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Title: Trends in the diagnosis of high grade cervical abnormalities in young women in the post vaccination era

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Sponsor: Cancer Society of New Zealand, Canterbury-West Coast Division Inc., Cancer Society Ashburton and Ellesmere Groups

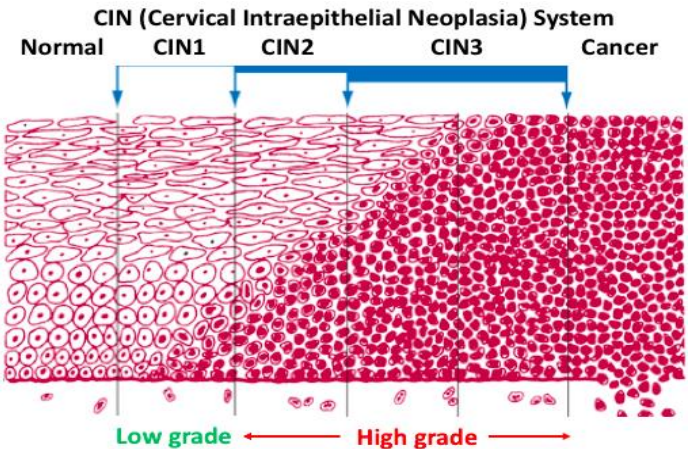
Introduction:
The Human papilloma virus or HPV, is the main cause of abnormalities in the cells that line the cervix. There are more than 100 different types of HPV, of which around 40 can affect the cervix. HPV infections are also very common. In most women, infection is only associated with low grade changes, and clears up naturally. In some women, the infection can persist, and cause high grade changes, which if untreated, can potentially progress to cervical cancer. Regular cervical screening, which currently starts at age 20 in New Zealand, helps detect these changes using a cervical smear, following which the person is referred to a clinic where they may take a biopsy.

There are two types of 'high risk' HPVs, HPV 16 and 18, that cause the majority of cervical cancers and a vaccine was developed that offered protection against these two types. In late 2008, a catch-up programme was started that offered this vaccine to girls born in 1990 and 1991 (aged 17 and 18) via secondary schools and GPs. The following year, a school based immunisation programme was started targeting girls in year 8 (aged 11-13), and the catch up programme was also extended to include girls in years 9 to 13 (born from 1992 onwards), to extend immunisation's benefits to these girls. This catch up programme ceased in 2010. Since 2010, around 55% of girls have been immunised. The reason this study is being done now is because these young women who were vaccinated, started entering cervical screening around 2012/13 onwards, and it is from this point onwards that abnormal changes will be picked up via screening. We predict that due to vaccination these changes would be reducing over time.

Aim and Impact:
The aim is to identify all women aged 20-24 at participating clinics from 2013 to 2017 and examine the burden of high-grade disease. Doing so will give us information about the real-life impact of the HPV vaccination program in New Zealand for which currently there is little published information. Furthermore, due to changing screening recommendations, women under 25 will not be screened in the future, and hence it's important to document the current disease load in women under 25 before screening ceases for these women.

Method:
We collected, de-identified and combined data from clinics that serve 3 DHBs.

The main outcome we are interested in, is that for each woman, what was her worst grade of cell abnormality, based on a biopsy result. A biopsy is a small sample of tissue from the cervix that is graded as low or high grade depending on how much of its thickness is



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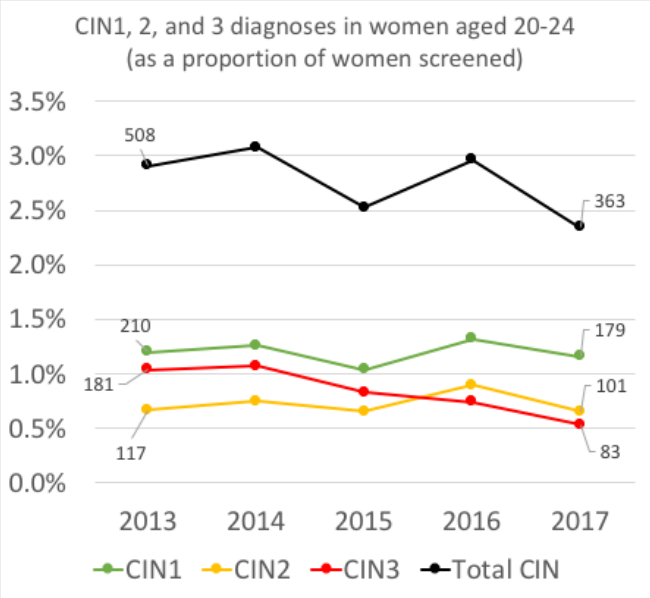
affected by abnormal cells. If up to a third of the layer is affected, it is called CIN1, which is considered low grade, and if two thirds or the entire layer is affected, it is called CIN2, and CIN3 respectively, both of which are considered high grade.

Results:
Our study sample consisted of 3,404 women, most of whom had been referred to a clinic due to an abnormal screening smear, and they provided 2,304 biopsies that ranged from low to high grade.

This graph below shows the proportion of women screened that have CIN1, 2, and 3, as well as the total of all 3 CIN types (Total CIN) over time. This was done by dividing the number of CIN1, 2 and 3 diagnoses per year by the number of women screened per year. The actual number of diagnoses are also shown for the start and end of the study period e.g. there were 210 cases of CIN1 in 2013.



Starting with total CIN, there was a 21% reduction in the proportion of women screened who were diagnosed with CIN from 2013 and 2017. This reduction in total CIN was mainly caused by a 48% reduction in the proportion of women screened with CIN3. Both decreases in total CIN and CIN3 were statistically significant. For CIN1 and CIN2 there was no significant decrease.

Other findings include a 17% reduction in the number of abnormal screening smears from 2013 to 2017. When comparing Maori and NZ European with a CIN diagnosis, the CIN3 proportion in Maori was 37% compared to 29% in NZ European, despite Maori women having a higher vaccination coverage than NZ European women. It was also possible to get the vaccination status for a subset of women in the Canterbury cohort. In women with a CIN diagnoses, Unvaccinated women had a higher proportion of CIN3 (35 vs 19%), and a lower proportion of CIN1 (38 vs 50%) compared to vaccinated. There was no difference in CIN2 (27 vs 31%).

Conclusion:
There was a large drop in the proportion of screened women with CIN3, which was reassuring. This drop is most likely due to vaccination preventing infection with types 16 and 18 and indicates that it is indeed reducing the burden of high grade disease. Reasons for seeing a bigger drop in CIN3 compared to CIN2 lesions include the fact that CIN3 lesions are more likely to be associated with types 16/18 and less likely to be associated with other high risk cancer causing types, such as types 31, 33 and 52. Even though CIN2 is also associated with types 16/18, many women have infections with multiple HPV types, like 31 and 33, which are not covered by the vaccine, which could be contributing to why CIN2 is not reducing. As for CIN1, low grade infections are less strongly associated with types 16/18 and all of the HPV types that affect the cervix, can cause low grade changes, which could explain why CIN1 is not reducing.

Despite vaccination rates being higher in Maori, the proportion of CIN3 in Maori women remains high, and this requires further research.