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McCullough Foundation Report: Determinants of Autism Spectrum Disorder

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Abstract

Introduction: Autism spectrum disorder (ASD) is now estimated to affect more than 1 in 31 children in the United States, with prevalence rising sharply over the past two decades and posing an increasing burden to families and public health systems. Most of the literature on ASD characterizes it as a complex neurodevelopmental condition shaped by multiple determinants, including genetic liability, immune dysregulation, perinatal stressors, and environmental toxicants. Since 1996, the *possible* role of childhood vaccination has also been discussed and debated. This review synthesizes the full range of evidence to clarify both vaccine-related and non-vaccine contributors to ASD risk.

Methods: We comprehensively examined epidemiologic, clinical, and mechanistic studies evaluating potential ASD risk factors, assessing outcomes, exposure quantification, strength and independence of associations, temporal relationships, internal and external validity, overall cohesiveness, and biological plausibility.

Results: We found potential determinants of new onset ASD before the age of 9 years old to include: older parents (>35 years mother, >40 years father), premature delivery before 37 weeks of gestation, common genetic variants, siblings with autism, maternal immune activation, in utero drug exposure, environmental toxicants, gut-brain axis alterations and combination routine childhood vaccination. These diverse genetic, environmental, and iatrogenic factors appear to intersect through shared pathways of immune dysregulation, mitochondrial dysfunction, and neuroinflammation, culminating in neurodevelopmental injury and regression in susceptible children. Of 136 studies examining childhood vaccines or their excipients, 29 found neutral risks or no association, while 107 inferred a possible link between immunization or vaccine components and ASD or other neurodevelopmental disorders (NDDs), based on findings spanning epidemiologic, clinical, mechanistic, neuropathologic, and case-report evidence of developmental regression. 12 studies comparing routinely immunized versus completely unvaccinated children or young adults consistently demonstrated superior overall health outcomes among the unvaccinated, including significantly lower risks of chronic medical problems and neuropsychiatric disorders such as ASD. The neutral

association papers were undermined by absence of a genuinely unvaccinated control group—with partial or unverified immunization even among those classified as unvaccinated—alongside registry misclassification, ecological confounding, and averaged estimates that obscure effects within vulnerable subgroups. Only a few case–control studies verified vaccination through medical records or parent-held cards, and none performed independent clinical assessments of the children for ASD. In contrast, the positive association studies found both population signals (ecologic, cohort, case–control, dose–response, and temporal clustering) and mechanistic findings converging on biologic plausibility: antigen, preservative, and adjuvant (ethyl mercury and aluminum) induced mitochondrial and neuroimmune dysfunction, central nervous system injury, and resultant incipient phenotypic expression of ASD. Clustered vaccine dosing and earlier timing of exposure during critical neurodevelopmental windows appeared to increase the risk of ASD. These findings parallel strong, consistent increases in cumulative vaccine exposure during early childhood and the reported prevalence of autism across successive birth cohorts. To date, no study has evaluated the safety of the entire cumulative pediatric vaccine schedule for neurodevelopmental outcomes through age 9 or 18 years. Nearly all existing research has focused on a narrow subset of individual vaccines or components—primarily MMR, thimerosal-containing, or aluminum-adjuvanted products—meaning that only a small fraction of total childhood vaccine exposure has ever been assessed for associations with ASD or other NDDs.

Conclusion: The totality of evidence supports a multifactorial model of ASD in which genetic predisposition, neuroimmune biology, environmental toxicants, perinatal stressors, and iatrogenic exposures converge to produce the phenotype of a post-encephalitic state. Combination and early-timed routine childhood vaccination constitutes the most significant modifiable risk factor for ASD, supported by convergent mechanistic, clinical, and epidemiologic findings, and characterized by intensified use, the clustering of multiple doses during critical neurodevelopmental windows, and the lack of research on the cumulative safety of the full pediatric schedule. As ASD prevalence continues to rise at an unprecedented pace, clarifying the risks associated with cumulative vaccine dosing and timing remains an urgent public health priority.

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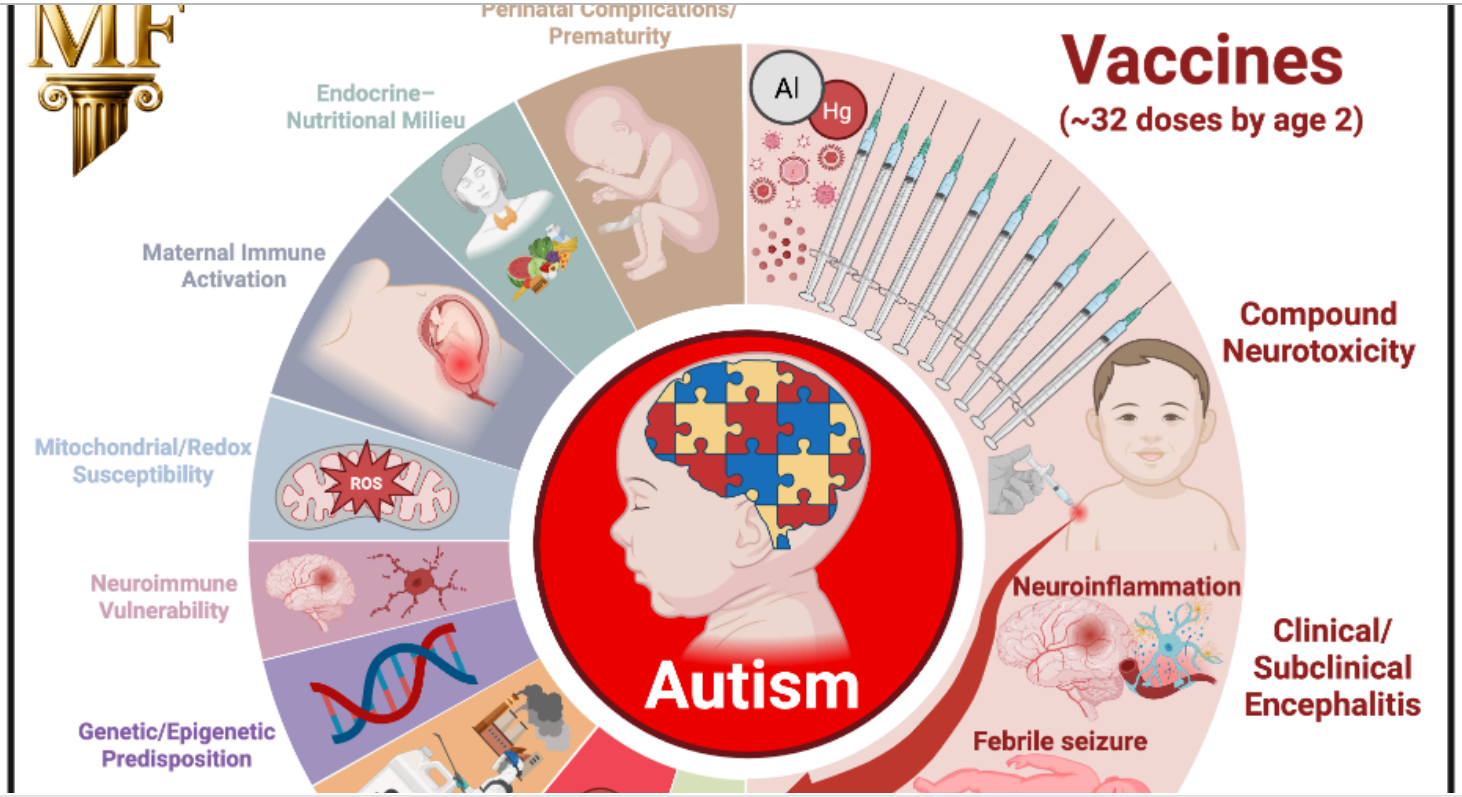

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