Reviewer’s report

Title: Autism, Circumcision and Analgesia: an Ecologic Link

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Reviewer: Philip J. J Landrigan

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This manuscript describes a very interesting ecological study examining the possibility that there exists a relationship between risk of autism use of the analgesic agent, paracetamol (acetaminophen) during circumcision. To explore the relationship between paracetamol exposure and Autism Spectrum Disorder (ASD) the authors compared population-weighted average autism prevalence rates obtained from CDC with region-specific paracetamol usage rates reported in the literature. Publications reporting rates for paracetamol use were identified through a systematic literature search conducted in PubMed.

This is fascinating study. Although it has all of the limitations that are associated with ecological studies, it is well done. Moreover the finding of an association between use of paracetamol in male circumcision and autism parallels two striking features of the autism epidemic:

1. The rapid recent increase in autism which parallels recent increases in use of paracetamol as an analgesic
2. The striking male/female discrepancy in rates of autism, which reflects the sex-specific nature of male circumcision

An ecologic study such as this is by definition never definitive. That said, the hypothesis that it generates is intriguing and is worthy of further investigation. I suggest that the authors reduce the length of the section of their paper entitled Biologic Plausibility and the subsequent sections that span pages 13 through 16. This is not their area of expertise, and the information presented is derivative in nature. For these reasons it should presented in one of the two brief paragraphs.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No competing interests