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Literature review and recommendations about current affairs concerning the parents of autistic children

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A. Vaccination:

The causal association of vaccinations, and especially of the one for Measles/Mumps/ Rubella (MMR), started from a paper published by Wakefield et al at the prestigious journal of Lancet in 1998.[1] This paper is a case series of 12 "consecutive" cases of normal development, who after receiving the MMR a new syndrome was presented with gastroenterological symptoms (colitis), that lead to regression autism in 8 of these cases. It admitted, though, that the study did not "prove" a correlation between MMR and autism. However, both the media and Wakefield himself continued to allege the corelation and advised to deliver the three vaccines separately, for "preventive reasons". This study had severe methodological flaws, with the sample carefully chosen and not consecutive cases, data were manipulated, the invasive tests done to the children were unjustified, while there was no official ethical approval. Furthermore, Wakefield had relations and got funded from a group of anti-vaccines lawyers that were preparing lawsuits for compensations from the vaccines' producers, while he has applied for a patent for single vaccine for measles. All these conflicts of interests were not declared to the journal. Based on all these, the paper was fully retracted from Lancet in 2010 and he was struck out the UK medical register rendering him unable to practice there.

Since then, some small studies with multiple methodological issues have been published by Geir MR and his son Geir DA that allege a relationship between autism and either the MMR or the preservative thimerosal that used to be found in it and other vaccines. NB that the medical licence of Marc Geir had been revoked in all the states of USA in which he practiced the medical profession. Finally, the study on which the latest revival of the subject is based upon is that of Mawson & Jacob that surveyed 47,155 children 9 years of age, and was published in a non-indexed journal.[2] The study didn't use medical files but rather the billing receipts in Florida State Medicaid where a code of vaccination was mentioned. Thus, it is neither known which vaccines and when were done nor if diagnosis was done before or after vaccination. Furthermore, confounding factors were not considered and accounted for, such as the amount of service usage (subjects with greater usage of the system have greater chance to be vaccinated but also higher chance to be diagnosed – a bias similar to

the association between coffee and lung cancer due to their higher use in smokers), family history, socio-economic factors, environmental exposures and how the way of diagnosis of autism has evolved in the 12 years of the study. Finally, the study had serious issues in the statistical analysis, the quality of data and the methodology (mainly cross-sectional) could reveal corelations but not causality. Note that a paper by Mawson with similar claims was submitted and published consecutively in two peer reviewed journals (first in Frontiers in Public Health and one year later in Journal of Translational Science), and was retracted both time by the journal in the first month.

The reaction to Wakefield's fraudulent paper and the relevant media storm it produced, was a series of big and rigorous studies that proved the lack of association between vaccinations or their ingredients with autism. I cite here few of the biggest and latest ones:

- Taylor et al (2014) run a meta-analysis of 5 cohort studies (1,256,407 children) and 5 case control studies (9,920 children).[3] No statistically significant association was found between vaccinations or their ingredients (Thimerosal or mercury) or multiple vaccines like MMR, with ORs around 1, signalling a not elevated risk for autism.
- Hviid et al (2019) surveyed 657,461 children born in Denmark between 1999-2010 (equivalent of over 5,000,000 subjects-years follow-up).[4] Comparing MMR-vaccinated with MMR-unvaccinated children yielded a fully adjusted autism hazard ratio of 0.93, that is no increase risk. Furthermore, MMR does not seem to trigger autism in susceptible children (e.g. with positive history).
- Becerra-Culqui et al (2022) studied 84,739 mother-child pairs comparing children whose mothers had influenza vaccination vs. infection during pregnancy.[5] No increase in autism risk was detected in the offspring from neither the vaccination nor the infection.
- Zerbo et al (2022) surveyed 14,947 children already diagnosed with autism and 1,650,041 children without autism, 4-7 years of age, that received a vaccine containing measle or pertussis.[6] Children with autism were not at increased risk for serious adverse events (fever, febrile seizures or emergency department visits) compared to those without autism.
- Andersson et al (2025) surveyed 1,200,000 children born between 1997 and 2018 to examine if the small amounts of aluminium used in many vaccines increase risk of 50 different health conditions including autism.[7] No statistical association with autism or any other conditions studied was found.

Thus, it is nor surprisingly that the official Health Agencies around the world have unanimously accepted and declared that there is no connection between MMR or other vaccines or some of their ingredients with autism. This position is held by the World Health Organization (WHO), the American Centers for Disease Control and Prevention (US CDC), the UK NHS Medicines-Information Services, the American Academy of Pediatrics (AAP), the Australian Academy of Health and Medical Sciences (AAHMS), and more.

What should be emphatically noted are the consequences of such unsubstantiated claims followed by the relevant conspiracy theories upon both the person's health but also on the level of public health: epidemics of preventable diseases, decrease of trust in the vaccines and erosion of people's trust in the health systems, as seen at the Covid 19 pandemic.

After the publication of Wakefield (1998) paper, MMR coverage in the UK fell from around 92% in 1996 to 80% by 2004, [8] and scepticism about its safety spread in USA and all around the world.[9] Subsequently, measles outbreaks re-emerged in the UK [10], but also in USA and Europe. Mumps and rubella also saw resurgences. Mortality rates are low in developed countries, but deaths increased world-wide from 95,000 in 2021 to 136,200 in 2022, following the vaccination drop during Covid 19. It is calculated that 57,000,000 measles deaths were averted by vaccination during 2000-2022. [11]

Finally, one should consider the financial costs of a measle outbreak which mounts several millions of US dollars per outbreak, and compare this to the cost to prevent it through achieving herd immunity by vaccination over several years. For instance, the Merseyside outbreak in UK (2012-2013) costed $5.5-6M [12], while the prevention approach would have costed around 4% of that figure. [12] It is well studied that childhood immunization programs are the most cost-effective public health interventions: according to CDC the US program (1994-2018) prevented >419M illnesses, 936,000 deaths and saved $406 billion in direct costs. [13] These figures disvalidate one of the main conspiracy theories of the vaccination sceptics, i.e. vaccines are promoted from the pharmaceutical companies for the sake of profits. Profits would have been multiple times higher for the industry if vaccines were not used, as the direct costs from the illness are multiple the costs of the vaccines.

Conclusion and recommendation: Vaccines are the most effective way to protect a person from preventable diseases and they have proven safe in their use not leading to autism or other developmental adversities. They are also safe for use in already diagnosed autistic children. Parents should NOT be worried or sceptic to follow the relevant recommendations for their child's vaccination program from the official paediatric associations.

B. Acetaminophen / Paracetamol:

Acetaminophen or Paracetamol, branded as Tylenol, Panadol, Depon etc, is an analgesic used more than a hundred years, and its use in children and pregnancy has intensified since the issue of warnings against aspirin and ibuprofen. Based on the published literature, FDA issued in 2020 a warning against the use of nonsteroidal anti-inflammatory drugs (NSAIDs), like aspirin, ibuprofen, diclofenac, celecoxib, or naproxen, around 20 weeks or later in pregnancy, as it may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications.[14] It advised also against the use of aspirin in all trimesters (bleeding, loss of the child, premature closure of the ductus arteriosus, etc). However, low doses of aspirin (80mg/d) are considered safe and recommended for preeclampsia prophylaxis.[15] Similarly, first the American Academy of Pediatrics (1982), then the FDA (1986) and with a final rule in 2003, issued a statement against its use in children and adolescents below 19 with viral illnesses mainly due to the danger of Reye syndrome.[16] In all instances, acetaminophen/ paracetamol was cited as a safe alternative. Ibuprofen was also considered safe for infants above 6 months that were not dehydrated, had not kidney problems, stomach ulcers or asthma.

First concerns were raised in 2008 by a small case control study that examined the use of acetaminophen for the adverse effects of the MMR in 12-18 months infants and reported a higher risk for those infants that took the medication.[17] The same group reported

similar results in couple of small studies [18] and hypothesized that acetaminophen disruption of the endocannabinoid system may underlie some of the increased likelihood for ASD, particularly in children with genetically compromised pathways that normally metabolize this drug.[19] Several other studies have reported association of prenatal or early postnatal use of acetaminophen with a modest increase of autism or autism symptoms or ADHD: in a Danish national birth cohort prospective study (2016) of over 64,000 children a higher risk for autism with hyperkinetic features was found but not autism alone.[20] Measuring metabolites in umbilical cord in 996 births and prospectively following up 9 years later, Ji et al (2020) reported a significant increase risk for ADHD and ASD, but because of the half-life of acetaminophen in adults (<3h), the cord plasma measurement may at most reflect maternal use of acetaminophen during the peripartum period and not generally prenatally.[21] In a European meta-analysis of 6 cohorts (2021), 73,881 mother child pairs were included and examined for prenatal and early postnatal exposure, to find associations with increased autism spectrum conditions and ADHD.[22] However, there was a big heterogeneity how the exposure and the outcome was measured in the different cohorts. Also, it was only the largest one among the 6 (83% of the total sample) that supported the association, while the other 5 studies didn't find evidence of such an association. The issue resurfaced recently after the publication in august 2025 of a new study which evaluated the published data from 46 studies of which 26 were positive.[23] However, as the American College of Obstetricians and Gynecologists , among others, pointed out the study "include the same methodological limitations—for example, lack of a control for confounding factors or use of unreliable self-reported data—that are prevalent in the majority of studies on this topic", [24] while its data can at the most add up to a possible association and not to causality.

Although these associations are interesting (though modest and not consistent), they don't add up in causation due to lack of controlling of the most important confounding factors. The more rigours designed studies do try to control for these, such as the underlying conditions that prompt acetaminophen use, like fever, infection or inflammation, that may contribute to the risk themselves. However, they usually don't control for residual confounders, such as shared genetic predispositions and shared family/environmental factors that should be accounted for. The late can be addressed through a sibling control analysis design in which we compare siblings where one is exposed and the other was not. This comparison controls for confounders that would be identical or similar between siblings like genetics, socioeconomic status, parenting style, maternal health characteristics, household exposures, etc. By doing this, we examine the possibility that one of these confounders "creates" this association between the acetaminophen and autism, e.g. higher maternal stress increase the use of acetaminophen and the risk of autism. Thus, in a recent prospective Swedish study (2024) of almost 2,5m subjects such methodology was implied.[25] Proving the need for such rigorous approach, the study reported acetaminophen exposure was more common among children born to birthing parents with a lower socioeconomic position, a higher early pregnancy body mass index, those who smoked during pregnancy, and those with diagnoses of any psychiatric conditions, neurodevelopmental disorders, indications for acetaminophen, and co-prescription of related therapeutics. As in most of the observation studies small population -level associations were found between acetaminophen exposure and the increased risk for autism, ADHD and intellectual disability, but these disappeared in sibling comparisons. Same held true for the dose-response pattern seen in this and other studies. Same pattern was

observed in the Norwegian sibling control study (MoBa), where the association between acetaminophen and ADHD disappeared in the within family level, once the sibling control model was used.[26] An earlier smaller sibling control study, using the MoBa sample, examined children at the age of 3, found an association with maternal report of externalising symptoms that survived in the within family level.[27] this difference could be attributed to the younger age or to the use of general symptoms instead of a clear diagnosis. These results indicate that the true reason of the autism risk might not be the use of acetaminophen but something shared across the families who tend to use it more often.

The current consensus among official health bodies such as WHO, American Academy of Pediatrics (AAP), the American College of Medical Toxicology (ACMT) and that of Obstetricians and Gynecologists (ACOG) and others, is that we cannot base our judgment on observational studies that can show association but not causation, and point to the fact that when other residual confounders are factored in (e.g. through sibling comparison studies) the small risk from the observation studies tend to disappear. [24, 28-30] In its latest statement, WHO explicitly states that "no consistent association" has been established, [28] while FDA speaks about possible association, mentioning the studies with opposite claims and also underscores that "a causal relationship has not been established".[31] Two reputable and leading Autism organizations, the International Society for Autism Research and Autism Speaks, are also going along with the above consensus. [32-33] Based on the literature, the only recommendation that could be given was cautious use (as most medications during pregnancy) concerning doses, duration and indications. One should factor in that acetaminophen is one of the few safe options (as mentioned above) to treat pain and fever in pregnancy which can be harmful for the foetus if untreated. As ACOG statement pointed out: "The conditions people use acetaminophen to treat during pregnancy are far more dangerous than any theoretical risks and can create severe morbidity and mortality for the pregnant person and the fetus".[24] NB that even fever itself is associated with a modest increase in the risk for autism, [34] and thus the advice to sustain the fever with no medications is unfounded.

Conclusion and recommendation: Observational studies show an inconsistent and modest association (and not causation) between the use of acetaminophen in pregnancy and autism risk. This association disappears in studies with more rigorous designs controlling for residual confounders such as genetics and environmental exposures. Acetaminophen/ Paracetamol is considered a safe medication for pregnancy and infants when taken following the relevant health professional guidelines.

C. Leucovorin:

Folate is a water-soluble B vitamin that is essential for a wide variety of essential metabolic systems and thus normal development.[35] The primary transporter for folate across the blood-brain barrier is the folate receptor α (FRα). Through energy dependent endocytosis, folate is transported attached to the FRα. Active transport is necessary because central nervous system folate concentration is several times higher than in the serum. If this mechanism is blocked, it is called Cerebral Folate Deficiency (CFD), which is characterized by low folate levels in the cerebrospinal fluid (CSF) despite normal serum folate levels and associated with developmental delays, speech and language issues, irritability or mood

problems and autistic behaviors (32%) and some neurological and motor symptoms.[36,37] CFD is caused usually by FRα autoantibodies (FRAAs), blocking and binding, which impair FRα function; but it can be caused, also by mitochondrial disorders due to a lack of energy for active transportation of folate.[35] FRAAs have been identified in children with autism in higher percentages compare to neurotypical adults or to non-ASD disabled children and mitochondrial disorders can be comorbid conditions in ASD.[36,37] In a meta-analysis the prevalence of CFD in autism, independent of causation) was calculated at 43% but with significant heterogeneity (from 0 to 100%), rendering this figure not reliable.[37] Furthermore, typical developing siblings of children with autism, as well as their parents, appeared to have similar prevalence of FRAAs [37,38], which cast doubt about the specificity of the findings.

Folinic acid (*d,l*-leucovorin), a long standing medication used in chemotherapy, is a reduced (active) form of folate which can enter the CNS through the Reduced Folate Carrier and has been reported to normalize folate levels in the CNS. Thus, it has been used to treat CFD and eventually, given the association of ASD with CFD, tried in autism treatment. A series of small studies with few controlled ones, have been performed to examine its effect on ASD. In a 2021 systematic review and meta-analysis, Rossignol & Frye identified 20 studies including four placebo-controlled studies, three prospective, controlled studies, nine prospective studies without a control group (two studies examined the same cohort of patients), and four case reports/series.[37] The studies included were small, mostly not controlled and with short follow up, while the authors state that it may take 1–2 years to observe maximal clinical improvements. Furthermore, the studies used a plethora of different outcome measures, whilst the effect of the concomitant interventions is not controlled for. The impact of the medication was of medium effect size at the best and it was more pronounced in those children positive for FRAAs. For instance, in the randomized double-blind placebo-controlled trial of Frye et al (2018), the authors report an overall significant effect with an effect size of 0.7, that jumps to 0.9 for the FRAAs positive cases, but becomes non-significant in those cases negative for FRAAs.[39] However, this finding is not highlighted, and both in this paper's conclusions and the ones in the systematic review by the same authors, leucovorin is proposed for all autistic children, and proposed to be given even blindly without checking the FRAAs status.[37,39] Finally, adverse events were reported similar to those in the control groups, even with the high proposed dose of 2mg/Kg/day and up to a maximum of 50mg/d.[37]

Two more small studies with short follow-up were subsequently published: Panda et al (2024) conducted a randomized double-blind, placebo-controlled trial and reported gains with medium effect size that were more prominent in those children with FRAAs.[40] Zhang et al (2025), in their single blinded study, examined children that were also getting the TEACCH intervention.[41] Their outcome measures were the 10 subscales of PEP-3 without defining a main outcome. NB that PEP-3 is also the guiding tool for the tailoring of the TEACCH interventions to the child's needs !!! A medium effect size gain was demonstrated in one of the 10 subscales, the social reciprocity.[41]

The current literature consists of small, mostly not controlled, with no rigorous design and short follow up studies that by no means can be considered enough to draw conclusions on the use of leucovorin in autism. At the best, the existing data could be pointing to folinic acid use in the Cerebral Folate Deficiency (CFD), and is towards that end that FDA announced that it is moving for. However, the existing data do not point to an answer in a

series of questions regarding its use in autism: a) what's the prevalence of CFD or FRAAs or any other index of folate insufficiency in ASD? Are these features reliably predicting benefit? b) which areas of autism folinic acid can have an effect upon? Are they the core symptoms or the accompanying symptoms and behaviors? c) Is Leucovorin useful in autistic children without folate insufficiency? The answers needed require a series of relevant well-designed phase 2 studies, and three of them are on their way. However, professionals and parents should be reminded that many medications that were initially supported with the kind of data leucovorin also has, were subsequently discarded in more robust phase 2 studies or in the larger multisite phase 3 ones. To quantify this, 28-35% of medications pass from phase 2 to phase 3 and 55-70% pass phase 3 to be FDA approved.

Often, the scientists introducing this kind of "medicines" argue for their use on the basis of "nothing to lose": even if their effect are not proven, they are free of side effects. We heard that for the DAN protocol or its parts, and we heard the same argument from the same group of researchers that now pioneered the leucovorin for the hyperbaric oxygen in autism. However, the lack of physiological side effects (in whatever extent) does not exclude the causing of as damaging psychological ones, especially when the "treatment" will be ineffective: parents can lose confidence in clinicians leading to non-compliance, scepticism or disengagement for other treatments, both autistic persons and their caregivers with repeated exposure to ineffective treatments may end up in hopelessness or learned helplessness and from there to depression, and the prioritization of the ineffective "miracle" pills can lead to delay or disregard of evidence based interventions, especially if they require way much more involvement of the parents.[42]

FDA initiated its approval process for use of leucovorin in patients with CFD. CFD is described by the FDA as a neurological condition that can cause developmental delays with autistic features (e.g., challenges with social communication, sensory processing, and repetitive behaviors), seizures, and problems with movement and coordination. However, FDA notes that its use in populations with neuropsychiatric symptoms, including autism, lack supporting data and additional studies are needed to assess safety and efficacy.[43] In the same line, the Society for Developmental and Behavioral Pediatrics underscores the lack of evidence for the safety and efficacy of leucovorin for autistic individuals, and points to the fact that current folate receptor autoantibody testing (FRAT) is unreliable.[44] Autism Speaks and INSAR also underscore the need for more studies, with the late mentioning that "such unproven claims have the potential to cause harm for autistic persons, their families, and society at large".[32,33]

Conclusion and recommendation: Some conclusions can be drawn from the published studies on leucovorin use in Cerebral Folate Deficiency (CFD), with a potential to treat autism-like *symptoms* in patients who have this very specific diagnosis. But its use for unselected autistic cases is discouraged, as its safety and effectiveness have not been established. Even with the use of folate receptor autoantibody testing (FRAT) as a predictor of response, we cannot suggest the experimental use of leucovorin, given the questions and issues raised above, as well as its unrealability.

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