

REVIEW ARTICLE

# Psychobiology of Vaccination Effects: Bidirectional Relevance of Depression

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## ABSTRACT

Emerging research on inflammation-mediated processes that underpin depressive syndromes reveals a possible link warranting greater exploration. Because of its often insidious onset and varied presentation, depression as a sequelae of pharmaceutical interventions can be difficult to assess. This review explores the available literature

considering the relevance of pre-existing depression to vaccination response as well as the association of vaccination with adverse psychiatric events/depression and the mechanistic plausibility of that association. (*Altern Ther Health Med.* 2015;21(suppl 3):18-26.)

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Emerging research on inflammation-mediated processes that underpin depressive syndromes reveals a possible link warranting greater exploration. Because of its often insidious onset and varied presentation, depression as a sequelae of pharmaceutical interventions can be difficult to assess. This review explores the available literature considering the relevance of pre-existing depression to vaccination response as well as the association of vaccination with adverse psychiatric events/depression and the mechanistic plausibility of that association.

## INFLAMMATORY MODEL

Previously thought to have a neurochemical basis in serotonin imbalance, depression is now coming under the etiologic umbrella of most chronic-disease models that ascribe pathology to inflammatory response.<sup>1</sup> In that model, often referred to as the cytokine theory, depression is a syndrome of evolutionary mismatch.<sup>2</sup> It is an expression, on the part of the immune system, of stress caused by an evolutionarily unprecedented environment that humans have not evolved to accommodate homeostatically. Those

stresses include lack of contact with nature and with the circadian rhythm of sunlight, together with consumption of a processed, nutrient-depleted diet, and exposure to industrial chemicals such as pesticides and plastics (eg, polychlorinated biphenyls) (PCBs).<sup>3</sup> Communication of the stress response is mediated through cytokines such as interleukin 6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), the specific role of which was first elucidated in hepatitis patients treated with interferon who developed depression at a rate of 45%.<sup>4</sup> Those cytokines have been shown to have a linear and predictive relationship with depressive states.<sup>5,6</sup>

Referred to as *sickness syndrome*,<sup>7</sup> models of inflammatory depression are characterized by symptoms that are designed to reallocate energy resources for recovery.<sup>8</sup> Those symptoms include loss of appetite, lack of social interest, irritability, slowed thinking, low libido, increased sleep, anhedonia, and lethargy. Depression was likely an adaptive response<sup>9</sup> in human history of acute infectious stressors but has been rendered disabling in a landscape of a chronic, unrelenting assault on response systems.

In fact, even psychological stress has been demonstrated to mobilize immature monocytes from the bone marrow that are glucocorticoid resistant and proinflammatory in nature, which then serve to initiate the central nervous system (CNS) inflammatory response through the microglia.<sup>10</sup>

In addition, signals from the gut<sup>11</sup> trigger an immune and inflammatory response that translates primarily through the vagus nerve to stimulate central production of cytokines and associated compounds that are neurotoxic when unremitting. Thought to play an increasingly important role

in the physiology of depressive symptoms, glutamate is a major mediator of brain inflammation. When inflammation is triggered systemically and translated to the brain, astrocytic recycling of glutamate is inhibited, and *N*-methyl-D-aspartate (NMDA) agonist compounds, such as quinolinic acid, are produced by activated microglia.<sup>12,13</sup>

## PSYCHONEUROIMMUNOLOGY

The study of the interconnectedness between the gut, the brain or mind, and the immune system is referred to as *psychoneuroimmunology* and refers to the bidirectional effects of the gut ecosystem on brain function and vice versa. The role of the gut microbiome in depression and mental health generally has been featured as a primary point of clinical intervention. For example, lipopolysaccharide (LPS), a highly proinflammatory component of the gram-negative bacterial cell wall, has been used in animal models to induce depressive states and can pass into the bloodstream in the setting of dysbiosis and intestinal permeability.<sup>14</sup> That research speaks to the vital role of commensal organisms as agents of homeostasis.

Not only did humans coevolve with microbes and eukaryotic organisms<sup>15</sup> during millions of years, but the very mitochondria powering the cellular machinery are themselves of bacterial origin.<sup>16</sup> The human genome is up to 8% viral, and the body uses those viruses and microbes to regulate gene expression, immunomodulation, nutrient synthesis, and, even, placental growth.<sup>17</sup> Given the flashpoint nature of awareness of the microbiome, biology as scientists know it must come under revision, particularly when applied to its direct human application in medical interventions.

Rene Dubos, the late microbiologist, warned the world of the dangers of classical germ theory one-half of a century ago, stating,

... man himself has emerged from a line descent that began with microbial life, a line common to all plant and animal species ... [he] is dependent not only on other human beings and on the physical world but also on other creatures—animals, plants, microbes—that have evolved together with him. Man will ultimately destroy himself if he thoughtlessly eliminates the organisms that constitute essential links in the complex and delicate web of life of which he is a part.

Awareness of the role of microbes in day-to-day life has brought scientists to a radical new understanding of the interconnectedness between the gut and the brain. In fact, the role of the brain-based immune system has only been elucidated in the past 10 years, and many questions remain.

Garay and McAllister<sup>18</sup> stated,

The link between environmental factors, the immune response, and neurological dysfunction is not completely clear at present, but it is receiving increasing attention and support ... the sheer number of immune molecules that could be important for nervous-system development and function is staggering. Although much progress has been made in the past 10 years in

scientists' appreciation that immune molecules play critical roles in the healthy brain, the large majority of immune molecules have not yet been studied for their presence and function in the brain. For the immune molecules that scientists know are important, almost nothing is understood about their mechanisms of action.

Incredibly, even basic anatomy is still being elucidated; Louveu et al<sup>19</sup> have recently identified the existence of brain lymphatics, stating,

The discovery of the central nervous system's lymphatic system may call for a reassessment of basic assumptions in neuroimmunology and sheds new light on the etiology of neuroinflammatory and neurodegenerative diseases associated with immune-system dysfunction.

Given the research discussed, immune-targeted pharmaceuticals recommended to healthy individuals must be reevaluated for their brain-based effects.

## CELL-DANGER RESPONSE

Designed more than a century ago—prior to the discovery of deoxyribonucleic acid (DNA) in 1953, reverse transcriptase in 1970, and the study of epigenetics—vaccines are intended to induce a persistent, low-grade immune response and are necessarily inflammatory by nature. Although antibody production was once held as the cornerstone of a robust and enduring immune response, newer data have undermined the primary role of increased antibody titers in an effective immunoprotection.<sup>20</sup>

The inextricable links between different elements of the immune system have revealed that stimulation of one arm, namely T helper cell 2 (Th2) immunity, may result in unintended effects related to Th1 immunity. For example, the flu vaccine is associated with increased vulnerability to viral infection. Specifically, data have suggested that (1) the vaccine can hamper the development of virus-specific, CD8 T-cell immunity<sup>21</sup>; (2) the pediatric flu vaccine can induce a 3-fold increase in hospitalization for recipients<sup>22</sup>; (3) the trivalent flu vaccine can produce a 4.4 relative risk (RR) for noninfluenza viral infection<sup>23</sup>; and (4) the receipt of the 2008 trivalent flu vaccine caused up to a 2.5-fold increased risk of medically attended H1N1.<sup>24</sup>

To increase the intensity and duration of the immune response, powerful xenobiotic and biological adjuvants are employed in the manufacture of vaccines, many of which hyperstimulate the Th2 response. In that way, vaccine adjuvants, as well as preservatives and live tissue ingredients, may provoke a cell-danger response<sup>25</sup> that may persist in a significant subset of the population, leading to possible unremitting, and potentially unresolvable, inflammation and autoimmunity.

## Mercury

Even though most vaccines recommended to children and adults contain no more than trace amounts of mercury

in the form of thimerosal (49.6% ethylmercury), a notable exception is the flu vaccine. For example, each adult flu shot contains 50 µg of thimerosal, in a soluble concentration of 1:10 000, or the equivalent of 50 000 parts per billion (ppb) of mercury relative to the 2 ppb that the Environmental Protection Agency (EPA) sanctions for oral ingestion through a liter of drinking water.<sup>26</sup> The cumulative burden of mercury exposure through the multiple recommended flu shots and tetanus and meningococcal vaccines, in addition to amalgams, fish, and air pollution, makes it difficult to generalize with regard to safety parameters. Encountered as elemental, inorganic, and organic substances, mercury can affect the immune system in different ways. Mercury, even at subtoxic levels, can induce an immune response,<sup>27</sup> potentially through the formation of metal-protein complexes.<sup>28</sup>

Thimerosal kinetics differ from those of methylmercury, and, potentially, are more relevant to brain physiology. Burbacher et al<sup>29</sup> investigated those kinetics in primates, stating,

Data from the present study support the prediction that, although little accumulation of Hg in the blood occurs over time with repeated vaccinations, accumulation of Hg in the brain of infants will occur. ... Absolute inorganic Hg concentrations in the brains of the thimerosal-exposed monkeys were approximately twice that of the MeHg monkeys.

Evidence exists that shows that ethylmercury can act as a mitochondrial toxin in brain astrocytes.<sup>30</sup> Thimerosal has also been found to promote overflow of the excitotoxic chemical, glutamate, in the prefrontal cortex<sup>31</sup> causing “behavioral, neurochemical, and neuropathological abnormalities” and “lasting neurobehavioral impairments and neurochemical alterations in the brain” in animal studies.<sup>32</sup> Longitudinal human studies have demonstrated developmental impairment from ethylmercury exposure.<sup>33</sup>

Notably, the toxicological assessment of injected quantities has never been examined, but due to the absence of liver-based detoxification mechanisms and the gut barrier, direct injection of heavy metals can be presumed to have a significantly greater potential toxicity compared with oral delivery.

## Aluminum

As mercury was phased out of most vaccines 10 years ago as a precautionary step, aluminum replaced it as a primary vaccine adjuvant, and it is now present in 18 vaccines in the current pediatric schedule—hepatitis B (HepB); diphtheria, tetanus, and pertussis (DTaP); hepatitis A (HepA); haemophilus influenza type B (Hib); and pneumococcal conjugate vaccine (PCV). A recent study<sup>34</sup> stated, “Aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation, and associated neurological complications, and thus, may have profound and widespread, adverse health consequences.”

Once thought to be efficiently cleared from the body, it has been known since 2001 that aluminum biopersist. Gherardi et al<sup>36</sup> have stated,

We previously showed that poorly biodegradable, aluminum-coated particles injected into muscle are promptly phagocytosed in the muscle and the draining lymph nodes and can disseminate within phagocytic cells throughout the body and slowly accumulate in brain.

One of the most relevant aluminum-containing vaccines is Gardasil, responsible for more than 34 000 reported adverse events,<sup>37</sup> and now Gardasil 9, which contains twice the aluminum dose (ie, now with 500 µg per 3 recommended doses).<sup>38</sup> Marketed for prevention of cervical cancer, the vaccine did not require clinical proof of effectiveness but instead used cervical intraepithelial neoplasia (CIN) 1/2 as a surrogate marker for cancer and death outcomes.

The diagnosis rate for cervical cancer in the United States is 7.9 per 100 000. Only 5% of human papillomavirus (HPV) infections progress to CIN, and 91% of early-stage cases of CIN resolve spontaneously within 36 months, with 70% of CIN-1 and 54% of CIN-2 cases doing the same within 12 months.<sup>39</sup> Using those pathologies as surrogate markers for cancer incidence may represent a scientific shortcoming, particularly in light of the preexisting effectiveness of the pap smear.<sup>40,41</sup> The combined pap smear and HPV vaccination have not been demonstrated to improve outcomes above Pap screening alone, and a recent review stated, “Pap screening will still be required in vaccinated women; hence, HPV vaccination programs are not cost-effective and may do more harm than good in countries where regular Pap screening and surgery have already reduced the burden of the disease.”<sup>42</sup>

## Other Toxicants

The field of toxicology is evolving to account for the potentially adverse effects of low-dose toxicants, the role of the hypothalamic-pituitary-adrenal (HPA) axis, and the relevance of chemical-toxicological synergy.<sup>43</sup> An important study also has supported the role of the inflammatory response itself in priming the brain for sensitivity to chemicals.<sup>44</sup> Chemical ingredients such as polysorbate 80 and formaldehyde have never been studied for safety by intramuscular injection, either singularly or in the combinations of antigens present in a single vaccine or in vaccines given simultaneously or serially. Polysorbate 80 has been demonstrated to traverse the blood brain barrier,<sup>45</sup> and intravenous data on it have demonstrated immunotoxic effects.<sup>46</sup> Formaldehyde is classified as a carcinogen<sup>47</sup> and has been implicated for its immunotoxicity.<sup>48</sup>

Of additional concern is monosodium glutamate in vaccines such as the measles, mumps, and rubella (MMR) vaccine. Dr Stephanie Seneff<sup>49</sup> of the Massachusetts Institute of Technology argued that the near ubiquitous exposure to glyphosate, which is the primary ingredient of the weed killer Roundup, primes the body to accumulate glutamate because it chelates minerals essential to its metabolism, such as manganese.<sup>50</sup> Many vaccine excipients interfere with cytochrome-p450 functioning, which itself is subject to genetic variance, thereby modifying the pharmacokinetics of coadministered agents.<sup>51</sup> The Centers for Disease Control

and Prevention (CDC) makes a list of excipients available for each vaccine.<sup>52</sup>

### Live and Adventitious Viruses

Live-virus vaccines employ attenuation techniques ostensibly to decrease virulence. One of the basic methods used to create those weakened vaccines is to pass the infectious agent through animal and/or diploid human cells and fluids serially. The process gives the vaccine's master seed stock an opportunity to become contaminated along the way with hidden disease vectors, including cancer-causing viruses, which the CDC has acknowledged to have infected millions of polio vaccine (SV40) recipients. In addition, the manipulation of those tissues introduces the possibility of activating normally benign, endogenous retroviruses that are latent in animal and human genomes, creating potentially infectious vectors<sup>53</sup> that have been linked to schizophrenia and bipolar disorder.<sup>54</sup> Those agents are assumed to be benign, and, therefore, are not screened for when vaccines are assessed; those adventitious agents are identified in many attenuated vaccines.<sup>55</sup>

With only theoretical mechanistic considerations for the ways in which foreign genetic material can cause chronic inflammation, one possibility is chronic, low-grade infection that defies immunosurveillance,<sup>56,57</sup> with another being the risk of insertional mutagenesis from human fetal cells, quantified by Deisher et al,<sup>58</sup> who discovered that the fetal DNA levels in vaccines, such as the MMR vaccine, ranged from 142 to 2000 ng, whereas the upper limit for the Food and Drug Administration (FDA) is 10 ng.<sup>58</sup>

### AUTOIMMUNITY AND DEPRESSION

With 50 million Americans suffering from diagnosed autoimmune disorders,<sup>59</sup> the relevance of those diagnoses to depression has been explored in the literature.<sup>60</sup> Patients with autoimmune disorders suffer from depression more often than can be accounted for by the struggle with their physical symptoms. In a population-based cohort study of 3.5 million people, autoimmune disease increased the risk of a mood disorder by 45%.<sup>61</sup> Some autoimmune disorders, specifically, carry near complete comorbidity. For instance, "Seventy-percent of systemic lupus erythematosus (SLE) sufferers exhibit nervous system (NS) disturbances collectively referred to as neuropsychiatric SLE (NPSLE), with as many as 15% to 75% of NPSLE sufferers exhibiting major depressive symptoms."<sup>62</sup>

Do vaccines play a role in self-antigen presentation (ie, in circumstances in which the immune system identifies self-structures as other)? Overwhelming evidence<sup>63,64,65,66,67,68</sup> has suggested that the relationship is an important consideration. Because the coinjection of animal and human tissues with structural homology, together with immune- and inflammatory-provocative adjuvants, bypasses mucosal barriers, molecular-mimicry mechanisms are highly plausible. Vaccine-induced immune effects differ from those induced through wild-type (natural) infection; most studies

have demonstrated that vaccines induce Th2 responses rather than the Th1 and Th17 associated with a response to wild-type, community-acquired infections.<sup>57</sup>

Although end-organ immune targets, such as thyroid autoimmunity, can result in psychiatric sequelae,<sup>69</sup> brain-based targets (ie, encephalitides) are of particular relevance to the current discussion. Encephalitis is a cited, potential sequelae of vaccine-preventable infections, such as measles. Measles is known to cause encephalitis through 3 means: (1) acute postinfectious encephalitis; (2) acute progressive infectious encephalitis; and (3) chronic, subacute sclerosing panencephalitis (SSPE)<sup>70</sup> involving trafficking of the virus along neurons.<sup>71</sup> In an analysis of the Vaccine Adverse Event Reporting System (VAERS), Rugole and Ležaić<sup>72</sup> stated that "background rates of measles-related encephalitis are difficult to ascertain because '(the) study of the issue is hampered by a lack of background encephalopathic rates in unvaccinated children.'" Comparatively, vaccine-induced encephalitis has an earlier onset (8-9 d) in many cases, with associated lymphoid hyperplasia.<sup>73</sup> Mumps and MMR vaccines have also been associated with up to a 12-fold increase in incidence of aseptic meningitis postvaccinally, according to assessments of outbreaks.<sup>74,75</sup>

A review<sup>76</sup> on postvaccination encephalitis stated that the incidences of the initially termed neuroparalytic accidents gained recognition in 1853 after the widespread introduction of the Jenner's smallpox (actually cowpox) vaccine, and, in 1885, with Pasteur's rabies vaccine. Postvaccination, acute disseminated encephalomyelitis (ADEM) is associated with several vaccines, including those for rabies, diphtheria-tetanus-polio, smallpox, MMR, Japanese B encephalitis, pertussis, influenza, HepB, and swine flu.<sup>72</sup>

Because of limitations in current population surveillance through the VAERS passive reporting system, which captures only approximately 1% to 10% of incidence,<sup>77</sup> the true nature of the association remains to be researched. An analysis of available reports to VAERS found that the seasonal flu and HPV vaccines accounted for almost 30% of encephalomyelitis reports, with the majority of case showing onset within 2 to 30 days of vaccine receipt.<sup>78</sup>

Although many protein targets are candidates in the CNS, NMDA-receptor autoimmunity<sup>60</sup> is a psychiatrically disabling condition that has been reported in connection to the DTaP vaccine.<sup>79</sup> That and other aluminum-containing vaccines have been documented in the medical literature as triggers for a host of autoimmune disorders, termed autoimmune/inflammatory syndrome induced by adjuvants (ASIA).<sup>80</sup>

Tomljenovic<sup>81</sup> summarized the concerns as follows:

Immune challenges during early development, including those vaccine-induced, can lead to permanent, detrimental alterations to the brain and immune function. Experimental evidence also shows that simultaneous administration of as little as 2 to 3 immune adjuvants can overcome genetic resistance to autoimmunity. In some developed countries, by

the time children are 4 to 6 years old, they will have received a total of 126 antigenic compounds, together with high amounts of aluminum (Al) adjuvants, through routine vaccinations. According to the FDA, safety assessments for vaccines have often not included appropriate toxicity studies, because vaccines have not been viewed as inherently toxic.

In addition, female patients, who are an understudied population, may be uniquely vulnerable to both depression and to autoimmunity, in that their inflammatory response may be entirely different from that of males, calling into question the universality of vaccine recommendations and the critical need to account for bioindividuality across age, gender, and race, to name but a few salient confounders.

## VACCINES AND DEPRESSION

If researchers acknowledge that depression can result from an inflammatory trigger that provokes the neuroendocrine system (ie, raising cortisol, inflaming the brain, and impacting immunity in unpredictable ways), they can logically extend that knowledge to the idea that depressed individuals could mount aberrant responses to vaccines.

Antibody response to vaccine antigens appears to be largely dependent on characteristics of the individual's HPA axis, environmental and lifestyle factors, and some contributions from genetics. As stated in a recent article "Variation in the Human Immune System Is Largely Driven by Nonheritable Influences," "Considerable heterogeneity exists in immunological parameters between individuals, but its sources are largely unknown."<sup>83</sup>

At the current time, vaccines have not been adequately researched with regard to their impact on the microbiome, ostensibly responsible for orchestrating some 70% to 80% of the human immune response.<sup>84,85</sup> This year, the American Society for Microbiology claimed to be the first ever to look at the impact of a live, attenuated, flu-vaccine virus on other microbes in mice, finding reversal of normal bacterial clearance and abnormal colonization.<sup>86</sup> The broad implications suggest that live, attenuated, viral vaccines may have unintended consequences on important human bacterial pathogens unrelated to the vaccine's target species. Preliminary data have implicated the absence of *Bifidobacterium* in potentially unexpected or adverse responses to vaccines, with diversity and phyla dominance playing a role in ethnic disparities in vaccine responses.<sup>87</sup>

It appears that individualized psychological stressors and immune factors can synergize to produce a number of inflammatory responses. For example, in a randomized, placebo-controlled trial of healthy men, the typhoid vaccine produced higher levels of the inflammatory cytokine IL-6 when the participants were subjectively stressed. Those stressed and inflamed participants had changes in hormones, neurotransmitters, and subjective mood states.<sup>88</sup> Sixty college students with high perceived psychological stress were found to mount lesser antibody responses to a meningococcal vaccine.<sup>89</sup> In the case of the flu vaccine, noted to cause an

inflammatory response in pregnant patients,<sup>62</sup> the response was even more persistent and amplified in pregnant depressed patients.<sup>90</sup>

Similarly, a study involving 126 eleven-year-olds, who were monitored for 6 months after vaccination, determined that those with internalizing mood symptoms exhibited an enhanced vaccine response characterized by elevated, and more persistently elevated, antibody titers.<sup>91</sup> The researchers stated,

The observed, enhanced vaccine response associated with depressive and anxious symptoms in early adolescence may reflect an important developmental difference in immune-system-brain interplay between adults and children, and it underscores the need for further developmental studies of psychoneuroimmunology.

Speculation has occurred in the literature that an increased incidence of shingles may be directly related to disturbance of wild-type immunity of varicella in the childhood demographic.<sup>92</sup> In a study of healthy adults who were offered the shingles vaccine, Irwin et al<sup>93</sup> found that those who were depressed had lessened cell-mediated immune responses.

Burns et al<sup>89</sup> have attempted to address age-related differences in immune responses, stating,

It is not easy to extrapolate from NK (natural-killer)-cell function, an index of innate immune response, to vaccine responses, a prototypic index of the adaptive immune system; however, the contrasting findings suggest that distinctly different patterns of interplay among psychological processes, the nervous system, and the immune system may be found in adult and pediatric samples.

Those early findings support the relevance of biochemical individuality and of at-risk stratification, which as of yet is not possible, around the medical intervention.

## DEPRESSION AS AN ADVERSE EFFECT

To date, the only longitudinal, case-controlled pilot study that has compared the entire vaccine schedule with unvaccinated controls was conducted in primates and identified neuroanatomical, volumetric, and ligand-binding disparities with the 1994–1999 schedule, which has since doubled in dosage recommendations.<sup>94</sup> It is appreciated, however, that gross end-organ damage is not always required for neurodegenerative and inflammatory sequelae to be clinically relevant. Vaccines have been largely understudied for their psychiatric effects.

In a placebo-controlled trial, typhoid vaccine recipients were found to have "produced a robust inflammatory response indexed by increased circulating IL-6, accompanied by a significant increase in fatigue, confusion, and impaired concentration."<sup>95</sup> The researchers discussed the complexity of the marker and the recruitment of specific neuroanatomical sites specific to the inflammatory response. Their paper is offered as primary support of the central effects of peripheral inflammation.

The role of lifestyle as a specific risk factor for psychiatric vaccine injury was explored in a study of 12-year-old girls who were vaccinated with live, attenuated rubella and demonstrated that vaccinated subjects from lower socioeconomic classes exhibited a more severely depressed mood, together with social, attentional, and behavioral problems.<sup>96</sup>

### ANTECEDENTS AND TRIGGERS

In a systems-biology frame, *allostasis* refers to the maintenance of stability in the face of change and is achieved through recruitment of mediators, including the endocrine system, immune system, and autonomic nervous system. Vaccines, singly or cumulatively, may impact allostasis, having drug-based effects that have not been sufficiently examined in the realm of psychiatric pathology. A study conducted in farmed salmon examined the impact of vaccines on allostasis by comparing fish that were vaccinated at baseline and then (1) vaccinated again and stressed; (2) stressed and then vaccinated again after 4 weeks (ie, the “stress and vaccine group”); or (3) received no further vaccinations (controls). The researchers stated,

A stressor’s effects on the immune system have mainly been attributed to elevated levels of cortisol, and huge complexity exists in the interactions between the immune and endocrine systems that is most likely governed by a bidirectional communication between the HPI axis and the immune system ... [In the current study,] the stress and vaccine group experienced elevated levels of plasma cortisol at 2 weeks prior to the second vaccination (post-stress) compared to prestress (baseline) levels, and the secondary vaccination at week 4 seemed just to be the additional stressor that pushed the animals into a chronic stress state or allostatic-overload, type-2 situation ... with dire consequences for animal welfare.<sup>97</sup>

It has been demonstrated that stress and associated hypercortisolemia, characteristic of depressive states, is an important variable in the persistent adverse effects of vaccination stimuli. In the setting of hypercortisolemia, receptor resistance may result in diminished intracellular control of innate immune and inflammatory signaling, allowing for the high-cortisol, high-inflammation state found in depression,<sup>98</sup> not unlike the hyperinsulinemic and hyperglycemic states found in type 2 diabetes.

Scientists now are stating clearly “that a developmental, psychoneuroimmunological (PNI) model will require multiple kinds of research paradigms across alternative definitions of immune-system response.”<sup>99</sup>

The role of the brain-based immune system in the emergence of depressive symptoms is highly relevant to an immune-provocative medical intervention (ie, vaccination). Depression and associated psychosocial stress, often insidiously emerging, may be an important consideration for risk stratification.

### EFFECTIVENESS AND SAFETY

The nature of modern medicine and the complexity of genetic-epigenetic-environmental interactions are best addressed by a personalized approach to interventions. Biochemical individuality, including genetic variants<sup>99</sup> such as methyl-tetrahydrofolate reductase (MTHFR) that have been demonstrated to be relevant to vaccination,<sup>100</sup> as well as nonheritable immune determinants,<sup>83</sup> microbiota,<sup>87</sup> mitochondrial integrity,<sup>101</sup> and baseline HPA-axis functioning,<sup>97</sup> are all important considerations for immune-based effects and potential risks. Until and if screening for those vulnerable to adverse effects can be implemented, a one-size-fits-all pharmaceutical product encompasses an unnecessary level of risk for difficult-to-establish effectiveness.

Vaccinations may have an effect without consistently established effectiveness. In the assessment of effectiveness, the following concepts are relevant and warrant further research: (1) the now-questioned relevance of antibody titers as a surrogate for effectiveness<sup>20,102</sup>; (2) the documentation of outbreaks in highly to completely vaccinated populations, including primary and secondary vaccine failure<sup>103-104</sup>; (3) the documentation of live viral shedding and spread postvaccination<sup>56,105-106</sup>; (4) the escape-mutant/serotype replacement effects of vaccination, which force the strain evolution of existing microbes in the same way that antibiotics force bacterial adaptation<sup>107</sup>; and (5) the original antigenicity in or the imprinting of an immune response by vaccination that is incomplete, resulting in increased risk of infection on reencounter of the pathogen.<sup>24,109,110</sup>

The inherent difficulty of proving a nonevent is an exercise in correlation (ie, the absence of illness after vaccination is difficult, if not impossible) to attribute to the vaccination intervention. For that reason, epidemiologic evidence of decline in illness mortality prior to vaccination mandates and widespread introduction of the vaccine program indicates that the declines were attributable to quality-of-life factors, including hygiene, sanitation, refrigeration, electricity, labor laws, etc.<sup>111</sup> In addition, the absence of mass universal vaccination for illnesses such as typhoid, which also declined in the early 1900s, supports the epidemiologic trend.<sup>112</sup>

To ascertain vaccination safety and effectiveness truly, large comparative studies of the longitudinal health outcomes of statistically significant numbers of fully vaccinated and fully unvaccinated children would have to be conducted. The studies would have to be independently overseen to assure regulatory checks and balances to outcomes data. The vaccine schedule has tripled in the past 3 decades, without true placebo-controlled trials (saline) to support its safety. Vaccines have never been studied as they are given, simultaneously and cumulatively, starting on the day of birth and with time, compared with an unvaccinated control group. The Institute of Medicine itself admits that “key elements of the entire vaccine schedule have not been studied.”<sup>7,113</sup>

It is the duty of trained clinicians to provide patients with the information necessary for true informed consent.

That information should include a discussion of clinical pharmacology, warnings, contraindications, precautions, and adverse reactions.<sup>114</sup> Patients or their parents should be encouraged to consult databases of peer-reviewed literature, including GreenMedInfo.com<sup>115</sup> and the National Vaccine Information Center<sup>116</sup> for self-education.

## CONCLUSION

Scientists must acknowledge the limitations of the scientific premise of vaccination and developments in immunology and personalized medicine and concede that vaccines can cause injury and death in an unpredictable manner. Every medical intervention should be evaluated in the context of an individual patient's belief system around health and in consideration of personal health conditions, including any history of immunocompromise, HPA axis dysfunction, dysbiosis, and familial mitochondriopathy. Only then can clinicians begin to practice evidence-based rather than eminence-based medicine,<sup>117</sup> with true informed consent leading a patient and parent-empowered paradigm.

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