The Good, the Bad and the Ugly of Vaccination

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Ever since the eighteenth century, beginning with Janner's inoculation of humans with cow's serum as a means of immunization against smallpox (*vaccinia* — *vacca* — cow) followed by Pasteur who perfected the technique and developed additional vaccines, the practice of vaccination has become a universal means of preventing infectious diseases. So much so, that it has become one of the cornerstones of modern medicine and no one of sound mind would challenge the practice of vaccination. Or should they?

During the last decade reports have accumulated on various side effects of vaccines that previously were not observed, or perhaps not acknowledged [1,2]. These include an entire range of autoimmune phenomena, and even full-blown illnesses, temporally related to the administration of vaccines. To be sure, vaccination is starting to emerge as a more complex issue than previously considered.

The Good

Since the beginning of vaccination and because of it, the quality of life for humankind (or at least a large portion of it) has improved significantly. Morbidity, and consequently mortality due to infectious diseases, especially childhood ones, have decreased considerably. Some diseases have even been completely eradicated, such as anthrax and the plague. In others, the efficacy of vaccination has been confirmed by its discontinuation; for example, the anti-tuberculosis vaccination that was used in Israel — throughout the country except for Jerusalem — until the end of the 1980s. In the early 1990s the mass vaccination against tuberculosis was discontinued, and today we are witnessing a surge of new cases of a disease once considered a relic of the past.

The Bad

On the other hand, a new aspect of vaccination has been making itself known over the last few years, as evidenced by the increasing number of reports in the literature on autoimmune phenomena, as well as full-blown autoimmune illness [3–5] [Table 1].

Two major diseases have troubled both the professional and the lay community. The first, multiple sclerosis, is related (temporally, though not causally in any conclusive way) to the hepatitis B virus vaccine [6]. The reported increase in MS cases following HBV mass vaccination prompted a public outcry and, in effect, brought this vaccination to a halt in France [7]. Lately the same issue — based on the same complaints — was raised before the U.S. congress, with the demand that anti-HBV mass vaccination be stopped in the U.S. [8].

Another cause of major public concern has been the suspected connection between the triple measles-mumps-rubella vaccine (more specifically the measles component) and the occurrence of autism in immunized children [5,6,9]. Autism, a neurodevelopmental disorder of unknown etiology, has been associated with the immune system since autoantibodies to brain components (such as myelin basic protein) were found in the sera of autistic children [2]. Extending this immune hypothesis even further, experimental treatments with IV immunoglobulin have been applied to autistic patients with encouraging results. The MMR vaccine has also been linked to a new type of inflammatory bowel disease diagnosed in children who developed symptoms of neuropsychological retardation shortly after receiving the vaccine. The new form of IBD was termed lymphoid nodular hyperplasia as it involves the bowel lymphoid tissue, which becomes hyperplastic, while the local immune defense system becomes deficient. This deficiency may explain to some extent the connection between the vaccine, the bowel inflammation, and autism. Publication of the first article on the apparent link between the vaccine and autism evoked a great deal of concern among parents and led to an almost 20% decrease in the immunization rate of children with the MMR vaccine. The link between MMR and autism has been and still is widely disputed [7].

Therein lies the rub. That these vaccines reduce child morbidity and mortality from measles, mumps and rubella is indisputable, and *not* immunizing children may leave them exposed to potentially dangerous infectious diseases. The rubella component of the MMR vaccine has also been implicated in causing autoimmune phenomena — mainly joint symptoms such as arthralgia and arthritis — since a significant proportion of children immunized against rubella developed joint symptoms within 6 weeks of the vaccination.

MS = multiple sclerosis
HBV = hepatitis B virus
MMR = measles-mumps-rubella
IBD = inflammatory bowel disease

Table 1. Autoimune diseases reported after vaccinations

Disease	No. of cases	Vaccine	Reference
SLE	10	HBV	2
	3	Typhoid/Paratyphoid	17
	4	Combination	17
	1	Anthrax	17
	1	Tetanus	17
RA	15	HBV	2, 17
	13	Tetanus	17
MS	More than 20	HBV	2
Autism	More than 10	MMR	2
Reiter's	1	BCG	Present
	1	Typhoid	17
	1	*Salmonella*	*Arthritis Rheum* 1987;30:1197
	1	Combination	*Br Med J* 1994;309:94
Dermatomyositis	1	Smallpox	17
	2	BCG	17
	2	Diphtheria	17
	1	DPT	17
PAN	4	Influenza	17
	1	Pertussis	17
GBS	More than 10	Influenza	2
	2	Polio	2
	2	Tetanus	2
Reactive arthritis	1	DPT	17
	2	MMR	*Arch Dis Child* 1995;72:348–9
	29	HBV	*Clin Exp Rheum* 1993;11:45
		Influenza	*Recenti Prog Med* 1994;85: 438–40
		Influenza	2, 17
			Clin Rheumatol 1994;13:645

However, it should be mentioned that the symptoms were milder than those often observed after infection with the wild strain of the virus.

The Ugly

A wide range of additional autoimmune manifestations has been described in relation to vaccines, including joint symptoms (as mentioned above, and even full-blown rheumatoid arthritis) [8,10], systemic lupus erythematosus [11] and others [12,13].

In this issue of *IMAJ*, Hodish et al. [14] describe a patient who presented with Reiter's syndrome, arthritis and urethritis that developed after intravesical inoculation with BCG as part of the treatment for urinary bladder carcinoma. Intravesical BCG inoculation has long been used as therapy for transitional cell carcinoma of the bladder. The effect of the BCG on the tumor is indirect, causing an increased immune response that locally fights the tumor. However, sometimes the reaction is not local but systemic; and fever, rash and even sepsis have been reported in relation to intravesical BCG administration. Infection with *Mycobacteria tuberculosis* has been connected to autoimmune disorders [15,16] including arthritic symptoms. In 1897 Poncet described an inflammatory arthritis in several patients with acute tuberculosis, but its existence has been disputed ever since [15]. Researchers have tried to explain the apparent connection between *M. tuberculosis* and autoimmune phenomena through the molecular mimicry theory. A molecule characteristic of the *M. tuberculosis* (heat-shock protein 65) has been implicated in the triggering of autoimmune phenomena [16], but no conclusive results have been obtained. Skin manifestations, namely lupus vulgaris, have been described after intravesical BCG administration, as well as after spontaneous infection with the bacteria. Table 1 summarizes the autoimmune diseases and the vaccines to which they have been connected.

The case described by Hodish et al. is unusual because of both the arthritis (which is an uncommon occurrence in relation to BCG inoculation) and the protracted course of the illness. An additional case of Reiter's syndrome following immunization against typhoid was recently reported [17]. In this 22-year-old man the symptoms of the disease first appeared 10 days after immunization. In the case described by Hodish and colleagues, the first symptoms of the disease manifested one week after the fifth treatment with BCG.

Arthritis has been described, as mentioned before, in connection with rubella vaccine, but also with other vaccines. Rheumatoid arthritis has been described following HBV vaccination, as well as other vaccines such as paratyphoid A and B [18]. The development of inflammatory arthritis first occurred 1–3 weeks following immunization (while neurological side effects have been described also during the first few days after vaccination) — a reaction similar to serum sickness. Unlike serum sickness, however, this disease persisted. Many of the patients who developed RA were carrying HLA class II genes expressing the RA shared motif, suggesting a genetic predisposition to the disease. In these cases the vaccination may have provided the trigger for the autoimmune reaction. In other cases, such as SLE described after various immunizations [Table 1], such an association was not always found.

Another interesting aspect of the post-vaccination autoimmune diseases is that they affect males and females equally [18], unlike the naturally occurring autoimmune diseases that have a clear female predominance.

In the meanwhile, even though we recognize that vaccination *can* and *does* have autoimmune side effects, and that it can trigger full-blown autoimmune diseases, we are unable to identify who is most prone to develop these side effects or diseases after immunization. This is not unlike our inability to anticipate which individuals from among those exposed to certain environmental factors, and/or carrying a given genetic baggage, will develop autoimmune disease. As more cases of systemic connective tissue diseases following vaccinations are reported, we may

BCG = bacillus Calmette-Guérin

RA = rheumatoid arthritis

be able to identify those that are genetically prone to be negatively affected by the immunization. It should be stated that patients already diagnosed with autoimmune diseases such as RA or SLE withstand immunization very well and even benefit from it. With these patients being at greater risk from infectious diseases, the vaccination actually reduces the morbidity and the mortality among them.

The dilemma of whether and when to vaccinate remains unresolved, and the polemic around this issue will surely continue until ongoing research provides us with more definite guidelines and answers.

References

1. Cohen AD, Shoenfeld Y. Vaccine-induced autoimmunity. *J Autoimmun* 1996;9:699–703.
2. Shoenfeld Y, Aron-Maor A. Vaccination and autoimmunity — vaccinosis; a dangerous liaison? *J Autoimmun* 2000;14:1–10.
3. Marshall E. A shadow falls on hepatitis B vaccination effort [Editorial]. *Science* 1998;281:630.
4. Dove A. Congress examines childhood vaccine safety. *Nat Med* 1999;5:970.
5. Singh VK, Sheren XL, Yang VC. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. *Clin Immunol Immunopathol* 1998;98:105–8.
6. Lee JW, Melgaard R, Clementa CJ. Autism, inflammatory bowel disease and MMR vaccine. *Lancet* 1998;351:905–9.
7. Peltola H, Patja A, Leinikki P, Valle M, Davidkin I, Paunio M. No evidence for measles, mumps and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. *Lancet* 1998;351:1327–8.
8. Grasland A, Vinceneux P. Rheumatic manifestations of vaccination. *Rheum Eur* 1999;28:25–7.
9. Wakefield AJ, Montgomery SM. Autism, viral infection and measles-mumps-rubella vaccination. *IMAJ* 1999;1:183–7.
10. Symmons DPM, Chakravarty K. Can immunization trigger rheumatoid arthritis. *Ann Rheum Dis* 1993;52:843–4.
11. Tudela P, Marti S, Bonal J. Systemic lupus erythematosus and vaccination against hepatitis B. *Nephron* 1992;62:236.
12. Stefanini M, Piomelli S, Ostrovski JF, Colpoys WP. Acute vascular purpura following immunization with asiatic influenza vaccine. *N Engl J Med* 1998; 259:9–12.
13. Joekes AM, Gabriel JRT, Goggin J. Renal disease following prophylactic inoculation. *Nephron* 1972;9:162–70.
14. Hodish I, Ezra D, Gur H, Strugo R, Olchovsky D. Reiter's syndrome after intravesical bacillus Calmette-Guérin therapy for bladder cancer. *IMAJ* 2000;2:240–1.
15. Shoenfeld Y, Isenberg DA. Mycobacteria and autoimmunity. *Immunol Today* 1988;9:178–82.
16. Tischler M, Shoenfeld Y. Tuberculose et immunite: ou en sommes nous? *Ann Inst Pasteur* 1996;7:133–6.
17. Maillefert JF, Serabian-Tonolli I, Cherasse A, Demoux AL, Tavernier C, Piroth L. Arthritis following combined vaccine against diphtheria, poliomyelitis and tetanus toxoid. *Clin Exp Rheumatol* (in press).
18. Older SA, Battafarano DF, Enzenauer RJ, Krieg AM. Can immunization precipitate connective tissue disease? Report of five cases of systemic lupus erythematosus and review of the literature. *Semin Arthritis Rheum* 1999;29:131–9.

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