthritis
C. thrombocytopenic purpura
D. paralytic poliomyelitis

18. Reports to the Vaccine Adverse Event Reporting System (VAERS) are required for adverse events listed in the Vaccine Injury Table.
A. True
B. False

19. Which of the following is one of the intricate criteria for assessing cause-and-effect relationships?
A. Any biological hypothesis is sufficient
B. Effect must occur before cause
C. Strength of association between exposure and outcome
D. Any one of several studies shows a statistically significant finding

20. Reports to the Vaccine Adverse Event Reporting System (VAERS) are required for adverse events listed as contraindications to additional doses of a vaccine.
A. True
B. False

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Answer Sheet

1.	A	B	C	D	E	6.	A	B	C	D	E	11.	A	B	C	D	E	16.	A	B.	C	D	E
2.	A	B	C	D	E	7.	A	B	C	D	E	12.	A	B	C	D	E	17.	A	B	C	D	E
3.	A	B	C	D	E	8.	A	B	C	D	E	13.	A	B	C	D	E	18.	A	B	C	D	E
4.	A	B	C	D	E	9.	A	B	C	D	E	14.	A	B	C	D	E	19.	A	B	C	D	E
5.	A	B	C	D	E	10.	A	B	C	D	E	15.	A	B	C	D	E	20.	A	B	C	D	E

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