

## **Reply by Authors – Re: Canadian Pediatrics Society position statement on newborn circumcision: a risk-benefit analysis revisited**

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Dear Editor,

We are pleased that representatives of the Canadian Pediatric Society (CPS) have written a Letter<sup>1</sup> responding to our criticisms<sup>2</sup> of its position statement on early infant (“newborn”) male circumcision (EIMC).<sup>3</sup> We also appreciate that the CPS authors accepted some of our criticisms. Their response, however, demonstrates ongoing misunderstandings.

First, we did not, “advocate for routine neonatal male circumcision” (MC). Any medical intervention in childhood requires parental consent.

Second, the CPS listed some data, but did not present key calculations for total risk, total benefit or benefit:risk ratio for EIMC. One of us, Brian Morris, recommended a standard risk-benefit analysis in a teleconference during planning of the CPS review. Participants in the teleconference included Todd Sorokan, the first author of the CPS position statement,<sup>3</sup> Neil Pollock, a co-author of our critique,<sup>2</sup> and Edgar Schoen, a former Chair of the American Academy of Pediatrics (AAP) Task Force on Circumcision. We note that Todd Sorokan is not an author of the CPS Letter.

Third, we question why the authors of the CPS Letter cite a website (their ref. 2) rather than the published CPS position statement.<sup>3</sup> We note that the first author of the Letter, Joan Robinson, is the Editor of the journal that published the CPS position statement. We also note that that journal published a Letter<sup>4</sup> by Brian Earp, a strident EIMC opponent, criticizing the CPS for recommending an evidence-based brochure for parents in the “Selected Resources” section of its position statement.<sup>3</sup> The link to that brochure no longer appears in the online version of the CPS position statement. The brochure (available on the Circumcision Academy of Australia website – <http://www.circumcisionaustralia.org>) included results of a risk-benefit analysis published in Mayo Clinic Proceedings.<sup>5</sup> Curiously, that risk-benefit analysis was not cited in the CPS position statement.

We will now respond to each point in the Letter.

1. The procedure is safe: A study by CDC researchers of 1.4 million circumcisions in the US collected inpatient data as well as data from “more than 870 000 unique outpatient medical providers”.<sup>6</sup> It documented adverse events for 0.4% for EIMC procedures, similar to rates cited by the AAP’s EIMC policy (0.19% and 0.22% for the US and 0.34% for Israel).<sup>7</sup> In contrast, the CPS selected a rate of 1.5% reported in a meta-analysis of medical and nonmedical circumcisions of newborns, infants and children across 21 countries globally. Adverse event frequency is 10-20 times higher in older children and adults.<sup>6</sup> In the absence of a rate for Canada, US figures should be more relevant than global figures. We agree that severe complications are indeed “incredibly rare.” Using the argument the Letter presents, one would not vaccinate a child either, since doing so, to quote the Letter, “may or may not benefit an individual patient”. Public health recommendations generally accept exposure to small risks if the benefit is substantial.
  
2. Circumcision prevents urinary tract infections (UTIs) in males of all ages: The CPS authors misstate the results of a meta-analysis of MC and UTI risk.<sup>8</sup> That analysis found, “32.1% (95% CI 15.6-49.8) of uncircumcised males experience a [UTI] in their lifetime compared with 8.8% (95% CI 4.15-13.2) of circumcised males (RR 3.65, 95% CI 1.15-11.8)”<sup>8</sup>. Thus, having a foreskin contributes  $(32.1-8.8)/32.1 = 72.6\%$  of lifetime UTI risk in an uncircumcised male UTI patient, 27.4% of the risk being from factors unrelated to the foreskin. Clearly, the CPS statement that, “23% of all UTIs [are] attributed to lack of circumcision”<sup>3</sup> is not accurate. Half of the 22 studies included in that meta-analysis involved urine collection by suprapubic bladder aspiration or urethral catheterization to avoid contamination. The higher UTI prevalence seen in those studies was little different from the relative risk of 9.91 (95% CI 7.49-13.1) for all studies of males in aged 0-1 years.<sup>8</sup> A large US study concluded that, “Although both urine cultures and urinalyses are more accurate in catheterized specimens, the magnitude of difference is small”.<sup>9</sup> The Letter cites a 2005 meta-analysis of EIMC and UTI, but seems unaware of the criticisms levelled at that article by Schoen.<sup>10</sup> The Letter states that UTIs, “can generally be treated with outpatient antibiotics.” But the Cochrane review they cite applied to older children with acute pyelonephritis, not newborns. Of infant males with UTI, 27.6% were hospitalized in a US study, so adding to costs.<sup>11</sup> Most of these UTIs could have been avoided by EIMC.<sup>11</sup> Swabs taken from under the foreskin of boys aged 7 days to 11 years identified 50 bacterial isolates, most multi-drug-resistant strains.<sup>12</sup> The continual rise in antibiotic-resistant uropathogens will further add to hospital admissions and poor clinical outcomes. The meta-analysis of lifetime UTIs used 11 (not 6) studies that included boys aged 1-16 years.<sup>8</sup> Although UTI risk is much higher in the first year of life, UTIs occur in older boys, and at a higher rate if not circumcised. For adult males, we agree that more studies are needed. Nevertheless, the meta-analysis used what data was available, namely that from a convenience sample of men attending a sexually transmitted infections (STI) clinic in Seattle that found 3.46-fold lower UTI prevalence in men who were circumcised. Uncircumcised males of all ages are more likely to harbor subpreputial uropathogenic bacteria. Foreskin swabs taken before MC (at age 2 months to 9 years; mean 5.7 years) contained 72 microorganisms, including 54 gram-positive bacteria (57% Enterococcus species) and 17 gram-negative bacteria (41% Escherichia coli) and Candida species.<sup>13</sup> Swabs from healthy uncircumcised males (mean age 26.5 years) contained a higher proportion of potentially uropathogenic gram negative rods (17%) than in circumcised males (4%).<sup>14</sup> Gram positive cocci, which are less likely to cause UTI, were seen in 62% and 80% of uncircumcised and circumcised males, respectively, while streptococci, strict anaerobes and genital mycoplasmas were only present in the uncircumcised males.<sup>14</sup> A randomized controlled trial (RCT) found that MC significantly reduced the prevalence and load of genital anaerobic bacteria.<sup>15</sup>
  
3. Circumcision prevents STIs: The CPS position statement was prompted in part by concerns about the rise in heterosexually acquired HIV in Canada, especially amongst its indigenous population.<sup>3</sup> The Letter does not dispute the evidence that MC provides substantial protection against heterosexually acquired HIV. Protection against other STIs in heterosexual men: For human papillomavirus (HPV), the recent meta-analysis cited by the Letter concluded that, “MC was strongly associated with reduced odds of genital HPV prevalence”. That meta-analysis treated all types of studies equally, whereas our risk-benefit analysis gave emphasis to RCTs, two meta-analyses, and a large multinational study published in the New England Journal of Medicine in which penile HPV was detected in 19.6% of uncircumcised and 5.5% of circumcised men.<sup>16</sup> After adjustment for age at

first intercourse, lifetime number of sexual partners, and other potential confounders, that study found circumcised men were less likely than uncircumcised men to be infected with HPV (OR 0.37; 95% CI 0.16-0.85).<sup>16</sup> The recent meta-analysis the Letter cites and the publications we cited<sup>2</sup> found MC was associated with reduced infection by high risk HPV types. An RCT in 2012 by Backes et al we cited found a 98% lower incidence of flat penile lesions among circumcised men and that men with, "high HPV16/18/31 [high risk HPV] viral load (OR = 5.2; 95% CI = 1.1-24.4) had higher odds of flat penile lesions". MC does not reduce infection by low risk HPV types responsible for warts, because these infect the shaft and genital area generally, whereas high risk types mostly infect the foreskin and underlying glans.

As for HPV clearance, a RCT found, "circumcised men had a shorter duration of infection of the glans/coronal sulcus".<sup>17</sup> That study found, "The duration of infection did not vary by circumcision status in the penile shaft, scrotum, or all genital sites combined". Thus, clearance is greatest in precisely the area of the penis exposed by MC. A US study found, "circumcision was significantly associated with an increased likelihood of clearance of any HPV infection (HR, 2.7 [95% CI, 1.3-5.7]) and of clearance of oncogenic HPV infection (HR, 3.2 [95% CI, 1.4 -7.4]), but not with an increased likelihood of clearance of nononcogenic HPV infection".<sup>18</sup> The meta-analysis in 2017 by Zhu et al the Letter cites conceded that, "sampling sites also played an important role in the final results", and that, "selection bias in our meta-analysis" (i.e., not taking into account penile sites used for sampling) affected the conclusions. Use of a single combined sample for the penis and scrotum was explained as the reason for a negative result in one study.<sup>19</sup> Thus, MC reduces penile infection and increases clearance of high-risk HPV genotypes.

For genital herpes (HSV-2), the three RCTs found significant decreases of 45%, 30%, and 28% in HSV-2 infection in men after MC, while one found a non-significant decrease of 12% (as cited in our Table<sup>2</sup>). The meta-analysis in 2006 by Weiss et al. that we cited predated the RCTs and found HSV-2 was 15% (OR 0.74–0.98) lower in circumcised men, after adjustment for confounding factors.

RCTs and other studies we cited<sup>2</sup> found approximately 50% lower syphilis, chancroid, genital ulcer disease, *Trichomonas vaginalis* and *Mycoplasma genitalium* rates among circumcised men. Genital ulcers of uncircumcised men contain a higher prevalence of anaerobic bacteria. RCT data showed that MC reduces total bacterial load and microbiota biodiversity.<sup>15</sup> The meta-analysis in 2006 by Weiss et al. that we cited found syphilis was 33% lower in circumcised men. Although an RCT by Tobian et al. cited in the Letter did not find a reduction in syphilis, this may have resulted from lack of power due to the small number of syphilis infections identified on follow-up testing.<sup>20</sup> The lead author of that RCT, Aaron Tobian, in an editorial covering another large study we cited that found 42% lower syphilis in circumcised men,<sup>21</sup> acknowledged that MC does reduce syphilis risk.<sup>22</sup> It is well-known, and unsurprising, that MC does not prevent sexually transmitted urethritis in men.

Protection against STIs in women: Findings on the impact of MC on STIs in women are mixed. For HPV, one might expect that by lowering high risk HPV infection in men, MC would reduce infection in women, and thus cervical dysplasia, which can progress to cervical cancer. In the large multinational study referred to in the Letter, Castellsague et al stated, "to minimize confounding as a result of the women's having had male partners other than the current partner, [they] restricted the analysis to 1420 men whose female partner reported having had only one sexual partner".<sup>16</sup> Contrary to the Letter, monogamous women whose male partner had either a high or an intermediate "sexual-behavior risk index" (n = 374 and 511, respectively) were more likely to have had a cervical cancer diagnosis (OR 0.18 [95% CI 0.04-0.89] and 0.50 [95% CI 0.27-0.94], respectively). A RCT found the prevalence and incidence of high-risk HPV after 2 years were, respectively, 28% and 23% lower among women with circumcised male partners than women with uncircumcised partners.<sup>23</sup>

The Letter makes the inaccurate claim that "routine" HPV vaccination, "is almost 100% effective in preventing acquisition of high risk [HPV] genotypes". In fact, current HPV vaccines are directed at only the two most common genotypes (HPV16 and HPV18) of over 14, high risk HPV genotypes. These two genotypes are found in approximately 70% of cervical cancers. In Canada, there was a 69% decrease in cervical intraepithelial neoplasia type 2 in girls under the age of 18 years who had been fully vaccinated by having received three doses of the quadrivalent HPV vaccine (see Figure 3C in a recent systematic review of real-world experience with HPV vaccination<sup>24</sup>). In Australia, one of the earliest countries to vaccinate girls (in early high school), there was an 86% decrease in vaccine genotypes (HPVs 6, 11, 16 and 18).<sup>24</sup> Thus, vaccination is not "almost 100%" effective. Moreover, as with other public health interventions, a package of multiple preventive measures is likely to have a greater impact than vaccination alone.

For genital herpes, the Pittsburgh study referred to in the Letter found HSV-2 was twice as high in women who had ever had intercourse with an uncircumcised man (OR 2.2; 95% CI 1.4-3.6; n = 1,207). Similarly, a RCT found

2-fold higher HSV-2 infection over 12 months in 783 wives of uncircumcised men.<sup>25</sup> But one RCT failed to find a significant decrease in HSV-2 acquisition by the female partners of circumcised men.

MC may also protect women against some other STIs. A RCT found women with circumcised male partners had 22% lower genital ulcer disease, 40% lower overall bacterial vaginosis, 61% lower severe bacterial vaginosis, and 48% lower *Trichomonas vaginalis*, but no difference in dysuria or vaginal discharge.<sup>25</sup> A large prospective cohort study of 2,946 HIV-negative couples found syphilis was 75% lower in the female partners of circumcised men.<sup>21</sup> A large multinational study found chlamydia trachomatis seropositivity was 5.6-fold higher in women with an uncircumcised partner.<sup>26</sup> The finding also applied to women who had only had one sexual partner. Prevalence of *C. pneumoniae*, which is not transmitted sexually, did not differ. The authors suggested that infected cervicovaginal secretions may be trapped under the prepuce for longer in uncircumcised men, increasing risk of penile urethral infection and transmission to the vagina during sex.<sup>26</sup> A prospective study in Uganda, Zimbabwe and Thailand found no difference in chlamydial, gonococcal or trichomonal infections in women as a function of MC status.

Protection against STIs in men who have sex with men [MSM]: It is implausible that MC could protect MSM against HIV infection during receptive anal intercourse with another man. Most MSM engage in this form of anal intercourse, perhaps explaining the overall negative finding from the meta-analysis the Letter cites. The meta-analysis and other work showed that MC protected those MSM who predominantly adopted an insertive role during anal intercourse. MC provided 57% protection against the major oncogenic HPV type, HPV16.<sup>27</sup> MC protected against incident syphilis (HR 0.35; 95% CI 0.15-0.85), particularly in the one-third of MSM who engaged predominantly in insertive anal intercourse (HR 0.10; 95% CI 0.01-0.81).<sup>28</sup> The authors suggested a reason for absence of association with, "prevalent (baseline)" syphilis was because, "Syphilis was ... virtually eliminated [in Australia] during the late 1980s and 1990s," so "One possible explanation for an association with incident but not prevalent syphilis is that participants who initiated MSM sexual activity during the late 80s and 90s would have been at very low risk of acquiring syphilis ... irrespective of their circumcision status," and that, "Only ... since 2001, has syphilis re-emerged in Australian MSM".<sup>28</sup>

4. Circumcision prevents male cancers: Phimosis is the primary risk factor for penile cancer, increasing risk 12-fold in the meta-analysis we cited in the discussion of our critique.<sup>2</sup> The authors of the Letter might agree that EIMC eliminates lifetime risk of phimosis. Other factors influenced by EIMC – balanitis and smegma – increased penile cancer risk 3.8-fold and 3.0-fold, respectively, in the meta-analyses we cited.<sup>2</sup> Our critique cited a meta-analysis that found 47% of penile cancers are positive for high risk HPV genotypes. Since HPV genotypes prevented by current HPV vaccines constitute approximately 70% of population prevalence of all high-risk HPV genotypes, one might predict that HPV vaccination offers the potential to reduce penile cancer by  $47 \times 0.7 = 33\%$ . This level of risk reduction is comparable to that conferred by MC. An early concern was that over time non-vaccine HPV genotypes might replace vaccine genotypes.<sup>29</sup> There is now evidence for this. Eight years after introduction of the HPV vaccination program for girls in Australia, although prevalence of HPV 16 and 18 decreased in heterosexual men from 13% to 3% ( $p < 0.0001$ ), there was no decrease in HPV genotypes overall, and, "prevalence of non-vaccine-targeted genotypes" increased from 16% to 22% ( $p < 0.0001$ ).<sup>30</sup> Regardless, all measures should be advocated for genital cancer prevention.

For prostate cancer, it was reasonable that the meta-analysis in 2015 by Pabalan et al we cited reduced heterogeneity by removing outlier studies. This study showed prostate cancer was significantly lower in circumcised men, especially in the post-PSA testing era ( $p = 0.01$ ). In Blacks, recent large Canadian and US studies we cited showed risk reductions of 60% (95% CI 0.19-0.86) and 36% (95% CI -8-61), respectively. MC prevalence worldwide is inversely correlated with prostate cancer incidence.<sup>31</sup> Countries with high MC prevalence have lower prostate cancer-related mortality, corrected for potential confounding factors.<sup>32</sup> In the US, in the absence of MC there would be 24%-40% more cases of prostate cancer and US \$0.8-1.1 billion extra in costs for treatment and terminal care per year.<sup>33</sup> The risk reduction associated with MC is similar to that from other commonly recognized risk factors.

5. Circumcision prevents other sequelae: Phimosis, balanitis and candidiasis were noticeable omissions from the CPS Table of benefits.<sup>3</sup> Each of these conditions often occur alone, but can occasionally co-occur. The Letter recognizes that meta-analyses represent high quality evidence, so it seems odd that it objects to a meta-analysis we cited that found 68% lower balanitis in circumcised males. For penile candidiasis, we cited a large Australian survey by Ferris et al in which 7.7% of uncircumcised men and 4.9% of circumcised men reported this condition. In boys aged 8 months to 18 years (mean 6.4 years) prevalence of fungal infection was 44% in

uncircumcised boys, compared with 18% in circumcised boys.<sup>34</sup> The fungal species were, in order of decreasing prevalence: *Malassezia globosa*, *M. furfur*, *M. slooffiae*, *C. albicans*, *C. tropicalis* and *C. parapsilosis*. Each was present in uncircumcised infants, but none in circumcised infants. A gradual accumulation with age occurred, increasing by age 18 years to 62.5% in uncircumcised boys versus 37.5% in circumcised boys. Annual incidence of *C. albicans* globally is approximately 400,000 and most cases occur in economically developed regions.<sup>35</sup> Crude (42%) and attributable (27%) mortality rates are very high.<sup>35</sup> Infected individuals are less able to mount a cytokine response to limit the damage caused by the *C. albicans* peptide toxin candidalysin, whereby hyphae (filamentous structures of yeast) breach the epidermal barrier of the host cell.<sup>36</sup> Recently, a strong direct link has been found between *C. albicans* antibodies and schizophrenia in men, independent of potential confounders.<sup>37</sup>

6. Circumcision is cost-effective: US studies we cited have confirmed that EIMC is cost-saving. Cost-saving should also apply in Canada.

7. The CPS statement is discordant with others: The current positions of the AAP and CDC favoring MC led to hostile responses from MC opponents via publication of critiques that presented contrary “evidence”, social media campaigns, and picketing of AAP conferences and the home of the Chair of the AAP Task Force. The AAP’s recommendation was as affirmative as might be formally stated in the current era of radical individualism, devaluation of scientific evidence, and promotion of autonomy, where even life-saving childhood vaccines may be refused by parents. An article in AAP News suggested that the AAP policy may require US pediatricians to modify their discussions about newborn health interventions with parents, since “physicians sometimes can be held accountable for harm that results from not telling patients about an available medical treatment or procedure.”

The Letter quotes from the AAP policy, but omitted the subsequent sentence, namely that, “It is important that clinicians routinely inform parents of the health benefits and risks of male newborn circumcision in an unbiased and accurate manner”. We fully support this position. In contrast, the CPS position statement does not present, “a balanced view to parents”.

As for the Letter’s accusation of conflict of interest, our cover letter that accompanied our manuscript stated, “It should be noted that two of the three Canadian authors (P. Crouse and N. Pollock) and one US author (J. Krieger) have a potential conflict of interest owing to the fact that they derive income from circumcision as part of their clinical work.” All medical procedures, including vaccinations, generate income for providers. We can therefore understand why the journal may not have thought it necessary to publish our disclosure.

The Letter mentions three deaths from EIMC in Canada over the past 15 years, but not the three deaths attributed to vaccination in Canada over a 15-year period.<sup>38</sup> Deaths from MC are extremely rare, but failure to circumcise can lead to deaths in infancy (see ref 47 in our Table<sup>2</sup>) and over the lifespan, where the Letter mentions, “40 [actually 43] deaths annually in Canada” from penile cancer,<sup>39</sup> a disease seen almost exclusively in uncircumcised men. A proportion of the 3,708 annual deaths in Canada from prostate cancer and 443 from cervical cancer<sup>39</sup> would likely have been avoided by EIMC.

In conclusion, we find the Letter by Robinson et al is one-sided. Scholarly evaluation of the literature leads us to reject many of the claims it makes. Our risk-benefit analysis withstands scrutiny. In the interests of its constituents, other medical practitioners, allied health professionals and parents, the CPS should have presented a proper risk-benefit analysis and should now issue a revised position statement based on the high-quality evidence that is currently available.

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