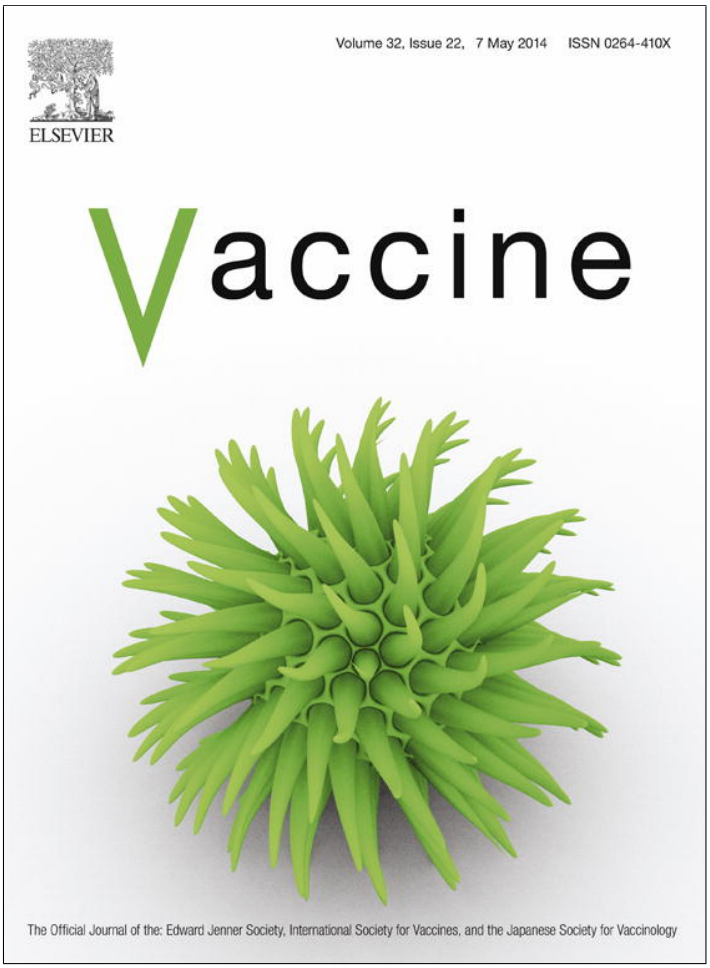

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# Cost-effectiveness and equity impacts of three HPV vaccination programmes for school-aged girls in New Zealand

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ABSTRACT

*Background:* As with many high-income countries, vaccination coverage against human papilloma virus (HPV) infection is not high in New Zealand (NZ) at 47% in school-aged girls for three doses. We estimate the health gains, net-cost and cost-effectiveness of the currently implemented HPV national vaccination programme of vaccination dispersed across schools and primary care, and two alternatives: school-based only (assumed coverage as per Australia: 73%), and mandatory school-based vaccination but with opt-out permitted (coverage 93%). We also generate estimates by social group (sex, ethnic and deprivation group).

*Methods:* A Markov macro-simulation model was developed for 12-year-old girls and boys in 2011, with future health states of: cervical cancer, pre-cancer (CIN I–III), genital warts, and three other HPV-related cancers (oropharyngeal, anal, vulvar cancer). In each state health sector costs, including additional health sector costs from extra life, and quality-adjusted life years (QALYs) were accumulated.

*Results:* The current HPV vaccination programme has an estimated cost-effectiveness of NZ$18,800/QALY gained (about US$9700/QALY gained using the OECD's purchasing power parities; 95% UI: US$6900 to $33,700) compared to the status quo in NZ prior to 2008 (no vaccination, screening alone). The incremental cost-effectiveness ratio (ICER) of an intensive school-based only programme of girls, compared to the current situation, was US$33,000/QALY gained. Mandatory vaccination appeared least cost-effective (ICER compared to school-based of US$117,000/QALY gained, but with wide 95% uncertainty limits from $56,000 to $220,000). All interventions generated more QALYs per 12-year-old for Māori (indigenous population) and people living in deprived areas (range 5–25% greater QALYs gained).

*Interpretation:* A more intensive school-only vaccination programme seems warranted. Reductions in vaccine price will greatly improve cost-effectiveness of all options, possibly making a law for mandatory vaccination optimal from a health sector perspective. All interventions could reduce ethnic and socioeconomic disparities in HPV-related disease.



## 1. Introduction

There is widespread acceptance that human papilloma virus (HPV) vaccination of adolescent girls, regardless of setting, is cost-effective [1,2]. Existing economic evaluations of HPV vaccination have addressed issues such as bivalent versus quadrivalent vaccines [2], inclusion of multiple future diseases (e.g., cancers other than cervical cancer, anogenital warts and cervical intraepithelial neoplasia states) [2,3], cross-protection [4], the marginal impact of vaccinating boys [2], and interacting effects with cervical screening programmes [5–7]. This paper presents disease modelling and economic evaluation of a quadrivalent vaccine using a multiple disease model for New Zealand, with a particular focus on two issues not yet well addressed internationally: (i) variation in health gains, costs and cost-effectiveness by socioeconomic and ethnic groups, and hence quantifying the impact of HPV vaccination on health inequalities; and (ii) examination of the incremental cost-effectiveness of interventions to increase vaccine coverage of girls, including a law for mandatory immunization (with opt-out permitted).

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Disease sequelae of HPV infection contribute to health inequalities. Between countries, there are higher rates of cervical cancer in low income countries. Projected increased HPV vaccination globally from 2011 to 2020 has been estimated to be capable of averting half a million future deaths, or 15.1 deaths per 1000 girls vaccinated [8], which will inevitably contribute to reducing between country cervical cancer inequalities. Within countries, cervical cancer rates [9–12] and other HPV-associated cancer rates are higher among lower socioeconomic, and minority and indigenous populations [13,14]. Accordingly, HPV vaccination should – so long as vaccine coverage is not lower among socially disadvantaged populations – lead to future reductions in health inequalities. Some modelling of the impact on HPV prevalence in social groups when either or both the vaccine coverage and the number of lifetime sexual partners vary has been undertaken [15]. But to our knowledge there has not previously been modelling which includes actual data on social group differences in baseline epidemiological parameters (e.g., cancer rates) taken through to quantified health gains (mortality and morbidity) and cost-effectiveness by social group.

In New Zealand there are also social inequalities in HPV-related disease [12], but at least the HPV vaccination uptake to date appears to be somewhat higher among Māori (indigenous) and Pacific peoples (compared to other New Zealanders), and so might be modestly contributing in closing health gaps [16]. But it is ideal to explore the potential for health inequalities reduction further by considering a wider range of vaccination scenarios and also the cost-effectiveness of vaccination by social group.

Many countries have struggled to obtain high HPV vaccination coverage. Herd immunity will reduce the marginal impact for further increases in vaccination coverage – especially for HPV 6/11 caused disease (i.e., largely anogenital warts) which appears to have more marked herd immunity than HPV 16/18 caused disease (primarily cancers) [17]. Most economic evaluations have assumed that the incremental cost of increasing vaccination coverage is simply that due to increased use of vaccine and delivery costs. However, increasing vaccination coverage may require a restructuring of current programmes or more intensive effort at the margin, both carrying costs; although prior modelling studies have suggested that this can be a cost-effective investment [18]. In New Zealand, a national girls' HPV vaccination programme began in 2008 with a catch-up phase (older adolescent girls), followed since by routine vaccination of 12-year-old girls either in school or through primary care providers. Achieved coverage is 47% for the third dose (Unpublished data for 2011 from the National Immunization Register), although higher coverage of 56% has been achieved for Māori (indigenous population) and Pacific peoples [16]. Possible reasons for low coverage are that the programme is not exclusively school-based (as in Australia, where coverage is 73%) [19], and that HPV immunization is free for females up to their 20th birthday, suggesting that 'choice' in provider and timing can also result in failure to be vaccinated.

The purpose of this study was to assess the health impact (quality-adjusted life years gained [QALY]), cost (health system perspective) and cost-effectiveness for three interventions: (1) the 2008 'as implemented' HPV vaccination programme of girls only in New Zealand; (2) modification to 'as implemented' to be a school-only programme as per Australia; (3) added inclusion of a new mandatory law requiring active opting-out of vaccination (as per some US states). All three interventions are compared to a baseline of no vaccination programme (i.e., business as usual pre-2008), as well as to each other. Due to existing social inequalities in HPV-related cancers and HPV infection rates and the rich availability of data in New Zealand by social group, different impacts (or heterogeneity) by ethnicity and socioeconomic deprivation was also a specific focus. Included in the evaluations are the spill-over effects for males and unvaccinated females (i.e., herd immunity leading to less HPV infection among these groups) and multiple disease and health state outcomes (e.g., anal cancers, cervical cancer, cervical neoplasia and anogenital warts). Scenario or sensitivity analyses about a range of variables are included, most importantly vaccine price, lesser herd immunity benefits in the first vaccinated cohort and the discount rate.

## 2. Methods

### 2.1. Perspective and general approach

Study methods followed the Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE$^3$) Protocol [20]. Briefly, a health system perspective was used, and so the various costs and consequences beyond the health system were out of scope (e.g., productivity costs). The eligible vaccination population was 12-year-old girls in 2011. This cohort, and the equivalent cohort of boys, was modelled through to death or age 110 years. HPV vaccination was modelled as contributing to the prevention of cervical cancer, a range of other cancers (oropharyngeal, anal, vulvar; vaginal and penile were not included as they contribute only 2–3% of HPV16/18-related cancer burden), cervical intraepithelial neoplasia (CIN I and CIN II/III) and anogenital warts. As much of the recurrent respiratory papillomatosis (RRP) burden is through vertical transmission to children, and the data on its incidence, severity, morbidity, mortality and health services utilization in New Zealand is sparse, we could not include it in the model. A 3% discount rate was applied to costs and QALYs gained, and unrelated health system costs were included (i.e., average expected costs to health system by sex and age).

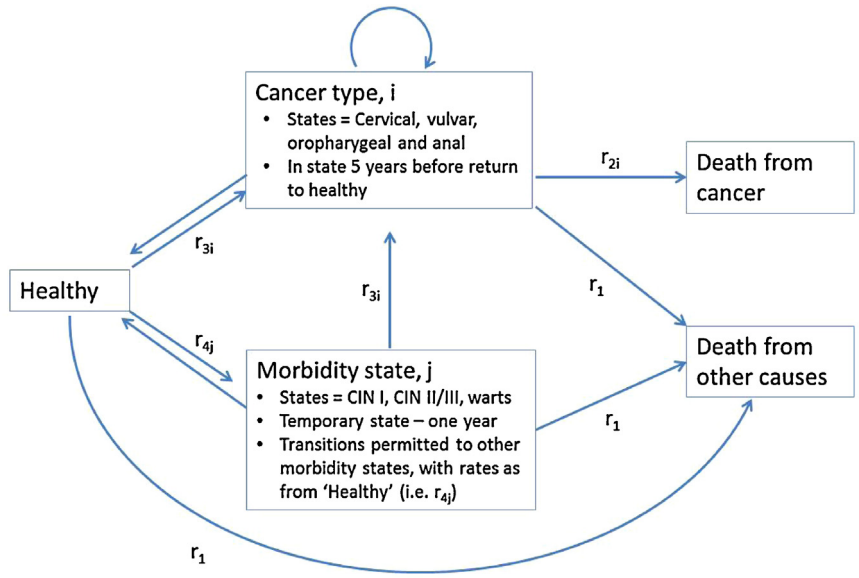
### 2.2. Core model structure

The core model was a Markov macro-simulation model, with annual cycles (Fig. 1). The population of 12-year-olds in 2011 commenced in a disease-free 'healthy state' and were followed for 98 cycles, until the residual cohort members reached age 110. The model structure was such that individuals could only have one disease condition at one time. Neither did we allow for different cancer rates based on previous CIN status. Disadvantages of our approach include that we may slightly misestimate costs and utilities (but given most states are rare these will be inconsequential compared with other uncertainties such as health-related quality of life for CIN states), and also that we could not extend our model to evaluate additional interventions (e.g., modifications to cervical screening programmes). The advantages include simplicity, parsimony to answer our research questions regarding HPV vaccination and ethnic and socioeconomic heterogeneity, and adherence to the available data (e.g., detailed data by socio-demographics of incidence and survival).

For equity analyses, we stratified the New Zealand 12-year-old population by sex, ethnicity (Māori, non-Māori) and area-based socioeconomic deprivation tertile, giving 12 discrete cohort populations.

### 2.3. Quality-adjusted life years

The QALY metric captures both years of life lost from premature death, and loss of quality of life through morbidity. QALYs use many different health status valuation methods (e.g., EuroQol (EQ5D) and Health Utilities Index questionnaire); we used disability weights (DW) on a scale from 0 (full health) to 1.0 (death) applied to the non-fatal health state in question (Supplementary Table 1). Expected population morbidity due to other diseases and injury was allowed for by using the average ethnic and age-specific prevalent years of




$r_1$ = rates of all-cause mortality from population lifetables, by sex, age, ethnicity (Māori, non-Māori) and area deprivation (approximate tertiles), and projected to future. Source: [32]

$r_{2i}$ = excess mortality rates of death from cancer i, by sex, age, ethnicity and deprivation, and by time since diagnosis. Source: [21] and see Supplementary Table 1.

$r_{3i}$ = incidence rates for cancer i, by sex, age, ethnicity and deprivation. Source: [33]

$r_{4j}$ = incidence rates for morbidity states j, by sex and age (and ethnicity for CIN I, CIN II/III and anogenital warts). Source: see Supplementary Table 1 and Appendix.

**Fig. 1.** Stylized Markov model for HPV-related disease states [32,33].

life lived in disability (YLD) from the New Zealand Burden of Disease Study [20], limiting the maximum health gain with increasing age. For example, a Māori woman aged 60–64 has an expected YLD of 0.288, meaning a year of life gained in this population group has a maximum value of 0.712. We formally use the term $QALY^{DW}$ in Sections 2 and 3 to denote the use of DWs and expected YLDs in estimation, but shorten it to QALY in Section 4.

### 2.4. Model input parameters

Input parameters are shown in Supplementary Table 1. Cancer incidence rates were those predicted for 2011 (and beyond to 2026 for cervical and oropharyngeal) based on regressions on New Zealand Cancer Registry data. Cancer excess mortality rates by time since diagnosis were modelled for 1994–2008 national cancer registrations, followed up to December 2010 for deaths [21]. Incidence rates for other states were obtained from various sources, and likewise the proportion due to HPV 16/18 or 6/11. Australian burden of disease models were used to allocate durations for each cancer in diagnosis and treatment, remission, pre-terminal and terminal states, with attendant DWs sourced from the Global Burden of Disease 2010 study [22], with modification to the New Zealand distribution of cancers [20]. For the cancer states in the Markov model, a survivor is in this state for 5 years accumulating $QALYs^{DW}$, then returns to the healthy state. There is considerable variation and uncertainty in the international literature of (dis)utilities to assign CIN and anogenital warts states. Our assumptions, and therefore generous specification of uncertainty about these DWs (i.e., 1 minus the utility weight), are described in Supplementary Table 1 and Appendix.

### 2.5. Health system costs

Just as $QALYs^{DW}$ are awarded to each individual as they travel through states, so are health system costs. For the healthy and cancer states, we used the New Zealand Ministry of Health's Health Tracker. This is a collection of datasets from administrative health data collections, including hospitalizations, mortality, cancer registrations, mental health and addiction service use, pharmaceutical and laboratory claims, primary health care enrolment, and outpatient/emergency department visits for the entire New Zealand population with costs attached as described elsewhere [20]. Thus, we assigned health system costs by sex and single year of age to the healthy state (i.e., the simple average of all health system use and attendant cost for each sex by age group, as estimated in 2012; we assumed real costs to be the same in the future). Using these data, the additional costs for cancer patients at different stages of their care (diagnosis, remission, terminal) were estimated. The costs for the other states in the model were estimated relying on other New Zealand-based data. Examples of the health system costs in 2011 are shown for selected age groups in Supplementary Table 2 (and detailed in Appendix). All costs were represented in 2011 New Zealand dollars.

### 2.6. Intervention effectiveness: vaccination coverage and future reduction in HPV prevalence

The vaccination coverage levels for the various scenarios are detailed in Table 1. The rationale for the vaccine coverage achieved with interventions 2 (73%) and 3 (93%) are given in Appendix; vaccine coverage for Intervention 1 is that observed as of 2011 in New Zealand. To determine the total impact of vaccination on future reduction in risk of HPV infection (both direct effect of vaccination and herd immunity effects for females, and herd immunity effects only for males), a meta-regression approach of Brisson et al.'s (2011) existing infectious disease model was used, with vaccine efficacy of 99% and vaccine duration of 20 years, at vaccine coverage levels of 30%, 50%, 70% and 90% [17]. The method is described in the Appendix, and distributions of the long-run HPV prevalence reduction are shown in Table 1 for the central estimate of vaccine coverage for each intervention. Summarizing to this point, for each intervention a random draw from the estimated vaccine coverage distribution was made (e.g., for intervention 2 from a Beta distribution with alpha = 56.8 and beta = 21.0), and then this value was used

**Table 1**
Intervention parameters: vaccination coverage, reduction in future HPV prevalence and intervention costs.

| Interventions | Vaccination coverage | Beta distribution for vaccination coverage | Reduction in HPV infection for central estimate of vaccination coverage only (i.e., 56%/45%, 73% and 93%, respectively, for the three intervention scenarios) (95% uncertainty interval) | | | | Vaccination costs (NZ$; incurred in 2012 only, only for girl recipients; SD as % of expected valued used for Gamma distribution) |
|---|---|---|---|---|---|---|---|
| | | | Females | | Males | | |
| | | | HPV6/11 | HPV16/18 | HPV6/11 | HPV16/18 | |
| Intervention 1: Programme as per NZ in 2011 | Māori: 56%, assumed SD = 2% | Alpha = 344, beta = 271 | Māori: 75% (57–83%) | Māori: 49% (41–59%) | Māori: 75% (56–83%) | Māori: 47% (41–53%) | Scenario A: $760 (10%) [($113 + $141) × 3] |
| | Non-Māori: 45%, assumed SD = 2% | Alpha = 278, beta =340 | Non-Māori: 67% (48–76%) | Non-Māori: 41% (33–50%) | Non-Māori: 66% (47–74%) | Non-Māori: 37% (32–43%) | Scenario B: $395 (10%) [($113 + $19) × 3] |
| Intervention 2: Enhanced uptake as per Australia with school-only delivery | 73% (no variation by ethnicity or deprivation level; assumed SD = 5%) | Alpha = 56.8, beta = 21.0 | 81% (67–88%) | 63% (53–73%) | 81% (65–88%) | 61% (53–67%) | Scenario A: $716 (10%) [($113 + $126) × 3] Scenario B: $395 (10%) [see Intervention 1] |
| Intervention 3: Mandated (with opt-out permitted) at school | 93% (no variation by ethnicity or deprivation level; assumed SD = 3%) | Alpha = 66.3,beta = 5.0 | 83% (77–89%) | 77% (63–87%) | 83% (77–89%) | 73% (65–81%) | Scenario A: $716 (10%) [see Intervention 2] Scenario B: $395 (10%) [see Intervention 1 and 2] Cost of a new law (pro rata per 12-year-old in the population,[a] 3% discount rate and 10-year annuitization period): $7.36 (25%) |

Scenario A = Top-down costing. Scenario B = bottom up costing (see Section 2 and Appendix).

[a] Note that the cost of a new law is a fixed total cost which is independent of vaccine coverage (unlike other costs in this column).

to generate a random draw of long-run HPV prevalence reduction (using equations described in Appendix).

This prevalence reduction was then multiplied by the percentage of cancer/disease due to HPV 6/11 or 16/18 (Supplementary Table 1), and then the disease incidence into the future reduced by this amount. These disease reductions will take some years to be realized after the introduction of HPV vaccination (see graphs in [17]), due to HPV circulation in older age cohorts and the long development time between infection and cancer. Thus our assumptions are more consistent with HPV vaccination in a future 'steady state'. However, even for the first vaccinated cohort herd immunity effects would be occurring: unvaccinated girls would still benefit from herd immunity effects from vaccinated girls in their age-cohort and younger cohorts and to an extent in older cohorts included in the catch-up programme (females up to 9 years older); boys would still benefit from lower risk sexual contact with vaccinated girls and emerging herd immunity more generally; given maximum sexual activity of the first cohort of 12-year olds probably occurs in the 5–20 years after they have been offered vaccination, there is 'time' for much of the herd immunity to emerge. Nevertheless, our method probably overestimated the benefits for the initial cohort, so we present 'no herd immunity' and 'low herd immunity' scenarios in Table 4 (details in footnotes to this table).

### 2.7. Intervention cost

The overall costs of each vaccination intervention are shown in the final column of Table 1, and detailed in Appendix. Briefly, the vaccination costs were calculated per fully vaccinated girl, which was in accordance with the vaccination schedule of three doses. The vaccine cost-per-dose was $113 based on the annual vaccine cost paid by the Ministry of Health. The delivery and administration costs of the three main interventions were $141 or $126 per dose depending on whether the vaccination was delivered through schools and primary care settings (Intervention 1) or schools only (Interventions 2 and 3), respectively. The third intervention also included the cost of enacting a new immunization law based on the average cost of new act in New Zealand [23]. We annuitized this cost of a law over 10 years (scenario analyses for 5 and 20 years also shown), and distributed it evenly across all girls and boys. In addition, separate scenario analyses (Scenario B in Table 1) were conducted involving alternative bottom-up costing estimates derived from information from a vaccination programme organizer in the Wellington Region and the GAVI vaccine purchase price resulting in delivery and administration cost of $19 per dose. More detailed information on deriving the costs by intervention is provided in Appendix.

### 2.8. Markov modelling and cost-effectiveness analyses

Monte Carlo simulation of 2000 iterations was run based on the Markov macro-simulation model for the HPV related disease states (Fig. 1). QALYs$^{DW}$ gained, net cost and incremental cost-effectiveness ratios (ICER) were calculated for each iteration to give the 'total population' results. Likewise, average values were calculated for 'Māori only' and other population groups of interest. Within each of the 2000 iterations the comparator and three intervention arms were run using the same random draw from the uncertainty intervals about all input parameters in Supplementary Table 1. (In additional modelling (Supplementary Table 5) we set a correlation of 1.0 between the long-run reductions in HPV prevalence between the three intervention arms. The uncertainty in both QALYs$^{DW}$ gained and costs reduced modestly, meaning uncertainty about the ICER changed little, except Intervention 3 compared to 2 where marginal changes are small and the ICER unstable (see Supplementary Table 5).) Net monetary benefit and cost-effectiveness acceptability were determined including parameter uncertainty. Scenario analyses were based on the expected values only excluding parameter uncertainty. One-way sensitivity analyses were conducted using the 2.5th and 97.5th percentile values for input parameters, with all other parameters at their expected value, and presented with tornado plots. Analyses were undertaken in TreeAge Pro 2012 and Microsoft Excel.

## 3. Results

Total costs and QALYs$^{DW}$ gained in the remainder of their lives for all 58,582 12-year-olds (girls and boys combined) in New Zealand in 2011 for Interventions 1–3 are shown in Table 2. Compared to no HPV vaccination, the current programme (Intervention 1) has an estimated additional net cost of NZ$4.65 million (95% uncertainty interval [UI] $2.44–6.97 million). This net cost is less than the actual cost of the intervention ($10.33 million), due to offsetting from health system costs averted in the future by preventing HPV-related disease. A total of 266 (95%UI: 164–413) QALYs$^{DW}$ were gained from the current programme, with anticipated reductions in anogenital warts contributing 45% of the QALYs$^{DW}$ gained for females, and 67% for males (Supplementary Table 3). Cervical (33% females), oropharyngeal (6% females and 24% males) and anal cancers (6% and 10%) were the next major contributors. The ICER for Intervention 1 (compared to no HPV vaccination) was $18,800 per QALY$^{DW}$ gained ($7300–35,400).

Regarding Intervention 2 (73% coverage in a school-based programme), there were diminishing marginal QALYs$^{DW}$ gained due to proportionately less herd immunity effects (especially for HPV 6/11) compared to Intervention 1. Specifically, total QALYs$^{DW}$ increased from 266 to 348 (24% increase) (Table 2). The mandated immunization law (Intervention 3; 93% coverage) led to a further increase in QALYs$^{DW}$ to 382 (9% increase). Percentage increases in net costs across interventions were more marked, increasing 31% from Intervention 1 to 2 and 24% to Intervention 3.

The plots of all 2000 simulations for each intervention compared to no HPV vaccination are shown as a cost-effectiveness plane in Fig. 2. Also shown in Fig. 2 as bold lines is the cost-effectiveness frontier, connecting the points of mean cost by QALYs$^{DW}$ gained. The slope of each segment is the ICER, respectively, for Intervention 1 compared to no HPV vaccination, Intervention 2 compared to 1 ($34,700 per additional QALY$^{DW}$ gained; Table 2), and Intervention 3 compared to 2 ($122,500 per additional QALY$^{DW}$ gained). Whilst there is considerable overlap in the three clouds of net cost by QALYs$^{DW}$ gained, the uncertainty about the ICER is less than this visual image suggests as there are actually 2000 separate frontiers (and hence ICERs) that can be formed by connecting up the dots from the same iterations (i.e., 2000 different random draws of parameter uncertainty). For Intervention 3 compared to 2, the 95% UI is $58,800–230,600. However, for Intervention 2 compared to 1, more than 2.5% of the incremental costs are negative (i.e., net cost saving) rendering the 2.5th percentile of the ICER 'dominant'.

To decipher the optimal intervention in cost-effectiveness terms, it is useful to examine the cost-effectiveness acceptability curves as shown in Fig. 3. This curve is constructed by calculating the probability that any of the three interventions (or having no HPV vaccination programme) is the optimal choice across all 2000 simulations, for selected values of a governmental willingness-to-pay ($x$-axis; $1000 increments of cost per one QALY$^{DW}$ gained). Up to a willingness-to-pay of about $17,000/QALY$^{DW}$ gained, having no vaccination programme is the optimal choice. Between $17,000 and $30,000 Intervention 1 is optimal, between $30,000 and $115,000 Intervention 2, and only above $115,000/QALY$^{DW}$ gained would Intervention 3 be optimal.

**Table 2**
Costs, QALYs$^{DW}$ and ICERs (95% uncertainty intervals) for all 12-year-olds in New Zealand in 2011, for the three interventions each compared to no vaccination programme and for incremental comparisons.

| | Each intervention compared to no HPV vaccination | | | Incremental comparisons | |
|---|---|---|---|---|---|
| | Intervention 1: replicating the NZ programme in 2011 | Intervention 2: intensive programme, school-based | Intervention 3: mandated, immunization law | Intervention 2 c.f. Intervention 1 | Intervention 3 c.f. Intervention 2 |
| Cost of intervention (NZ$; 1000s) | $10,333 ($8275–12,587) | $14,885 ($11,706–18,532) | $19,392 ($15,763–23,340) | $4552 ($557–870) | $4507 ($2221–6970) |
| Net cost (NZ$; 1000s) | $4650 ($2443–6973) | $7423 ($4114–10,943) | $11,207 ($7227–15,179) | $2773 (dominant–$6626) | $3784 ($1980–5814) |
| QALYs$^{DW}$ gained | 266 (164–413) | 348 (224–527) | 382 (246–573) | 82 (47–128) | 35 (12–71) |
| ICER | $18,800 ($7300–35,400) | $22,600 ($9800–40,200) | $31,000 ($15,400–$52,000) | $34,700 (dominant–$88,100) | $122,500 ($58,800–230,600) |

ICERs rounded to nearest 100. Discount rate 3%.

### 3.1. Heterogeneity and equity analyses around ethnicity

Table 3 shows how the expected QALYs$^{DW}$ gained, net cost and ICER per 12-year-old vary by sex, ethnicity and deprivation. Note that these analyses do not involve Monte Carlo simulation or parameter uncertainty, and accordingly the sum of these expected values for individuals do not (quite) match the total population results in Table 2.

About 75% of the total QALYs$^{DW}$ gained was for females. Regarding differences by ethnicity and deprivation, all three interventions appear pro-equity in that there were greater health gains for Māori and those living in the most deprived areas (tertile 3) compared to no HPV vaccination programme. For example, Māori had 26% greater QALYs$^{DW}$ gained per person for Intervention 1 than non-Māori (0.0053 and 0.0042, respectively). This larger Māori gain was partly a function of the higher vaccine coverage for Māori in Intervention 1, but there was still an approximately 10% greater QALYs$^{DW}$ gained per Māori for Interventions 2 and 3, which had equal vaccination coverage across ethnicities. The greater QALYs$^{DW}$ gained from Interventions 2 and 3 arise from higher background burden of HPV-related disease among Māori (e.g., cervical cancer has both higher incidence and worse survival for Māori). To explore this further, we conducted a Māori 'equity analysis' (also in Table 3) by recalculating the Māori QALYs$^{DW}$ using non-Māori mortality and morbidity rates, because the higher background mortality and morbidity rates for Māori meant that in the baseline analysis a life saved for Māori is weighted less compared to a life saved for non-Māori. We found an approximately 20% increase in QALYs$^{DW}$ gained and commensurate favourable reductions in the ICER. The increased QALYs$^{DW}$ gained for the most deprived population (tertile 3) compared to the least deprived (tertile 1) were less pronounced than differences across ethnic groups. The pattern of net costs tend to follow those for QALYs$^{DW}$ gained, thus the ICERs do not vary greatly by ethnicity or deprivation – although the ICERs for Māori are lower than for the total population.

### 3.2. Uncertainty analyses

Fig. 4 shows the impact on the ICER for univariate sensitivity analyses using the 2.5th and 97.5th percentile values from the uncertainty distribution for each input parameter, with all other input parameters held at their expected value. For all three incremental comparisons, uncertainty in the vaccination cost results in large variation in the ICER. Uncertainty in future cervical cancer

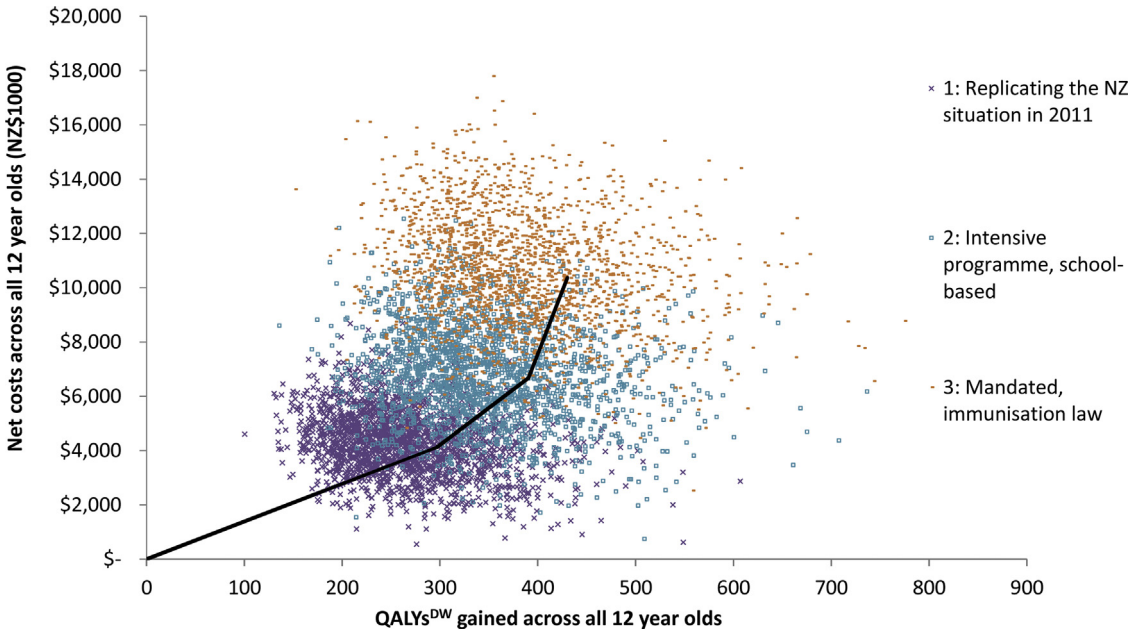



**Fig. 2.** Cost-effectiveness plane for the three HPV vaccination programmes compared to no HPV vaccination (bold black lines join average values).

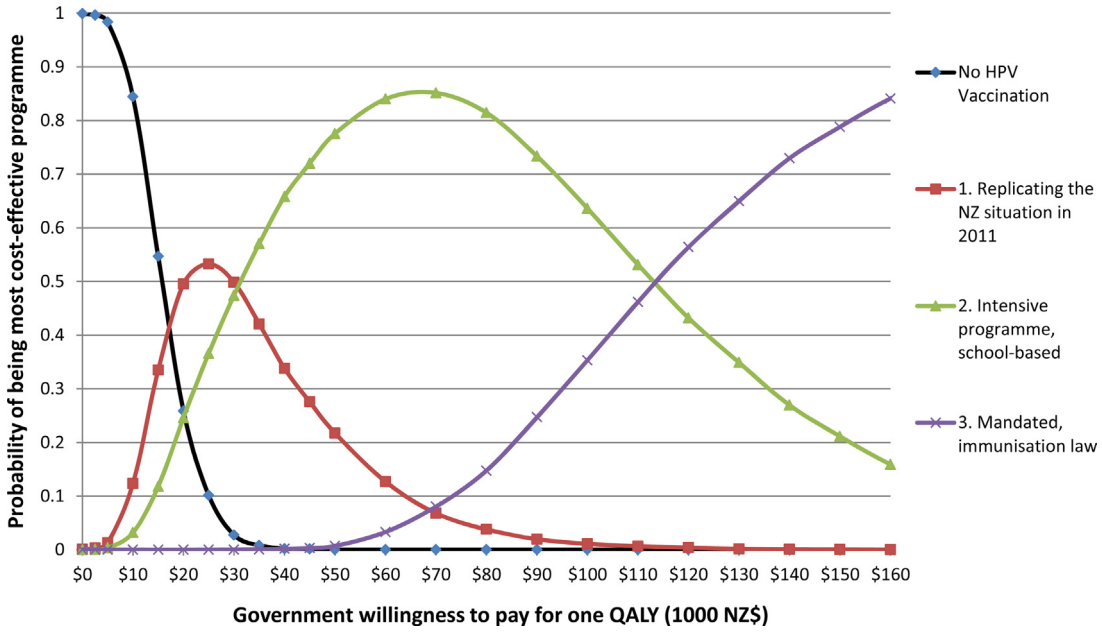



**Fig. 3.** Multiple cost-effectiveness acceptability curves for the three HPV vaccination programmes and no HPV vaccination from our 'best' model.

incidence, DW for genital warts, and incidence rate of genital warts also resulted in notable variation in the ICERs. Still, the variation in ICERs for these univariate sensitivities was considerably less than the variation in ICERs reported in the scenario analyses below.

### 3.3. Scenario analyses

Model outputs were clearly sensitive to differing assumptions. The net costs were very sensitive to vaccination programme costs and vaccine price (Table 4). For example, halving the vaccine price – a plausible expectation in the short-term future – shifted all ICERs to be less than \$19,000/QALY$^{DW}$ gained, except for Intervention

**Table 3**
Sub-population heterogeneity within our 'best' model: incremental costs, QALYs$^{DW}$ and ICER per 12-year-old (expected value analysis).

| | No HPV vaccination (baseline) | Each intervention compared to no HPV vaccination | | | Incremental comparisons | |
|---|---|---|---|---|---|---|
| | | Intervention 1: replicating the NZ programme in 2011 | Intervention 2: intensive programme, school-based | Intervention 3: mandated, immunization law | Intervention 2 c.f. Intervention 1 | Intervention 3 c.f. Intervention 2 |
| Net cost (NZ$) | | | | | | |
| Total population | $43,807 | $81 | $128 | $193 | $47 | $65 |
| Māori | $41,166 | $98 | $126 | $190 | $28 | $64 |
| Māori: equity analysis[b] | $44,286 | $98 | $126 | $190 | $27 | $64 |
| Non-Māori | $44,621 | $76 | $129 | $194 | $53 | $65 |
| Least deprived tertile | $45,103 | $82 | $135 | $200 | $53 | $65 |
| Most deprived tertile | $42,336 | $88 | $132 | $197 | $44 | $65 |
| QALYs$^{DW}$ gained | | | | | | |
| Total population | 26.2830 | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| Māori | 24.7895 | 0.0053 | 0.0064 | 0.0070 | 0.0010 | 0.0006 |
| Māori: equity analysis[b] | 26.6423 | 0.0068 | 0.0080 | 0.0089 | 0.0013 | 0.0008 |
| Non-Māori | 26.7432 | 0.0042 | 0.0057 | 0.0063 | 0.0015 | 0.0006 |
| Least deprived tertile | 26.7357 | 0.0041 | 0.0055 | 0.0060 | 0.0014 | 0.0005 |
| Most deprived tertile | 25.7543 | 0.0045 | 0.0058 | 0.0064 | 0.0013 | 0.0006 |
| Males[a] | 26.3533 | 0.0024 | 0.0032 | 0.0036 | 0.0007 | 0.0004 |
| Females[a] | 26.2092 | 0.0067 | 0.0087 | 0.0095 | 0.0021 | 0.0008 |
| ICER | | | | | | |
| Total population | | $18,000 | $21,800 | $29,800 | $33,700 | $111,500 |
| Māori | | $18,400 | $19,800 | $27,100 | $27,100 | $98,800 |
| Māori: equity analysis[b] | | $14,500 | $15,600 | $21,400 | $21,400 | $77,200 |
| Non-Māori | | $17,900 | $22,400 | $30,700 | $35,100 | $116,100 |
| Least deprived tertile | | $19,900 | $24,600 | $33,400 | $39,000 | $126,100 |
| Most deprived tertile | | $19,500 | $22,700 | $30,800 | $33,900 | $111,300 |

All costs and ICERs rounded to nearest 100.

[a] QALYs$^{DW}$ only are shown by sex. Calculating cost and ICERs by sex is somewhat artificial given that there is no vaccination cost attributed to males.

[b] As Māori have higher background mortality rates and higher morbidity, this essentially 'penalizes' health gain for Māori in the analyses. So we present an equity analysis with non-Māori morbidity and mortality rates applied to Māori.

**Table 4**
Scenario analyses (expected value analysis; costs and $QALYs^{DW}$ gained per 12-year-old in 2011).

| | Output | Compared to no HPV vaccination | | | Incremental comparisons | |
|---|---|---|---|---|---|---|
| | | Intervention 1: replicating the NZ programme in 2011 | Intervention 2: intensive programme, school-based | Intervention 3: mandated, immunization law | Intervention 2 c.f. Intervention 1 | Intervention 3 c.f. Intervention 2 |
| 'Best' model from Table 3, but for expected value only analysis | Net cost (NZ$) | $81 | $128 | $193 | $47 | $65 |
| | $QALYs^{DW}$ gained | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| | ICER | $18,000 | $21,800 | $29,800 | $33,700 | $111,500 |
| Scenario analyses | | | | | | |
| Low delivery/administration cost (bottom-up estimate – scenario B) | Net cost (NZ$) | $−4 | $14 | $47 | $18 | $33 |
| | $QALYs^{DW}$ gained | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| | ICER | $−800 | $2300 | $7300 | $12,600 | $57,400 |
| Vaccine price halved (effective negotiating by government/purchaser) | Net cost (NZ$) | $42 | $68 | $116 | $26 | $48 |
| | $QALYs^{DW}$ gained | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| | ICER | $9200 | $11,500 | $17,9400 | $18,900 | $83,000 |
| Very low vaccine price ($7.46), equivalent to the GAVI price of 5US$ – scenario C) | Net cost (NZ$) | $8 | $16 | $50 | $8 | $34 |
| | $QALYs^{DW}$ gained | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| | ICER | $1700 | $2700 | $7700 | $6000 | $58,500 |
| Discount rate 0% | Net cost (NZ$) | $−28 | $−24 | $23 | $5 | $46 |
| | $QALYs^{DW}$ gained | 0.0136 | 0.0187 | 0.0207 | 0.0051 | 0.0020 |
| | ICER | Dominant | Dominant | $1100 | $900 | $22,800 |
| Discount rate 6% (double baseline) | Net cost (NZ$) | $123 | $186 | $258 | $63 | $72 |
| | $QALYs^{DW}$ gained | 0.0024 | 0.0031 | 0.0034 | 0.0007 | 0.0003 |
| | ICER | $50,400 | $59,900 | $76,200 | $95,800 | $257,000 |
| Excluding unrelated health system costs[a] | Net cost (NZ$) | $73 | $116 | $179 | $44 | $63 |
| | $QALYs^{DW}$ gained | 0.0045 | 0.0059 | 0.0065 | 0.0014 | 0.0006 |
| | ICER | $16,200 | $19,700 | $27,700 | $31,200 | $109,100 |
| Excluding disease DWs (i.e., no morbidity impacts of HPV-related disease)[b] | Net cost (NZ$) | $81 | $128 | $193 | $47 | $65 |
| | $QALYs^{DW}$ gained | 0.0011 | 0.0016 | 0.0018 | 0.0006 | 0.0002 |
| | ICER | $74,800 | $78,400 | $105, | $85,400 | $322,900 |
| Excluding both background morbidity and disease DWs (i.e., life years gained analysis, ignoring morbidity) | Net cost (NZ$) | $81 | $128 | $193 | $47 | $65 |
| | Life yrs gained | 0.0016 | 0.0023 | 0.0026 | 0.0008 | 0.0003 |
| | ICER | $52,000 | $55,400 | $74,300 | $62,500 | $231,300 |
| Set annuitization period for cost of law to 5 years | Net cost (NZ$) | | | $200 | | $71 |
| | $QALYs^{DW}$ gained | n.a. | n.a. | 0.0065 | n.a. | 0.0006 |
| | ICER | | | $31,000 | | $127,000 |
| Set annuitization period for cost of law to 20 years | Net cost (NZ$) | | | $190 | | $62 |
| | $QALYs^{DW}$gained | n.a. | n.a. | 0.0065 | n.a. | 0.0006 |
| | ICER | | | $29,500 | | $110,000 |
| Initial cohort – assume no herd immunity[c] | Net cost (NZ$) | $116 | $168 | $230 | $52 | $62 |
| | $QALYs^{DW}$ gained | 0.0028 | 0.0041 | 0.0046 | 0.0013 | 0.0006 |
| | ICER | $41,500 | $41,300 | $49,600 | $40,700 | $110,000 |
| Initial cohort – assume low herd immunity[d] | Net cost (NZ$) | $99 | $146 | $202 | $47 | $56 |
| | $QALYs^{DW}$ gained | 0.0037 | 0.0051 | 0.0059 | 0.0014 | 0.0009 |
| | ICER | $27,000 | $28,700 | $34,000 | $32,800 | $65,400 |

*Note*: All ICERs below $100,000 rounded to the nearest $100. All ICERs above $100,000 rounded to the nearest $1000.

[a] That is ignoring the health costs from diseases other than those specifically modelled, which increase net costs as living longer is associated with costs from (other) future disease and disability.

[b] That is, the DWs for cancers, CIN and anogenital warts states are all set to zero – but the background morbidity is retained. The health gain realized from HPV vaccination is therefore only from preventing premature death from cancer.

[c] For the first cohort vaccinated, they will not enjoy the full herd immunity benefits of the future steady state (i.e., once vaccination in place for 10 or more years). In this 'most pessimistic' scenario, we 'turn off' all future reduction in HPV-related disease for males and set future HPV-related disease reduction for females to a minimum of the vaccine coverage or central estimate used in main analyses. (Occasionally the estimated reduction in HPV prevalence is less than vaccine coverage due to less than perfect vaccine efficacy and attenuation of effect after 20 years).

[d] As per above scenario, but now assuming half the herd immunity benefits for the first vaccinated cohort (i.e., males get half of the reduction in future HPV-related disease that is estimated in the main or 'best' model, and females get a value half way between the vaccine coverage and that estimated in the main model. For example, for girls only vaccination of 73%, the 'best' estimate of future reduction in HPV 6/11-related disease is 81% (Table 1), so we assign 77% (=73% + 0.5 [81–73%]).

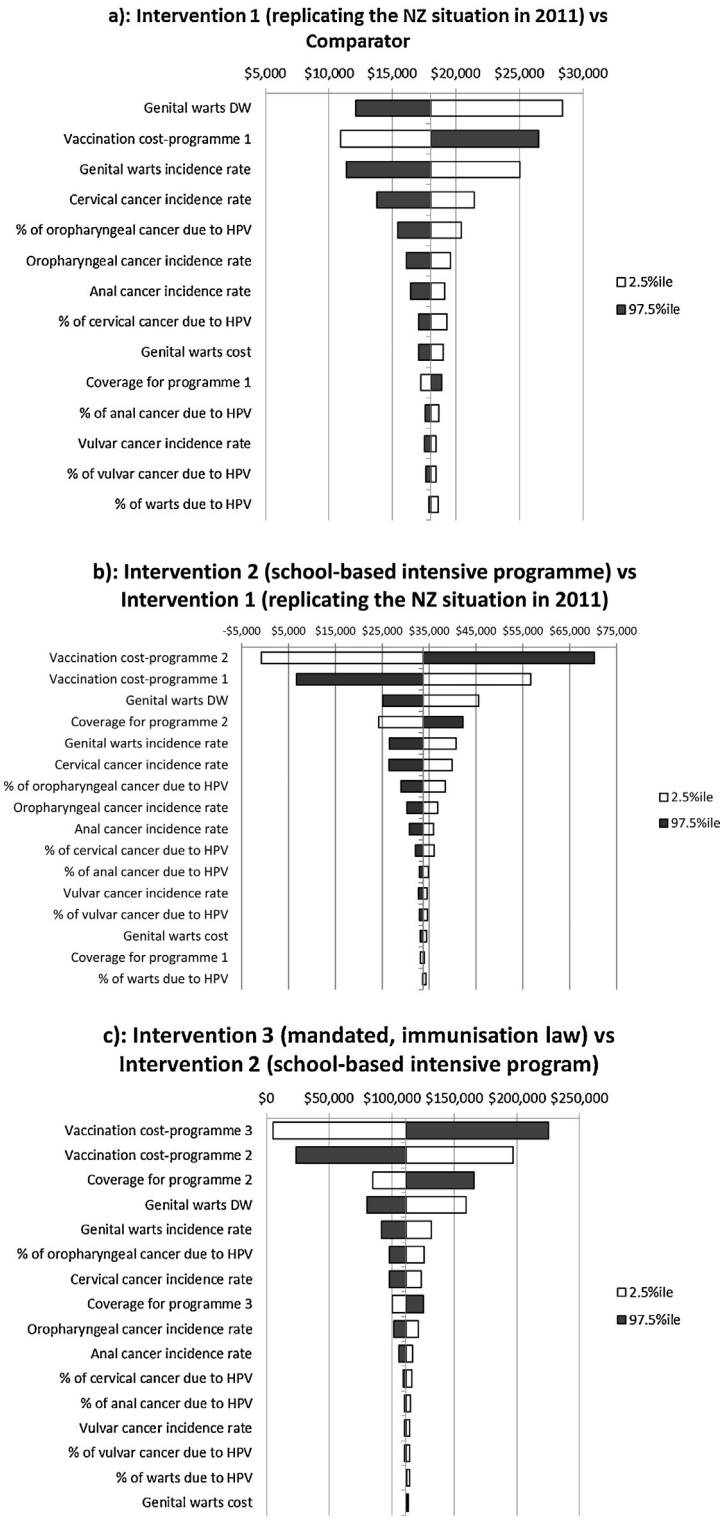



**Fig. 4.** Tornado plots for one-way sensitivity analyses of the ICER, for the three interventions. DW, disability weight; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus infection. Vaccination cost includes vaccine price and administration/delivery cost. New Zealand GDP per capita (NZ$40,000) may be used as a rough rule of thumb of the society's willingness to pay per QALY gained.

3 compared to 2 ($83,00/QALY$^{DW}$ gained). As expected, using the even lower GAVI price for the vaccine improved cost-effectiveness (lower ICERs). A 0% discount rate made Interventions 1 and 2 cost saving. Conversely, doubling the baseline discount rate (to 6%) shifted all ICERs to be above $50,000/QALY$^{DW}$ gained. The other scenarios that shifted all ICERs to be about $50,000 or higher were those that excluded the morbidity impacts of HPV-related disease (i.e., setting disease DWs to zero). That is, on a life years gained basis HPV vaccination is much less cost effective, highlighting the sensitivity to how quality of life of common states such as anogenital warts is quantified – also reflected in the above univariate uncertainty analyses for the anogenital warts DW (Fig. 4).

Excluding unrelated health system costs (i.e., the costs incurred in the future due to people not dying of HPV-related diseases) made no meaningful difference to any of the results. Two-way scenario analyses of the discount rate and vaccination cost or vaccine price are shown in Supplementary Table 4.

Finally, scenario analyses about low herd immunity (that would be the case for the initial 12-year-old cohort vaccinated; see Section 2) find less health gains and higher net costs (due to less future prevented disease), such that the ICER for Intervention 1 was $27,000/QALY$^{DW}$ gained. The ICER for Intervention 2 compared to Intervention 1 was little changed from the 'best' model and the ICER for Intervention 3 compared to Intervention 2 was now considerably less, at $65,400/QALY$^{DW}$ gained (due to more incremental health gain at higher vaccination coverage due to less herd immunity). A scenario analysis about no herd immunity (biologically implausible in our view and inconsistent with emerging data from other countries, for example Australia which shows a reduction in genital warts in males after the commencement of the female-only programme [24]) saw all ICERs increase to over $40,000.

## 4. Discussion

### 4.1. Main findings and interpretation

Using the best data we could assemble for the current and projected situation in New Zealand, and noting our structural assumptions (e.g., model structure and disease shown in Fig. 1; and utilization of other simulation model outputs [17] to capture herd immunity), we conclude that the current HPV vaccination programme in New Zealand has a cost-effectiveness of NZ$18,800/QALY gained (about US$9700/QALY gained using the OECD's PPP; 95% UI: NZ$7200 to NZ$33,400). We also conclude that the incremental cost-effectiveness of an intensive school-based only programme in New Zealand that achieves 73% vaccine coverage of girls, compared to the current vaccination programme dispersed across schools and primary care (that achieves 56% coverage for Māori and 45% for non-Māori), has an ICER of $34,700/QALY gained. A mandatory immunization law appears cost-ineffective, although this assumes that such a law only applies to HPV vaccination – if other vaccinations were included in such a law, then the cost would be shared beyond HPV-related diseases.

Using New Zealand GDP per capita (NZ$40,000) as a rough rule of thumb of the society's willingness to pay per QALY gained, then our model suggests the optimal decision on cost-effectiveness grounds alone is Intervention 2 (school-only) which has the highest probability of being cost-effective from a societal willingness-to-pay per QALY of $30,000–115,000 (Fig. 3).

As with many preventive interventions, and especially those for infectious diseases, there is considerable uncertainty in projected health gains. HPV vaccination is no exception. Our modelling suggests that both uncertainty about the current cost of vaccination delivery, and possible future reductions in vaccine price, moderately to dramatically alter ICERs. Apart from negotiated price reductions, the cost of the vaccine and of delivering the vaccine could potentially reduce in future if the vaccine schedule was adjusted to be two doses rather than the current three doses.

There is emerging evidence that two doses confer a similar level of immunity and protection as three doses [25]. To a lesser extent, uncertainty in future cervical cancer and warts incidence, and the morbidity experienced from having warts, impact on QALYs gained and thence ICERs. Alternative structural assumptions about herd immunity effects may be important. In this paper we used model outputs from research by Brisson et al. [17], resulting in diminishing marginal increases in QALYs gained over the population for increasing vaccine coverage. Thus, further research to improve quality of life impacts of warts and the degree of herd immunity would improve accuracy of model estimates. However, these aspects dwarf into insignificance (and do not warrant further research from the decision-makers' perspective) if the price of the vaccine can be reduced as seems plausible given recent international trends in HPV vaccine prices, and the possibility that two vaccine doses may be sufficient.

A priori, we expected that HPV vaccination would especially benefit Māori and low socioeconomic populations more because of higher cervical cancer incidence rates [12], and worse survival in these groups [26]. The modelling results obtained supports this hypothesis, with greater QALY gains for Māori and deprived populations even allowing for higher background mortality and morbidity from other causes in these groups. In an 'equity analysis' where we assumed Māori were not 'penalized' by these higher background mortality and morbidity rates, the QALY gains for Māori increased further. Thus, we conclude that HPV vaccination is a pro-equity intervention, so long as attained vaccine coverage is as high or higher for Māori and deprived populations (as might be expected with school-based vaccination programmes).

### 4.2. Comparison to previous modelling and cost-effectiveness studies

Comparisons between cost-effectiveness analyses are inherently challenging due to variations in model assumptions and parameter inputs. In particular to HPV vaccination analyses, the difficulty is due to differences in vaccination cost estimates, and assumptions about vaccine efficacy, coverage, and years of protection. We found that the current programme in New Zealand had an ICER of about US$9700/QALY gained (2011) and the school-based programme (73% coverage) had an ICER of US$11,700/QALY gained (2011) compared to no vaccination programme. Broadly, both of our findings were more cost-effective than estimates from Australia [27]. The Australian study used screening alone as the comparator, assumed life-long protection and 100% coverage, however it only considered cervical disease outcomes, which led to an estimated ICER of US$28,601/QALY gained (in 2011, using OECD inflation data). In New Zealand, analyses of 3-year screening of women from 20 to 60 years old and 50% coverage of vaccination produced an estimated ICER of US$3465/QALY gained (2011) compared to screening alone as per the current programme in New Zealand [6]. These estimates are much lower than ours, likely due to differences in cost and screening assumptions and inclusions (as that analysis also reflects cost savings from not screening women older than 60 years), and the fact that we include a cohort of all 12-year-old boys and girls in our analyses rather than an age and sex subset of the population. However, using the New Zealand GDP (US$20,800) as a reference point, both the current programme and a school-based programme are considered good value from a willingness-to-pay perspective, while the Australian estimate is not.

### 4.3. Strengths and limitations of this study

Key strengths of this study include the modelling of a range of HPV-related diseases, the use of detailed New Zealand data on disease rates (including by socioeconomic status and ethnicity; and projecting future changes in incidence where possible) and costs, incorporating updated disability weights based on the Global Burden of Disease Study [22], and considering the health benefits from herd immunity for both the female and the male population. Novel features of this study, and not previously reported to our knowledge, include the modelling of population heterogeneity (by ethnicity and socioeconomic status) and equity analyses in a real world setting, and inclusion of the cost of a new law mandating vaccination.

The limitations include the (inevitable) uncertainty in some projections, although the inclusion of a range of scenario and uncertainty analyses can be seen as a strength in light of 'true' uncertainty. We estimate that had we included penile and vaginal cancers, the QALYs gained would have increased by perhaps 1% at most. Also modelling recurrent respiratory papillomatosis (RRP) (which is relatively expensive to treat surgically) would probably further improve the results for health gains and cost-effectiveness. The magnitude of the benefits of HPV vaccination has been found to be sensitive to the rate of RRP [28], consequently more precise estimates on the incidence of RRP are ideally required in New Zealand.

A key assumption of our method is that sexual behaviour in New Zealand is broadly similar to that modelled for Canada [17], in order for the herd immunity 'benefits' of HPV vaccination to be applied to New Zealand. We are not aware of comparable data comparing sexual contact patterns in Canada and New Zealand. However, if they are such that herd immunity effects in New Zealand might be less than in Canada, then the 'low herd immunity' scenario in Table 4 provides an alternative perspective. Conversely, if they were such that herd immunity effects were greater in New Zealand, then we would expect the ICER for Intervention 1 versus no vaccination to improve, but the ICER for Intervention 3 versus 2 to deteriorate further. Such uncertainty is inherent in most HPV vaccination models.

Related, for the comparisons of Māori and non-Māori, and by deprivation, we are implicitly assuming that sexual behaviour, and thus herd immunity effects, are similar by social group. Malagon et al. (2013) have found that modelled future reductions in HPV prevalence could vary substantially between social groups if sexual activity levels also varied substantially. For example, central estimates of future relative reductions in HPV16/18 prevalence for groups with 0–2, 3–10, 11–39 and 40+ lifetime sexual partners were 62%, 74%, 40% and 28%, respectively (vaccine efficacy = 100%, average duration of protection = 20 years, vaccine coverage = 50%). We are not aware of reliable data on the lifetime number of sexual partners by ethnicity or deprivation in New Zealand, but data from various youth (school-age) studies found that Māori were more likely to start having sex at a younger age, were more likely to be sexually active at a given age, and less likely to use condoms (summarized in [29]). Rates of presentation for genital warts, however, do not suggest marked ethnic differences (Appendix). Our results by ethnicity and deprivation must, therefore, be treated cautiously. It is our view though that HPV vaccination should secure greater health gains for Māori and deprived populations, supported by the results in this paper. The genital warts data suggest that the sexual contact patterns do not vary profoundly enough between these social groups so as to dramatically alter the herd immunity effects. Also, given the lower cervical cancer screening coverage for Māori, ceteris paribus one would expect a larger impact on future cervical cancer rates for Māori – amplified by the higher cervical cancer incidence rates.

We also did not model intersections with likely future changes in existing cervical cancer screening programmes. The impact of HPV vaccination will be to both reduce future costs of managing and testing screen-detected abnormalities and to reduce the cost-effectiveness of cervical screening [30] (unless screening is done less frequently, to reflect the reduction in disease risk post-vaccination). Conversely, if there was a major reduction in cervical screening then some of the projected future cervical cancer incidence reductions included in our baseline data may be overstated – if true, then the QALY gains from HPV vaccination would increase due to a larger counterfactual burden of cervical cancer to address. However, it must be noted that cervical cancer only contributes about a third of the female QALYs gained under a 3% discount rate assumption and other structural assumptions in our modelling (Supplementary Table 1 for Intervention 1 compared to no HPV vaccination; [34–43]).

## 5. Conclusion

The current HPV vaccination programme appears cost-effective and pro-equity. Our results suggest however that a more intensive school-only programme may be a more optimal intervention in terms of health gain at reasonable cost-effectiveness, if the 73% vaccination coverage that we assumed is achieved (as it has been in Australia). Nevertheless, all interventions modelled are considered pro-equity and could contribute to lowering HPV-related disease inequalities. There is considerable uncertainty in many input parameters and the model structure which could be improved by future research. Still, this uncertainty pales into insignificance if the vaccine price can be successfully reduced. If price can be reduced, then a mandatory law may achieve cost-effectiveness and would maximize health gain. Alternatively, with low vaccine costs, there may be additional health gains from vaccinating boys, but this was not explored in the current research. Finally, if the vaccine price does not reduce in the near future, further consideration could be given to modelling two dose vaccination schedules [25,31].

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.02.071.

## References

[1] Seto K, Marra F, Raymakers A, Marra CA. The cost effectiveness of human papillomavirus vaccines: a systematic review. Drugs 2012;72:715–43.
[2] Canfell K, Chesson H, Kulasingam SL, Berkhof J, Diaz M, Kim JJ. Modeling preventative strategies against human papillomavirus-related disease in developed countries. Vaccine 2012;30(Suppl. 5):F157–67.
[3] Smith MA, Lew JB, Walker RJ, Brotherton JM, Nickson C, Canfell K. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. Vaccine 2011;29:9112–22.
[4] Horn J, Damm O, Kretzschmar ME, Delere Y, Wichmann O, Kaufmann AM, et al. Estimating the long-term effects of HPV vaccination in Germany. Vaccine 2013;31:2372–80.
[5] Canfell K. Models of cervical screening in the era of human papillomavirus vaccination. Sex Health 2010;7:359–67.
[6] Sopina E, Ashton T. Cost-effectiveness of a cervical screening program with human papillomavirus vaccine. Int J Technol Assess Health Care 2011;27:290–7.
[7] Coupe VM, Bogaards JA, Meijer CJ, Berkhof J. Impact of vaccine protection against multiple HPV types on the cost-effectiveness of cervical screening. Vaccine 2012;30:1813–22.
[8] Lee LA, Franzel L, Atwell J, Datta SD, Friberg IK, Goldie SJ, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccine 2013;31(Suppl. 2):B61–72.
[9] McDougall JA, Madeleine MM, Daling JR, Li CI. Racial and ethnic disparities in cervical cancer incidence rates in the United States, 1992–2003. Cancer Causes Control 2007;18:1175–86.
[10] Parikh S, Brennan P, Boffetta P. Meta-analysis of social inequality and the risk of cervical cancer. Int J Cancer 2003;105:687–91.
[11] Shack L, Jordan C, Thomson CS, Mak V, Moller H, UKAoC Registries. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. BMC Cancer 2008;8:271.
[12] Blakely T, Shaw C, Atkinson J, Cunningham R, Sarfati D. Social inequalities or inequities in cancer incidence? Repeated census-cancer cohort studies, New Zealand 1981–1986 to 2001–2004. Cancer Causes Control 2011;22:1307–18.
[13] Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst 2013;105:175–201.
[14] Brisson M, Drolet M, Malagon T. Inequalities in Human Papillomavirus (HPV)-associated cancers: implications for the success of HPV vaccination. J Natl Cancer Inst 2013;105:158–61.
[15] Malagon T, Joumier V, Boily MC, Van de Velde N, Drolet M, Brisson M. The impact of differential uptake of HPV vaccine by sexual risks on health inequalities: a model-based analysis. Vaccine 2013;31:1740–7.
[16] Turner N. HPV vaccination coverage in New Zealand: closing the equity gap. HPV Today 2011:23.
[17] Brisson M, van de Velde N, Franco EL, Drolet M, Boily MC. Incremental impact of adding boys to current human papillomavirus vaccination programs: role of herd immunity. J Infect Dis 2011;204:372–6.
[18] Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of male HPV vaccination in the United States. Vaccine 2011;29:8443–50.
[19] Gertig D, Brotherton J, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. Sex Health 2011;8:171–8.
[20] Blakely T, Foster R, Wilson N, BODE$^3$ Team. Burden of Disease Epidemiology, Equity and Cost-Effectiveness (BODE$^3$) study protocol. Version 2.0. Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme – technical report No. XXX. Wellington: Department of Public Health, University of Otago; 2012.
[21] Blakely T, Costilla R, Soeberg M. Cancer excess mortality rates over 2006–2026 for ABC-CBA. Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme – technical report No. 10. Wellington: Department of Public Health, University of Otago; 2012.
[22] Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012;380:2129–43.
[23] Wilson N, Nghiem N, Foster R, Cobiac L, Blakely T. Estimating the cost of new public health legislation. Bull World Health Organ 2012;90:532–9.
[24] Ali H, Donovan B, Wand H, Read TRH, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ 2013;346:f2032.
[25] Dobson SM, McNeil S, Dionne M, Dawar M, Ogilive G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309:1793–802.
[26] Soeberg M, Blakely T, Sarfati D, Tobias M, Costilla R, Carter K, et al. CancerTrends: trends in cancer survival by ethnic and socioeconomic group, New Zealand 1991–2004. Wellington: University of Otago and Ministry of Health; 2012.
[27] Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, et al. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health 2007;4:165–75.

[28] Chesson HW, Forhan SE, Gottlieb SL, Markowitz LE. The potential health and economic benefits of preventing recurrent respiratory papillomatosis through quadrivalent human papillomavirus vaccination. Vaccine 2008;26:4513–8.
[29] Ministry of Health. Our children's health: key findings on the health of New Zealand children. Wellington: Ministry of Health; 1998.
[30] Canfell K, Lew JB, Clements M, Smith M, Harris J, Simonella L, et al. Impact of HPV vaccination on cost-effectiveness of existing screening programs: example from New Zealand. In: 28th international human papillomavirus conference & clinical and public health workshops. 2012.
[31] Kahn Ja BDI. Hpv vaccination: too soon for 2 doses? JAMA 2013;309:1832–4.
[32] Kvizhinadze G, Blakely T. Projected New Zealand lifetables. Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE$^3$) – technical report No. 4. Wellington: Department of Public Health, University of Otago; 2011.
[33] Costilla R, Atkinson J, Blakely T. Incorporating ethnic and deprivation variation to cancer incidence estimates over 2006–2026 for ABC-CBA. Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme – technical report No. 5. Wellington: Department of Public Health, University of Otago; 2011.
[34] Smith M, Walker R, Canfell K. National cervical screening programme monitoring report No. 34: 1 July–31 December 2010. Wellington: National Screening Unit, Ministry of Health; 2012.
[35] Brotherton JM. How much cervical cancer in Australia is vaccine preventable? A meta-analysis. Vaccine 2008;26:250–6.
[36] Clifford G, Franceschi S. Members of the human papillomavirus type 18 family (alpha-7 species) share a common association with adenocarcinoma of the cervix. Int J Cancer J Int Cancer 2008;122:1684–5.
[37] Watson M, Saraiya M, Ahmed F, Cardinez CJ, Reichman ME, Weir HK, et al. Using population-based cancer registry data to assess the burden of human papillomavirus-associated cancers in the United States: overview of methods. Cancer 2008;113:2841–54.
[38] Brestovac B, Harnett GB, Smith DW, Shellam GR, Frost FA. Human papillomavirus genotypes and their association with cervical neoplasia in a cohort of Western Australian women. J Med Virol 2005;76:106–10.
[39] Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003;88:63–73.
[40] Stevens M, Tabrizi S, Quinn M, Garland S. Human papillomavirus genotype prevalence in cervical biopsies from women diagnosed with cervical intraepithelial neoplasia or cervical cancer in Melbourne, Australia. Int J Gynecol Cancer 2006;16:1017–24.
[41] Kvizhinadze G, Blakely T. Projected NZ life tables. Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme – technical report No. 4. Wellington: Department of Public Health, University of Otago; 2011.
[42] Jeffreys M, Rachet B, McDowell S, Habib AG, Lepage C, Coleman MP. Survival from rectal and anal cancers in England and Wales, 1986–2001. Eur J Cancer 2006;42:1434–40.
[43] Klint A, Tryggvadottir L, Bray F, Gislum M, Hakulinen T, Storm HH, et al. Trends in the survival of patients diagnosed with cancer in female genital organs in the Nordic countries 1964–2003 followed up to the end of 2006. Acta Oncol 2010;49:632–43.