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Association of prior HPV vaccination with reduced preterm birth: A population based study

Beverley Lawton [a,*], Anna S. Howe [b], Nikki Turner [b], Sara Filoche [c], Tania Slatter [d], Celia Devenish [e], Noelyn Anne Hung [d]

[a] Centre for Women's Health Research, Faculty of Health, Victoria University of Wellington, New Zealand
[b] Department of General Practice and Primary Care, University of Auckland, New Zealand
[c] Department of Obstetrics and Gynaecology and Department of Pathology and Molecular Medicine, Department of Obstetrics and Gynaecology, University of Otago, Wellington, New Zealand
[d] Department of Pathology, University of Otago Dunedin School of Medicine, University of Otago, New Zealand
[e] Children's and Women's Health, University of Otago Dunedin School of Medicine, University of Otago, New Zealand

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ABSTRACT

Background: Emerging evidence suggests that HPV infection is associated with negative pregnancy outcomes such as preterm birth (PTB), and pre-eclampsia. We aimed to determine if prior HPV vaccination reduced adverse pregnancy outcomes.
Methods: A New Zealand population-based retrospective study linking first pregnancy outcome data (2008–2014 n = 35,646) with prior quadrivalent HPV vaccination status. Primary outcomes were likelihood (odds ratios, ORs) of PTB, pre-eclampsia, and stillbirth. Exposure groups were based on HPV vaccination. Adjusted ORs were calculated for each outcome, controlling for mother's age at delivery, ethnicity, socioeconomic status, health board region at time of delivery, and body mass index and smoking status at time of registration with maternity care provider.
Results: Mother's mean age at delivery was 19 (SD 2.1) years. Of 34,994 the pregnancies included in the final study analyses 62.3% of women were unvaccinated, 11.0% vaccinated with one or two doses and 27.7% vaccinated with three doses prior to pregnancy. PTB (OR: 0.87; CI 0.78, 0.96)) was significantly lower for women who previously received the HPV vaccine. A dose response effect was found with each successive dose received decreasing the likelihood of PTB. No associations between the vaccinated and unvaccinated groups were shown for pre-eclampsia or stillbirth.
Conclusions: Prior receipt of the quadrivalent HPV vaccine was associated with a significant reduction in PTB (13%); suggesting that HPV vaccination may be effective in reducing PTB. The potential global public health impact is considerable and there is urgency to undertake further research to replicate and explore these findings.

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1. Background

Human papilloma virus (HPV) is one of the most common sexually transmitted infections in the world [1,2]. Persistent infection with oncogenic HPV types is associated with an increased risk of cervical and other cancers (including anal, penile, oropharyngeal and vaginal/vulvar) causing an estimated 5.2% of the total global cancer burden (approximately 7.7% and 2.2% of all cancers in developing and developed countries, respectively) [2].

There is an emerging body of evidence that suggesting HPV infection may be associated with adverse delivery outcomes [3]. Some observational evidence suggests that HPV infection both of the cervix and and/or the upper female genital tract may be associated with negative pregnancy outcomes including miscarriage [4,5], preterm birth (PTB) [6–8], pre-clampsia [9,10] and that vertical transmission of HPV to the fetus can occur [11]. HPV infection, has been found in the placentas of pregnancies that have resulted in PTB [12]. Histological abnormalities, including acute chorioamnionitis and lymphohistiocytic villitis in association with placental HPV infection (including HPV types 16 and 18) have also been observed in adverse pregnancy outcomes including PTB and

* Corresponding author.
E-mail addresses: bev.lawton@vuw.ac.nz (B. Lawton), a.howe@auckland.ac.nz (A.S. Howe), n.turner@auckland.ac.nz (N. Turner), sara.filoche@otago.ac.nz (S. Filoche), tania.slatter@otago.ac.nz (T. Slatter), celia.devenish@otago.ac.nz (C. Devenish), noelyn.hung@otago.ac.nz (N.A. Hung).

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pre-eclampsia [12]. This is a new and promising area of work. Studies are preliminary and still limited by small cohort number [6] with retrospective [8] and cytological [9] methodology rather than prospective HPV testing. Nevertheless collectively, they suggest there may be biologic plausibility to HPV infection being associated with adverse pregnancy outcomes and this provides the rationale for this present investigation.

PTB and pre-eclampsia are associated with substantial morbidity and mortality worldwide and significant public and personal health costs [13]. PTB alone is the leading cause of perinatal morbidity and mortality in developed countries and accounts for approximately 75% of neonatal mortality and 50% [14] of long term neurological disability in children [7,14]. Of the 3.98 million births in the USA in 2015, 9.63% were PTBs (approximately 380,000) with marked racial disparities (non-Hispanic black (14.71%) non-Hispanic white (8.88%) [15]. Globally PTB accounts for 965,000 neonatal deaths annually and 125,000 deaths in children aged between one and five years [16]. Any intervention that reduces PTB by even a small percentage is liable to accrue major global health benefit [16]. Therefore if HPV virus infection is a co-factor contributing to these globally-significant adverse pregnancy outcomes there is potential for prior HPV vaccination to mitigate these outcomes. New Zealand (NZ) has the ability to investigate this question with a standardised national vaccination programme, national immunisation register, standardised maternal outcomes databases and a unique patient identifier.

NZ introduced a three dose regime of HPV vaccination for females with the quadrivalent vaccine Gardasil® containing virus-like particles derived from HPV vaccine types 6, 11, 16 and 18 from 1 September 2008. The vaccine was initially offered to all females born in 1990 and 1991 (i.e. 17 and 18 years old) then extended in 2009 to all females born from 1992 onwards. Since 2011 the programme has been offered primarily in school year 8 (aged around 11 years), with catch up in primary care for all young women up the age of 20 years. All immunised individuals are entered on the NZ National Immunisation Register (NIR) [17].

This study uses linked national databases to investigate the hypothesis that prior vaccination with the quadrivalent HPV vaccine reduces adverse pregnancy outcomes.

2. Material and methods

A national retrospective cohort study was conducted using routinely collected maternity data, which was linked to individual level information on maternal HPV vaccination status and delivery outcome. This study is reported as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[18] An overview of the study showing data sources, variables, and inclusion and exclusion criteria is shown in Fig. 1.

2.1. Ethical approval

Ethical approval for this study was granted by the Health and Disability Ethics Committee of New Zealand (16/NTA/43). All data were non-identifiable, and individual informed consent from participants was not required.

2.1.1. Inclusion criteria

The study population comprised women whose date of birth was on or after 1st January 1990, were eligible to have received funded HPV vaccination, and subsequently became pregnant and sustained the pregnancy to at least 20 weeks' gestation and/or delivered an infant weighing at least 400 grams. For each woman only the first pregnancy following her eligibility to receive HPV vaccine was considered. Only singleton pregnancies were included.

2.1.2. Exclusion criteria

Women were excluded if their record stated an alternative had been given, the vaccine was administered overseas, if the vaccine had been provided before June 2008, or if women were pregnant between receipt of HPV vaccine dose 1 and 3. Women were also excluded if they had received multiple doses in one day, a dose less than 3 weeks after the previous dose, or if they had received more than three doses (n = 1450). Women with missing data regarding the primary outcome of interest were excluded from the final analyses.

2.2. Data sources and linking

Data were collected from three nationally held health collections [19]: the Maternity Collection (MAT) which comprises records about all pregnancies that are sustained to at least 20 weeks gestation and/or result in an infant weighing at least 400 g the National Immunisation Registry (NIR which comprises records of HPV vaccination given since June 2008 including vaccine antigen, vaccination date and dose number; and the National Minimum Dataset (NMDS) which comprises records of all public hospital discharges, including records of delivery events and ICD-10-AM discharge diagnoses (Fig. 1). Study personnel linked data using an encrypted National Health Index number (NHI number), present in each collection and it is a unique identifier assigned to every person who uses health and disability support services in NZ [19]. The NHI number was encrypted by the NZ Ministry of Health (MOH) across each of the data sources using a unique key for each woman. The ICD codes were deemed associated with the pregnancy if they were recorded as being between the date of last menstruation (LMP) and date of delivery (inclusive). HPV immunisation prior to pregnancy was based on being prior to LMP; and during pregnancy as having occurred between LMP and date of delivery.

2.3. Primary outcomes

The primary outcomes of interest were PTB, defined as delivery before 37 weeks' completed gestation (ICD-10-AM codes P072 and P073), pre-eclampsia (ICD-10-AM codes P00.0, O13, and O14), and delivery outcome (ICD-10-AM codes Z37.0 (live born) and Z37.1 (stillborn)). All outcomes were coded as 0 'did not have the outcome' or 1 'had outcome of interest'.

2.4. Exposure

HPV vaccine was identified in the NIR dataset by the antigen 'Human Papilloma Virus vaccine'.

2.4.1. Confounders

Major risk factors (confounding variables) available from the MAT dataset included in analyses were: maternal age, socio-economic status (SES) as area deprivation [20], ethnicity, health board region of residence (to account for variations in vaccine coverage), and body mass index and smoking status at the time of booking (registration) with a maternity care provider. It is important to note that maternal ethnicity is not a risk per se, but a potential marker of differential exposure to risk factors.

Maternal age was calculated based on age at the time of delivery. Area deprivation at the time of delivery was based on the mother's place of residence using the NZ Deprivation Index (NZDep06) [20] and derived from the maternity dataset. NZDep06 combines nine variables from the 2006 NZ census which reflect

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