

## Review Article

# Autism vs Vaccines: The Case Reopened

Crawford SA\*

Department of Biology, Southern Connecticut State University, USA

## \*Corresponding author

Crawford SA, Department of Biology, Southern Connecticut State University, New Haven, CT 06515, USA, Tel: 203-321-6972; Email: crawfords2@southernct.edu

Submitted: 09 July 2018

Accepted: 27 July 2018

Published: 30 July 2018

## Copyright

© 2018 Crawford

## OPEN ACCESS

## Keywords

- Regressive autism
- Vaccines
- Immune system
- Spileptic seizures
- Neurodevelopment

## Abstract

Regressive autism is the rapid-onset loss of previously acquired milestones in central nervous system development often associated with seizures that occurs within the first 1-3 years of life. The dramatic CNS changes associated with regressive autism sometimes rapidly follow the administration of vaccines, highly suggestive of a causal connection that has been the subject of clinical studies worldwide; however, clinical research studies to date have failed to validate an association between vaccines and autism. Despite this, recent genetic studies have demonstrated extensive overlap of immune system components shown to be dysregulated in autism and those essential to the establishment of vaccine based immunity. Moreover, the genetic links between autism and the immune system extend to physiological differences in immune system functions that may directly affect central nervous system maturation during critical developmental windows. In this model, vaccine-associated regressive autism (VARA) is the result of the combined effects of predisposing genetic (and/or other) epidemiological factors on immune system functions that predispose at-risk individuals to central nervous system impairment following the administration of routine childhood vaccines.

## ABBREVIATIONS

VARA: Vaccine Associated Regressive Autism; CNS: Central Nervous System; ASD: Autism Spectrum Disorder; IS: Immune System; PRR: Pattern Recognition Receptor; DC: Dendritic Cell; TLR: Toll-Like-Receptor; NFkB: Nuclear Factor kappa B; NK: Natural Killer Cell; HLA: Human Leukocyte Antigen; IL: Interleukin; CDC: Centers for Disease Control

## INTRODUCTION

## Conceptual definition of vaccine associated regressive autism (VARA)

Regressive autism may be defined as a rapid-onset loss of previously acquired milestones in central nervous system (CNS) development that occurs usually within the first several years of life [1]. The behavioral characteristics of regression often include loss of language and social skills; epileptic seizures may also be involved [1]. Nordahl et al. [2], have identified abnormal brain enlargement as a distinctive feature of regressive autism. This research showed that total brain volume in 3-year-old boys with regressive autism was approximately 6% larger than non-autistic age-matched boys. Moreover, 22% of boys with regressive autism showed megalencephaly as compared to 5% boys who did not have this disorder. The increase in brain volume was first detectable at 4-6 months of age, preceding the onset of autism symptoms, and was associated only with the regressive form of the disorder. In addition to abnormalities in

CNS morphology, regressive autism has been specifically linked to mutations in genes encoding postsynaptic density; in contrast, autism-associated mutations in embryonic genes were less likely to be associated with the regressive form of this disorder [3].

The term itself, "regressive autism", is loaded; increasingly, researchers and clinicians alike have attempted to describe the onset of autism as an accumulation of CNS impairments that may ultimately present as developmental losses rather than as deficits of gain if early signs are missed. In 2014, the overall prevalence of autism spectrum disorder (ASD) among the 11 (Autism Disorder and Disability Monitoring) ADDM sites was 16.8 per 1,000 (one in 59) children aged 8 years and did not distinguish between purely developmental and regressive forms of the disorder [4]. Evidence suggests that true clinical regression occurs only in a small subset of patients with autism; however, the level of disability, including intellectual disability, on average, is greater in this group [1]. The timing of onset of regressive autism ranges between ranges between 15 and 30 months, 24-81 months, with a mean of 20 months, and demonstrates a dramatic, sudden clinical onset [5,6]. This is an important distinction, because it suggests that a critical trigger mechanism responsible for CNS impairment may occur in the same temporal timeframe as the onset of developmental regression. To this end, early childhood vaccines have been implicated in the etiology of sudden onset regressive autism by parents and primary health care providers who have witnessed sudden changes in behavioral and neurological functions in some young children following

the administration of vaccines [7]. Clinically, this abnormal response to vaccination is termed “vaccine encephalopathy”, in which apparently normal infants or children display a sudden, permanent developmental regression and/or seizures with rapid onset following vaccine administration. That the dramatic CNS changes associated with regressive autism can so rapidly follow the administration of vaccines is highly suggestive of a causative connection that has been the subject of epidemiological studies worldwide [8]. To date, these studies have failed to validate an association between vaccines and any type of autism, leading to a widespread consensus that there is no connection between vaccines and autism spectrum disorder (ASD) [8]. The premise of this paper is that these epidemiological studies, investigating a potential link between vaccines and autism, have failed to do so because they have not considered the limitations of population based studies in identifying rare case occurrences, nor have these studies addressed the physiological basis for causality that suggests a connection between the onset of autism and immune system (IS) responses to vaccines in some individuals. The highly disturbing association between vaccines and CNS dysfunction clearly deserves a second look.

**Epidemiological data**

Broad-based retrospective and prospective epidemiological studies conducted over the past decade have provided strong

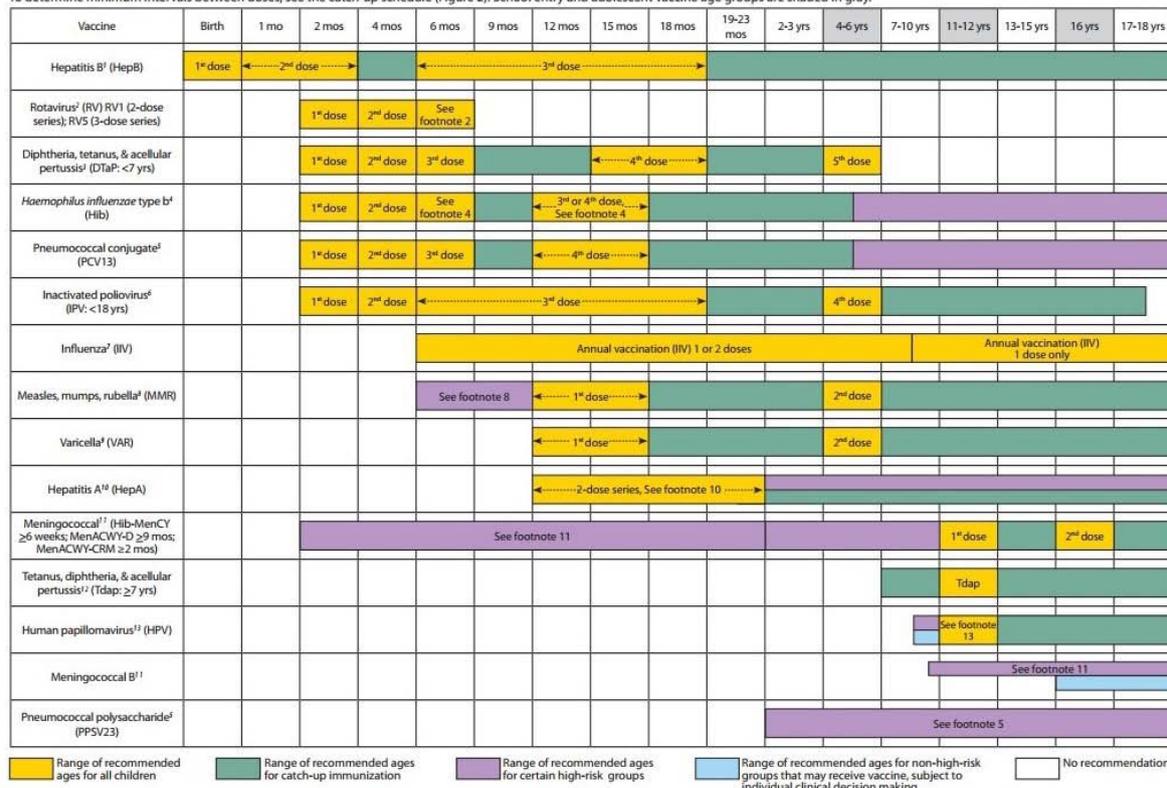
evidence that the common vaccines administered in infancy and childhood (Figure 1) are safe and highly effective in preventing infections that were once associated with high mortality rates in the years before vaccines were available [9]. Moreover, research designed to assess the potential association of vaccines with autism have failed to produce a statistically significant association. A retrospective study of all children in Denmark born between 1991-1998 examined the association between the measles-mumps-rubella vaccine administered at 15 months and the incidence of autism [10]. This study showed that the relative risk for autism in the vaccinated versus unvaccinated group was statistically similar. A 2013 study by the Centers for Disease Control (CDC) measured both the cumulative and single day exposures to antigens in vaccines administered to a group of several hundred children and found that the risk of acquiring autism spectrum disorder (ASD) was not correlated with the level of antigen exposure from vaccines between 0-2 years of life [11]. The consensus of these studies was that there was no link between autism and early childhood vaccines.

A closer inspection of the study data, however, reveals that there are several areas in which these studies failed to present a definitive statement on the potential association of vaccines with autism in some individuals. Much of this research was based on the false cause-and-effect premise that the number of types

**Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2017.**

**(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE (FIGURE 2)).**

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.



**Figure 1** Recommended Immunization Schedule for Infants/Children/Adolescents (Centers for Disease Control, 2017).

of antigens is the only immune-stimulating facet of vaccines. In reality, other components such as adjuvants or the amount of a single type of immune-active antigen are likely as or more important than the number of types of antigens. A second factor of significance is that these large-scale population studies were not designed to detect rare events or associations; therefore, null findings may lack the power to identify these events and cannot be concluded to rule out such occurrences [12]. Thirdly, these studies were not designed to assess the hypothesis that vaccines are not a sole cause of autism but, instead, may play a contributory role in the development of autism in individuals predisposed to this disorder due to additional risk factors. Moreover, none of these studies specifically addressed the subgroup of regressive autism in vaccine recipients which is the subject of this paper.

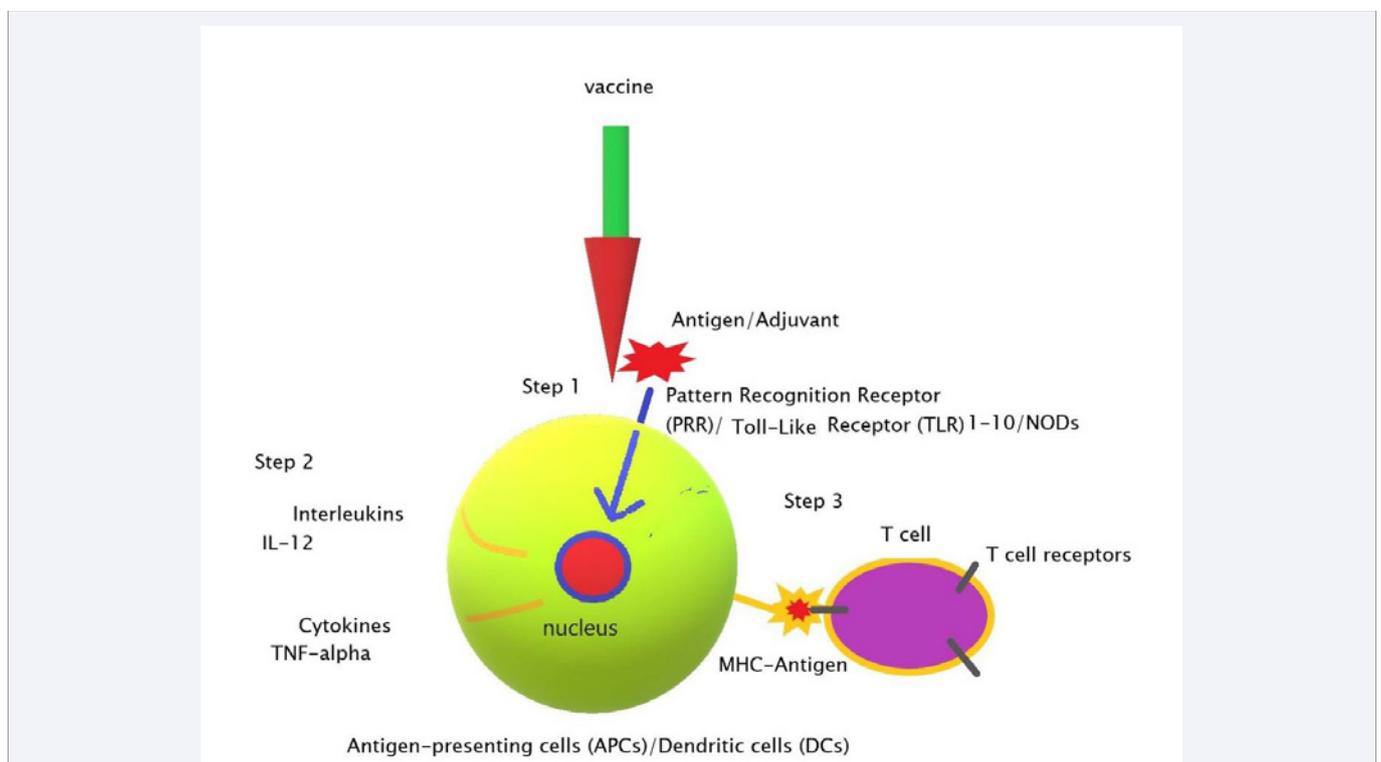
### Immune system responses to vaccines with potential links to autism

The plethora of physiological responses induced by antigen/adjuvant presentation by vaccines presents the possibility for a varied and complex profile of immune system (IS) responses based on genetic and/or environmentally associated differences in the activities of each of these players in vaccine-associated immunity. To assess critically the relationship between regressive autism and vaccine administration, it is essential to define early, immediate physiological responses to vaccine antigens and adjuvants to determine whether, and under what conditions, any or all IS responses to vaccines have the potential to disrupt normal brain function in early childhood (Figure 2). As our general understanding of the relationship between the IS and autism has increased, combined with new research illuminating the early stages of IS activation post vaccine administration,

it is now possible to define a comprehensive paradigm demonstrating the points at which these two systems converge to define mechanistically the role of vaccines in the onset of autism in infants/young children in whom significant IS/autism risk factors are present.

Available data suggest a link between genetic polymorphisms in the innate IS genes that may influence vaccine responses [13]. The innate immune system plays an important role in programming early life responses to vaccine immunization. The immediate innate IS response involves pattern recognition receptors (PRRs) on dendritic cells (DCs), such as the Toll-like-receptors (TLRs) that determine the nature of the antigens recognized by receptors on T and B cells; PRRs are first responders to immune system activation by vaccines. Variations in pattern recognition receptor genes (PRRs) encoding Toll-like receptors (TLRs), human leukocyte antigen (HLA) proteins, cytokines and their receptors have been linked to heterogeneous responses to many different types of vaccines, including measles, hepatitis B, bacillus Calmette-Guerin (BCG), Haemophilus influenzae type b, tetanus toxoid, pneumococcal polysaccharide vaccine, varicella vaccine, and themeasles, mumps, and rubella vaccine (MMR) [14,15]. For example, bacillus Calmette-Guerin activates innate immune responses involving toll-like receptors (TLRs), monocytes, natural killer (NK) cells, cytokines and interferon production immediately after immunization at birth, followed by T cell responses at 13 weeks post-vaccination [15].

Genetic polymorphisms in these innate IS response genes have also been linked to autism. For example, many genes linked to autism code for immune and inflammatory response functions. Garbett et al. [16], identified 31 sets of genes



**Figure 2** Early innate immune responses to vaccines.

differentially expressed in patients with autism as compared to controls. Of these, 19 were associated with IS functions, including antigen-specific immune response, inflammation, cell death, natural killer (NK) cell function and cell migration. Each of these genes showed increased structural variability in the autism cohort. The expression of inflammatory genes, signaled by nuclear factor kappa-B (NF- $\kappa$ B) or interferon regulatory factor, stimulates the production of cytokines that trigger the maturation of activated DCs to antigen-presenting cells that, in turn, activate T cell receptors vis-à-vis specific human leukocyte antigen (HLA) receptor-antigen complexes. Specific HLA allelic haplotypes have been linked both to autism and variations in vaccine induced immune responses [17]. Individuals with a family history or other risk factors for autoimmune disorders are more likely to experience vaccine-related sequelae than non-affected individuals [18]. Likewise, individuals with a family history of autoimmune disorders are significantly more likely to develop autism [18]. Research studies have identified genetic variants of the HLA gene family that are associated with vaccine-induced autoimmune activation, including HLA DRB1, HLA DRB2, HLA DR4, and HLA DRQ8 [19]. Several reports have suggested grouping different autoimmune conditions that are triggered by external stimuli (e.g., exposure to vaccine) as a single syndrome called “autoimmune syndrome induced by adjuvants” (ASIA) [20]. Among the alleles linked to autism are class II DRB1, particularly in Han Chinese, Egyptian and Saudi populations [21]. DRB\*11 and DRB\*1104 alleles occur more frequently in children with autism. HLA-DR-4 alleles occur at increased rates in children with ASD and their mothers [21]. Nazeen et al. [22], performed an integrative genetic data analysis that revealed that genes involved in TLR and chemokine signaling pathways are significantly associated with ASD and its co-morbidities and that genetic variants in the innate IS can be used to classify these cases versus controls with a minimum of 70% accuracy. The study authors suggested that these dysregulated signaling pathways not only represent a functional genetic commonality implicating the innate IS in the causation of autism, but may also serve as a connection to environmental triggers of ASD. As the innate IS is an important determinant of adaptive IS responses to vaccines, dysregulation of this pathway may affect IS pathways activated by vaccine administration. Dysregulation of the KEGG TLR and chemokine signal pathway were shown to be statistically linked to autism with 97% or greater probability [23]. Additional functional studies have shown an association of abnormal TLR/chemokine signal mechanisms in autism [24]. The NOD-like receptor signal pathway was also shown to be linked to autism in a comprehensive genetic data analysis [22]. NOD-like receptors are important in the formation of inflammasomes and in the production of pro-inflammatory cytokines. Other genes linked to autism include CCL4, the most highly unregulated chemokine in NK cells in autistic children [22]. SPP-1 mediated up regulation of IFN- $\gamma$  and TBK1 activation of NF- $\kappa$ B has also been detected in children with autism [22]. These findings indicate that dysregulation of the innate IS is one of the most reproducible genetic associations linked to autism. To this end, differences in innate IS gene expression levels have been documented both in the CNS and peripheral blood of patients with autism [25].

Epileptic seizures sometimes occur within a relatively short timeframe post vaccine administration; moreover, epileptic

seizures are a frequent accompaniment of autism [26]. Thus, the onset of epileptic seizures concomitant with vaccine administration is highly relevant in this context. The National Institute for Public health and the Environment in the Netherlands reviewed clinical data of 990 children who experienced epileptic seizures in response to vaccines between 0-2 years of age between 1997 and 2006 [27]. The data showed that the risk of seizures in infants and young children in the general population increases by 2.5-fold on the day of administration of an inactivated vaccine. Moreover, the risk of developing seizures continues from day 5 to 14 after administration of live attenuated vaccines. The study authors concluded that this elevated risk was the result of underlying genetic or structural disorders of the brain [27].

### **Abnormal IS a response to vaccines: links to brain function**

IS activation of microglial excitotoxicity is emerging as a primary physiological cause of impaired neurodevelopment. In the CNS, differences in microglial activation, physiology and localization have been observed in autistic brains [28]. There are extraordinarily tight connections between the CNS and IS. The duality of microglia structure/function relationships in CNS immune surveillance and neurodevelopment represents a critical connection between the immune system and the developing brain [29]. Autopsies of individuals with ASD characteristically show evidence of neuroinflammation resulting from the production of cytokines, interleukins, NF- $\kappa$ B and other pro-inflammatory molecules from activated microglia [30]. In the CNS, PRRs / TLRs are expressed in microglia, astrocytes and neurons [31]. Microglia has been shown to express high level cell surface TLR2 as well as intracellular expression of TLR3 and TLRs1-9 [32]. In addition, expression of high level TLR3 and low-level expression of TLRs 1, 4, 5 and 9 have been detected in brain astrocytes [32]. TLR 3 activation in brain microglia induces high level production of IL-12, IL-6, CXCL-10, IL-10, and IFN- $\beta$  [32]. In astrocytes, TLR-3 activation resulted in gene expression of IL-6, CXCL-10 and IFN- $\beta$  [33]. Even neurons appear to produce components of the innate IS, including TLRs 3, 7, 8 and 9 [34].

The chemokine receptor, CXCR-1, plays a critical role in embryonic brain development; moreover, CXCR-L1 ligand, fractalkine, is an important player in inflammatory disease resulting from IS dysregulation [35]. Recent research suggests that CXCR-3 plays a critical role in the establishment of adaptive IS responses via regulation of myeloid cell activation [34]. Increased levels of CXCR-3 have been observed in patients with autism [35]. Moreover, two variant alleles of this receptor have been identified in 20-30% of the population [36]. Additional studies in mice have shown that increased levels of CXCR-3 are associated with brain inflammation [37]. Dysregulated expression of the HCK gene, a Src related tyrosine kinase which plays an important role in microglial regulation, has also been observed in autistic children [22]. Defects in the leukocyte transendothelial migration pathway have been linked to autism via genetic analysis, which may facilitate their migration across the BBB into brain tissue to produce inflammation [22].

Substantial research implicates IS dysfunction in the etiology of epilepsy; for example, altered innate IS signal patterns from brain tissues causes inflammation that may trigger epileptic

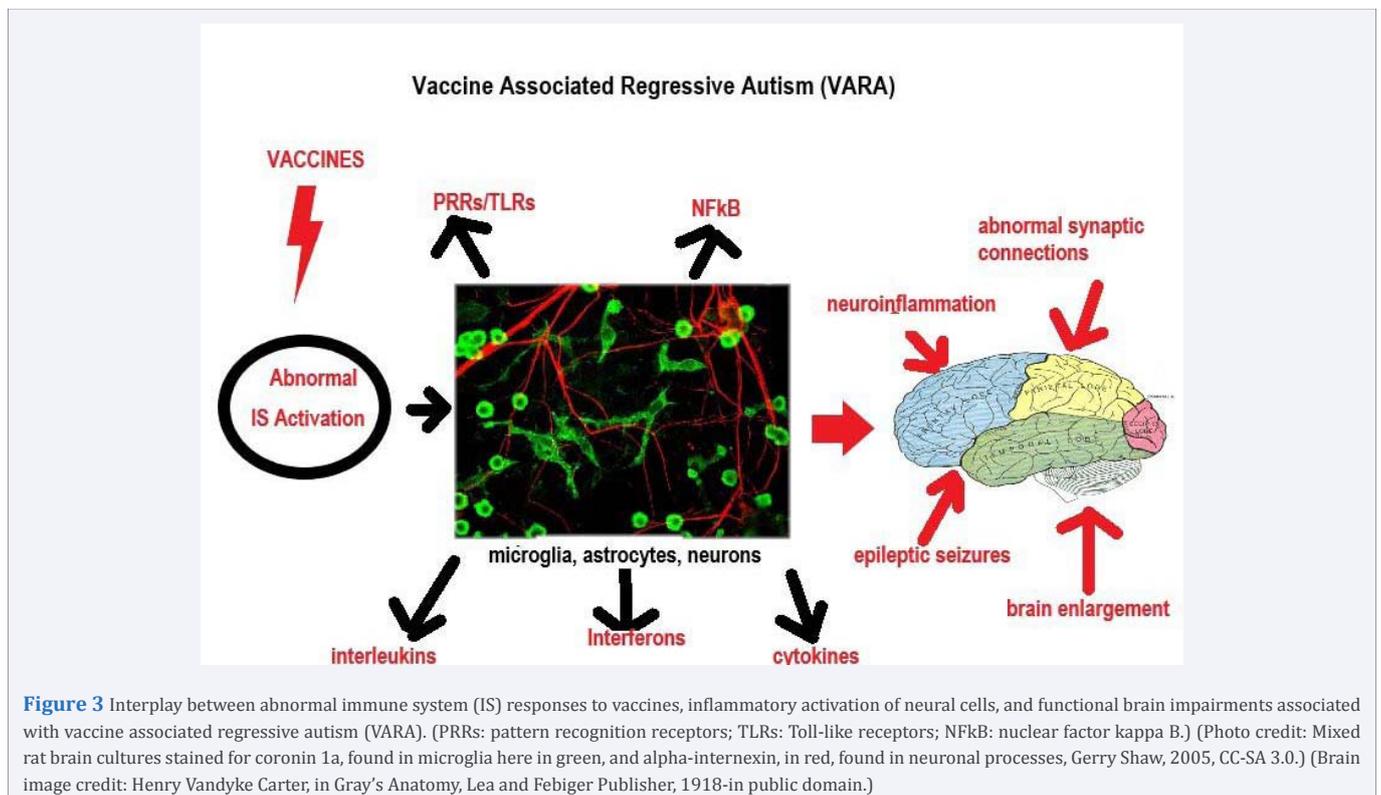
seizures [38]. Studies of brain tissue pathology in patients with epilepsy have provided evidence of neuroinflammation associated with the secretion of pro-inflammatory cytokines that increase the permeability of the blood/brain barrier and activate brain microglia [39]. Microglial activation has been linked to epileptic seizures, which occur in 20-30% of patients with ASD [40]. Additional research suggests that the onset of recurrent epileptic seizures is linked to innate and adaptive IS actions that can cause brain damage in ways that are not fully understood [41]. Innate IS components implicated in this causation include TNF, interleukins and interferon's. TLR expression in brain tissues has been shown to initiate CNS inflammation in experimental systems, which may result in disruption of ion channel and inhibitory neuron regulation and subsequent epileptogenesis [41]. This conception is supported by physiological studies indicating increased levels of pro-inflammatory cytokines in the sera and CSF of patients with epilepsy [42]. The elevated production of pro-inflammatory cytokines may be induced by either endogenous or exogenous factors that trigger innate IS signal pathways. Innate IS TLR activation leads to the production of NF- $\kappa$ B, which in turn results in the phosphorylation N-methyl D-aspartic acid (NMDA) to trigger influx of calcium and elevated neuronal excitability [43]. In addition, IL-1b both blocks glutamate reuptake by astrocytes and stimulates its production in microglia to further exacerbate neuronal excitability [44].

## DISCUSSION

The prevailing consensus of the scientific community, that the temporal association between the administration of vaccines and the onset of regressive autism is not indicative of a causal connection, is based on population studies that were not designed

to identify rare events and did not assess potential causal physiological connections between IS responses to vaccines and CNS function. This combined study of the IS components activated by vaccines and those implicated in the etiology of autism shows that many of the same molecules are involved in both processes (Figure 3). The notion that ASD results from underlying genetic and/or physiological conditions that cause impaired CNS development, and that vaccines have no role in the etiology of this disorder, is belied by empirical research showing that many of the genes linked to autism are innate IS genes activated by vaccine administration. That the innate IS also plays a critical role in orchestrating first-line responses to vaccines indicates a point of convergence between vaccines and autism that cannot be ignored. The extensive overlap of IS components shown to be dysregulated in autism and, at the same time, essential to the establishment of vaccine based immunity presents a compelling physiological explanation for the onset of autism in response to vaccines in individuals at the threshold of IS/CNS dysfunction.

The immunological evidence linking vaccines to IS linked neurodevelopment parameters presented in this paper establishes a direct physiological connection between neurological impairment and abnormal IS responses to vaccines. To this end, vaccines may induce rapid onset CNS impairment in children who show no previous signs of ASD but, nevertheless, possess IS risk factors predisposing them to brain inflammation and CNS damage in response to vaccine administration. This multifactorial concept is embodied in the Quantitative Threshold Exposure (QTE) Model of autism (Figure 4) [45]. This model proposes that neurological impairments associated with Autism Spectrum Disorder (ASD) are the result of quantitative exposure during critical CNS developmental windows to diverse genetic and

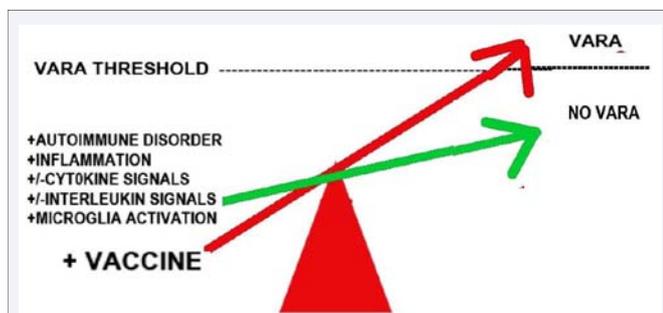


environmental factors that, upon attaining a pathophysiological threshold, cause impaired brain development/functions. In this model, vaccine-associated regressive autism (VARA) is the result of the combined effects of predisposing genetic (and/or other) epidemiological factors in addition to vaccines that contribute cumulatively to IS overload and CNS functional impairment. This model explains why most children who receive vaccines do not experience CNS effects, while vaccine administration may trigger CNS pathophysiology in a subset of children with additional risk factors, both genetic and environmental.

The consensus of the epidemiological data that failed to identify any association between vaccines and autism is not inaccurate; rather, the study designs were not appropriate for detecting an indirect, multifactorial cause-and-effect association between vaccines and neurodevelopmental disorders in at-risk individuals. The conclusion reached by the CDC study authors, that autism risk is not associated with vaccines based on the observed uniform antigen exposure levels measured in all vaccine recipients, fails to address the effect of these antigen exposure levels on brain development in a group of at-risk children who possess significant autism risk factors, genetically or otherwise determined. This reductionist approach represents a fundamental misunderstanding of the complex, multifactorial causes of autism and its physiological association with immune system activities. The premise of this paper is that sudden-onset, regressive autism may occur in a select group of “at risk” infants and young children in whom the presence of risk factors associated with altered immunological responses to antigenic stimulation may present a direct cause and effect relationship between vaccine administration and autism.

This paper specifically addresses a subset of ASD, termed “vaccine associated regressive autism” (VARA) that is characterized by a dramatic and rapid loss of previously demonstrated developmental milestones and/or the onset of seizure disorder in a short (0-14 days) timeframe following vaccine administration in the absence of traumatic injury or other variables during this timeframe that could account for this CNS event. The proposed clinical criteria for diagnosis of “vaccine associated regressive autism” VARA includes:

- Defined temporal relationship of 0-14 days between vaccine administration and onset of disorder;
- Age of onset between 3-80 months;



**Figure 4** Application of the Quantitative Threshold Exposure (QTE) Model to the role of vaccines in the multifactorial causation of vaccine associated regressive autism (VARA).

- Demonstrable loss of previously acquired behavioral and/or cognitive developmental milestones and/or initial onset of seizures within 0-14 days of vaccine administration;
- Observed changes in cognitive, behavioral and/or neural function do not subside over time.

It should be noted; however, that vaccines may potentiate neural impairment also in children with the developmental form of the disorder as its effects on IS interactions with the CNS may exacerbate pre-existing neurodevelopmental conditions. Moreover, vaccine associated neural impairments are not only pertinent to sudden regression but may be also in play in cases where there is latency between the vaccine administration and the manifestation of autism.

## CONCLUSION

Taken together, the IS dysfunctions observed in patients with autism provide a compelling explanation for the observed neurological impairments associated with this disorder. Furthermore, the IS /autism connection provides a physiological basis for the effects of vaccines on CNS integrity in individuals with risk factors for impaired IS function. The challenge now confronting clinicians and researchers is to develop protocols to identify infants at risk for adverse reactions to vaccines that may precipitate the onset of ASD/seizures.

## REFERENCES

1. Barbeau W. Neonatal and regressive forms of autism: Diseases with similar symptoms but a different etiology. *Med Hyp*. 2017; 109: 46-52.
2. Nordahl CW, Lange N, Li DD, Barnett LA, Lee A, Buonocore MH, et al. Brain enlargement is associated with regression in preschool-age boys with autism spectrum disorders. *Proc Natl Acad Sci U S A*. 2011; 108: 20195-20200.
3. Atladóttir HÓ, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, et al. Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics*. 2009; 124: 687-694.
4. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States. *MMWR Surveill Summ*. 2018; 67: 1-23.
5. Ozonoff S, Gangi D, Hanzel EP, Hill A, Hill MM, Miller M, et al. Onset patterns in autism: Variation across informants, methods, and timing. *Autism Res*. 2018; 11: 788-797.
6. Goldberg WA, Osann K, Filipek PA, Laulhere T, Jarvis K, Modahl C, et al. Language and other regression: assessment and timing. *J Autism Dev Disord*. 2003; 33: 607-616.
7. Ozonoff S, Williams BJ, Landa R. Parental report of the early development of children with regressive autism: the delays-plus-regression phenotype. *Autism*. 2005; 5: 461-486.
8. Maglione MA, Das L, Raaen L, Smith A, Chari R, Sydne Newberry, et al. Safety of vaccines used for routine immunization of US children: a systematic review. *Pediatrics*. 2014; 134.
9. Madsen K, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, et al. A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism. *N Engl J Med*. 2002; 347: 1477-1482.
10. Taylor L, Swerdfeger A, Eslick G. Vaccines are not associated with autism: an evidence-based meta-analysis of case-control and cohort studies. *Vaccine*. 2014; 32: 3623-3629.

11. DeStefano F. Vaccines and autism: evidence does not support a causal association. *Clin Pharmacol Ther.* 2007; 82: 756-759.
12. Thygesen LC, Ersbøll AK. When is a null finding in register-based epidemiology convincing? *Eur J Epidemiol.* 2014; 29: 551.
13. Newport MJ. The Genetic Regulation of Infant Immune Responses to Vaccination. *Front Immunol.* 2015; 6.
14. Dowling DJ, Levy O. Ontogeny of Early Life Immunity. *Trends Immunol.* 2014; 35: 299-310.
15. Kleinnijenhuis J, Quintin J, Preijers F, Benn CS, Joosten LA, Jacobs C. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. *J Innate Immun.* 2014; 6: 152-158.
16. Garbett K, Ebert PJ, Mitchell A, Lintas C, Manzi B, Persico AM, et al. Immune transcriptome alterations in the temporal cortex of subjects with autism. *Neurobiol Dis.* 2008; 30: 303-311.
17. Atladóttir HÓ, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, et al. Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics.* 2009; 124: 687-694.
18. Vadalà M, Poddighe D, Laurino C, Palmieri B. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? *EPMA J.* 2017; 8: 295-311.
19. Singh VK. Phenotypic expression of autoimmune autistic disorder (AAD): a major subset of autism. *Ann Clin Psychiatry.* 2009; 21: 148-161.
20. Shoenfeld Y, Agmon-Levin N. 'ASIA'-autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun.* 2011; 36: 4-8.
21. Torres AR, Maciulis A, Stubbs EG, Cutler A, Odell D. The transmission disequilibrium test suggests that HLA-DR4 and DR13 are linked to autism spectrum disorder. *Hum Immunol.* 2002; 63: 311-316.
22. Nazeen S, Palmer NP, Berger B, Kohane IS. Integrative analysis of genetic data sets reveals a shared innate immune component in autism spectrum disorder and its co-morbidities. *Genome Biol.* 2016; 17: 228.
23. Zeidán-Chuliá F, Rybarczyk-Filho JL, Salmina AB, De Oliveira BH, Noda M, Moreira JC. Exploring the multifactorial nature of autism through computational systems biology: calcium and the Rho GTPase RAC1 under the spotlight. *Neuromolecular Med.* 2013; 15: 364-383.
24. Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. *Neuro psychopharmacol.* 2017; 42: 284.
25. Xu N, Li X, Zhong Y. Inflammatory cytokines: potential biomarkers of immunologic dysfunction in autism spectrum disorders. *Mediat Inflamm.* 2015; 1-10.
26. Tuchman R, Hirtz D, Mamounas LA. NINDS epilepsy and autism spectrum disorders workshop report. *Neurol.* 2013; 81:1 630-1636.
27. Verbeek N, Jansen F, Vermeer-de Bondt P, de Kovel C, van Kempen M. Etiologies for Seizures around the Time of Vaccination. *Pediatrics.* 2014.
28. Suzuki K, Sugihara G, Ouchi Y, Nakamura K, Futatsubashi M, Takebayashi K, et al. Microglial activation in young adults with autism spectrum disorder. *JAMA Psychiatry.* 2013; 70: 49-58.
29. Crawford SA. Prenatal screening of maternal immune antigen biomarkers linked to microglial regulation of brain development may predict autism risk. *J Autism Epilepsy.* 2016; 1.
30. Weir RK, Bauman MD, Jacobs B, Schumann CM. Protracted dendritic growth in the typically developing human amygdala and increased spine density in young ASD brains. *J Comp Neurol.* 2018; 526: 262-274.
31. Bsibsi M, Ravid R, Gveric D, van Noort JM. Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol.* 2002; 61:1013-1021.
32. Jack CS, Arbour N, Manusow J, Montgrain V, Blain M, McCrea E, et al. TLR signaling tailors innate immune responses in human microglia and astrocytes. *J Immunol.* 2005; 175: 4320-4330.
33. Farina C, Krumbholz M, Giese T, Hartmann G, Aloisi F, Meinl E. Preferential expression and function of Toll-like receptor 3 in human astrocytes. *J Neuroimmunol.* 2005; 159: 12-19.
34. Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. *Clin Sci.* 2011; 121: 367-387.
35. Kara T, Akaltun İ, Cakmakoglu B, Kaya İ, Zoroğlu S. An Investigation of SDF1/CXCR4 Gene Polymorphisms in Autism Spectrum Disorder: A Family-Based Study. *Psychiatry Investig.* 2018; 15: 300-305.
36. Mangino M, Roederer M, Beddall MH, Nestle FO, Spector TD. Innate and adaptive immune traits are differentially affected by genetic and environmental factors. *Nat Commun.* 2017; 8.
37. Paton MC, McDonald CA, Allison BJ, Fahey MC, Jenkin G, Miller SL. Perinatal brain injury as a consequence of preterm birth and intrauterine inflammation: designing targeted stem cell therapies. *Front Neurosci.* 2017; 11: 200.
38. Matin N, Tabatabaie O, Falsaperla R, Lubrano R, Pavone P, Mahmood F, et al. Epilepsy and innate immune system: A possible immunogenic predisposition and related therapeutic implications. *Hum Vaccin Immunother.* 2015; 11: 2021-2029.
39. Lee AS, Azmitia EC, Whitaker-Azmitia PM. Developmental microglial priming in postmortem autism spectrum disorder temporal cortex. *Brain Behav Immun.* 2017; 62: 193-202.
40. Hiragi T, Ikegaya Y, Koyama R. Microglia after Seizures and in Epilepsy. *Cells.* 2018; 7: 26.
41. Bauer J, Becker AJ, Elyaman W, Peltola J, Rüegg S, Titulaer MJ, et al. Innate and adaptive immunity in human epilepsies. *Epilepsia.* 2017; 58: 57-68.
42. Cordero-Arreola J, M West R, Mendoza-Torreblanca J, Mendez-Hernandez E, Salas-Pacheco J, Menendez-Gonzalez M, et al. The Role of Innate Immune System Receptors in Epilepsy Research. *CNS Neurol Disord Drug Targets.* 2017; 16: 749-762.
43. Stephenson J, Nutma E, van der Valk P, Amor S. Inflammation in CNS neurodegenerative diseases. *Immunol.* 2018; 154: 204-219.
44. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev.* 2018; 281: 8-27.
45. Crawford S. On the origins of autism: The quantitative threshold exposure hypothesis. *Med Hypotheses.* 2015; 85: 798-806.

#### Cite this article

Crawford SA (2018) Autism vs Vaccines: The Case Reopened. *J Autism Epilepsy* 3(1): 1014.