

Effect of HPV on cervical cancer screening in Alberta

Kim and colleagues evaluated the dose-stratified effectiveness of the quadrivalent human papillomavirus (HPV) vaccine on reduction of cervical abnormalities in Alberta, using a nested case-control approach in data linked between the Alberta Health Care Insurance Plan and the Alberta provincial immunization repository.¹ As expected, the authors found strong protection against high-grade cervical abnormalities among women who received three doses. The data appear to indicate similar protection conferred by one and two doses (odds ratio [OR], 0.45 and 0.17, respectively), albeit with nonsignificant effect estimates, given the small case counts in these dose groups. Yet, the authors concluded that three doses were required for HPV vaccination to reduce high-grade cervical abnormalities. When we conducted an analysis of their results by combining women who received one or two HPV doses, significant protection against high-grade cervical abnormalities was seen (crude OR 0.29, 95% confidence interval [CI] 0.09–0.93] when the controls were defined as normal cytology results).

We also have concerns about the study methods in Kim and colleagues' article. First, no HPV genotyping data were available (as is usually the case for these types of linkage studies). This is more problematic for outcomes such as low-grade squamous intraepithelial lesions and abnormal squamous cells of undetermined significance, where carcinogenic types other than HPV16/18 contribute to a great proportion of lesions.^{2,3} The data in their study indicated that vaccine effectiveness was greater with a high-grade endpoint, rather than with the less progressed endpoint(s).

Second, there was a lack of data about age at vaccination and covariates that might reflect prevaccination HPV exposure. Evaluation of age at first vaccination by dose group should

have been possible because vaccination data were obtained from a provincial immunization repository. If reduced-dose recipients are systematically older or have an earlier age at sexual debut, they likely have more prevalent HPV infections at the time of vaccination that artificially lower the estimated effectiveness. A dose-specific analysis by time since vaccination, or application of a buffer period before case counting, could address this concern. Other published studies of post-licensure vaccine effectiveness by number of doses have had similar limitations.^{4,5}

In conclusion, Kim and colleagues state that three doses were required for the vaccine to be effective against cervical abnormalities, thereby raising concerns about the effectiveness of reduced doses of HPV vaccination. We believe that this conclusion does not reflect the study data and that the inherent limitations in record linkage studies to address HPV vaccine effectiveness by dose were not adequately addressed. Further, the growing body of evidence from post-hoc analyses nested in trial settings continue to suggest that two doses (maybe even one) protect as well as three doses, at least in the short term.^{6,7}

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References

1. Kim J, Bell C, Sun M, et al. Effect of human papillomavirus vaccination on cervical cancer screening in Alberta. *CMAJ* 2016;188:E281-8.

2. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer* 2012;131:2349-59.
3. Clifford GM, Rana RK, Franceschi S, et al. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1157-64.
4. Herweijer E, Leval A, Ploner A, et al. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. *JAMA* 2014;311:597-603.
5. Blomberg MR, Dehlendorf C, Sand C, et al. Dose-related differences in effectiveness of human papillomavirus vaccination against genital warts: a nationwide study of 550,000 young girls. *Clin Infect Dis* 2015;61:676-82.
6. Kreimer AR, Rodriguez AC, Hildesheim A, et al. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. *J Natl Cancer Inst* 2011;103:1444-51.
7. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. *Lancet Oncol* 2015;16:775-86.

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Functional impairment, not FASD

The publication of new guidelines for fetal alcohol spectrum disorder (FASD) raises concerns about the ongoing push for FASD-specific assessment and support programs.¹ Many children present with evidence of pervasive brain dysfunction who do not have FASD. Current developmental practice emphasizes interaction of function and environment, not etiologic labels.²

FASD is clinically indistinguishable from other causes of neurobehavioural disorders (e.g., antenatal alcohol or other teratogens, complex trauma, genetic).³ Treatment for neurobehavioural disorders is nonspecific (e.g., environmental supports) and based on function (e.g., cognitive, memory, executive, self-regulation). Emphasizing an etiologic label with no specific treatment is misleading to the public and unethical.

Function-based, nonmedical diagnosis-specific services are compatible with a vigorous public health program in preventing antenatal alcohol exposure. Basing resources on an etiologic label marginalizes individuals with neurobehavioural disabilities without a unifying diagnostic label.

FASD-specific programs will increase wasteful diagnosis-seeking behaviour (as seen in autism spectrum disorder). A universal FASD-specific diagnostic program based on current guidelines is not tenable⁴ and emphasizes the question of qualification for an FASD diagnosis, which is of low practical clinical relevance. The label of FASD carries potential harm to many through stigmatization and prejudice, particularly for those who are in the “at risk of FASD” category.⁵ Ironically, FASD-specific programs will exclude many who are affected by antenatal alcohol but do not meet the criteria.

There is no good quality evidence indicating a need to diagnose children early with FASD (as opposed to diagnosing function-based problems). We need equitable, nonetiologic diagnosis-based services for all people with neurobehavioural disorders. Prioritization for assessment and intervention programs should be based on severity of functional disability, not on etiology. Diagnosticians need to focus on functional impairment rather than often futile (and sometimes damaging) attempts to attribute causality.

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References

1. Cook JL, Green CR, Lilley CM, et al., for the Canada Fetal Alcohol Spectrum Disorder Research Network. Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan. *CMAJ* 2016;188:191-7.
2. Rosenbaum P, Gorter JW. The ‘F-words’ in childhood disability: I swear this is how we should think! *Child Care Health Dev* 2012;38:457-63.
3. Malone M, Koren G. Alcohol-induced behavioural problems in fetal alcohol spectrum disorders versus confounding behavioural problems. *J Popul Ther Clin Pharmacol* 2012;19:e32-40.
4. Goulden KJ. Are FASD guidelines practical and sustainable? *CMAJ* 2005;173:1070-1.
5. McLennan JD. Alcohol-exposed? Next. *CMAJ* 2015;187:682-3.

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Incentive payments: the correct lesson

Lavergne and colleagues found that incentive payments to primary care physicians for the care of patients with complex disease had no impact on health care outcomes.¹ That’s an

important finding, but the wrong lesson is easily drawn from it.

The correct lesson is not that incentives do not work, but that incentives alone do not work. The key is contained in the first paragraph of their methods section: “British Columbia retained the fee-for-service payment system and made no structural changes to primary care provision, such as the introduction of team-based models of practice.”¹ Our team studied the introduction of incentive payments statewide in Michigan and found substantial reductions in presentation to emergency departments, admission to hospital and cost.² However, that incentive program was implemented with explicit ties to the medical home model. It also included supports such as learning collaboratives to aid practices in transformation.

Incentives are necessary, but they’re not sufficient. This point must be made clear to policy-makers, lest they make the error of discarding incentives rather than connecting them to the structures needed to make them work.

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References

1. Lavergne MR, Law MR, Peterson S, et al. A population-based analysis of incentive payments to primary care physicians for the care of patients with complex disease. *CMAJ* 2016 Aug. 15 [Epub ahead of print]. DOI:10.1503/cmaj.150858.
2. Paustian ML, Alexander JA, El Reda DK, et al. Partial and incremental PCMH practice transformation: implications for quality and costs. *Health Serv Res* 2014;49:52-74.

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Assisted dying for patients with psychiatric disorders

The article by Kim and Lemmens contains several important errors and omissions.¹

First, it was Carter, not just the Parliamentary Special Joint Committee on Physician-Assisted Dying, that stated that patients are not required to accept all treatments to be considered “irremediable.”²

Second, the authors failed to reference the judgement from the E.F. case, heard by the Alberta Court of Appeal, which confirmed that Carter neither

requires that death be “reasonably foreseeable” nor excludes people with primary psychiatric illness.³ E.F. was granted access to medical assistance in dying (MAID) by three judges, based exclusively on a psychiatric diagnosis.

Third, Kim and Lemmens reference a study stating that “most” patients with depression achieve remission if given high-quality treatment; however, that “most” was only 60.2%.⁴ We cannot ignore the remaining 39.8%.

Finally, the authors imply that MAID in refractory mental illness would only be acceptable with a zero error rate. Nowhere else in medicine do we require zero risk of error. Unnecessary deaths are tragic; yet so is the counterpart: ceaseless unbearable pain, deplorable quality of life, and loss of self. It is not MAID, but rather denying MAID, that puts “many vulnerable and stigmatized people at risk.” Without MAID, the most irremediable but competent patients would be consigned to years of suffering or a horrific death by suicide.

We must recall the intent of Carter and should trust doctors and patients to make careful decisions, collaboratively, that honour patient autonomy and reduce suffering in the most ethical manner.

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Competing interests: Derryck Smith is a board member of The Committee of the World Federation of Right to Die Societies, and both authors are members of the Physician Advisory Council, Dying With Dignity Canada.

References

1. Kim S, Lemmens T. Should assisted dying for psychiatric disorders be legalized in Canada? *CMAJ* 2016;188:E337-9.
2. *Carter v. Canada (Attorney General)* 2015 SCC 5. Available: <https://scc-csc.lexum.com/scc-csc/scc-csc/en/item/14637/index.do> (accessed 2016 July 11).
3. *Canada (Attorney General) v E.F.* 2016 ABCA 155 (CanLII). Available: www.canlii.org/en/ab/abca/doc/2016/2016abca155/2016abca155.html (accessed 2016 July 11).
4. Fekadu A, Rane LJ, Wooderson S et al. Prediction of longer-term outcome of treatment-resistant depression in tertiary care. *Br J Psychiatry* 2012; 201:369-75.

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