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Discussion

Unusual positive effects from vaccines need to be reported – They represent a resource that could lead to new treatment strategies

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In the practice of medicine a select number of patients stand out as distinctly remarkable and hence unforgettable. This article relates to a single patient encounter with an exceptional middle-aged woman, whom on presentation, was elated because of a change in her health. She had a 10 year history of severe intrinsic asthma and for the first time in years was breathing normally. Her husband was waking her at night because he could not hear her breathing and thought she may have died. The only recent event was a flu vaccine within the previous 2 weeks. She continued doing well until 3 months later when her asthma returned and again she was on intermittent systemic steroids. A study protocol was set up to vaccinate her with the same antigens plus investigate changes in her T cell response but due to poor health, the patient declined participation.

Remission of asthma is rare in the middle aged and elderly and is associated with mild disease and cessation of smoking [1]. Resolution of adult onset asthma, occurring after flu vaccine, has not been previously reported.

Vaccines introduce pathogen specific antigens. Hence if a positive or negative effect on a chronic disease occurs within the time frame when the immune system is selectively expanding in response to these defined antigens, we have a window of opportunity to determine mechanisms that can tip the balance between cure and chronic disease.

Currently systems are set up in many places to detect adverse effects of vaccines, by definition noxious unintended effects. However, we do not have similar tradition for registering unexpected positive effects. A positive event occurring in a single patient that is biologically not easily explained is likely to be ignored. Furthermore, larger than predicted drops in population morbidity and mortality occurring after modification of a vaccination program are likely ascribed to environmental factors rather than the vaccine. This unfortunately means that an opportunity to find new approaches to treatment can be lost. This brief article will discuss unexpected positive effects from vaccines, briefly review altered innate immunity, cross-reactivity and how the immune response can be redirected. If by chance the immune system can so powerfully be modified by a vaccine, then perhaps it can also happen by design.

Although vaccines were originally conceived as a method to generate a selective immune response against a microbe, subsequent studies have shown that numerous unexpected protective effects also occur [2]. Anecdotally, *Vaccinia* immunization did not only protect against smallpox but had protective effects against measles, scarlet fever, syphilis and atopic diseases [3]. In recent randomized trials in low-income countries, both measles vaccine and BCG vaccine were associated with benefits far from what could be explained based on the specific effects. Measles vaccines administered at 4.5 or 9 months of age in reduced mortality in the 4.5–36 month

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age group by 30% while measles death related events could only account for a 4% reduction of deaths [4]. BCG reduced neonatal mortality by more than 40% although TB as a cause of death in neonates is very rare [5]. These *non-specific effects* from vaccines may be partly due to "trained innate immunity" mediated via epigenetic reprogramming of innate immune cells, leading to a heightened state of activation of the innate immune system, increased expression of pattern recognition receptors and enhanced protective inflammatory responses toward unrelated pathogens [2]. This window of time when the innate system is functionally on alert status lasts several months and potentially years [6]. Furthermore, the adaptive immune response, through T cell cross-reactivity, may diverge from clonal proliferation of T cells selected for dominant antigens of the inducing vaccine antigens to spread of reactivity to other peptide-MHC molecular mimics. This confers protection against many unrelated microbes. However, epitope spread may be detrimental if self antigens are inadvertently targeted leading to immunopathology or if it compromises the development of protective immune responses [7]. Past immunizing events, the sequence of infections or vaccines, the T cell repertoire emerging from the thymus when an immunizing event occurs plus inter-individual genotypic variances defining host tissue and its responsiveness all modulate the outcome [2,7]. Of definite interest, from the perspective of lung pathology related to influenza A virus (IAV) vaccines, is a mouse model initially immunized against IAV and latter infected with lymphocytic choriomeningitis virus (LCMV). The mice developed a cross-reactive memory response between 2 proteins on each virus. The severity of the subsequent lung pathology was directly correlated to the frequency of the IAV memory responses rather than the response to LCMV. Ablating the IAV memory cells inhibited severe lesion such as bronchiolization from developing [8].

Hence, compelling epidemiological evidence for non-specific effects of vaccines is now backed by immunological studies supporting that vaccines may have effects on the immune system which go far beyond the effect on the target disease. These effects may be due to increased or decreased pro-inflammatory innate and adaptive responses to other pathogens: the direction of the effect is not easy to predict. Thus, any immune event, including a positive change in disease status, which occurs with such a sharply defined onset after a vaccination, should be considered an effect of this vaccine. Such findings provide a chance of finding mechanisms central to disease pathogenesis.

We will not know how often vaccines have beneficial effect on non-related illnesses unless we encourage reporting of beneficial effects. The intent of this viewpoint article is to stimulate interest in reporting and registering unintended positive events in a manner similar to what is done for negative effects after vaccination. Hence we propose that national and international "vaccine adverse event reporting" registers are renamed "vaccine associated event reporting" registers and that reporting of both positive and negative associated events are encouraged. Alternatively a separate "positive vaccine associated event" register could be created.

Patients with chronic inflammatory disease, like the woman with asthma, who developed unexplained significant improvement in symptoms after vaccination represent an important subset to study. Clearly such patients may be rare but since hundreds of millions of patients receive vaccines yearly, it remains to be established the extent to which this type of positive event actually occurs. At the population level, it is also important to keep a watch for unexpected drops (or increases) in overall morbitity and mortality associated with changes in vaccination schedule, introduction or removal of vaccines. In likening with patient-related events, a vaccine associated unexpected drop in morbidity or mortality at the population level should likewise be reported as a "positive vaccine associated event".

Medical breakthroughs not uncommonly arise through pursuit of unusual responses noted in single patients. "Happy Accidents" have been reported to play a major role in innovative discovery [9]. Those patients who deviate positively post vaccination are an opportunity to better understand how the immune system functions with the potential benefit of improved patient and population specific treatment.

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Conflict of interest

None of the authors has any potential financial conflict of interest related to this article.

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