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## Round Table

# Vaccine adverse events in the new millennium: is there reason for concern?

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As more and more infectious agents become targets for immunization programmes, the spectrum of adverse events linked to vaccines has been widening. Although some of these links are tenuous, relatively little is known about the immunopathogenesis of even the best characterized vaccine-associated adverse events (VAAEs). The range of possible use of active immunization is rapidly expanding to include vaccines against infectious diseases that require cellular responses to provide protection (e.g. tuberculosis, herpes viral infections), therapeutic vaccines for chronic infections (e.g. human immunodeficiency virus (HIV) infection, viral hepatitis B and C), and vaccines against non-infectious conditions (e.g. cancer, autoimmune diseases). Less virulent pathogens (e.g. varicella, rotavirus in the developed world) are also beginning to be targeted, and vaccine use is being justified in terms of societal and parental "costs" rather than in straightforward morbidity and mortality costs. In the developed world the paediatric immunization schedule is becoming crowded, with pressure to administer increasing numbers of antigens simultaneously in ever simpler forms (e.g. subcomponent, peptide, and DNA vaccines). This trend, while attractive in many ways, brings hypothetical risks (e.g. genetic restriction, narrowed shield of protection, and loss of randomness), which will need to be evaluated and monitored. The available epidemiological and laboratory tools to address the issues outlined above are somewhat limited. As immunological and genetic tools improve in the years ahead, it is likely that we shall be able to explain the immunopathogenesis of many VAAEs and perhaps even anticipate and avoid some of them. However, this will only happen if the human and financial resources needed for monitoring and studying vaccine safety stay in step with the accelerating pace of vaccine development. Failure to make such a commitment would put all immunization programmes at risk.

**Keywords:** adverse drug reaction reporting systems; antigens, bacterial and immunology; drug monitoring; immunization schedule; vaccination trends; vaccine, adverse effects.

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*Voir page 212 le résumé en français. En la página 213 figura un resumen en español.*

## Introduction

During the past century of increasing use of vaccines, those who support and promote immunization have been in the large majority. However, there have been and still are a few who oppose individual vaccines or the whole concept of vaccination. Although precise data on the risk and incidence of adverse reactions are relatively difficult to obtain, vaccines certainly compare favourably with other pharmaceutical agents in terms of adverse reactions (Table 1) (1, 2). Extraordinarily high safety standards have been imposed on vaccines, as a result of several characteristics of vaccines and of vaccine use. These characteristics include the fact that most vaccines are given to otherwise healthy individuals (usually children, and often repeatedly), the widely held view that infectious diseases are "natural" (so too, are heart attacks and cancer, of course) and the fact that many

governments have made vaccination mandatory. For those who support immunization programmes, there is considerable irony in the observation that the very success of the vaccines introduced to date has contributed significantly to the growing rumble of anti-vaccination sentiment (i.e. by decreasing perception of the risks) (3). So that the ideas outlined below are not taken out of context and add to the anti-vaccination rumble, it is crucial that the reader should keep in mind the difference between *hypothesis* and *scientific confirmation*. The ideas aired in this article are hypotheses rather than established scientific "facts", and are meant to generate discussion. Some of the hypotheses may appropriately be considered for testing at the present time. Others are more speculative and are likely to be proved (or disproved) only with the passage of time.

## Current status

Over the last 40–50 years, vaccines have had a spectacular impact on human health. However, even this relatively short history of modern vaccine development includes several unexpected incidents,

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Table 1. Frequency of known adverse events with selected vaccines and pharmaceutical agents (2, 12–14)

Vaccine/pharmaceutical agent	Adverse event		
	Death	Anaphylaxis	Other
Measles–mumps–rubella	Case reports <sup>a</sup>	1–20 per 1 000 000	2–5 % rash approximately 40 per 100 000 thrombocytopenia 13–15% arthritis (in adults)
Diphtheria–pertussis–tetanus <sup>b</sup>	None	2 per 100 000	0–10.5 per 1 000 000 encephalopathy 3.5–291 per 100 000 unusual shock-like state 0.1–6% inconsolable crying
Hepatitis B vaccine	None	Case reports	
Penicillin	1 per 100 000	4–40 per 100 000	0.7–10% rash/hypersensitivity
Isoniazid (anti-tuberculosis agent)	14–23 per 100 000	None reported	15% elevated liver enzymes 520 per 100 000 hepatitis 1–5% peripheral neuropathy
Clindamycin (antibiotic)	Case reports	Case reports	10% rash 2–20% diarrhoea 0.01–10% pseudomembranous colitis
Non-steroidal anti-inflammatory drugs (e.g. aspirin, indometacin)	Case series		10–50% intolerance approximately three-fold increased risk of gastrointestinal bleeding
Sulfonylureas (e.g. glibenclamide, glipizide) (oral hypoglycaemic agents)	Case reports	Case reports	4% hypoglycaemia 10–15% disulfiram-like action 5% hyponatraemia
Lovastatin (cholesterol-lowering agent)	Case reports	None reported	0.1–1.5% elevated liver enzymes 5–10% elevated creatine kinase

<sup>a</sup> Not including experimental high titre formulations (see Table 4).

<sup>b</sup> Formulations with whole cell pertussis vaccine.

some of which resulted in a number of unfortunate casualties (Table 2) (4–11). Furthermore, the broad spectrum of adverse events linked to vaccines is growing (12–14). Although the strength of these associations ranges from definite to highly “creative”, it is incontestable that a small number of individuals are harmed by vaccines (e.g., vaccine-associated paralytic poliomyelitis, anaphylaxis to vaccine components). In many cases, we have only limited understanding of the correlates of immune protection and the mechanisms of immunopathogenesis of the vaccine-targeted diseases themselves. As a result, it is not surprising that the search for tools to predict vaccine-associated adverse events (VAAEs) has proved to be quite frustrating. Despite the considerable efforts of the Institute of Medicine in the USA as well as others to assemble the available data (12, 13), what is known with certainty about the causality and pathogenesis of VAAEs is quite limited (Table 3). Of course, it should be acknowledged that the task of

understanding VAAEs has been made particularly challenging by the very safety and efficacy of the vaccines introduced to date. Indeed, we are very unlikely to fully understand some of the adverse events associated with measles vaccination (e.g. excess mortality with high-titre formulations, atypical measles after exposure to inactivated vaccine) (6, 7) and poliomyelitis vaccination (e.g. vaccine-associated paralytic poliomyelitis) (4) before these diseases follow smallpox into vaccine-induced oblivion (15).

### VAAEs: how and when to maintain surveillance

To date, vaccine manufacturers and national licensing bodies have shared the responsibility for monitoring VAAEs during phase I to phase III studies (16). Typically, the safety data accumulated during this stage of vaccine development have actively been acquired

over the 15–30-day period immediately after vaccination. With multiple-dose vaccines (e.g. diphtheria–pertussis–tetanus (DPT), hepatitis B), the period of general “watchfulness” may extend to 1–2 years but the period of active “surveillance” for VAAEs is much more limited. Although there is great variability, it has historically been unusual to enrol and actively monitor more than 5000–10 000 subjects at this stage of vaccine evaluation (16). As a result, the total number of subjects studied prior to licensing is often under 10 000. After licensing, the responsibility for monitoring VAAEs typically shifts from the licensing bodies to the public health authorities. At this stage, the vaccine manufacturers often conduct a small number of phase IV studies to address questions of particular interest to the industry (e.g. so-called “post-marketing”) or to major vaccine customers (e.g. the military, governments, health maintenance organizations (HMOs)). The monitoring of VAAEs is not always a major component of these studies, but short-term active surveillance is often performed. These studies can substantially increase the amount of data actively collected during the first 15–30 days after vaccination, but the total number of subjects actively monitored rarely surpasses 30 000–40 000 (note that these numbers are far higher than those required prior to the introduction of many therapeutic agents such as antibiotics or anti-inflammatory drugs — reflecting the higher standards to which vaccines are often held). As a result, only unusual events (few of them occur for other reasons in the vaccinated population) or relatively frequent events (e.g. those that occur after vaccination and are well above the expected frequency) come to the attention of investigators/monitors during the initial phase of enhanced watchfulness. Thereafter, VAAEs are “monitored” primarily by passive surveillance systems with occasional bursts of information provided by projects linked to mass campaigns or initiated by individual investigators addressing specific research questions (14). Although an attempt is now being made to increase the power of post-marketing surveillance by combining databases nationally and internationally (i.e. large linked databases) (14), these efforts will always be limited by the passive nature of the reporting. The Canadian IMPACT system (Immunization Monitoring Program—Active) is a rare example of publicly funded, active surveillance for VAAEs that covers about 80% of the tertiary care, paediatric hospital admissions in the country (17). However, even this excellent system is limited by its focus on childhood vaccines and events serious enough to merit hospitalization, the relatively small size of the population base (annual birth cohort of about 400 000), the absence of data on the expected frequency to permit the calculation of attributable risk, and the bias towards “acute” events associated with vaccination. Certainly, a major limitation of all the current approaches to monitoring VAAEs is the insensitivity or outright inability to detect events caused or initiated by vaccination which manifest more than 3–4 weeks after vaccination. Although the occurrence of such late events with some vaccines is

Table 2. Selected incidents in the history of vaccine development

	Year	Incident
<b>Incidents resulting in death or serious disability</b>		
Smallpox	1800–1900s	Bacterial sepsis and transmission of syphilis with early arm-to-arm inoculation (15)
Yellow fever	1942	Contaminated human serum used as vaccine stabilizer: approximately 28 000 hepatitis B cases (5)
Poliomyelitis	1955	Cutter incident involving incomplete inactivation of vaccine resulting in 204 cases of paralytic poliomyelitis (13)
Measles	1980s–1990s	“Excess mortality” in children who received high titre measles vaccines (7)
<b>Near misses</b>		
Poliomyelitis	1960s	Some early oral poliovirus vaccine (OPV) lots contaminated with oncogenic monkey virus (simian virus 40)
	1960s–present	Sabin trivalent OPV can return to near full neurovirulence with only two back-mutations (4)
Hepatitis B	1981–present	Processing of serum-based vaccines inactivated viruses unknown at the time (e.g., human immunodeficiency virus and hepatitis C) (10)
Many		Apparent ability to transmit prions with bovine and/or human serum fractions present in trace amount or used as excipient (11)

incontestable (Table 4) (4, 6–8, 18, 19), it is far from simple to design a systematic approach for their detection. This is particularly true for vaccines that are rapidly accepted for “universal” administration since investigators are often reduced to using epidemiological tools based upon “historical” or other suboptimal control groups for comparison. It has recently been suggested that the detection limit of such epidemiological tools is in the range of 1 event per 1–2 million vaccinations under ideal circumstances (20). Events such as vaccine-associated paralytic poliomyelitis (4) and Guillain–Barré syndrome after influenza A vaccination (21) probably occur in this range. A further complication in the monitoring of VAAEs is likely to be added in the coming decade as vaccines become more complex (i.e. multivalent, conjugated,

Table 3. **Serious vaccine-associated adverse events for which causality is established or highly likely (12–14)**

	Adverse event		
	Dissemination/death <sup>a</sup>	Anaphylaxis	Other
BCG	Yes	No	No
Diphtheria–pertussis–tetanus	No	Yes	Whole pertussis: inconsolable crying, shock-like episodes, encephalopathy Tetanus: serum sickness with too frequent repeat doses
<i>Haemophilus influenzae</i>	No	No	No
Hepatitis B	No	Yes	No
Influenza A	No	No	Guillain–Barré syndrome
Measles–mumps–rubella <sup>a</sup>	Yes	Yes	Measles: thrombocytopenia, excess mortality with high titre formulations Rubella: acute arthritis (adult women)
<i>Pneumococcus</i>	No	No	Serum sickness with too frequent repeat doses (adult)
Poliovirus (live)	Yes	No	Transmission of back-mutated (revertant), vaccine-strain virus to contacts
Varicella	Yes	Yes	Transmission of vaccine-strain virus to immunocompromised contacts

<sup>a</sup> Predominantly in individuals with severe immunological deficits.

Table 4. **Vaccine-associated adverse events that occur more than 30 days after vaccination**

Vaccination for	Adverse event
Measles	Atypical and severe measles developed in some individuals upon exposure to wild type measles months to years after receipt of the inactivated vaccine. Although the precise cause remains unknown, it is possible that a formalin-induced change in the protein resulted in an unbalanced immune response to measles proteins and variable susceptibility to atypical disease (13).
Measles	Recipients of measles vaccine formulations containing 100–1000-fold higher numbers of viral particles than the standard titre vaccine (approximately 10), appear to have suffered increased mortality (relative risk 1.3; CI 1.02–1.73) for a 2–3 year period after vaccination. The cause of this excess mortality remains unknown (7).
Respiratory syncytial virus	In early vaccine trials, enhanced respiratory syncytial virus disease was reported in children who received inactivated vaccines when exposed to wild-type virus months to years later. Similar effects can be induced in mice due to vaccine-induced changes in the Th1-Th2 pattern of response to wild-type virus challenge (8).
Measles, BCG, poliomyelitis and others	Delayed dissemination often leading to death has been reported for many of the live attenuated vaccines in immunocompromized hosts: <ul style="list-style-type: none"> <li>– BCG adenitis 30 years after vaccination in AIDS patients (53)</li> <li>– Disseminated BCG leading to death months after vaccination in Canadian native children (19)</li> <li>– Disseminated measles pneumonitis and death in an HIV-positive man approximately one year after vaccination (18)</li> <li>– Progressive central nervous system disease evolving over months after poliovirus vaccination (4)</li> </ul>

vectored) and also simpler (i.e. individual peptides, proteins or polysaccharides, or cocktails of defined components). Genetic restriction in the immunogenicity of our “simplest” vaccine (e.g. recombinant hepatitis B) has already been demonstrated (22). It is highly likely (indeed certain) that reactogenicity is also influenced by our polymorphic immune response genes (e.g. HLA, TAP, TNF $\alpha$ ) (23). As we deliver immunogenic quantities of ever-simpler antigens (see below), the profile of adverse events for an identical

vaccine may plausibly be quite different in sub-Saharan Africa and downtown Tokyo.

### The changing vaccine environment

Despite the limitations to our knowledge outlined above, the last decade has witnessed enormous advances in basic immunology, molecular biology and genetics that have opened a wide range of

possibilities for the development of new vaccines (24). Large numbers of products are now being tested including preventative vaccines directed against many human pathogens, “therapeutic” vaccines directed against pre-existing, chronic infections (e.g. hepatitis B and C, HIV, *Helicobacter pylori*, human papilloma virus), anti-cancer vaccines, anti-fertility vaccines, and therapeutic vaccines for autoimmune illnesses (24). Compared with the currently available vaccines, these new products are also extraordinarily heterogeneous in their form (e.g. peptide, protein, fusion protein, carbohydrate, conjugated carbohydrate, cocktail of proteins, killed whole organism, live attenuated, live vectored, DNA, and whole autologous or allogeneic cells with or without genetic manipulation), in their formulation (e.g. novel adjuvants such as cytokines, co-stimulatory molecules, and CpG DNA motifs as well as physical carriers such as liposomes, immune stimulating complexes (ISCOMs) and proteosomes), and in their route of administration (e.g. mucosal, gene gun, food-based) (24). While enormously exciting, this impending flood of new products and novel uses of vaccination to treat and prevent both infectious and non-infectious illnesses must be accompanied by a commitment to secure the necessary resources to “keep up” the evaluation of vaccine safety. Indeed, the same level of resources and up-to-date science applied to the generation of the vaccines must be available for monitoring all aspects of vaccine safety. This commitment is important both for the evaluation of the new vaccines and to protect the “reputation” of the global vaccination effort as a whole. For good and ill, all products labelled as “vaccines” are linked in the public conscience and any serious breach in safety is likely to have far-reaching repercussions.

## Are there particular reasons for concern with the coming vaccines?

### The crowded paediatric vaccination schedule

The next generation of physicians will probably look back at the 15–20 vaccines currently available as the products of an age of remarkable simplicity. Even with this limited number of vaccines, there is already considerable pressure to combine antigens to minimize vaccine-related visits as well as the number of injections required (25). We have long been accustomed to diphtheria–tetanus–pertussis (DTP), measles–mumps–rubella (MMR), trivalent oral poliovirus vaccine/inactivated poliovirus vaccine (OPV/IPV), and the multivalent polysaccharide vaccines (e.g. pneumococcus and meningococcus), but many countries have recently introduced new bivalent (e.g. hepatitis A and B), quadrivalent and pentavalent vaccines (e.g. DTaP–IPV–*Haemophilus influenzae* b (Hib)). Furthermore, there are active efforts to build on these successes by creating ever more complex mixes of microbial antigens. On the one hand, multivalent vaccines can have great advantages such as reduced administration costs, increased coverage,

and decreased exposure to vaccine excipients which may be relatively common causes of VAAEs (e.g. gelatin) or lightning rods for anti-vaccine sentiments (e.g. thimerosal) (26–28). On the other hand, the increasing complexity of antigen mixtures may make the determination of VAAE causality very difficult (29).

Many of these new multivalent, multi-organism vaccines will also induce immune responses which are quantitatively and qualitatively different from those engendered by single antigen or single organism products. It is now well established that simultaneous administration of antigens A+B can alter the magnitude and pattern of immune response to both A and B (30, 31). Whether or not the altered immune responses generated by these vaccines are equally efficacious, durable and safe will have to be carefully monitored despite, in some cases, our many years of experience with the individual component antigens. The recently described immunological principles of immune balance between Th1-type versus Th2-type responses (32), original antigenic “sin” (i.e. the first exposure more or less permanently determines the pattern of response) (33), as well as epitopic competition and dominance (34, 35) may assume particular importance as investigators target organisms that require Th1-type responses for protection (e.g. papilloma virus and the agents responsible for tuberculosis and leishmaniasis — see below). To some extent, we have been fortunate to date with our combined vaccines in that the targeted organisms/diseases can all be prevented with sufficiently high antibody titres (DTP, MMR, hepatitis A and B). It is interesting that the possible exception to this “rule” is the relatively poor performance of the whole-cell pertussis component of trivalent and higher valency formulations (36). Neither the correlates of protection nor reactogenicity are well understood for *Bordetella pertussis*, although it appears that some degree of cell-mediated immunity (CMI) is necessary for protection from infection (37). To date, pertussis antigens have certainly been the most problematic component of multivalent vaccines in terms of both efficacy and reactogenicity.

### More subtle consequences of pressure to develop polyvalent vaccines

In addition to the immunological concerns regarding polyvalent vaccine administration discussed above, the pressure to combine microbial antigens may have very subtle influences on the risk of developing VAAEs. For example, the drive to combine antigens is one of the factors pushing investigators to create ‘simpler’ vaccines (e.g. component versus whole organism, peptide versus protein). Simpler vaccines that provide the same degree of protection are widely considered to be “better” (24) because of a lower chance of malignant antigen–antigen interactions, fewer non-essential antigens to elicit unwanted responses, and tremendous cost savings in many cases through the application of modern molecular tech-

niques. Although such simple vaccines hold tremendous promise for reducing VAAEs, we should still acknowledge that, in most cases, we do not know which B and T cell epitopes of a given vaccine are responsible for either protection or reactogenicity. We simply “hope” that the two effects can be dissociated by making simpler vaccines. As has recently been suggested by Behr & Small for BCG, it may not always be possible to dissociate virulence/reactogenicity and efficacy (38). When a complex vaccine is replaced by a simple antigen or a defined antigen cocktail (e.g. whole cell replaced by acellular pertussis vaccine), the dose of recombinant or purified antigen is titrated to biological effect (e.g. antibody production) and is measured in precise terms (e.g. µg per dose). However, we often do not know the precise concentrations of the component protein antigens in the original vaccine. If the same component is responsible for both efficacy and reactogenicity, we may deliver a higher dose of the VAAE-inducing antigen in a simple vaccine than in a more complex vaccine. In other words, the absolute number of potentially reactogenic epitopes present in an immunogenic protein or peptide vaccine may be far greater than in an intact, whole organism vaccine. While the population as a whole might benefit from the highly effective and non-reactogenic protein/peptide vaccine, the individual predisposed to respond inappropriately to epitopes within the protein/peptide may be more likely to suffer a VAAE.

Another way in which the drive to vaccinate ever larger proportions of the world’s population with polyvalent vaccines may have an untoward effect is through the progressive loss of randomness in antigen exposure. Although there are no convincing data to support this contention at the current time, several investigators have suggested that the age or order of vaccine antigen exposure can have a significant impact on the development of autoimmune diseases (39, 40). Such a hypothesis is biologically plausible since immunopathology associated with natural infections can vary enormously with the age at exposure (e.g. hepatitis viruses, Epstein–Barr virus) (41, 42) and the genetic make-up of the individual (e.g. Reiter syndrome, Behçet disease, reactive arthritis, rubella arthralgias) (43–45). Infectious agents have played a major role in driving the polymorphism of immune response genes (e.g. HLA, TAP, TNF) (45), and heterogeneity at these loci is very likely to be protective at a population level. Under “natural” conditions, human immune response genes interact with the plethora of infectious agents in a more or less random way over the first several years of life, with many factors influencing the timing of initial exposure to a given microbial antigen (e.g. season of birth, family order, social setting). Immunization programmes are inherently non-random. Young children are typically exposed to a large number of antigens in a relatively short period of time, but very few children have ever “naturally” experienced several childhood diseases simultaneously. Although current combination vac-

cines have been used for decades without obvious untoward effects, the possible influence of altered patterns of antigen exposure on infectious and non-infectious diseases *not targeted* by the vaccines will deserve more attention in the future.

## The “classic” vaccine paradigm is changing

### Organisms requiring a cell-mediated response

To date, the large majority of the infectious diseases against which vaccines have been developed share certain typical characteristics:

- illnesses with severe morbidity and/or significant mortality (e.g. smallpox, measles, rabies);
- monophasic illnesses with long-lasting immunity after infection;
- illnesses that are preventable by the induction of high titres of appropriate antibodies.

Note that even though cell-mediated immunity (CMI) is required to clear many viral infections once they are established (e.g. hepatitis A, measles), high titres of pre-formed, neutralizing antibody can often prevent infection.

Without disparaging the efforts of early vaccine pioneers, these vaccines were relatively “straightforward” to develop. They have also been spectacularly successful. It is probably not by chance that BCG, the least effective of the licensed vaccines, is directed against an organism for which cellular rather than humoral immunity plays an essential role (46). Relatively few “simple” infectious targets remain for vaccine development. For example, although neutralizing antibodies can be effective against respiratory syncytial virus (RSV) and dengue virus, these organisms exist as multiple serotypes and enhanced pathology can occur in the presence of sub-optimal or imbalanced antibody titres (7, 47). Worldwide, major targets for vaccine development include new or improved preventative vaccines for infectious agents with high associated mortality (e.g. HIV, influenza A, tuberculosis, malaria, leishmania, and diarrhoeal and respiratory diseases in the developing world), preventative vaccines for the chronic infections associated with cancer development (e.g. hepatitis B and C, papilloma virus, Epstein–Barr virus, *H. pylori*) or severe disability (e.g. *Chlamydia trachomatis*), vaccines against sexually transmitted diseases (STDs) (e.g. syphilis and STDs caused by herpes simplex virus 1, *Chlamydia* spp. and *Neisseria gonorrhoeae*), and therapeutic vaccines for chronic infections (e.g. hepatitis B and C, HIV infections) (24). Other organisms actively being pursued as vaccine targets are those that cause significant morbidity and mortality in limited circumstances (e.g. *Shigella* spp., *Campylobacter jejuni*, herpes simplex virus 1, cytomegalovirus, *Toxoplasma gondii*) (24). The induction of effective CMI is either an absolute or a

relative requirement for many of these targets. The pro-inflammatory nature of the Th1-type cytokines associated with cellular responses (e.g. interleukin-2, interleukin-12, interferon- $\gamma$ ) (32) raises the possibility that vaccines specifically designed to elicit this type of response will be quite reactogenic.

### Wisdom of targeting co-evolutionary "partner" pathogens

While diseases such as measles and syphilis probably had limited geographical distribution until relatively modern times, humans have co-evolved with other infectious agents such as malaria and the herpesviruses over millennia. These microorganisms have repeatedly or persistently infected essentially 100% of humans from an early age through a large part of our evolution as a species. The probability that the human immune system has *not* evolved to "assume" the presence of these organisms is essentially zero. Indeed, Margulis & Sagan make the eloquent argument that humans would not even exist as a species had such intimate co-evolution not occurred (48). A stunning example of this phenomenon is the recently described similarity between rickettsial DNA and eukaryote mitochondrial DNA (49). Other obvious evidence of our shared evolution with microorganisms includes the genetic legacy of Duffy-antigen-negative black Africans, the malaria-protective haemoglobinopathies (e.g. sickle cell, Hgb C), and the human cytokine genes that have been "stolen" by members of the *Herpesviridae* (e.g. vIL-10 in Epstein-Barr virus and vIL-6 in human herpesvirus-8) (50–52). Scientists have only just begun to analyse how microbial pressure may have moulded our polymorphic immune response genes (23, 43–45). The consequences for human health of "removing" some of this microbial pressure are unknown. Although the antigenic mass represented by 20–30 pathogens is trivial compared with the total antigen exposure that human infants experience during the first years of life, it is certainly plausible that some pathogenic organisms have a disproportional impact (e.g. those with high fatality rates, or the capacity to reinfect/persist, or immunomodulatory actions due to cytokine genes, superantigens, etc.).

While the case in favour of developing vaccines against tuberculosis and malaria is compelling, due to the enormous morbidity and mortality associated with these infections, the situation is potentially more complicated for organisms such as the herpesviruses and *Toxoplasma gondii*. To date, only two vaccines targeting such hypothetical co-evolutionary pathogens have been licensed (e.g. BCG for tuberculosis and varicella vaccine); both are live attenuated organisms (53, 54). In the case of varicella zoster virus, the vaccine strain virus appears to share many characteristics with wild-type virus including the establishment of latency for prolonged periods of time (54). This type of vaccine would appear to be the least likely to cause the hypothetical problem of loss of an infection-induced "advantage". In contrast, an inactivated or

component vaccine capable of completely preventing infection with one of these ubiquitous organisms could plausibly deny the developing immune system of an "essential" stimulus. Note that this discussion should not be misconstrued as an argument against the development of vaccines against herpes simplex virus 1/2, Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii*; rather, there are at least theoretical grounds to favour live attenuated formulations or vaccines that permit subsequent wild-type infection without pathology.

### Justification of vaccination using parental and societal costs

The latest aspect of the paradigm shift currently underway is the move to use parental/societal costs (e.g. time lost at work) in the cost-benefit analysis of products targeting less virulent pathogens (55). Theoretical and actual examples of such products include rotavirus and other gastroenteral virus vaccines in the developed world, and varicella and rhinovirus vaccines. This shift is particularly problematic when a third party (e.g. government, industry) has interests in addition to the health of the intended vaccinee, such as time-off-work, productivity, etc. Although annual influenza virus vaccination may well keep healthy young adults on the job and justify a corporate vaccination policy (56), there would likely be little support for a company that made annual influenza vaccination mandatory or a condition of employment.

Given the scope of the worldwide vaccination effort over the last 3–4 decades, the relative lack of organized opposition has been quite extraordinary. This has been due, in large part, to the general understanding of parents that smallpox, tuberculosis, pertussis, measles and poliomyelitis are fatal or maiming infections. Similarly, adults who consider themselves to be at high risk of acquiring rabies typically line up for the vaccination. However, concerns regarding VAAEs are heightened and the "sell" becomes much harder when the real or perceived *individual* risk is less obvious. Although many infectious diseases remain for which vaccines will be warmly welcomed (e.g. HIV, malaria), we may now be approaching a convergence of opinion between those who view some childhood illnesses as necessary "rites of passage" and those who feel that not every infection needs to be prevented by vaccination. As noted above and eloquently discussed by Rook & Stanford (57), it is virtually certain that we have evolved to "expect" a certain number of infections in our lifetime and particularly during infancy. Systematic prevention or modification of these exposures may not benefit the individual or the species in the long run.

### Conclusions

Recent advances in our understanding of basic immunology as well as of vaccine immunology are

leading the vaccine community into relatively uncharted waters. We now appear to have the capacity to make vaccines against a wide range of organisms that have frustrated 3–4 decades of sustained effort. Molecular tools in particular have accelerated the pace of vaccine development against a wide variety of microorganisms. Many of these products are either in, or rapidly approaching, clinical trials. It would be naive to assume that these new vaccines will be uniformly less problematic than their predecessors. Certainly, in terms of VAAEs, recent experience suggests that we should anticipate both successes (e.g. acellular pertussis vaccines) and possible failures (e.g. rotavirus vaccine (58)).

Both the resources and the epidemiological and laboratory tools to address the potential problems are strictly limited. In some cases, the limitations are factual (i.e. simple lack of knowledge). In other cases, the limitations come as part of the “vaccine package”; truly impressive vaccines tend to make large-scale, long-term, placebo-controlled (natural history) trials unethical. It is essential that adequate resources are made available not only to ensure the safety of ‘new’ products but also to protect our enormous investment in the vaccines already in place. We have recently seen the consequences of loss of commitment in the resurgence of diphtheria (59) and pertussis in some parts of the world (60). The human and economic costs of a large-scale return of measles or poliomyelitis would be marked. In order to protect the gains made by vaccines and vaccination programmes, there is an urgent need to learn more about the basic biology, the correlates of immunity, and the immunopathology of the diseases targeted by vaccines.

The evaluation of VAAEs should be standardized internationally and both public and private resources should be made available to evaluate VAAEs in genetically disparate societies. Every effort should be made to expand *active* surveillance for VAAEs and to encourage the linkage of VAAE databases. VAAE reporting should also be standardized such that the evidence “for” or “against” any given association can be presented in terms of simple incidence (e.g. the infection occurs in  $X$  persons per 100 000 Caucasians) or preferably, in terms of attributable risk (e.g. the risk of event  $Y$  following vaccination minus the background risk of the same event). It would be particularly useful to be able to compare the attributable risks of adverse events that occur following natural infection and vaccination. For example, it would be of great interest to know the

precise incidence and immunopathogenesis of Guillain–Barré syndrome occurring after natural influenza A infection (21). Of course, there is a simultaneous need to learn a great deal more about both appropriate (i.e. protective) and inappropriate immune responses to vaccination.

Despite the difficulties inherent in evaluating the potential, long-term, adverse effects of vaccines that are successful in the short term, the focus of current VAAE surveillance programmes on the first month after vaccination is too narrow (61).

The vaccination community also needs to formally examine the “costs”, which can be used to justify the vaccination of an individual (62).

The success of vaccination programmes to date and the swarm of new vaccines approaching the market raise the question of whether or not there is an “optimal” set of microbial exposures for the development of the immune system and for human health. Although this question is enormously complex compared to the presence or absence of a sore arm after vaccination, it *can* be approached experimentally in both humans and animal models of vaccination if sufficient resources are made available. We need to begin a discussion about where to draw the line: which of the remaining infectious agents deserve to be targeted?

As our epidemiological, immunological and genetic tools improve in the coming decade, it is likely that we shall be able to explain the immunopathology of some infectious processes as well as the immunopathology of the vaccines used to prevent them. If we are diligent, we may even acquire the capacity to anticipate and avoid some immunologically mediated VAAEs. Although the development of the required laboratory tools will probably occur independently of questions of vaccine safety, neither the application of these tools to VAAE issues nor the sophisticated epidemiological investigations that will be required will come cheap. As the pace of vaccine development accelerates, it is crucial that we find the political will and financial resources to ensure that surveillance systems and support for basic and epidemiological studies of VAAEs keep pace. Such a commitment will help to secure the status of vaccines as one of the crowning achievements of modern medicine well into the new millennium. ■

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### Résumé

#### Les manifestations postvaccinales indésirables au nouveau millénaire : faut-il s'inquiéter ?

L'histoire des vaccins comporte de magnifiques réussites mais aussi un certain nombre d'incidents fâcheux. D'après des mesures objectives de leur innocuité, les vaccins se comparent favorablement aux autres produits

pharmaceutiques. On assiste cependant à une augmentation des manifestations postvaccinales indésirables. Si certaines des associations rapportées sont largement infondées, il est vrai que les vaccins provoquent des



réactions graves chez un petit nombre de personnes. Bien que l'on connaisse mal l'immunopathogénie des effets indésirables associés aux vaccins actuels, la pratique de la vaccination est en augmentation rapide. Le « paradigme » vaccinal classique évolue pour inclure aussi des vaccins contre les maladies infectieuses qui, pour protéger, font appel à des réponses cellulaires pro-inflammatoires (tuberculose, infections herpétiques), des vaccins à usage thérapeutique contre des infections chroniques (comme le syndrome d'immunodéficience acquise (SIDA) ou les hépatites virales B et C) et des vaccins contre des affections non infectieuses (comme le cancer ou les maladies auto-immunes). Nous avons de plus commencé à prendre comme cible des agents pathogènes moins virulents, comme la varicelle, ou les rotavirus en Amérique du Nord, et à justifier l'utilisation des vaccins par les coûts sociétaux et parentaux plutôt que par de simples coûts en termes de morbidité et de mortalité.

Le calendrier vaccinal chez l'enfant devient pléthorique dans les pays développés où l'on cherche à administrer en même temps des antigènes de plus en plus nombreux sous une forme de plus en plus simple (par exemple les vaccins sous-unités, à ADN, peptidiques). Bien que séduisante à maints égards, cette tendance comporte aussi des risques théoriques tels que restriction génétique, diminution de l'étendue de la

protection offerte, disparition de l'exposition naturelle « aléatoire » aux antigènes, tous risques qui devront être évalués et surveillés. Les outils épidémiologiques et biologiques dont on dispose pour l'étude de ces phénomènes sont limités. Dans certains cas, ces limitations sont d'ordre factuel, tandis que dans d'autres, elles sont inhérentes au vaccin lui-même : les vaccins les plus prometteurs tendent à rendre contraires à l'éthique les essais cliniques en situation réelle. Il est probable qu'avec le progrès des connaissances en immunologie et en génétique nous serons bientôt en mesure d'expliquer l'immunopathologie de certaines manifestations post-vaccinales indésirables. Si nous faisons vite, nous pourrions même anticiper et éviter certaines de ces manifestations qui sont à médiation immunitaire. L'application de ces outils ne sera toutefois ni rapide ni bon marché. Avec l'accélération du développement des vaccins, il est indispensable que nous trouvions la volonté politique et les ressources financières pour assurer que les systèmes de surveillance et l'appui à la recherche fondamentale et épidémiologique sur les manifestations postvaccinales indésirables suivent le rythme. Un tel engagement permettra de confirmer le rôle des vaccins en tant que réalisation majeure de la médecine moderne et cela bien avant dans le nouveau millénaire.

## Resumen

### Episodios adversos asociados a las vacunas en el nuevo milenio: ¿hay motivos de preocupación?

La historia del desarrollo de las vacunas está jalonada de extraordinarios logros, pero también tiene en su haber algunos incidentes lamentables. En términos de medidas de seguridad objetivas, las vacunas constituyen una solución mejor que otros productos farmacéuticos. Sin embargo, el amplio espectro de episodios adversos asociados a las vacunas va en aumento. Algunas de las asociaciones notificadas tienen mucho de imaginario, pero está claro que las vacunas provocan un daño importante a un número reducido de personas. Si bien sabemos poco de la inmunopatogénesis de los episodios adversos asociados a las vacunas actuales, el uso de las vacunas va en rápido aumento. El «paradigma» clásico de la vacuna se está ampliando e incluye ahora a agentes infecciosos que exigen una respuesta celular (es decir, proinflamatoria) para ofrecer protección (p. ej., la tuberculosis, los herpesvirus), vacunas terapéuticas para infecciones crónicas (p. ej., el síndrome de inmunodeficiencia adquirida (SIDA), las hepatitis víricas B y C), y vacunas contra estados patológicos no infecciosos (p. ej., el cáncer, las enfermedades autoinmunitarias). Además, hemos comenzado a centrar nuestro interés en agentes patógenos menos virulentos (p. ej., la varicela, los rotavirus en América del Norte) y a justificar el uso de las vacunas por sus costos sociales y familiares y no ya sólo por los costos de morbilidad y mortalidad.

El calendario de vacunación pediátrica se está «recargando» en el mundo desarrollado, debido a la presión para simultanear y simplificar la administración

de un número creciente de antígenos (por ejemplo, en forma de vacunas de subcomponentes, de ADN y de péptidos). Si bien resulta atractiva desde muchos puntos de vista, esta tendencia también acarrea riesgos hipotéticos (p. ej., restricción genética, reducción del frente de protección, pérdida de aleatoriedad), que tendrán que ser evaluados y vigilados. Los instrumentos epidemiológicos y de laboratorio disponibles para abordar los problemas que se han expuesto son limitados. En algunos casos, las limitaciones son factuales, mientras que en otros son inherentes al efecto de la vacuna: cuando ésta es claramente eficaz, no es ético realizar ensayos masivos a largo plazo controlados con placebos. A medida que mejoren nuestros conocimientos en los campos de la inmunología y la genética, es probable que podamos explicar la inmunopatología de algunos episodios adversos asociados a las vacunas (EAAV). Si trabajamos con dedicación, podremos incluso llegar a prever y evitar algunos de los EAAV de tipo inmunológico. La aplicación de esos instrumentos a los interrogantes que plantean los EAAV no será ni rápida ni barata. A medida que se acelere el ritmo de desarrollo de vacunas, será decisivo contar con la voluntad política y los recursos financieros necesarios para que los sistemas de vigilancia y el apoyo a los estudios básicos y epidemiológicos de los EAAV se mantengan a la par. Tal compromiso contribuirá a que las vacunas se consideren como uno de los mayores logros de la medicina moderna hasta bien entrado el nuevo milenio.

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