AUTISM, SURGE IN THE PREVALENCE AND LINKAGE WITH CHILDHOOD VACCINATION - A REVIEW

Aliyu, I. A.*[1,2], Bala, J. A. [2,3]and Maqsood, M. [1,4]

[1]Department of Medical Microbiology and Parasitology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang Selangor, Malaysia

[2]Department of Medical Laboratory Science, Faculty of Allied Health Sciences, Bayero University Kano, P.M.B 3011, Kano, Nigeria

[3]Department of Pathology and Microbiology, Faculty of Veterinary Medicine, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

[4]Department of Microbiology, Faculty of Natural Sciences, SBKW University Quetta 87300, Pakistan.

Corresponding author; isahaa97@gmail.com

Abstract

Autism a neurodegenerative disorder characterised by an abnormal child behaviour like isolation, learning difficulties, general abnormality in communication and social reciprocity, inability to maintain eye contact or point at something, looking at thing with the peripheral vision and many other neurological disorders, the aetiology of autism is multifactorial including among other social, environmental, genetics, epigenetics and neurological factors, in recent years vaccines have drawn large interest of scientific community for its asserted role in the development of autism, this is largely due to the presence in higher concentration of a mercury containing compound thimerosal in many vaccines, and due to some evidence which link some vaccines including measles, mumps and rubella vaccines with autism, moreover several authentic scientific studies were undertaken to falsified those findings. Here we critically review those assertion, examined some implicating component of vaccine and relate them with neurobiology of autism.

Keywords: autism, neuropathology, thimerosal, vaccination, children

Introduction

A short in the dark is a book written by Harris C and Barbara L. one of the earliest book written to extensive outline the relationship of vaccine and autism, in which the authors who are US family physicians try to link the number of vaccine doses required to be given to child within certain age limit with the number of neurological and immunological disorders (Coulter and Fisher, 1991) the authors reported that following years of observation from various dimension both government, parent and doctors realised a rapid increase in the rate of children who develop autism (Coulter and Fisher, 1991), learning disability, juvenile diabetes, attention deficit disorder, asthma, rheumatoid arteritis, sudden infant death syndrome and other medical conditions(Coulter and Fisher, 1991)

A collection of chronic degenerative developmental disorders manifested by repetitive or stereotypic behaviours, interest and activities coupled with marked impairment in children ability to socialised and communicate is termed as Autism Spectrum Disorders (ASDs) (Murphy, 2011) even though many disease condition are now with medication or treatment but the medication to these syndrome remain to be identified (Murphy, 2011).

Citation: Aliyu, I. A, Bala, J. A. and Maqsood, M**.** (2016): Autism, Surge in the Prevalence and Linkage with Childhood Vaccination- A Review. *BJMLS, 1(1): 14 - 25*

Another report of Autism –Vaccine link was reported in Europe in a paper co-authored by Wakefield et al. (1998) in the paper the authors determine the association of vaccine with gastrointestinal disorders and the autism in which they found profound association of measles, mumps and rubella (MMR) vaccine to be associated with autism.

In a separate paper, Wakafield *et al.,* (1998)have studied the association of MMR with gastrointestinal disorders and come with an autistic gastroenteritis linking leaky gut theory with autism, it was reported in the paper that: that measles virus from the live-attenuated MMR vaccine caused intestinal inflammation, the inflamed intestines became "leaky," allowing undefined harmful proteins to enter the bloodstream, travel to the brain and cause autism. Their assertion was justified by the results of a study published in 2000 by Kawashima et al, in which measles virus RNA were identified in the leucocytes of the autistic enterocolitis patient and not in control group (Kawashima *et al.,* 2000).

Another interesting report correlating vaccine and autism was that of Bernard R,in which he noted that in early 1980s were solidly reported in children right from birth and in the first year of birth, he also observed in his data analysis of sudden change in the trend of families reporting that their children behaving normally for the first 18^{th} month of their life and later develop sudden behavioural changes diagnostic of autism in mid 1980s, and the number of families reporting such an incidence increase exponentially. This doubled incidence were linked to the addition of the combination of Measles-mumps-rubella vaccine in to the routine child vaccination schedule in 1979 and was administered to children at age of 12-15 month(Coulter and Fisher, 1991)

Other theories and reason for linking vaccines and autism or ASD were

i) Thimerosal a mercury containing vaccines preservative which for very long time been used in the childhood vaccine as a preservative, the compound is notoriously known for its toxic effect on the developing central nervous system

ii) Measles Mumps Rubella (MMR) containing thimerosal vaccine are believed to have double enhanced toxic implications on the child developing central nervous system

Thimerosal and autism

Thimerosal is an organic, ethyl mercury-containing compound with broad antimicrobial activity that has been used since the 1930s as a vaccine preservative (Offit and Jew, 2003), metabolism of Thimerosal has been reported produced ethylmercry and thiosalicylate, in general thirmerosal contain 49.6% mercury by weight 0.1 μg/kg -0.47 μg/kg body weight/day has been approved to be the maximum safe exposure limit of methyl mercury by WHO and other US regulatory agencies EPA and FDA, Chatterjee MD in a review said that it is worth of noting most of the guidelines and studies on the toxicity of mercury both epidemiological and laboratory were based on methyl mercury not ethylmercury which thermerosal metabolised to and argue that the two are different individual compound, while Stephanie and Deborah reported that even though the amount of literatures on metabolism of thimerosal and ethylmercury poisonous effects is limited, some toxicologist have assumed that the toxicity of ethylmercury is the same as that of methylmercury which was found to be extremely toxic (Coulter and Fisher, 1999)exposure to mercury and mercury containing compound have found to associated with degenerative nerve cell (Clements *et al.,* 1995), adverse behavioural changes (Buchholz, *et al.,* 1999)and brain developmental impairment (Clements *et al.,* 1995). Degenerative chronic condition such as Alzheimer's disease has also been associated with the mercury toxicity, to

worsen the situation it has been reported else were that foetal developing nervous system is more sensitive to mercury toxic effect, it has been known to cause mental retardation and cerebral palsy (Johnson, *et al.,* 1997), a lots of debate was going in US over the role played by thimerosal (mercury containing compound) in childhood vaccine and whether thimerosal has played role in the increasing incidence of autism seen in US, Analysis from vaccine safety data link VAERS found tremendous association between thimerosal preserved vaccine and neuro-developmental disorders(Takayama, *et al.,* 1997) infant body with juvenile premature immune system and been injected with vaccine doses containing ethylmercury from thimerosal cannot get rid properly of these toxic compound as adult did when they consumed toxic containing food like fish which have mercury. And the blood-brain barrier in infant is not fully develop,(this is a membrane between circulating blood and the brain which prevent the brain from exposure to certain harmful substances) as such it cannot protect brain from harmful effect of ethylmercury, therefore can enter brain stay and damage the brain Once in the brain, mercury gathers in the areas that affect motor skills and attacks the nerves, affecting emotional and mental functioning(Coulter & Fisher, 1991). After some of the US states has noted these entire problems pressure ware mounted on the manufacturers to remove thimerosal from vaccine. By 2006, Washington State was the seventh state to pass a law prohibiting thimerosal in childhood and pregnant women vaccines(Wise *et al.,* 2000) it was reported that more state pass same later, as such now childhood vaccines are devoid of thimerosal or it has been reduced to the lowest level except for some few childhood approved vaccinesalthough some scholars are of the opinion why should there be approval of such a toxic compound in the first place. But at same time many scientist are arguing the association of autism with thimerasol, many series of epidemiological and laboratory studies have been conducted world widely to ascertain the claim of thirmerosal autism association but all fail to prove same(Galil, *et al.,* 2002; Tugwell *et al.,* 2004; Bernstein *et al.,* 1993)

Measles-Mumps-Rubella Vaccines

The first published claim relating MMR with autism was made by Wakefield et al. a study conducted among 12 paediatric patients, these patient shows developmental disorders and gastrointestinal abnormal features. Nine of the patients were seen to have autism have autism which were associated with the MMR vaccine they received (Wakefield *et al.,* 1998). These led to the theory of autistic enterocolitis or leaky gut, Wakefield et al. further proved their theory is later paper which they isolated the RNA of measles virus in the white blood of some of their patients (Kawashima *et al.,* 2000). The Wakefield leaky gut theory suggested that measles virus from the live-attenuated MMR vaccine caused intestinal inflammation, the inflamed intestines became “leaky,” allowing undefined harmful proteins to enter the bloodstream, travel to the brain and cause autism (Kawashima *et al.,* 2000).Concurrent with the presence of thimerosal in the vaccine leaking into the blood stream to the brain the situation may even be worst. The incidence of autism were seen to shoot rapidly in 1980s in US and these was attributed to the introduction in 1979 of combination of measles-mumps-rubella vaccine to be given to children 12-15 month, at first the coverage of the vaccine were low and the incidence were also reported low, but there were larger coverage later (Coulter and Fisher, 1991). As the number of childhood vaccination increases so does the dramatic increases of autism was notice in US, from 1993 and 1998 there were recorded rise in the autism incidence by 513 per cent in Maryland (Coulter and Fisher, 1991), and also 300% increase of

autism were reported from 24 states between 1992 and 1997, these dramatic increase was as a result of the free MMR vaccine given in the US, this is supported by the fact that observation were made concerning reported autism cases in 1940s and 1950s, cases of autism were mainly confined to upper and upper-middle class families these class of families were the ones that could afford to pay for their child vaccines and other health care expenses, but as the US government made vaccine free the incidence of autism now crossed class line and autism is now wide spread in all socioeconomic group (Coulter and Fisher, 1991).

However, subsequently, enormous effort has been made by different group of researches employing different and various research methodologies to correlate MMR vaccines with autism, and the result from all these research confirm no linkage between vaccines MMR in particular with autism and disproved the Wakefield hypothesis, and regard the hypothesis as not having scientific basis(Madsen *et al.,* 2002;Black *et al.,* 2002 and Honda *et al.,* 2005). Other scientific researches which involves large group of patients for over a decade also conclusively and collectively show no relationship between MMR vaccines with autism (Peltola *et al.,* 1998; Taylor *et al.,*1999; Klein and Diehl, 2004; DeStefano *et al.,* 2004).Research has recently found in an interesting studies that the incidence of autism is lower in children who receive MMR compared with those that do not received (Mroz˙ek-Budzyn *et al.,* 2010)

Neuropathology of ASD

To compare the assertions of authors trying to link autism to vaccines and its constituents with those opposing presence of any linkage between the two let's look at some of the neuropathological events happening in ASD and the possible correlation of these events with the vaccines or any of the vaccine constituents. Even though, studies in this aspect were grossly limited despite their significance, and the limited published data are presented with many irregularities and contradictions, possibly because of the lack of tissue sample, subject population variations, medication and many other factors. As such the information here will be very brief. Neuropathology is defined as a study of nervous system in disease and healthy state, this involved examination of autopsied tissues and or surgical biopsies of brain tissues, it is a combined studies of neurology, neuroanatomy and neurosurgery (Fatemi *et al.,* 2002).

Early neuropathological studies of autism

Neuropathological studies in autism spectrum disorders (ASD) started from the review by (Darby, 1976) who in a retrogressive studies and enquiries, studied 33 brain sample of patients diagnosed to have ASD, the sample type in this study ranges from whole brain to a single slide of post-mortem sample, using light microscopic examination cerebral lipidosis were diagnosed in most sample, a condition mostly associated with phospholipid metabolism disorder, but also noted other different disorders which the author draw a conclusion that autism is heterogeneous disorder. Even though light microscopic findings was earlier reported by Aarkrog (Aarkrog, 1968), in which thickening of connective tissue in leptomeninges was observed from frontal lobe biopsy(Williams*et al.,* 1980). Study using brain cell count to differentiate autistic and non-autistic patient was reported by (Coleman, *et al*., 1985), in which tissue embedded in celloidin and stain differentially with histological stains show no significant differences in brain cell count between autistic and non-autistic subject, but ischemic neurons (eosinophilic neurons) were observed at the base of gyri in ASD subject, suggesting process of ulegyria, in which case scarring occur in sulci depth, often due to hypoxic-ischemic injury of the brain at perinatal stage of life(Coleman, *et al*., 1985).

Another neuropathological scenario assumed to be diagnostic of autism was reported in a 29 year old male patient who previously shows stereotypical behaviour and delayed development, he demonstrated short attention span, did not respond to his name and have no eye contact, and had major motor seizure at the age of 21, Photoconvulsive pattern was diagnosed from the EEG examination, Smaller than normal neurons in the hippocampus, amygdala and entorhinal, in the subcortical region of the brain at post-mortem examination was reported. Bauman and Kemper, (1985) added new cases later with similar diagnosis, with loss of Purkinje cell but normal olivary nuclei (Kemper and Bauman, 1993). In contrast Fatemi *et al*. (2002) found no difference in Purkinje cells densities between case and control subject. Immunohistochemistry studies of hippocampus for calretinin, calbindin and parvalbumin shows variables results at various position of the brain in autistic patient compared to their aged match control subject (Lawrence, *et al*., 2010). Which was also contrary to what Bailey et al. reported earlier(Bailey *et al.,* 1998), in which no neuronomorphometric significance differences from various CA subfields was observed in autistic subjects compared to controls.

Neuropathological findings in ASD based on brain anatomical site

Cortical Modularity

Human brain pyramidal cell array were mostly examined by Nissl stain and distance of between 30 and 80 um were reported between these units depending on the brain region. These units were reported to be one cell wide this might be because they originate from ontogetic minicolumn (Casanova, *et al.*, 2007). The degree of separation between minicolumn were reported to be same with that in pyramidal cell somas (Buxhoeveden, *etal*., 2000), even though this might not be the case in those laminae where stellar or granular neurons bound, it is true in supragranular layers (Casanova, 2007). In a study on Brodmann areas 9, 21 and 22 in post-mortem brain tissues of nine autistic patients, significant minicolumnal separation distance reductions was reported compared with the controls subject, peripheral neuropil compartment shows the greatest reduction(Casanova, *et al.*, 2002). This study was based on the computerised semi-automated minicolumnar morphometry imaging methods based on the pyramidal cell arrays.

Cerebellum

Cerebellum is the important part of the brain in which dysplastic histopathological abnormalities has been reported in many neuropathological studies of autistic individuals. Some of the vaccines constituent have also seen to cause some damage at this anatomical structure, but before this is discussed lets study some of these abnormalities reported from the cerebellum of autistic patients. Most of these anomalies seen in autistic individual were as a result of the organisational deviation of cerebellum which occurs during brain development. It was also reported that dysplasia was generally seen in the context of the widespread cerebral malformation (Soto-Ares, *et al*., 2000).

Purkinje cells are the largest human brain neurons, characterised by large number of dendritic spine and have elaborated dendritic arbor, they are buttressed and linearly arranged between cell poor molecular layer and underlined granular layer. Diminished Purkinje cells number has been reported in autism by many researchers, because these cells are the only sources of efferent projection of the cerebellar cortex, some of the autistic symptoms might be related to these abnormalities. Neocerebellum bilateral Purkinje cell loss was also reported (Bauman and Kemper, 1985). While wide spread Purkinje cell loss was recorded with ten autistic patients (Bauman and Kemper, 1985). In these cases archicerebellar cortices and posterolateral neocerebellar Purkinje cell loss were observed.

Bauman and Kemper (1985) concluded finally that Purkinje cell loss result in the formation of early developmental lesion in cerebellum of autistic patient.

Recently, studies involving western blotting and immunohistochemistry of Glial Fibrillary Acidic Protein (GFAP), suggest that astrocytosis is present in the autistic patient cerebellum (Laurence and Fatemi, 2005; Vargas*et al*., 2005). GFAP is an intermediate filament protein which is expressed by numerous central nervous system cell types including astrocytes (Jacque *et al.,* 1978). This protein was reported to have been expressed during the glial scar formation and in the process of reactive astrocytosis (Sofroniew and Vinters, 2010). In autism it has been reported that GFAP expression was up regulated and appear to demonstrate hypertropic cell bodies and processes in a narrow and compact spread along the Purkinje cell layer (Fatemi, 2015). And it was also suggested that the GFAP astrocytic response were there due to reactive process to the loss of Purkinje cell. This loss of cell or neurons cell dead has been extensively documented in the poisoning caused by some of the vaccine component like mercury (Cave and Mitchell, 2007)

Brainstem

Absence of facial nuclei and superior olivary with distance shortening between inferior olive and trapezoid body were reported in the sections examination of the lower cranial nuclei of a single ASD patient, which suggest the injury to neural tube closure which occur during development (Rodier, *etal*., 1996). This was later vindicated in a study by (Kulesza and Mangunay, 2008), which reported morphological significant abnormalities of the medial superior olivary nuclei in five ASD cases as compared to the control.

Axons

In the post-mortem examination of a patient with premature closure of cranial sutures, microscopic investigation of the superficial layer of the entorrhinal and perirhinal cortex, layer 2 and 3 of the neocortex shows neurofibrilla tangles, but the gyral pattern was found to be normal and there were no sign of concomitant accumulation of amyloid (Hof, *et al*., 1991). The patient in this study was microcephalic ASD patient who show different self-injurious characters like self-biting, head banging, and eye gouging, considering these characters the authors relate the neurofibrillary tangles finding to a degenerative condition worsen by recurrent trauma to the brain during his life(demetia pugilistica) (Hof *et al.,* 1991).

Relationship between Vaccines and Some of Neuropathological Findings of ASD

Thimerosal is a compound used as a preservatives in vaccines since 1930s and still been used in some vaccines, it is a compound of sodium ethylmercury thiosalicylate, which compose of about 50% mercury. Recently, this compound received tremendous attention for its toxicity especially in pregnant women, infant and young children (Qvarnström, *et al*., 2003). This compound was found to accumulate after its metabolism at various organs including brain where it was reported to remain there for years and cause a lot of damages to the brain (Olczak, *etal*., 2009). With recent increase in the number of paediatrics vaccines in developed, developing and even underdeveloped countries which mostly contain this compound, the fear of toxicity of this compound is at higher rate. For example Hepatitis B vaccines which is given to children at birth or within 24hours of birth. There is reported to contain 12.5 micrograms of thimerosal in each dose, this dose will then be followed with other doses of same vaccine, and other vaccines that also contain mercury at early postnatal life, (DTP, Hib) when combined these doses about 187.5 microgram of mercury will be administered to a child before his six month of life, while the accepted tolerated dose according to EPA was 0.1microgram/kg body weight (Cave and Mitchell, 2007).

When this mercurial compound accumulated in the body of the infant with juvenile immune system, and the system fail to get rid of it, they travel to brain and metabolised to inorganic mercury, attached themselves to neurons cells and damage them, it has been found that the areas most affected are hippocampus, cerebellum and amygdala which are part of the brain mostly involved in autism (Cave and Mitchell, 2007). Because of the similarities in symptoms between mercury poisoning and that of autism it was hypothesis that the mercury in vaccine might be the cause of autism in many infants (Bernard, *et al*., 2001). This assertion was further tested and published by many authors (Gallagher and Goodman, 2008; Geier and Geier, 2006).

This early postnatal period at which this thimerosal containing vaccines was administered has been reported in rat to be the most active neurons developmental stage, and it is characterised with synaptogenesis, gliogenesis, apoptosis, continuing neural cells proliferation and cerebellum and hippocampus dynamism, migration and myelinisation (Rice and Barone, 2000; Seaberg and Van Der Kooy, 2002). It has been suggested that neurodevelopmental abnormalities might have ensue due to mercury interference with these or part of these neurodevelopmental stages.

Neurobehavioral alteration was reported in rats treated with thimerosal in a vaccine like manner, administered in early postnatal time, symptoms resembling those of autism were observed after six weeks of administration, including locomotors deficits, impaired social interactions and pain sensation, also noted was increased anxiety in this rats (Olczak *et al.,* 2009). Other different sets of neuropathological abnormalities in animals treated neonatally with thimerosal were reported in mice (Hornig, *et al*., 2004) and in hamster (Laurente *et al.,* 2007).

Brain cells death by necrosis and apoptosis due to exposure to varying concentration of thimerosal at nanomolar concentration was also reported both invivo and invitro (Humphrey, *et al*., 2005; Nagashima, 1997; Yel, *et al*., 2005). Methyl mercury induced apoptosis was also reported in neural cell of cerebellum (Vendrell *et al.,* 2007). Also programmed cell death in cortical neurons which are triggered due to oxidative stress caused by mehtylmercury has also been reported elsewhere (Higgins, *et al*., 2009). Olczak *et al*. (2010) suggest that neural necrosis and apoptosis induced by thimerosal might be dependent on many factors including animal developmental stage and the amount of mercury in a distinct cellular compartment at a varying time after injection of thimerosal.

Mechanism of mercury induced neural damage

Hypoxaemic or anoxaemic effect due to perivascular oedema and blood circulation disturbance as well as strong direct toxic effect on neurons were reported to be the mechanism of brain cortex injury caused by methylmercury (Takeuchi, 1981). Another mechanism by which mercury containing compound cause brain or neural damage was by induced DNA damage and mitochondrial injury which subsequently lead to oxidative stress and bioenergetics crises (Baskin, *et al*., 2003; Yin *et al.,* 2007). Exposure to methylmercury has also been shown to cause brain oedema and disseminated ischaemia in human and monkeys (Eto, *et al*., 2002; Eto *et al.,* 2001). In a yet another experiment with rat, two phases of neural damage was reported by Olczak *et al*. (2010), acute neurotoxicity occurring shortly after thimerosal administration, few days or hours, at this phase Purkinje cell homogenising degeneration was noted together with ischemic neuronal degeneration, this coincided with the highest mercury concentration in the brain. The second phase was as a result of chronic neuronal poisoning caused by mercury accumulation in the brain this is called dark neurons, this phase was more extended then the former.

It has also been noted that administration of thimerosal in a doses comparable to those in paediatrics vaccine and in the same way vaccine is administered in suckling rats results in astroglia and neuronal injuries in various region of the brain (Olczak*et al*., 2010). Associations of these neuropathological disorders with many neurodevelopmental abnormalities including ASD has been documented (Gallagher and Goodman, 2008; Geier and Geier, 2006; Hewitson, *et al.*, 2010). It is obvious from these findings one can suggest that the rise in the incidences of autism seen world widely in recent years might have been related in a way to the increased and large doses of mercury (thimerosal) containing paediatrics vaccines administered to this category of the population, which may warrant the urgent need to do something so as to address the problem.

Conclusion

Autism a heterogeneous neurodevelopmental condition, manifestation of which usually started at the early age of the patient but in most cases unnoticed until age of 2 or 3 years when the child should be active and should have started communication, it is characterised by an abnormal children behaviour like isolation, learning difficulties, with general deficit in social reciprocity and communication, inability to maintain eye contact or point at something, looking at thing with the peripheral vision and many others neurological disorders, the diagnosis of autism is a subject of discussion, having no fixed standard criteria, because of the heterogeneity of the symptoms, as no two patients have exactly similar symptoms.Aetiology of autism is rather sophisticated, with the underlying pathology and pathophysiology remaining to be elucidated, some factors which were implicated includes; genetics, epigenetics, neuropathological, social, environmental, or immunological factors, the role either play in the symptomatology of autism remain unclear in most cases, the assertion of possible linkage of vaccines in autism also require critical examination and elucidation, the fact that dramatic surge in the incidence of autism which coincided with era of massive childhood vaccination need to be fully vindicated. The observed detrimental effect of vaccine and the benefit need to be fully weighed, investigated and revisited. Campaign for manufacture of thimerosal (mercury containing compound) and other harmful preservatives free vaccine is worth encouraging, the vaccine manufacturing companies should think of using safer component. And finally “anti-vaccine” propaganda need holistic address to prevent re-emergence of already eradicated infectious diseases, the task on the scientist should consider switching to less harmful vaccine production.

Conflict of interest

The authors were hereby given a declaration that no conflict of interest existed throughout the preparation of the manuscript.

REFERENCES

Aarkrog, T. (1968). Organic factors in infantile psychoses and borderline psychoses. A retrospective study of 46 cases subjected to pneumoencephalography. *Danish Medical Bulletin, 15*(9), 283-288.

Bailey, Aea, Luthert, P, Dean, A, Harding, B, Janota, I, Montgomery, M, Lantos, P. (1998). A clinicopathological study of autism. *Brain, 121*(5), 889-905.

Baskin, David S, Ngo, Hop, & Didenko, Vladimir V. (2003). Thimerosal induces DNA breaks, caspase-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts. *Toxicological Sciences, 74*(2), 361-368.

Bauman, M., and Kemper, T.L., (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology, 35*(6), 866-866.

Bernard, Sallie, Enayati, A, Redwood, L, Roger, H, & Binstock, T. (2001). Autism: a novel form of mercury poisoning. *Medical Hypotheses, 56*(4), 462-471.

Bernstein, Henry H, Rothstein, Edward P, Watson, Barbara M, Reisinger, Keith S, Blatter, Mark M, Wellman, Catherine O, White, C Jo. (1993). Clinical survey of natural varicella compared with breakthrough varicella after immunization with live attenuated Oka/Merck varicella vaccine. *Pediatrics, 92*(6), 833-837.

Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case–control study using data from the UK General Practice Research Database. BMJ. 2002;325:419–21.

Buchholz, Udo, Moolenaar, Ron, Peterson, Carol, & Mascola, Laurene. (1999). Varicella outbreaks after vaccine licensure: should they make you chicken? *Pediatrics, 104*(3), 561-563.

Buxhoeveden, Daniel P, Switala, Andrew E, Roy, Emil, & Casanova, Manuel F. (2000). Quantitative analysis of cell columns in the cerebral cortex. *Journal of neuroscience methods, 97*(1), 7-17.

Casanova, Manuel F, Buxhoeveden, Daniel P, Switala, Andrew E, & Roy, Emil. (2002). Minicolumnar pathology in autism. *Neurology, 58*(3), 428-432.

Casanova, Manuel F, Trippe, Juan, & Switala, Andrew. (2007). A temporal continuity to the vertical organization of the human neocortex. *Cerebral Cortex, 17*(1), 130-137.

Casanova, M.F. (2007). The neuropathology of autism. *Brain Pathology, 17*(4), 422-433.

Cave, Stephanie, & Mitchell, Deborah. (2007). *What Your Doctor May Not Tell You About (TM) Children's Vaccinations*: Grand Central Publishing.

Clements, Dennis A, Armstrong, Christine B, Ursano, Amy M, Moggio, Mary M, Walter, Emmanuel B, & Wilfert, Catherine M. (1995). Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents. *The Pediatric infectious disease journal, 14*(10), 874-878.

Coleman, Paul D, Romano, John, Lapham, Lowell, & Simon, William. (1985). Cell counts in cerebral cortex of an autistic patient. *Journal of Autism and Developmental disorders, 15*(3), 245-255.

Coulter, H.L., and Fisher, B.L. (1991). *A shot in the dark: why the P in the DPT vaccination may be hazardous to your child's health*: Penguin.

Darby, J.K. (1976). Neuropathologic aspects of psychosis in children. *Journal of Autism and Childhood Schizophrenia, 6*(4), 339-352.

DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C (2004). Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics:113:259–66.

Eto, Komyo, Tokunaga, Hidehiro, Nagashima, Kazuo, & Takeuchi, Tadao. (2002). An autopsy case of Minamata disease (methylmercury poisoning)—pathological viewpoints of peripheral nerves. *Toxicologic Pathology, 30*(6), 714-722.

Eto, Komyo, Yasutake, Akira, Kuwana, Takashi, Korogi, Yukunori, Akima, Michio, Shimozeki, Toshie, Kaneko, Yosuke. (2001). Methylmercury poisoning in common marmosets—a study of selective vulnerability within the cerebral cortex. *Toxicologic pathology, 29*(5), 565-573.

Fatemi, S Hossein, Halt, Amy R, Realmuto, George, Earle, Julie, Kist, David A, Thuras, Paul, & Merz, Amelia. (2002). Purkinje cell size is reduced in cerebellum of patients with autism. *Cellular and molecular neurobiology, 22*(2), 171-175.

Fatemi, S.H. (2015). *The Molecular Basis of Autism*: Springer.

Galil, Karin, Fair, Elizabeth, Mountcastle, Norine, Britz, Phyllis, & Seward, Jane. (2002). Younger age at vaccination may increase risk of varicella vaccine failure. *Journal of Infectious Diseases, 186*(1), 102-105.

Gallagher, Carolyn, & Goodman, Melody. (2008). Hepatitis B triple series vaccine and developmental disability in US children aged 1–9 years. *Toxicological and Environmental Chemistry, 90*(5), 997-1008.

Geier, D.A, and Geier, M.R. (2006). A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States. *Neuroendocrinol Lett, 27*, 401-413.

Hewitson, Laura, Lopresti, Brian J, Stott, Carol, Mason, N Scott, & Tomko, Jaime. (2010). Influence of pediatric vaccines on amygdala growth and opioid ligand binding in rhesus macaque infants: A pilot study. *Acta neurobiologiae experimentalis, 70*(2), 147-164.

Higgins, Gavin C, Beart, Philip M, & Nagley, Phillip. (2009). Oxidative stress triggers neuronal caspase-independent death: endonuclease G involvement in programmed cell death-type III. *Cellular and molecular life sciences, 66*(16), 2773-2787.

Hof, PR, Knabe, R, Bovier, P, & Bouras, C. (1991). Neuropathological observations in a case of autism presenting with self-injury behavior. *Acta neuropathologica, 82*(4), 321-326.

Honda H, Shimizu Y, Rutter M. (2005). No effect of MMR withdrawal on the incidence of autism: a total population study. J Child Psychol Psychiatry:46:572–9.

Hornig, Mady, Chian, David, & Lipkin, W Ian. (2004). Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Molecular psychiatry, 9*(9), 833-845.

Humphrey, Michelle L, Cole, Marsha P, Pendergrass, James C, & Kiningham, Kinsley K. (2005). Mitochondrial mediated thimerosal-induced apoptosis in a human neuroblastoma cell line (SK-N-SH). *Neurotoxicology, 26*(3), 407-416.

Jacque, CM, Vinner, C, Kujas, M, Raoul, M, Racadot, J, & Baumann, NA. (1978). Determination of glial fibrillary acidic protein (GFAP) in human brain tumors. *Journal of the neurological sciences, 35*(1), 147-155.

Johnson, Candice E, Stancin, Terry, Fattlar, Deborah, Rome, Leonard P, & Kumar, Mary L. (1997). A long-term prospective study of varicella vaccine in healthy children. *Pediatrics, 100*(5), 761-766.

Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hashika A, Wakefi eld A. (2000) Detection and sequencing of measles virus from peripheral mononuclear cells from patients with infl ammatory bowel disease and autism. Dig Dis Sci.:45:723–9.

Kemper, T.L, and Bauman, M.L. (1993). The contribution of neuropathologic studies to the understanding of autism. *Neurologic clinics*.

Klein K, Diehl E. Relationship between MMR vaccine and autism. Ann Pharmacother. 2004;38:1297–300.

Kulesza, R.J, and Mangunay, K. (2008). Morphological features of the medial superior olive in autism. *Brain research, 1200*, 132-137.

Laurence, JA, & Fatemi, SH. (2005). Glial fibrillary acidic protein is elevated in superior frontal, parietal and cerebellar cortices of autistic subjects. *The Cerebellum, 4*(3), 206-210.

Laurente, Jonny, Remuzgo, Fany, Ávalos, Betthina, Chiquinta, Johnnie, Ponce, Bladimir, Avendaño, Ronald, & Maya, Luis. (2007). Neurotoxic effects of thimerosal at vaccines doses on the encephalon and development in 7 days-old hamsters. *An Fac Med Lima, 68*(3), 222-237.

Lawrence, YA, Kemper, TL, Bauman, ML, & Blatt, GJ. (2010). Parvalbumin-, calbindin-, and calretinin-immunoreactive hippocampal interneuron density in autism. *Acta Neurologica Scandinavica, 121*(2), 99-108.

Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohlfahrt J, Thorsen P, et al. (2002) A population-b ased study of measles, mumps, and rubella vaccination and autism. N Engl J Med.:347:1477–82.

Mroz˙ek-Budzyn D, Kiełtyka A, Majewska R. (2010). Lack of association between measles-mumps- rubella vaccination and autism in children. A case–control study. Pediatr Infect Dis J:29:397–400.

Murphy JF (2011). Fallout of the enterocolitis, autism, MMR vaccine paper. Ir Med J 104(2):36

Nagashima, K. (1997). Review Article: A Review of Experimental Methylmercury Toxicity in Rats: Neuropathology and Evidence for Apoptosis. *Toxicologic Pathology, 25*(6), 624-631.

Offit P, and Jew R.(2003) Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics. 112(6):1394–7.

Olczak, M, Duszczyk, M, Mierzejewski, P, & Majewska, M. (2009). Early postnatal thimerosal administration, in a vaccination-like scheme, causes vast structural damage in rat brain: implication for autism. *Acta Neurobiologiae Experimentalis, 3*(69).

Olczak, Mieszko, Duszczyk, Michalina, Mierzejewski, Pawel, Wierzba-Bobrowicz, Teresa, & Majewska, Maria Dorota. (2010). Original paper Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal. *Folia Neuropathol, 48*(4), 258-269.

Peltola H, Patja A, Leinikki P, Valle M, Davidkin I, et al. (1998). No evidence for measles, mumps, and rubella vaccine-associated infl ammatory bowel disease or autism in a 14-year prospective study. Lancet:351:1327–8.

Qvarnström, Johanna, Lambertsson, Lars, Havarinasab, Said, Hultman, Per, & Frech, Wolfgang. (2003). Determination of methylmercury, ethylmercury, and inorganic mercury in mouse tissues, following administration of thimerosal, by species-specific isotope dilution GC-inductively coupled plasma-MS. *Analytical chemistry, 75*(16), 4120-4124.

Rice, D., and Barone, S. (2000). Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 108 (suppl 3): 511–533.

Rodier, Patricia M, Ingram, Jennifer L, Tisdale, Barbara, Nelson, Sarah, & Romano, John. (1996). Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology, 370*(2), 247-261.

Seaberg, Raewyn M, & Van Der Kooy, Derek. (2002). Adult rodent neurogenic regions: the ventricular subependyma contains neural stem cells, but the dentate gyrus contains restricted progenitors. *The Journal of neuroscience, 22*(5), 1784-1793.

Sofroniew, M.V, and Vinters, H.V. (2010). Astrocytes: biology and pathology. *Acta neuropathologica, 119*(1), 7-35.

Soto-Ares, Gustavo, Delmaire, Christine, Deries, Berengere, Vallee, Louis, & Pruvo, Jean Pierre. (2000). Cerebellar cortical dysplasia: MR findings in a complex entity. *American journal of neuroradiology, 21*(8), 1511-1519.

Takayama, Naohide, Minamitani, Mikio, & Takayama, Michiko. (1997). High incidence of breakthrough varicella observed in healthy Japanese children immunized with live attenuated varicella vaccine (Oka strain). *Pediatrics International, 39*(6), 663-668.

Takeuchi, T. (1981). Pathology of Minamata disease. With special reference to its pathogenesis. *Acta Pathologica Japonica, 32*, 73-99.

Taylor B, Miller E, Farrington CP, Petropoulos MC, Favot-Mayaud I, et al. (1999) Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet:353:2026–9.

Tugwell, Barna D, Lee, Lore E, Gillette, Hilary, Lorber, Eileen M, Hedberg, Katrina, & Cieslak, Paul R. (2004). Chickenpox outbreak in a highly vaccinated school population. *Pediatrics, 113*(3), 455-459.

Vargas, Diana L, Nascimbene, Caterina, Krishnan, Chitra, Zimmerman, Andrew W, & Pardo, Carlos A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of neurology, 57*(1), 67-81.

Vendrell, Iolanda, Carrascal, Montserrat, Vilaró, Maria-Teresa, Abián, Joaquín, Rodríguez-Farré, Eduard, & Suñol, Cristina. (2007). Cell viability and proteomic analysis in cultured neurons exposed to methylmercury. *Human & experimental toxicology, 26*(4), 263-272.

Wakefield AJ, Murch SH, Linnell J, et al (1998). Ileal-lymphoid-nodular hyperplasia, non-specifi c colitis, and pervasive developmental disorder in children [retracted]. *Lancet.* 351:637–41.

Williams, Roger S, Hauser, Stephen L, Purpura, Dominick P, DeLong, G Robert, & Swisher, Charles N. (1980). Autism and mental retardation: neuropathologic studies performed in four retarded persons with autistic behavior. *Archives of Neurology, 37*(12), 749-753.

Wise, Robert P, Salive, Marcel E, Braun, M Miles, Mootrey, Gina Terracciano, Seward, Jane F, Rider, Lisa G, & Krause, Philip R. (2000). Postlicensure safety surveillance for varicella vaccine. *Jama, 284*(10), 1271-1279

Yel, Leman, Brown, Lorrel E, Su, Kevin, Gollapudi, Sastry, & Gupta, Sudhir. (2005). Thimerosal induces neuronal cell apoptosis by causing cytochrome c and apoptosis-inducing factor release from mitochondria. *International journal of molecular medicine, 16*(6), 971-977.

Yin, Zhaobao, Milatovic, Dejan, Aschner, Judy L, Syversen, Tore, Rocha, Joao BT, Souza, Diogo O, Aschner, Michael. (2007). Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. *Brain research, 1131*, 1-10