Potential for HPV vaccination and primary HPV screening to reduce cervical cancer disparities: example from New Zealand

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1 **Abstract**   [word count: 286/ 300]

2 ## Background

3 Cervical cancer rates are over twice as high, and screening coverage is lower, in Māori women

4 compared to other women in New Zealand, whereas uptake of HPV vaccine is higher in Maori

5 females. We aimed to assess the impact of HPV vaccination and the proposed transition to 5-yearly

6 primary HPV screening in Māori and other women in New Zealand, at current participation levels; and

7 additionally to investigate which improvements to participation in Māori females (in vaccination,

8 screening, or surveillance for screening-defined higher-risk women) would have the greatest impact

9 on cervical cancer incidence/ mortality.

10 ## Methods

11 An established model of HPV vaccination and cervical screening in New Zealand was adapted to fit

12 observed ethnicity-specific data. Ethnicity-specific models were used to estimate the long-term impact

13 of vaccination and screening (vaccination coverage 63% vs 47%; five-year screening coverage 68%

14 vs 81% in Maori vs European/Other women, respectively).

15 ## Results

16 Shifting from cytology to HPV-based screening is predicted to reduce cervical cancer incidence by

17 17% (14%) in Maori (European/Other) women, respectively. The corresponding reductions due to

18 vaccination and HPV-based screening combined were 58% (44%), but at current participation levels

19 long-term incidence would remain almost twice as high in Māori women (6.1/100,000 compared to

20 3.0/100,00 in European/Other women). Among strategies we examined, the greatest impact came

21 from high vaccine coverage and achieving higher attendance by Māori women under surveillance for

22 screen-detected abnormalities.

23 ## Conclusion

24 Relative reductions in cervical cancer due to vaccination and HPV-based screening are predicted to

25 be greater in Maori than in European/Other women. While these interventions have the potential to

26 substantially reduce between-group differences, cervical cancer incidence would remain higher in

27 Maori women. These findings highlight the importance of multiple approaches and the potential

28 influence of factors beyond HPV prevention.

Highlights *(3-5 points; max 85 chars each incl spaces)*

- Cervical cancer rates are higher in Māori vs other women in New Zealand
- Both HPV vaccination and HPV screening are predicted to reduce this disparity
- Increased vaccine and screening coverage could further reduce but may not close gap
- Multiple approaches will be required, including beyond vaccination and screening
- These potentially include access to cervical cancer treatment, and tobacco control

1   **Potential for HPV vaccination and primary HPV screening to reduce cervical cancer**

2   **disparities: example from New Zealand**

3   **Keywords:** HPV, cervical cancer, screening, vaccination, New Zealand, ethnicity, equity, disparities

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Background

New Zealand is an example of a country with a well-established organised cytology-based screening program. New Zealand's National Cervical Screening Programme (NCSP) commenced in 1990, and recommends three-yearly liquid-based cytology (LBC) screening for women aged 20-69 years[1]. Prior to the inception of the NCSP, cervical cancer incidence was approximately three times higher in Māori women (who comprise ~14% of the population) than in New Zealand European women (~75%)[2, 3]. Since the NCSP was introduced, cervical cancer incidence rates have declined substantially in both Māori and non-Māori women,[3-5] and the relative reduction appears to be similar in these two groups.[5] While absolute disparities between the groups has reduced markedly since the NCSP began, and relative disparities have also tended to decrease, incidence rates are still approximately twice as high in Māori women as in New Zealand European women[3, 6], and screening coverage and re-attendance for surveillance in women with screen-detected abnormalities is consistently lower in Māori women[7].

New Zealand introduced HPV vaccination in 2008; initially for females only and using the quadrivalent HPV vaccine (HPV4), but switching to nonavalent HPV vaccine (HPV9) and including males since January 2017[8]. HPV vaccine uptake has been higher in Māori girls than in non-Māori non-Pacific girls (three-dose uptake by age 15 approximately 60% and 47% respectively) [9]. Prompted in part by the advent of vaccination, the NCSP is planning to transition to five-yearly cervical screening for women aged 25-69 years using human papillomavirus (HPV) testing in the near future [10]. The greater sensitivity and longer duration of protection from a negative screening test offered by HPV testing compared to cytology will provide better protection for women who are screened less frequently [11, 12]. Thus, both HPV vaccination and these changes to screening are likely to play a role in further decreasing disparities in cervical cancer between Māori and New Zealand European women in future.

We have previously evaluated the impact of primary HPV screening in New Zealand, and its population-level effectiveness relative to the current cytology-based NCSP [13]. In addition to population-level effectiveness, delivery of equitable screening services is a core objective of the National Screening Unit in New Zealand [14]. The National Screening Unit commissioned the current study to ascertain whether the proposed changes to cervical cancer screening in New Zealand would

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35   benefit Māori women to the same extent as other women (given differences in vaccine uptake,

36   screening participation and cervical cancer rates); and additionally to investigate which improvements

37   to current participation levels in Māori females (in screening or vaccination) would have the greatest

38   impact on cervical cancer incidence and mortality. Although the original aims also included

39   specifically evaluating these effects in Pacific women (~7% of the NZ population [2]), uncertainty in

40   deriving accurate estimates of cervical cancer rates in Pacific women who were resident in New

41   Zealand (as distinct from Pacific women resident in another country who were in New Zealand to

42   access cancer treatment) unfortunately precluded estimating intervention effects in this specific

43   group. Our general findings for Maori women are likely to be broadly applicable to Pacific women

44   residing in New Zealand, however, since Pacific females also currently have lower participation rates

45   in cervical screening but higher participation in rates in HPV vaccination than New Zealand European

46   females [7, 9].

47   **Methods**

48   *Model used*

49   We adapted a comprehensive model, *Policy1-Cervix*, that had been previously used to evaluate

50   cervical screening in the New Zealand population overall [13, 15]. The model design,

51   parameterisation and fit has previously been described in detail [13]. Briefly, it comprises a dynamic

52   model of HPV transmission and vaccination, coupled with a cohort-based model of HPV natural

53   history, cervical screening, diagnosis and treatment of cervical abnormalities, and cervical cancer

54   treatment and survival. Screening behaviour was modelled in detail for each management

55   recommendation and age group, using data on cumulative attendance over time from the NCSP

56   Register. The model had previously been fitted to local population-wide observed data on a range of

57   age-specific outcomes, including rates of histologically-confirmed high grade detection, cervical

58   cancer incidence and mortality, three- and five-year screening coverage, HPV type distribution in

59   histologically-confirmed high grade lesions, HPV-positivity in women undergoing triage of low grade

60   abnormalities, and the proportion of cytology tests reported as negative, ASC-US, LSIL, ASC-H, and

61   HSIL [13]. The model was also calibrated to results across all ages for the distribution of HPV types in

62   diagnosed cervical cancer cases.[13] The underlying model platform has also been previously

63   adapted to other settings and used to evaluate various vaccination, cervical screening and screening

3

64 management policies in Australia [15-21] and England [15, 22, 23]. The existing New Zealand

65 population model was adapted to separately model Māori women and a reference group of European/

66 Other women. European/ Other women were chosen as the reference group as they are the largest

67 ethnicity grouping in New Zealand (approximately 70% of the female population), and the largest of

68 the four ethnicity grouping for which cervical screening and cancer data are routinely reported (Māori,

69 Pacific, Asian and European/ Other) [6, 7]. Screening behaviour (including attendance for

70 surveillance and diagnostic tests) was adjusted to be ethnicity-specific, based on observed data [24,

71 25]; however HPV prevalence data did not suggest that HPV incidence differed in Māori and

72 European/ Other women [26], and so HPV incidence was not altered to be ethnicity-specific.

73 Calibration targets in this fitting process were ethnicity-specific rates of: 3- and 5-year screening

74 coverage; early re-screening; histologically-confirmed CIN2/3 and CIN1 detection; cervical cancer

75 incidence; detection of HPV16 vs 18 vs non16/18 types in diagnosed cervical cancers, and stage

76 distribution at cancer diagnosis (data sources detailed in the following section). We decided *a priori*

77 that if the observed differences in screening behaviour were insufficient to explain differences in

78 cervical cancer incidence (including stage at diagnosis and HPV type distribution) and CIN2/3

79 detection rates, then a small adjustment in HPV natural history would be allowed, to reflect the much

80 higher prevalence of tobacco use in Māori women than in both European/ Other women and the

81 overall female population (40% vs 13% and 15% respectively) [27]. Tobacco is a known co-factor for

82 cervical cancer,[28] associated with increased rates of HPV persistence and progression, and

83 potentially also lower rates of HPV clearance [29-31]. After fitting cervical cancer incidence, cancer

84 survival was also adjusted to be ethnicity-specific, consistent with observed data [4], in order to fit

85 observed differences in cervical cancer mortality [25].

86 ***Data sources for calibration targets and model inputs***

87 Data on CIN2/3 detection rates, cervical screening behaviour and attendance for follow-up tests were

88 based on data from the NCSP Register obtained from routine NCSP monitoring reports [24, 25]. The

89 NCSP Register is an opt-off national collection of routinely-collected data on all women attending for

90 screening and all pathology with a cervical component [32, 33]. Cervical cancer incidence, stage at

91 diagnosis, and mortality data were from the New Zealand Cancer Registry (NZCR) and provided by

92 the New Zealand Ministry of Health [25, 34]. Both the NCSP Register and NZCR are able to record

93 multiple ethnicities for an individual, but also report data according to a prioritised ethnicity

4

94 classification, which classifies women to a single ethnicity group in the priority ordering of Māori,

95 Pacific, Asian, European/ Other. That is, if any of the recorded ethnicities is Māori, the record is

96 classified as having occurred in a Māori person, and where ethnicity data are missing, it is classified

97 as European/ Other.

98 Ethnicity-specific vaccine uptake and other-cause mortality were based on published data [35-37]

99 (details in Appendix 1). Model fit against ethnicity-specific observed data is detailed in Appendix 2.

Scenarios considered

101 The baseline analysis examined the predicted impact of the proposed changes to cervical screening

102 policy (Figure 1), compared to current practice (3-yearly LBC for women aged 20-69; HPV triage

103 testing for women aged 30+ with ASC-US/LSIL[1, 13]), assuming no increase in screening

104 participation. This was considered separately for cohorts offered HPV vaccination (uptake as in

105 Appendix 1) and unvaccinated cohorts. Adherence to the recommended five-year interval assumed

106 that the proportion of women re-attending early, on-time and late for screening remained similar to

107 that observed under current practice, but for the new HPV-based screening program these categories

108 were defined in relation to on-time being five years, rather than three years [13].

109 Hypothetical scenarios examined the impact of different improvements to either vaccination or

110 screening coverage in Māori females, assuming no change in European/ Other women. Vaccination

111 scenarios considered the impact of increasing vaccine uptake in Māori females by age 16 years from

112 63% to 70%, 75%, or 85%. Screening scenarios separately examined potential changes to different

113 aspects of screening attendance, specifically: better on-time attendance (a higher proportion are re-

114 screened at five years after a negative HPV test); less under-screening (the proportion of women who

115 more than two years overdue for a routine screening test is lower); faster initiation of screening

116 (women who are ever screened attend for their first test closer to the recommended start age of 25

117 years); and improved attendance for surveillance testing among women recommended to return

118 earlier than the routine interval (for example women who are screen-positive but triage negative, or

119 previously treated for high grade lesions). The scenarios are described in more detail in Table 1 and

120 Appendix 1.

121 All scenarios involving vaccination were considered separately in the context of either female-only

122 vaccination with HPV4 (the program prior to 2017), and female and male vaccination with HPV9 (the

123   program since 1st January 2017). In the absence of available vaccine uptake data for males, all

124   scenarios involving male vaccination assumed uptake equivalent to that across the overall female

125   population (53% by age 16) [35, 36]. Uptake in males has been broadly similar to that in females in

126   other settings with school-based vaccination programs [38-41].

127   In each scenario, cervical cancer incidence and mortality were calculated over the lifetime of a cohort

128   of females who entered the model at age 10, until they reached age 84 (inclusive). In order to

129   maintain comparability with prior population-level results [13], the cohort born in 1997 and first offered

130   vaccination at age 12 in 2009 was chosen, Although male vaccination did not in practice start until

131   2017, in order to better capture the herd effects that would be expected in females in the context of

132   both-sex vaccination, scenarios that included male vaccination assumed it started at the same time.

133   Both relative and absolute disparities in cervical cancer incidence and mortality between the groups

134   were examined for each scenario.

135   **Results**

136   ***Impact of current vaccination and proposed changes to screening (no change in coverage)***

137   In the absence of HPV vaccination, the proposed change to HPV-based screening in New Zealand

138   would lead to slightly greater reductions in cervical cancer incidence and mortality in Māori females

139   than in European/ Other females (reductions of 17% vs 14% in incidence and 19% vs 16% in

140   mortality) (Figure 2). The relative reductions further improve in cohorts offered HPV vaccination. The

141   combination of the proposed change to HPV-based screening and HPV vaccination is predicted to

142   reduce cervical cancer incidence by 58% and 48% in Māori and European/ Other women respectively

143   in the context of female-only vaccination with HPV4, and by 63% and 72% in the context of both-sex

144   vaccination with HPV9 (Figure 2). Absolute and relative disparities in cervical cancer incidence and

145   mortality are predicted to decrease, but even in the context of HPV-based screening and both-sex

146   HPV9 vaccination, incidence and mortality are predicted to be approximately 1.9 and 2.5 times higher

147   respectively in Māori women than in European/ Other women in the long term (Figure 2, Table 2).

148   The combined impact of HPV4 vaccination and HPV-based screening is predicted to reduce cervical

149   cancer incidence and mortality at all ages, in both Māori women and European/ Other women (Figure

150   3).

151   ***Impact of improvements in vaccine uptake and screening participation***

152   The impact of different improvements to either vaccination or screening coverage is shown in Figure

153   4. The improvements which are predicted to have the greatest impact are increasing vaccination

154   coverage (to 75% or more by age 16) or an increase in the proportion of women attending for

155   surveillance tests. The effect of increased attendance for surveillance tests was further explored,

156   stratifying by two reasons for the surveillance recommendation: follow-up after a low-grade test result

157   in HPV-positive women (either cytological via triage or histological); or follow-up after a high grade

158   result (including post-treatment for CIN2/3 and following a high grade cytology result not

159   histologically-confirmed at first referral)(Figure 1). Both had important effects, but the reduction in

160   rates was greatest from increasing attendance after a low grade abnormality (Table 2). The relative

161   impact of each of the improvements considered tended to be slightly higher for mortality than for

162   incidence, but the impact was very similar in both cases. In all scenarios examined, cervical cancer

163   incidence and mortality rates remained higher in Māori women than in European/ Other women, but

164   the absolute disparity was further reduced (Figure 5). This was true both in the context of female-only

165   HPV4 vaccination and both-sex HPV9 vaccination, but the magnitude of the reductions compared to

166   current levels was greater with HPV9, ranging from 72% to 83% for Māori women, compared to 63%

167   for European/ Other women (Figure 5).

168   **Discussion**

169   Both absolute and relative reductions in cervical cancer incidence and mortality due to HPV

170   vaccination and HPV-based screening are predicted to be larger in Māori women than in European/

171   Other women in New Zealand. Therefore both HPV vaccination and HPV-based screening appear to

172   represent improvements to health equity in this setting. In terms of further reducing disparities, our

173   analysis suggests that the greatest impact would come from improving HPV vaccine coverage and

174   ensuring more Māori women under surveillance attend for follow-up; the combined impact of these

175   interventions has potential to reduce rates by up to 70-80% or more in Maori women over the long

176   term.

177   The most effective strategy to further reduce cervical cancer in Māori women was predicted to be

178   increasing vaccine uptake to 75% or more by age 16. This seems achievable, as since this analysis

179   was undertaken more recent data have become available that show three-dose uptake in the 2002

180   birth cohort was 74% in Māori females before age 15 [9]. However this higher uptake is unlikely to

181   narrow the gap between Māori and European/ Other females to the extent predicted in our analysis,

182   because coverage is also higher in European/ Other females in this cohort (60%) compared to our

183   base case (47%). In practice, it is unlikely that very high vaccine uptake (eg 85%) would be achieved

184   in Māori females while coverage remained at 47% in European/ Other females. This suggests that

185   while improving vaccine uptake is very important in terms of reducing the absolute burden of cervical

186   disease in Māori females, it will not be sufficient on its own to close the gap between Māori and

187   European/ Other women; addressing other factors are also required.

188   Vaccine coverage is routinely monitored and reported by ethnicity in New Zealand, so it will be

189   straightforward to monitor improvement on this aspect of participation. Screening coverage and other

190   aspects of screening participation and follow-up are also routinely monitored by ethnicity in New

191   Zealand, however the current study suggests that monitoring attendance by women recommended to

192   return for surveillance by ethnicity could be useful. One aspect of this has recently been included in

193   routine NCSP monitoring reports, and confirms that among women who are re-attending for

194   surveillance under the current NCSP, approximately 65% of Māori women are attending more than

195   three months later than recommended, compared to just over 50% for European/ Other women [42].

196   However, the current NCSP indicators do not quantify the proportion of women under surveillance

197   who do not re-attend at all. This gap in the monitoring could be filled to provide a more complete

198   measure of attendance for surveillance. Our assumptions for higher attendance for Māori women

199   under surveillance were set to be the same attendance rates as for European/Other women, but in

200   practice this increased attendance over the medium term (~four years) and not at the recommended

201   time of 12 months *per se*. Therefore monitoring attendance over longer time periods, and not only at

202   the recommended timepoint, would be important to assess whether some women are being lost to

203   follow-up.

204   While the strategies we examined would help reduce the gap between Māori and European/ Other

205   women in terms of cervical cancer burden, none were able to completely close the gap. This suggests

206   that multiple strategies are needed, and also that there are other important factors beyond

207   participation in screening and vaccination. These could potentially include access to cervical cancer

208   treatment, and tobacco control. Disparities in cervical cancer mortality and survival between Māori

209 and non-Māori women have improved over time, but some differences remain [4]. Māori women tend

210 to be diagnosed with more advanced disease, and increased attendance for screening or surveillance

211 would improve this – but observed differences in survival are only partially explained by stage at

212 diagnosis [4]. Tobacco smoking is well-established as being a co-factor for cervical cancer [28], and is

213 three times more common in Māori women than European/Other women in New Zealand [27]. While

214 this is likely to be a smaller factor in the current disparities compared to current differences in

215 screening behaviour, it is recognised as playing a role [43].

216 The strengths of the current analysis include that a well-established model of HPV natural history and

217 cervical screening was used, and fitted to age- and ethnicity-specific observed data for a large

218 number of outcomes. It is one of only a small number of modelled analyses that have examined how

219 HPV vaccination will affect absolute and relative rates of cervical cancer in ethnic groups who

220 currently have different levels of risk [44-47], and to our knowledge the first that has looked at the

221 ethnicity-specific impact of HPV-based screening, or HPV vaccination in the context of HPV-based

222 screening. New Zealand is also relatively unusual in that ethnic disparities in HPV vaccine uptake

223 differ to those for cervical screening participation, such that the majority population group in New

224 Zealand has the lowest vaccine uptake. Therefore this analysis provides some insight into how these

225 two factors combine.

226 Our analysis also has some limitations. Future screening behaviour is unknown, and so our base

227 case assumes similar patterns of behaviour to those observed in the context of the current NCSP

228 (although stretched to a longer interval of five years), including lower screening coverage in Māori

229 women than in European/ Other women. While it is not possible to rule out a future decrease in

230 participation in Māori women, this should be unlikely as the NCSP in New Zealand funds dedicated

231 services to help support Māori women (and other priority groups) participate in cervical screening [48],

232 and is additionally exploring the acceptability of HPV testing using self-collected samples to Māori

233 women through pilot studies [49]. Another limitation is that separate HPV transmission models were

234 used for Māori women and European/ Other women. This may have led to an overestimate in the

235 extent of herd effects in Māori women (although we assumed that vaccine uptake in the male partners

236 of both groups was the same and equal to that in the overall population, thus lower than in Māori

237 females). Herd effects may differ somewhat in reality, as previous analyses for Canada and England

238   have shown that groups with lower coverage can benefit from higher coverage in a different ethnic

239   group depending on the extent of sexual mixing, however the extent of this benefit varied depending

240   on the size of the groups [45, 47]. The Canadian analysis found that the variability in herd effects with

241   degree of cross-ethnic sexual mixing was much smaller in the majority ethnic group than in ethnic

242   groups with smaller population numbers - but in this previous analysis coverage was assumed to be

243   higher in the majority population group [45], whereas the reverse is true in New Zealand. Potentially

244   this suggests herd effects in the majority group of European/Other females would be relatively

245   unaffected by our assumption, but as previously herd effects may have been overestimated for Māori

246   females. Another limitation is that, while we considered the impact of the updated vaccination

247   program in New Zealand, which uses HPV9, this was done in the context of five-yearly HPV-based

248   screening. Previous analyses for New Zealand [15] and other countries [15, 50, 51] have suggested

249   that these younger cohorts offered HPV vaccination could be screened less frequently than this,

250   because their cancer risk is greatly reduced in absolute terms, and the HPV types that vaccines do

251   not protect against are less aggressive than vaccine types. Another limitation is that this exploratory

252   analysis has produced point estimates for the impact of different improvements, based on our fitted

253   baseline parameter set, although the range of improvements considered was intended to be relatively

254   broad (for example a wide range of possible vaccine uptake in Māori women). Finally, we were unable

255   to perform an analysis for Pacific women (~7% of the New Zealand population [2]). This is because

256   cancer statistics incorporate all cancer histology in New Zealand, including an unknown number of

257   cancers diagnosed in Pacific women who reside in another Pacific Island country, but who access

258   treatment in New Zealand. Deriving accurate estimates of cervical cancer rates in Pacific women who

259   reside in New Zealand would allow more detailed modelling of this group, and importantly, it would

260   also improve the ability to monitor the effectiveness of cervical screening and HPV vaccination in this

261   group. Additionally, these estimates relate to cohorts offered vaccination in early adolescence and

262   HPV-based screening from age 25, and thus the long-term impact of both HPV-based screening and

263   vaccination. In the shorter term, reducing disparities in screening participation in unvaccinated cohorts

264   will be critical and reduce disease disparities more rapidly, as it will take decades before vaccination

265   reduce incidence at the population level [47].

266   **Conclusions**

267 HPV vaccination and the change to HPV-based screening appear likely to improve equity in New

268 Zealand, because both are predicted to lead to greater absolute and relative reductions in cervical

269 cancer incidence and mortality in Māori women than in European/ Other women in New Zealand.

270 However while these prevention activities represent improvements, they are unlikely in themselves to

271 completely close the gap in cervical cancer between Māori women and European/ Other women in

272 New Zealand. Doing so will potentially involve changes beyond the screening and vaccination

273 programs, although important gains could be made by increasing vaccination coverage in Māori girls

274 and ensuring timely follow-up for Māori women under surveillance.

275

286 Disclosure of potential conflicts of interest

287 KC is co-PI of an investigator-initiated trial of cytology and primary HPV screening in Australia

288 ("Compass") (ACTRN12613001207707 and NCT02328872). The organisation conducting the trial, the

289 VCS Inc have received equipment and a funding contribution from Roche Molecular Systems and

290 Ventana, USA. KC is also a PI on Compass in New Zealand, ("Compass NZ"; ACTRN

291 12614000714684), which is conducted and funded by Diagnostic Medlab (DML), now Auckland

292 District Health Board. DML received an equipment and a funding contribution from Roche Molecular

293   Systems. However, neither KC nor her institution on her behalf (Cancer Council NSW) receive

294   funding from industry for Compass Australia or Compass NZ or any other project.

295 ## Ethical clearances
296   Cancer Council NSW Human Research Ethics Committee approved the study (reference 314).

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463

Figure captions and footnotes

464

465 **Figure 1 – Management of test results in primary HPV screening program**


466
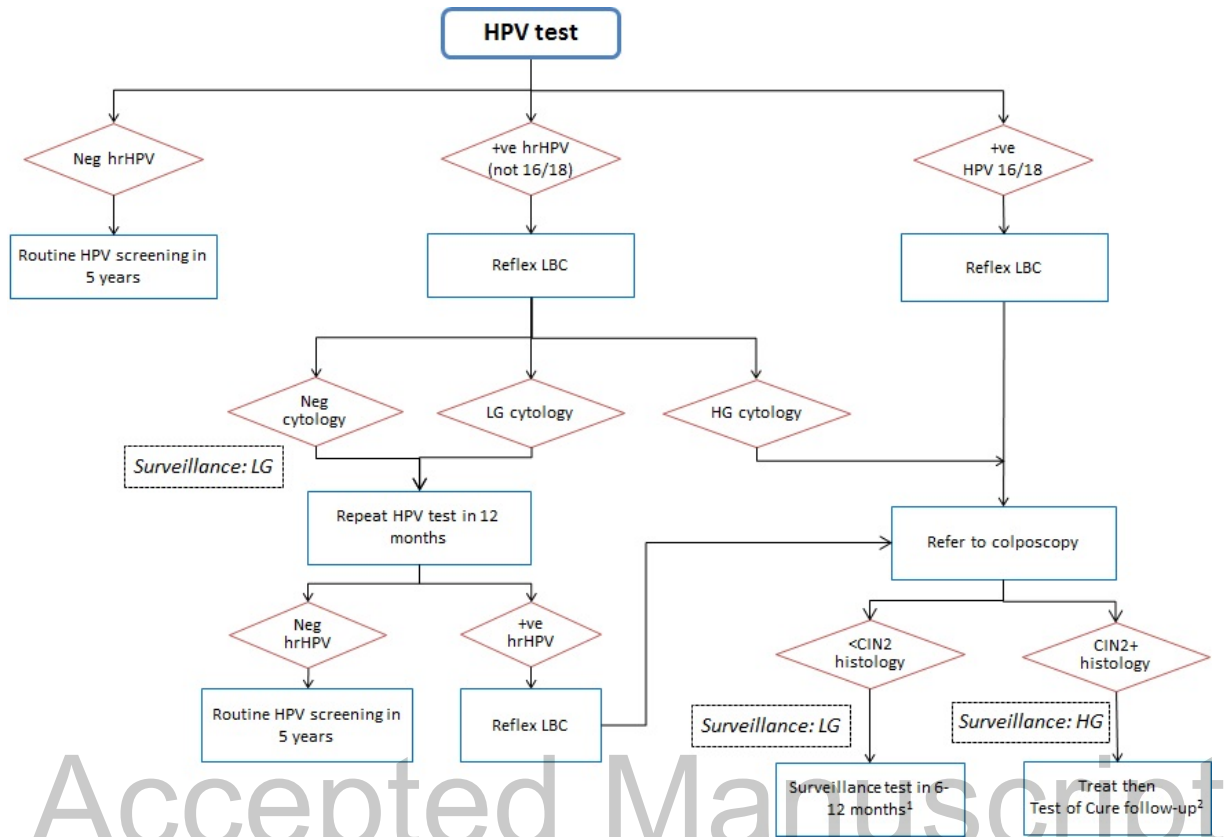
467 *Adapted from draft guidelines released for public consultation [52]. 1) Type of testing at 6-12 months varies*
468 *depending on reflex LBC result at time of colposcopy referral. Exceptions: diagnostic excision if LBC HSIL. See*
469 *Lew et al 2016 Appendix for detailed management [13]. 2) Test of Cure follow-up = co-testing with HPV and LBC*
470 *at 12 months post-treatment then every 12 months until negative on both tests in two consecutive rounds of*
471 *testing (thereafter, women returned to routine screening). Colposcopy referral occurs if HPV16/18 detected or if*
472 *LBC = ASC-H , HSIL, or any glandular abnormality*

473

Figure 2 - Cervical cancer incidence (a) and mortality (b) in Māori women and European/ Other
women, and relative rates (c), under different HPV vaccination and cervical screening
scenarios, assuming no change in coverage
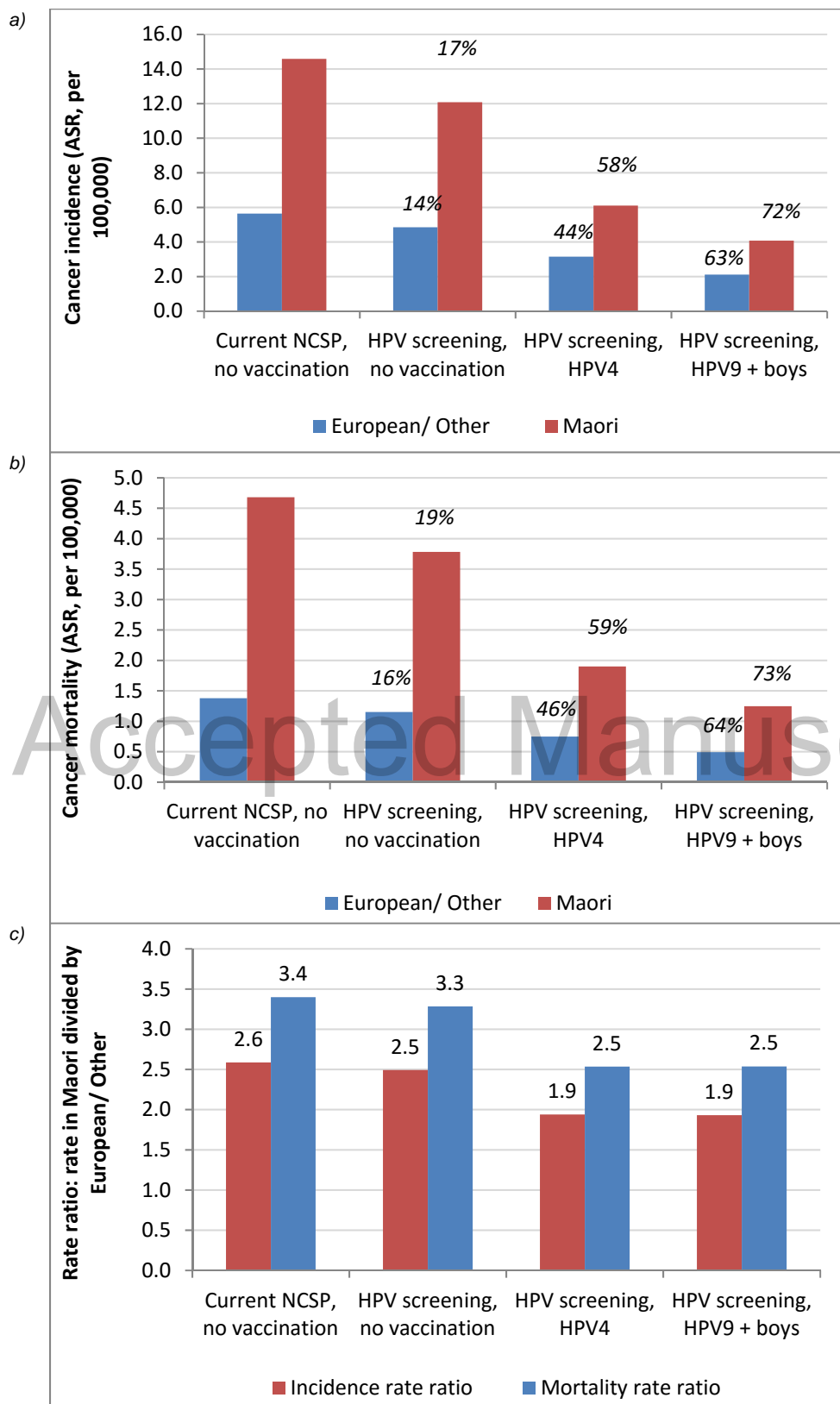
a)

b)

c)

Incidence and mortality rates are age-specific rates over the life of a cohort of females from age 10 until 84 years,

age-standardized using the WHO population [53]. % indicates the percentage reduction compared to rates in the

current NCSP, without vaccination.

Figure 3 – Combined impact of HPV4 vaccination and HPV-based screening on age-specific rates of cervical cancer incidence (a) and cervical cancer mortality (b) in Māori women and European/ Other women
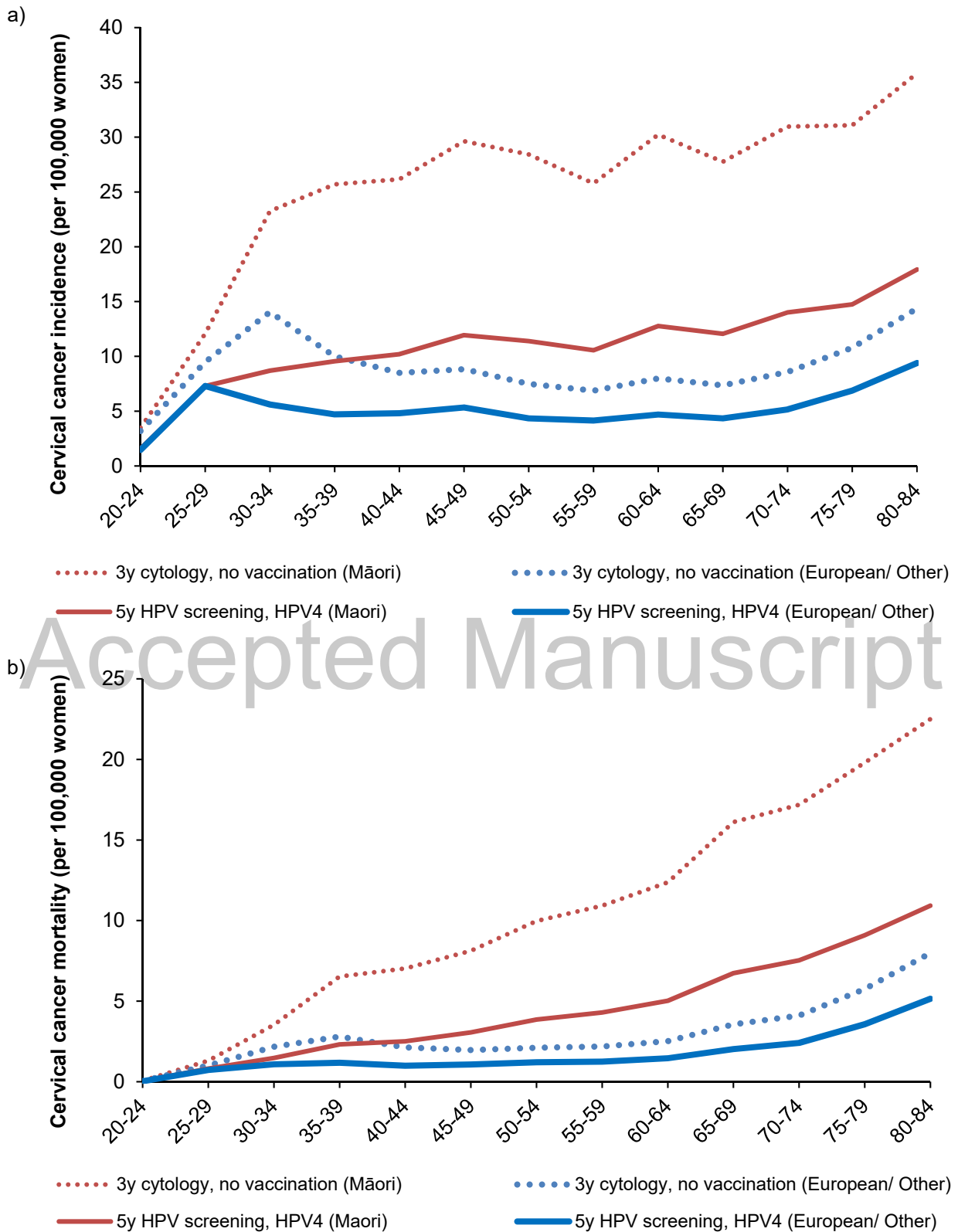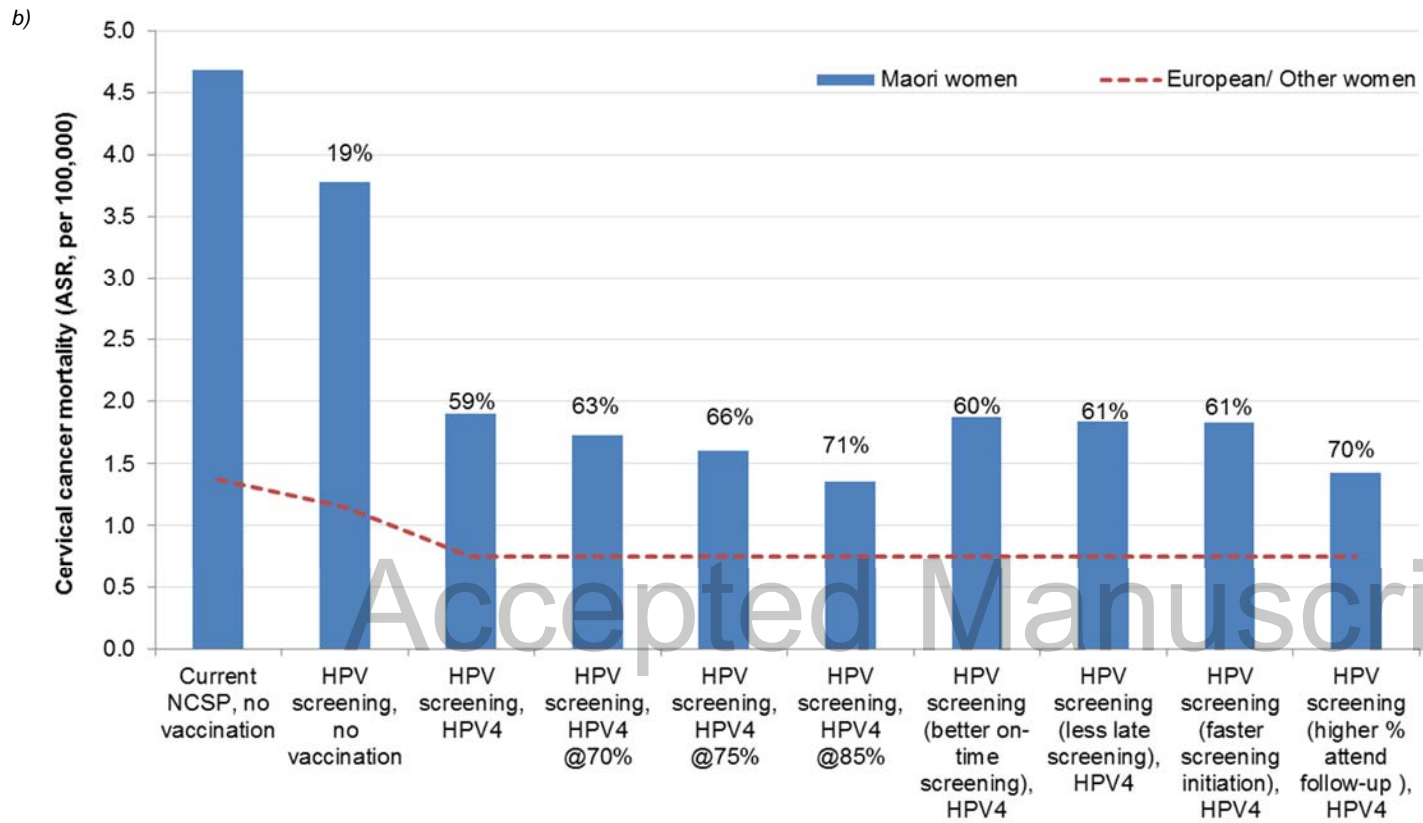

a)

b)

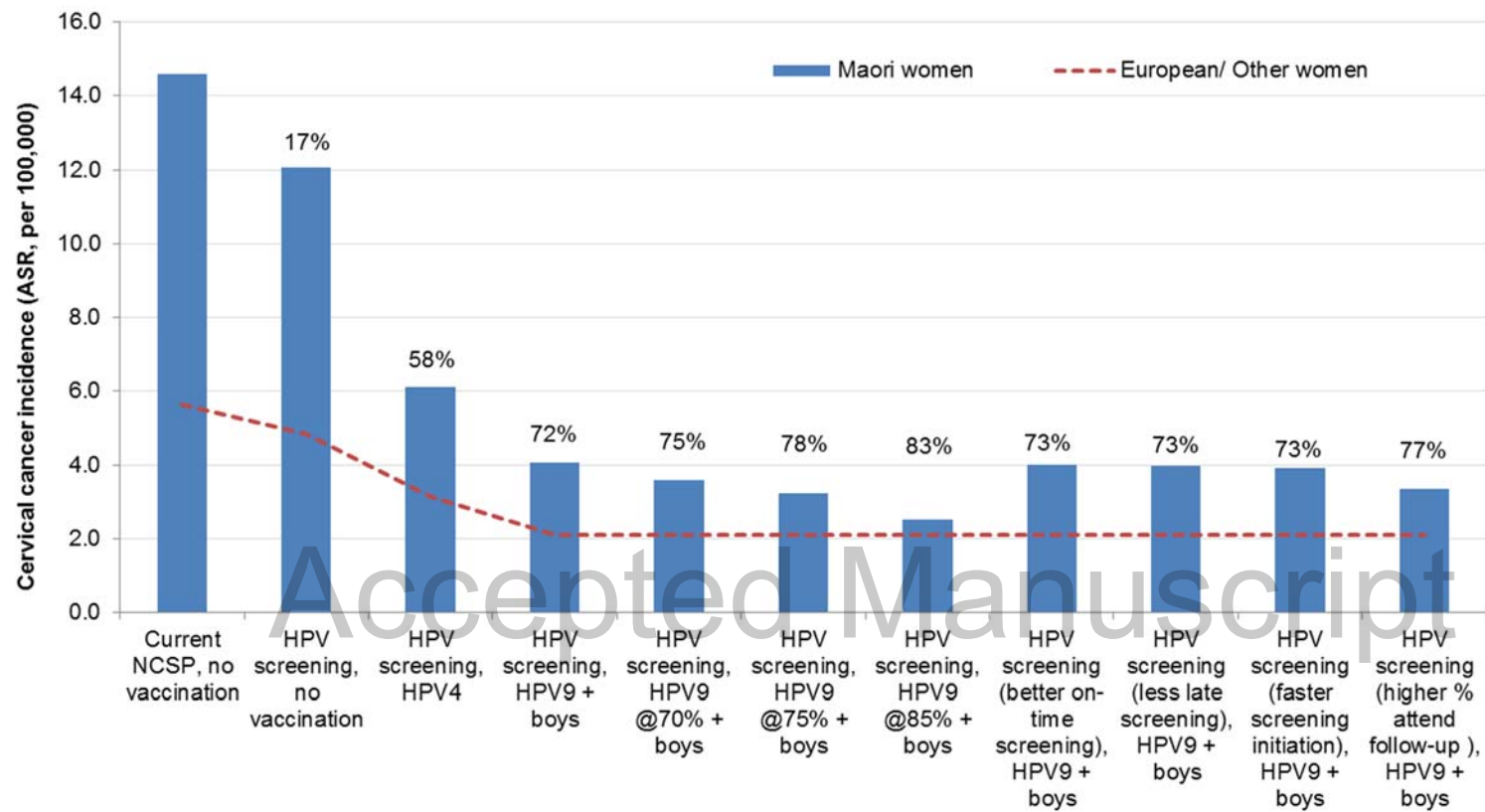*Incidence and mortality rates are age-specific rates over the life of a cohort of females from age 10 until 84 years,*

age-standardized using the WHO population [53]

485 **Figure 4 – Cervical cancer incidence and mortality in Māori women and European/ Other women, and relative reduction in the rates, in the context of**
486 **various improvements to cervical screening coverage or vaccination coverage in females, in the context of a),b) female-only HPV4 or c),d) both-sex**
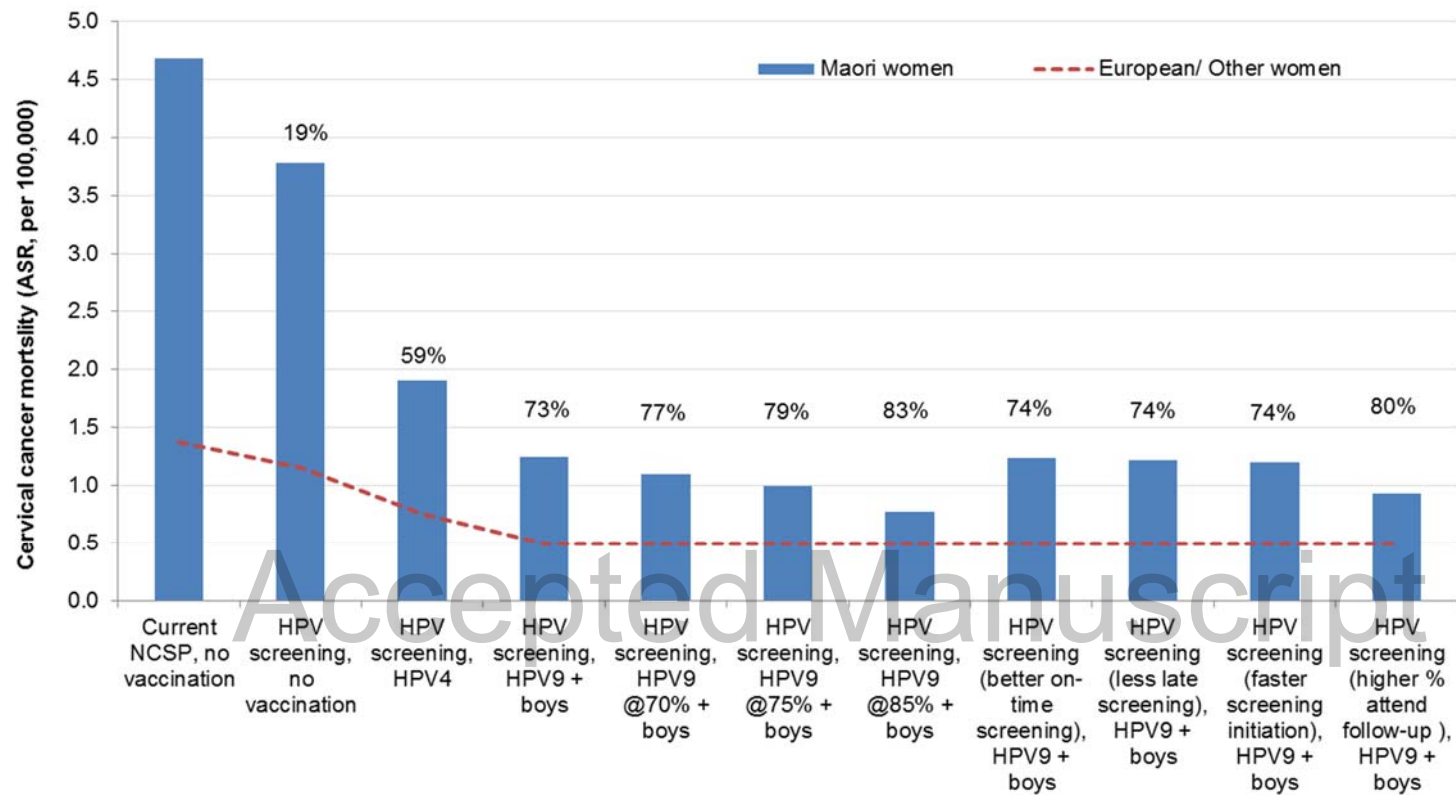487 **HPV9 program**

a)

b)
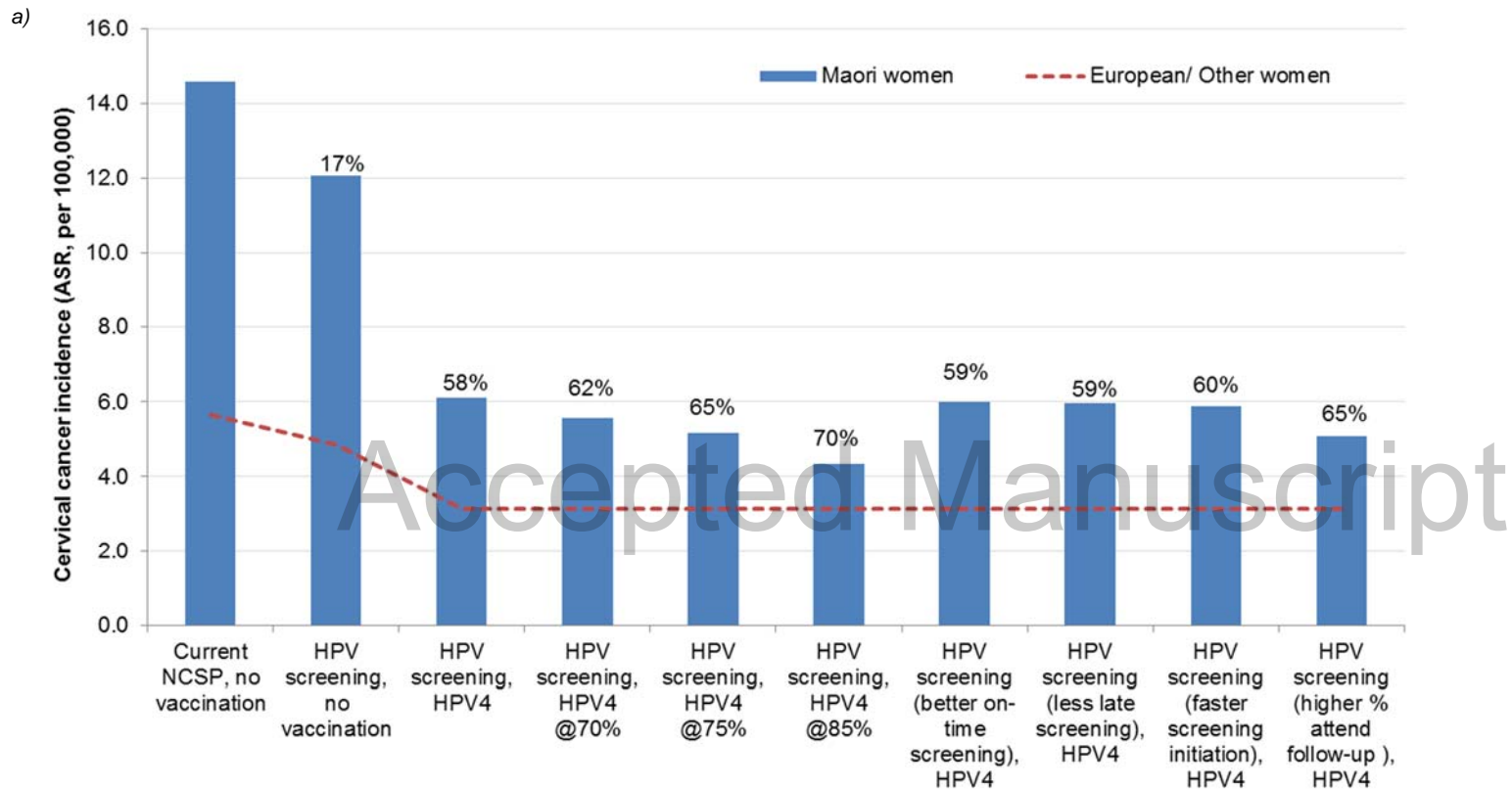
c)

d)

488   *Incidence and mortalityrates are age-specific rates over the life of a cohort of females from age 10 until 84 years, age-standardized using the WHO population [53]*

489   *% indicates the percentage reduction compared to rates in the current NCSP, without vaccination.*

490 **Figure 5 – Ratio of cervical cancer incidence and mortality rates in Māori women, relative to**
491 **rates in European/ Other women, in the context of various improvements to HPV4 vaccination**
492 **or cervical screening coverage**

493

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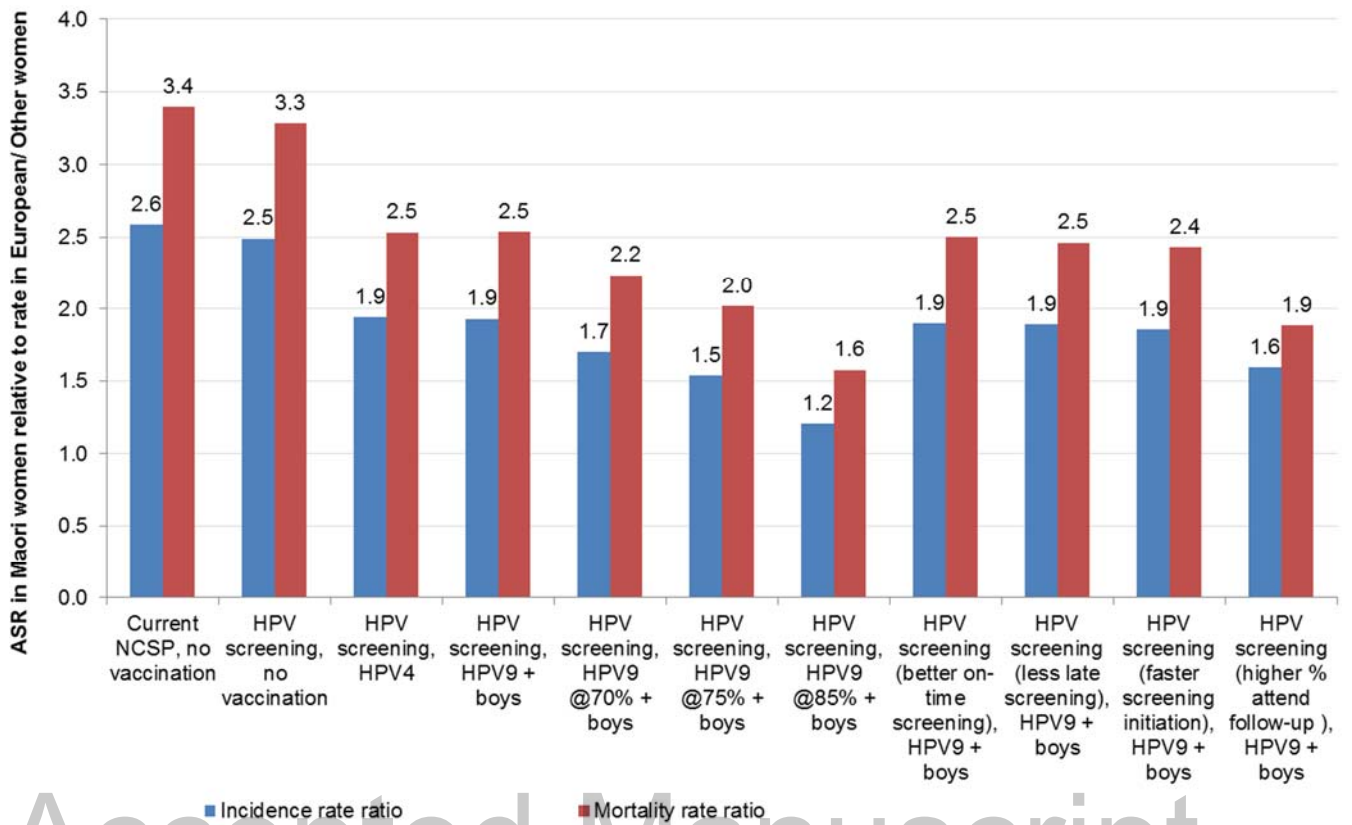
Tables

496 **Table 1 – Summary of scenarios considered**

Scenario	Relates to	Baseline value for Māori women [European/ Other women]	Improved value
HPV screening			
Better on-time screening	Proportion of women aged 25-74 years who re-attend for routine screening at the recommended interval of 5 years* †	43.3% [50.3%]	69.8%
Less late screening	Proportion of ever-screened women aged 25-74 years who re-attend for routine screening :		
	>7 years after their last screen (> 2 years overdue)*	3.5% [5.1%]	3.5%
	>8 years after their last screen (> 3 years overdue)*	3.3% [3.5%]	2.0%
	>10 years after their last screen (> 5 years overdue)*	2.9% [2.3%]	1.1%
Faster screening initiation	Proportion of women who attend for their first screen:		
	At or by age 25:	68.0% [68.7%]	75%
	At or by age 30:	81.7% [81.5%]	85%
Higher attendance for surveillance:	Proportion of women who re-attend for surveillance screening:		
After HG histology	At the recommended interval of 12 months*	29% [14%]	14%
	Cumulative by 4 years*	79% [94%]	94%
Other surveillance	At the recommended interval of 12 months*	28% [14%]	14%
	Cumulative by 4 years*	75% [84%]	84%
HPV vaccination			
HPV4 @ X%	Proportion of females fully vaccinated with HPV4 by age 16 (no male vaccination)	63% [47%]	70%; 75%; 85%
HPV9 @ X%	Proportion of females fully vaccinated with HPV9 by age 16 (53% of males vaccinated by age 16)	63% [47%]	70%; 75%; 85%

497 *Each scenario alters only the described screening/ vaccination parameters; all other screening/ vaccination parameters remain at baseline values (see Appendix1) NCSP =*
498 *National Cervical Screening Programme in New Zealand HPV4 = quadrivalent HPV vaccine that protects against HPV 6/11/16/18 HPV9 = 9-valent HPV vaccine that protects*
499 *against HPV 6/11/16/18/31/33/45/52/58   * Varies by age; value shown is age-standardised † Value shows cumulative proportion of women screened up to 5 years after their*
500 *last screen, however scenario change only affects women who are re-screened at exactly 5 years (ie no change in early re-screening).*

501

502 **Table 2 – Model-predicted cervical cancer incidence and mortality (ASR, per 100,000 females), in Māori and European/ Other women, in the context of different**
503 **vaccination and/or screening scenarios**

	ASR cervical cancer incidence (WHO, 0-84 years)				ASR cervical cancer mortality (WHO, 10-84 years)			
	Māori	European/ Other	Absolute difference	Rate ratio Māori: European/ Other	Māori	European/ Other	Absolute difference	Rate ratio Māori: European/ Other
Current NCSP (3y cytology), no vaccination	14.6	5.6	8.9	2.6	4.7	1.4	3.3	3.4
5y HPV screening, no vaccination	12.1	4.8	7.2	2.5	3.8	1.2	2.6	3.3
better on-time screening	11.9		7.0	2.5	3.7		2.6	3.2
less late screening	11.8		6.9	2.4	3.7		2.5	3.2
faster screening initiation	11.6		6.8	2.4	3.6		2.5	3.1
higher surveillance attendance	9.8		5.0	2.0	2.8		1.6	2.4
LG surveillance only	10.5		5.7	2.2	3.1		1.9	2.7
HG/ post-treatment surveillance only	11.4		6.6	2.4	3.5		2.3	3.0
5y HPV screening, HPV4	6.1	3.1	3.0	1.9	1.9	0.7	1.1	2.5
70% vaccine uptake	5.6		2.4	1.8	1.7		1.0	2.3
75% vaccine uptake	5.2		2.0	1.6	1.6		0.9	2.1
85% vaccine uptake	4.4		1.2	1.4	1.4		0.6	1.8
better on-time screening	6.0		2.9	1.9	1.9		1.1	2.5
less late screening	6.0		2.8	1.9	1.8		1.1	2.5
faster screening initiation	5.9		2.7	1.9	1.8		1.1	2.4
higher surveillance attendance	5.1		1.9	1.6	1.4		0.7	1.9
LG surveillance only	5.4		2.2	1.7	1.6		0.8	2.1
HG/ post-treatment surveillance only	5.8		2.6	1.8	1.8		1.0	2.3
5y HPV screening, HPV9	4.1	2.1	2.0	1.9	1.2	0.5	0.8	2.5
70% vaccine uptake	3.6		1.5	1.7	1.1		0.6	2.2
75% vaccine uptake	3.2		1.1	1.5	1.0		0.5	2.0
85% vaccine uptake	2.5		0.4	1.2	0.8		0.3	1.6
better on-time screening	4.0		1.9	1.9	1.2		0.7	2.5
less late screening	4.0		1.9	1.9	1.2		0.7	2.5
faster screening initiation	3.9		1.8	1.9	1.2		0.7	2.4
higher surveillance attendance	3.4		1.2	1.6	0.9		0.4	1.9
LG surveillance only	3.6		1.5	1.7	1.0		0.5	2.1
HG/ post-treatment surveillance only	3.8		1.7	1.8	1.1		0.7	2.3

504 *ASR = age-standardised rate; derived from age-specific rates over the life of a cohort of females from age 10 until 84 years, age-standardized using the WHO population* [53]

Potential for HPV vaccination and primary HPV screening to reduce cervical cancer disparities: example from New Zealand

Appendix 1:

Summary of vaccination and screening parameters

Contents

Accepted Manuscript

1 Vaccination

Vaccination uptake was based on observed data (including specific data downloads for coverage as at May, October and December 2013, February 2014 and September 2015) (1, 2). For comparability with an earlier analysis of HPV-based screening and vaccination across the overall female population in New Zealand (3), the primary cohort considered in the analyses was the one born in 1997. Vaccine uptake in other cohorts is included to take into account indirect protection from herd effects.

Where uptake data were not available above the age of 16 (as the cohorts had not attained that age at the time coverage data were reported), it was assumed that there was no further uptake after age 16, as data showed uptake was greatest at ages 12 and 13, with relatively small increase in coverage by age 15-16.

Vaccine uptake in the 1997 birth cohort was based on observed three-dose coverage at different time points, when they were aged 13, 15 and 16 years, and uptake at other ages was based on cohorts of similar age or with similar age-specific coverage patterns.

For catch-up cohorts of females born 1992-1996, it was assumed that the final observed uptake was achieved over the course of 2009 (the first year of the school-based program), when most of these females were offered vaccination at school.

Uptake in younger cohorts (born in 2002 or later) was based on two-dose coverage data for the cohort, and patterns observed in other cohorts (for example, that three-dose coverage by age 14-16 was similar to two-dose coverage achieved by age 13).

1.1 Māori females

Supplementary Table S 1 - Modelled vaccine uptake in Māori females

Birth year	Cumulative uptake by end of year when cohort turns that age (complete vaccine course)							
	12	13	14	15	16	17	18	19
1990	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**28.0%**
1991	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**28.0%**	**38.2%**
1992	0.0%	0.0%	0.0%	0.0%	0.0%	44.5%	44.5%	**44.5%**
1993	0.0%	0.0%	0.0%	0.0%	50.0%	50.0%	50.0%	**50.0%**
1994	0.0%	0.0%	0.0%	53.0%	53.0%	53.0%	53.0%	**53.0%**
1995	0.0%	0.0%	55.0%	55.0%	55.0%	55.0%	**55.0%**	55.0%
1996	0.0%	56.0%	56.5%	61.2%	63.0%	**64.0%**	64.0%	64.0%
1997	21.9%	**56.0%**	56.5%	**61.2%**	**63.0%**	63.0%	63.0%	63.0%
1998	21.9%	56.0%	**56.5%**	**60.0%**	60.5%	60.5%	60.5%	60.5%
1999	**35.3%**	**61.6%**	**64.0%**	67.5%	67.5%	67.5%	67.5%	67.5%
2000	**21.9%**	**59.0%**	64.0%	66.0%	66.0%	66.0%	66.0%	66.0%
2001	**21.0%**	61.6%	**64.0%**	70.0%	70.0%	70.0%	70.0%	70.0%
2002	35.3%	72.6%	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%

Bold cells are observed data

Hypothetical scenarios that explored higher coverage in Māori females (described in the main text) adjusted vaccine uptake in the cohort born in 1997 from age 12, and in cohorts born in later years, but not those born in earlier years. Coverage was scaled at all ages to achieve the higher hypothetical coverage by age 16 (as previously, it was assumed that there was no additional vaccine uptake after age 16 in cohorts offered vaccination when aged 12-13). While it is not in practise possible to alter the uptake in this birth cohort from age 12, this was a hypothetical scenario and it was desirable that the cohort used was consistent with the earlier population-level analysis (3). Use of this earlier cohort is likely conservative for two reasons: i) because vaccine uptake has increased over time and is higher in younger birth cohorts born after 1997 than the 1997 birth cohort, and ii) because herd effects

3

would be expected to be greater in cohorts born after 1997 than in the 1997 birth cohort, as more of the population is vaccinated.

1.2 European/ Other females

Supplementary Table S 2 - Modelled vaccine uptake in European/ Other females

Birth year	Cumulative uptake by end of year when cohort turns that age (complete vaccine course)							
	12	13	14	15	16	17	18	19
1990	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**42.0%**
1991	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**42.0%**	**50.8%**
1992	0.0%	0.0%	0.0%	0.0%	0.0%	52.5%	52.5%	**52.5%**
1993	0.0%	0.0%	0.0%	0.0%	50.0%	50.0%	50.0%	**50.0%**
1994	0.0%	0.0%	0.0%	49.0%	49.0%	49.0%	49.0%	**49.0%**
1995	0.0%	0.0%	47.0%	47.0%	47.0%	47.0%	**47.0%**	47.0%
1996	0.0%	40.0%	42.8%	44.5%	47.0%	**50.0%**	50.0%	50.0%
1997	16.6%	**40.0%**	42.8%	**44.5%**	**47.0%**	47.0%	47.0%	47.0%
1998	16.6%	40.0%	**42.8%**	**47.0%**	47.0%	47.0%	47.0%	47.0%
1999	**26.6%**	**48.0%**	**50.0%**	52.0%	52.0%	52.0%	52.0%	52.0%
2000	**16.6%**	**48.0%**	50.0%	52.0%	52.0%	52.0%	52.0%	52.0%
2001	**16.0%**	55.0%	**57.0%**	61.0%	61.0%	61.0%	61.0%	61.0%
2002	26.6%	55.0%	59.0%	59.0%	59.0%	59.0%	59.0%	59.0%

Bold cells are observed data

1.3 Males

Data on vaccine uptake in males were not available at the time of the current analysis (as this only commenced in 2017). We assumed uptake in males was equivalent to that in the female population overall (based on 53% by age 16) (1, 2). Uptake in males has been broadly similar to that in females in other settings with school-based vaccination programs (4-7). In the absence of more specific data on uptake and partnerships by ethnicity, vaccine uptake was assumed to be the same in the population of partners of Māori women and European/ Other women.

Supplementary Table S 3 - Modelled vaccine uptake in males

Birth year	Cumulative uptake by end of year when cohort turns that age (complete vaccine course)							
	12	13	14	15	16	17	18	19
1990	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**39.0%**
1991	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**39.0%**	**48.0%**
1992	0.0%	0.0%	0.0%	0.0%	0.0%	51.5%	51.5%	**51.5%**
1993	0.0%	0.0%	0.0%	0.0%	52.0%	52.0%	52.0%	**52.0%**
1994	0.0%	0.0%	0.0%	51.0%	51.0%	51.0%	51.0%	**51.0%**
1995	0.0%	0.0%	51.0%	51.0%	51.0%	51.0%	**51.0%**	51.0%
1996	0.0%	46.0%	48.4%	51.0%	53.0%	**55.0%**	55.0%	55.0%
1997	18.7%	**46.0%**	48.4%	**51.0%**	**53.0%**	53.0%	53.0%	53.0%
1998	18.7%	46.0%	**48.4%**	**52.0%**	52.2%	52.2%	52.2%	52.2%
1999	**29.8%**	**53.7%**	**56.0%**	59.0%	59.0%	59.0%	59.0%	59.0%
2000	**18.7%**	**53.0%**	56.0%	58.0%	58.0%	58.0%	58.0%	58.0%
2001	**18.0%**	58.7%	**61.0%**	66.0%	66.0%	66.0%	66.0%	66.0%
2002	29.8%	58.7%	66.0%	66.0%	66.0%	66.0%	66.0%	66.0%

Bold cells are observed data for overall New Zealand female population

4

2 Screening

## 2.1 Māori females

2.1.1 Screening initiation

The modelled analysis considered three screening initiation strategies. The first scenario, current practice, assumes conventional cytology offered for women aged 20-69 years. This scenario was modelled in order to compare model predictions with current practice, and also as a counterfactual, in order to compare the predicted impact of the proposed HPV-based program with what would have occurred had the existing cytology-based program continued. The second and third scenarios are the baseline and faster-initiation primary HPV screening strategies, where women are recommended to attend for routine screening in the age range of 25-74.

Supplementary Table S 4 - Summary of screening initiation assumptions under three uptake scenarios

Screening intervention	Model assumptions
Current screening practice (three-yearly cytology)	o Women do not initiate screening within the program until the age of 20, and women aged 70 who have never entered the screening program will not do so. o The median initiation age of Māori women is 21 years, which is based on observed data. [1]
Primary HPV screening with partial genotyping and LBC triage – baseline scenario	o Women do not initiate screening within the program until the age of 25, and women aged 70 who have never entered the screening program will not do so. o The proportion of women who initiates screening program at the age of 25 is the same as the proportion of women to have initiated screening by the age of 25 under the current screening practice intervention.
Primary HPV screening with partial genotyping and LBC triage – higher screening uptake scenario	o Women do not initiate screening within the program until the age of 25, and women aged 70 who have never entered the screening program will not do so. o Uptake patterns are based on the primary HPV screening with partial genotyping and LBC triage baseline scenario. Here we assume that women who have initiated screening by the age of 70 remains constant for both scenarios, however in this scenario women initiate screening at a faster rate (see Table 1 in main text).

Supplementary Figure S 1 summarises the cumulative age-specific proportion of Māori women to have screening at least once under the three screening initiation scenarios.

Supplementary Figure S 1 - Age-specific proportion of Māori women who have been screened at least once
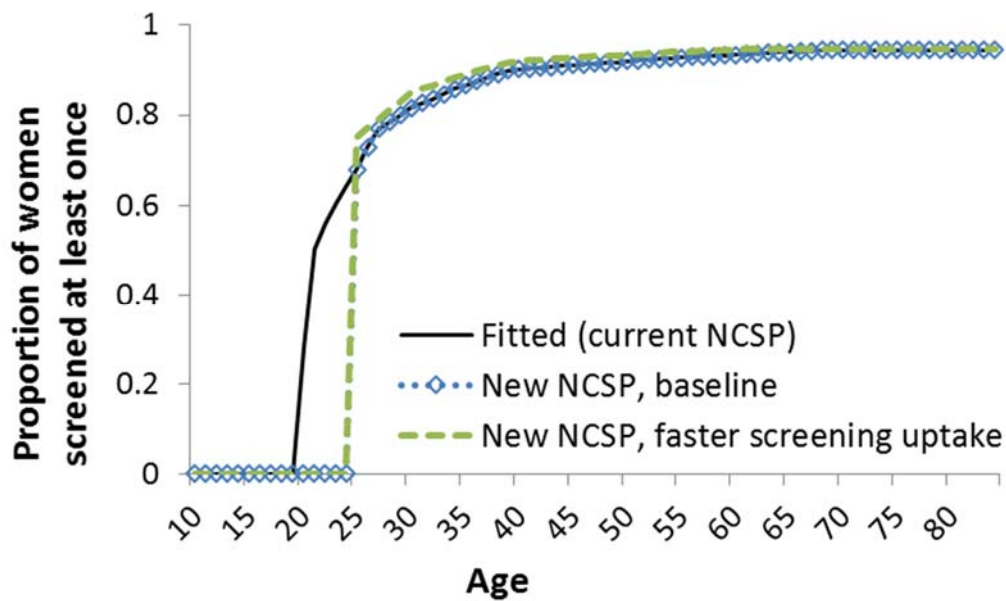

2.1.2 Rescreening probabilities

Age-specific re-screening probabilities under current practice are based on outcome of a woman's previous screening/follow-up test (including colposcopy and histology, where these were performed), the type of test she has been recommended to re-attend for, and the length of time since her previous test. These probabilities are obtained via calibration to observed early re-screening, three-year screening coverage and five-year screening coverage rates in Māori women from 2012 to 2014. The outcome of this calibration can be found in the calibration report (Appendix 2).

To obtain the age-specific routine re-screening probabilities under baseline five-yearly primary HPV screening with partial genotyping and cytology triage, re-screening probabilities under current practice were altered to maintain a similar proportion of women attending on-time, early and late for screening, but aligned with a five-year intervals, rather than the current three-year interval (Supplementary Figure S 2). We assume that the cumulative number of women to have attended for a routine screening test by seven years under five-yearly primary HPV screening is the same the cumulative number of women to have attended for a routine screening test by seven years under current screening practice. Additionally, we assume that compliance to follow-up management (including colposcopy) is the same under the new program as in the previous program.

As part of the main analysis, we explored the impact of higher screening participation in closing the disparity gap between Māori women and women of European/Other ethnicities. These additional scenarios are outlined in Table 1 in the main text.

Age standardised cumulative probabilities of re-attendance by time since last screen for Māori current practice, primary HPV screening (baseline), primary HPV screening (higher participation) and primary HPV screening (less under-screening) is visualised in Supplementary Figure S 2.

Supplementary Figure S 2 - Age-standardised* cumulative re-attendance probability for current screening practice (three-yearly) and three five-yearly screening scenarios in Māori women
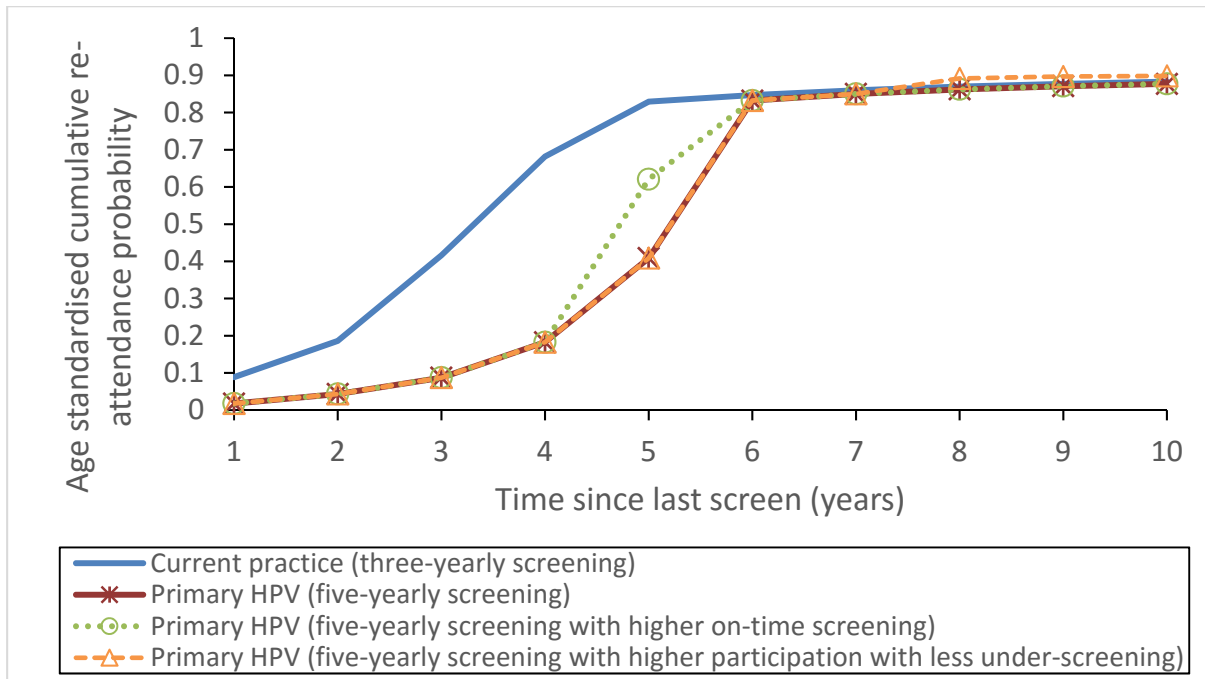
* Age-standardised (ages 25-74 years) using the estimated 2012 New Zealand female population

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2.2 European/Other females

2.2.1 Screening initiation

The modelled analysis considered two screening initiation strategies. The first scenario is relevant to current practice, where conventional cytology is offered for women aged 20-69 years. The second and third scenarios are for the baseline and faster-initiation primary HPV screening strategies, where women are recommended to attend for routine screening in the age range of 25-74.

Supplementary Table 1 - Summary of screening initiation assumptions under three uptake scenarios

Screening intervention	Model assumptions
Current screening practice (three-yearly conventional cytology)	o Women do not initiate screening within the program until the age of 20, and women aged 70 who have never entered the screening program will not do so.
	o The median initiation age of European/ Other women is 23 years, which is based on observed data. [1]
Primary HPV screening with partial genotyping and LBC triage - baseline	o Women do not initiate screening within the program until the age of 25, and women aged 70 who have never entered the screening program will not do so.
	o The proportion of women who initiates screening program at the age of 25 is the same as the proportion of women to have initiated screening by the age of 25 under the current screening practice intervention.

Supplementary Figure S 3 summarises the cumulative age-specific proportion of European/ Other ethnicity women to have screening at least once under the two screening initiation scenarios.

Supplementary Figure S 3 - Age-specific proportion of European/Other women who have been screened at least once
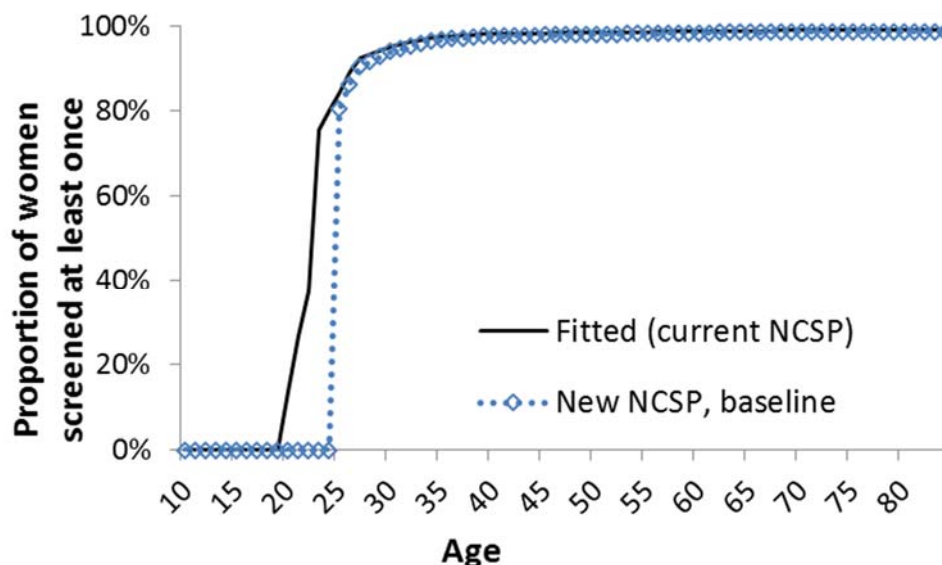
2.2.2 Rescreening probabilities

Age-specific re-screening probabilities under current practice are based on outcome of a women's previous screen, the type of test she will next attend, and the length of time since her previous test. These probabilities are obtained via calibration to observed early re-screening, three-year screening coverage and five-year screening coverage rates in European/ Other ethnicity women from 2012 to 2014. The outcome of this calibration can be found in the calibration report, supplementary text S1.

To obtain the age-specific routine re-screening probabilities under baseline five-yearly primary HPV screening with partial genotyping and cytology triage, re-screening probabilities under current practice were altered to prevent most early re-screening and assumes a high proportion of on time screening. However, we assume that the cumulative number of women to have attended for a routine screening test by seven years under five-yearly primary HPV screening is the same the cumulative number of women to have attended for a routine screening test by seven years under current screening practice. Additionally, we assume that compliance to follow-up management is the same under the new program as in the previous program.

Age standardised cumulative probabilities of re-attendance by time since last screen for European/ Other ethnicity current practice and primary HPV screening baseline is visualised in Supplementary Figure S 4.

Supplementary Figure S 4 - Age-standardised* cumulative re-attendance probability for current screening practice (three-yearly) and three five-yearly screening scenarios in European/ Other women
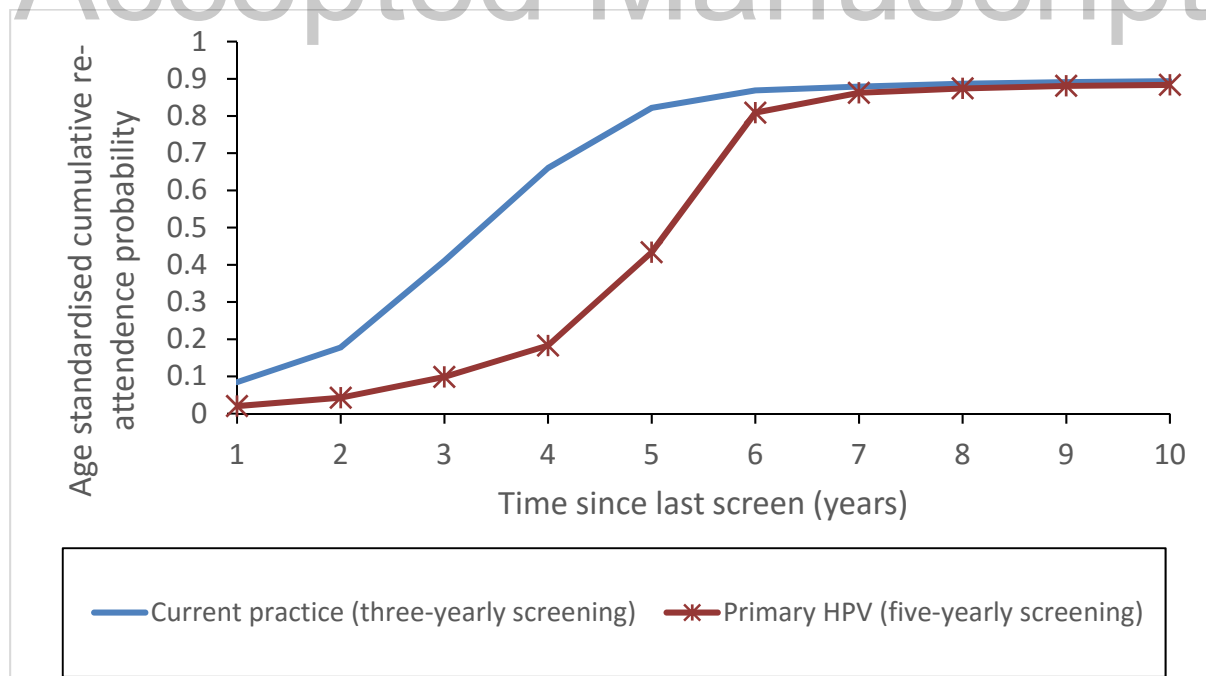
* Age-standardised (ages 25-74 years) using the estimated 2012 New Zealand female population

3 Colposcopy

The colposcopy compliance parameters for the overall female population for the current NCSP in New Zealand were based on reported data and fitting. Women who are recommended to attend colposcopy are assumed to have the same patterns of attendance in the new (5-yearly) primary HPV NCSP as they do in the current (3-yearly cytology) NCSP (ie whether or not a woman attends colposcopy is unaffected by the routine screening interval). In the current NCSP, there were some observed differences in colposcopy attendance based on the referral cytology result. This difference was also maintained in the new NCSP; however in the new NCSP women who test positive for HPV 16/18 will be referred directly for colposcopy, regardless of their cytology result. As there was no direct equivalent to this situation in the current NCSP, we assumed that the probability of these women attending would be midway between the probabilities for women referred following a low grade cytology result and following a high grade cytology result.

These existing baseline compliance parameters for the overall female population in New Zealand were varied for Māori women by scaling the attendance rate for New Zealand women overall according to the observed relative attendance for follow-up by Māori women in the current NCSP (8).

Supplementary Table S5 – Percentage of women attending colposcopy within 12 months of receiving a recommendation, by ethnic group

Reason for colposcopy	NZ overall		Māori women		European/ Other women	
	Aged <70[a]	Aged 70+	Aged <70[a]	Aged 70+	Aged <70[a]	Aged 70+
High grade cytology[b]	90% (85.9 – 91.5%)	70.5%	86% (82.3 – 87.7%)	67.5%	90% (85.9 – 91.5%)	70.5%
Low grade cytology[c]	87% (82.3 – 91.7%)	85.6%	82% (77.8 - 86.8%)	81.0%	87% (82.3 – 91.7%)	85.6%
Post-treatment [d]	75% (51.5 – 97.8%)	38.6%	73% (49.3 – 93.8%)	37.0%	75% (51.5 – 97.8%)	38.6%
HPV16/18 positive [e]	88% (86.0 - 89.7%)	78.0%	84% (81.9 – 85.5%)	74.3%	88% (86.0 - 89.7%)	78.0%

a Range reflects variation by age b Includes women referred following high grade cytology (ASC-H+; current NCSP) or women who are test positive for non-16/18 types and ASC-H+ (primary HPV NCSP)   c Includes women referred following a positive HPV triage test, or with persistent LG cytology (current NCSP) d Includes women referred following e In the primary HPV NCSP, these women are referred directly to colposcopy regardless of cytology result; set to the midpoint of compliance following HG and LG cytology

4   References

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Potential for HPV vaccination and primary HPV screening to reduce cervical cancer disparities: example from New Zealand

Appendix 2:

Calibration report for models of HPV vaccination, cervical screening and natural history for Maori and European/Other women in New Zealand

Contents

1   Maori women

1.1   Summary

The output of the Maori-specific natural history and cervical screening model were calibrated to the following data observed in New Zealand:

- The early-rescreening rate observed in Maori women in 2014.(1)
- Age-specific three- and five- year coverage rates observed in Maori women from 2012-2014. (1)
- Histologically-confirmed abnormalities rate observed in Maori women in 2012.(2)
- Age-specific histologically-confirmed CIN2/3 rates observed in Maori women in 2012 (based on an analysis of NCSP Register data).
- The age-specific and age-standardised rates of cervical cancer observed in 2008-2012 and cervical cancer mortality rate observed in 2006-2010. (2)
- Cervical cancer stage distribution in Maori women analysed from New Zealand Cancer Registry data.(3)
- Proportion of HPV 16 and HPV 18 infections among cervical cancer cases diagnosed in Maori women based on the findings Sykes e.t al. 2014. (4)

1.2   Screening participation

We modified screening and follow-up re-attendance assumptions, given a women's last test result, to calibrate the model-predicted early-rescreening rate and 3- and 5- years screening coverage rates with data observed in Maori women in 2014. (1, 2) For a detailed description of model input parameters relating to screening uptake and participation, please refer to supplementary text S2. The calibrated model's predictions compare well with the observed rates in New Zealand shown in Figure 1 and Figure 2.

Figure 1 Proportion of Māori women re-screened within 30 months: model prediction vs observed New Zealand data
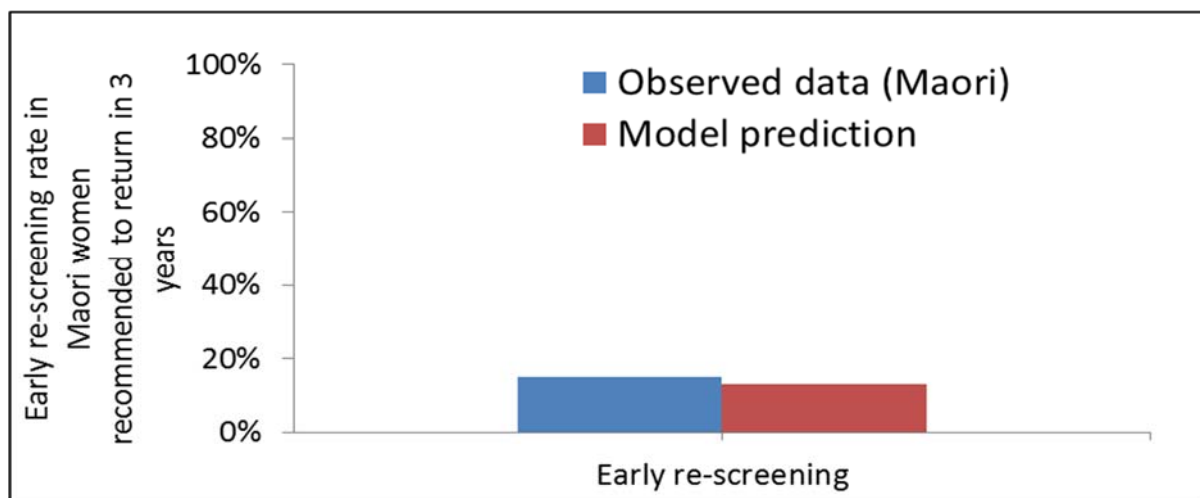
Observed data for the proportion of women with an index test recommendation in 2011 to return at the routine interval of 3 years who are re-screened early (within 30 months) of their index screening test (1).

Figure 2 Age-specific proportion of Maori women screened in the preceding (a) three and (b) five years: model predictions vs observed New Zealand data
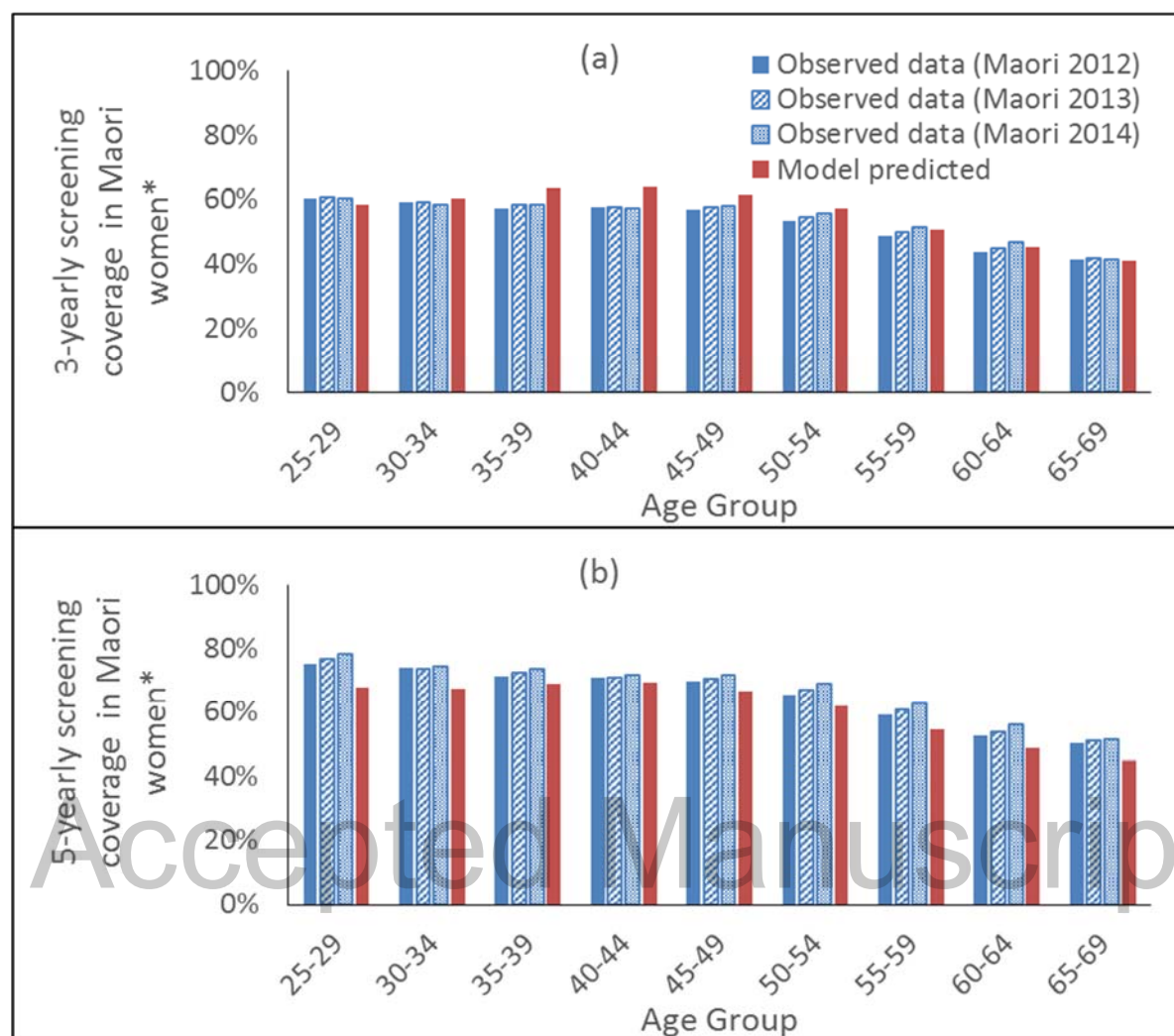

Observed data for women screened in the 3-year periods ending 2012, 2013, 2014, as a proportion of the hysterectomy-adjusted female population [2].

1.3 Histology outcomes

Model-predicted histologically-confirmed abnormalities rates among Maori women are calibrated to data observed in New Zealand in 2012, from the National Cervical Screening Program (NCSP) Register. Figure 3 compares the model-predicted histologically-confirmed Negative/HPV, CIN1 and CIN2/3 per 1,000 Maori women screened with observed data (age-standardised rates; women aged 20-69 years)(2). The estimated histology-confirmed CIN1 and CIN2/3 rate are consistent with the observed data. The estimated histologically-confirmed negative/HPV rate is lower than the data observed (Figure 3); however, this is related to the data recorded on the NCSP Register. The observed data from the NCSP Register includes all histology with a cervical component, including benign hysterectomy samples, not all of which are related to the screening program (whereas only program-related histology samples are captured in the model). More recent monitoring reports show that approximately 35% of

the negative/ benign histology recorded on the NCSP Register data originate from benign hysterectomy samples (5).

Figure 3 Histology outcomes per 1,000 Maori women screened (age 20-69 years): model prediction vs observed New Zealand data
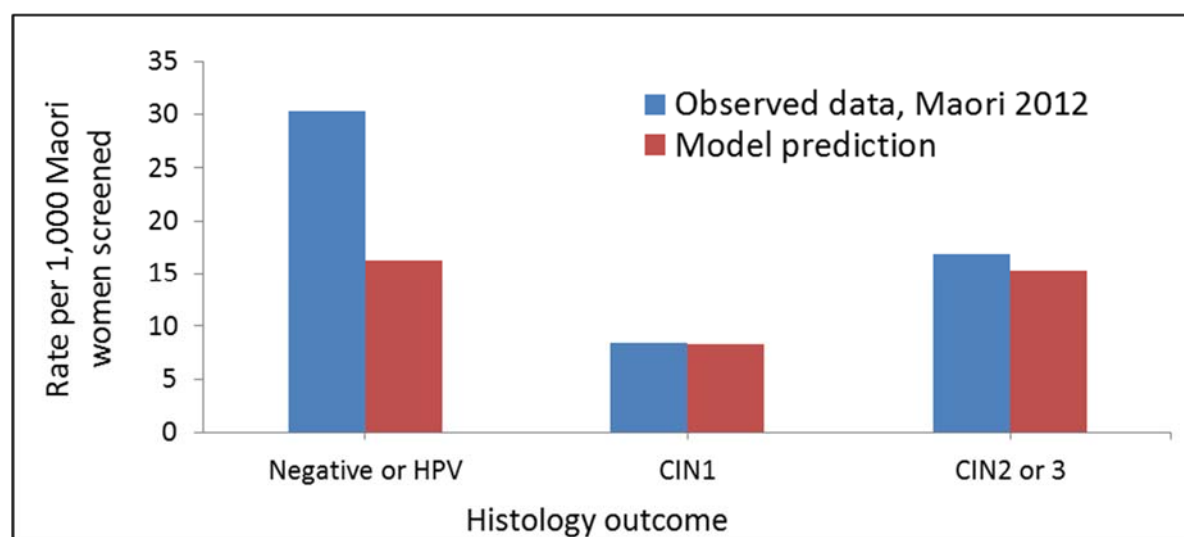
*Observed data in 2012**(2)***

Model-predicted histologically-confirmed CIN2/3 rates per 1,000 Maori women screened were further calibrated by five-year age group to observed data (based on an analysis of data from the NCSP Register), and rates are broadly consistent with the observed data (Figure 4).

Figure 4 Age-specific rates of histologically-confirmed CIN2/3 per 1,000 Maori women screened: model prediction vs observed New Zealand data
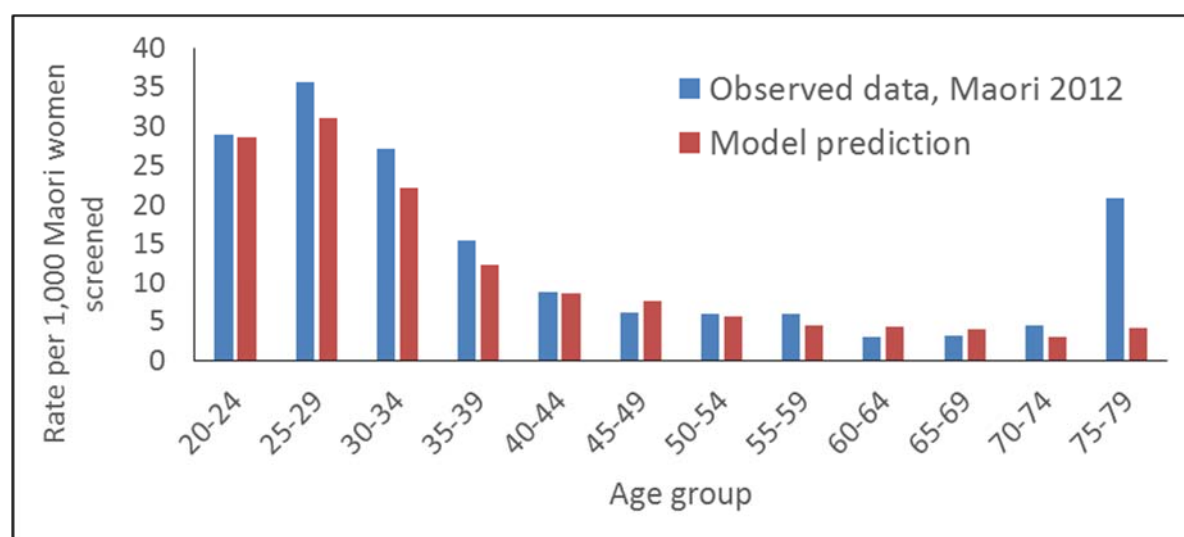
Table 1 compares the model estimated number of women undergoing histology evaluation with data observed in 2012. (2) Discrepancies between the model predictions and observed data are larger when comparing case numbers. The model predicted a total of 1,546 Maori women aged between 20 and 69 years had a histology evaluation in 2012 (based on estimated 2012 Maori population(6)). These are

broken down further by histological result in Table 1. All of the model-predicted numbers are lower than the observed data (2), in particular for negative/HPV histology (Table 1).

As many other predicted outcomes compare well with observed targets for New Zealand, it is possible that factors other than model or parameterisation error contribute to the target rate of women with histology (and particularly women with negative/HPV histology) being higher than model predictions. In particular, and as noted earlier in relation to rates, the large difference in predicted numbers of negative/ HPV histology is likely due to the broader range of samples captured in the observed data from the NCSP Register (which includes all histology with a cervical component, including benign hysterectomy samples, not all of which are related to the screening program) than in the model (which only captures screening program-related histology samples). More recent monitoring reports show that approximately 35% of the negative/ benign histology recorded on the NCSP Register data originate from benign hysterectomy samples (5). Additionally, more women with low-grade cytology outcome underwent colposcopy and histology evaluation in the observed data than what was modelled.

Table 1 Histology results in Maori women aged 20-69 years: model prediction vs observed New Zealand data (2012)

	Negative/ HPV	CIN1	CIN2/3	Cancer	Other	Total
Observed data(2)	1,374	402	800[a]	43[b]	14 [c]	2,633
Model prediction[d]	688	297	560	41[d]	n/a	1,546

a Includes women with the following histology outcomes: CIN2, CIN3 and HSIL not otherwise specified b Includes women with the following histology outcomes: microinvasive, invasive SCC, invasive adenocarcinoma, adenosquamous carcinoma and other cancer c Includes women with the following histology outcomes: glandular dysplasia, adenocarcinoma in situ d Assuming 2012 Maori population (ages 20-69 years)(6)

This result is consistent with results presented in Figure 5, which displays age-specific model-predicted number of histology tests performed in 2012 on Maori women, against data observed in 2012 (based on an analysis of NCSP Register data).

Figure 5 Age-specific number of Māori women with histology tests: model prediction vs observed New Zealand data
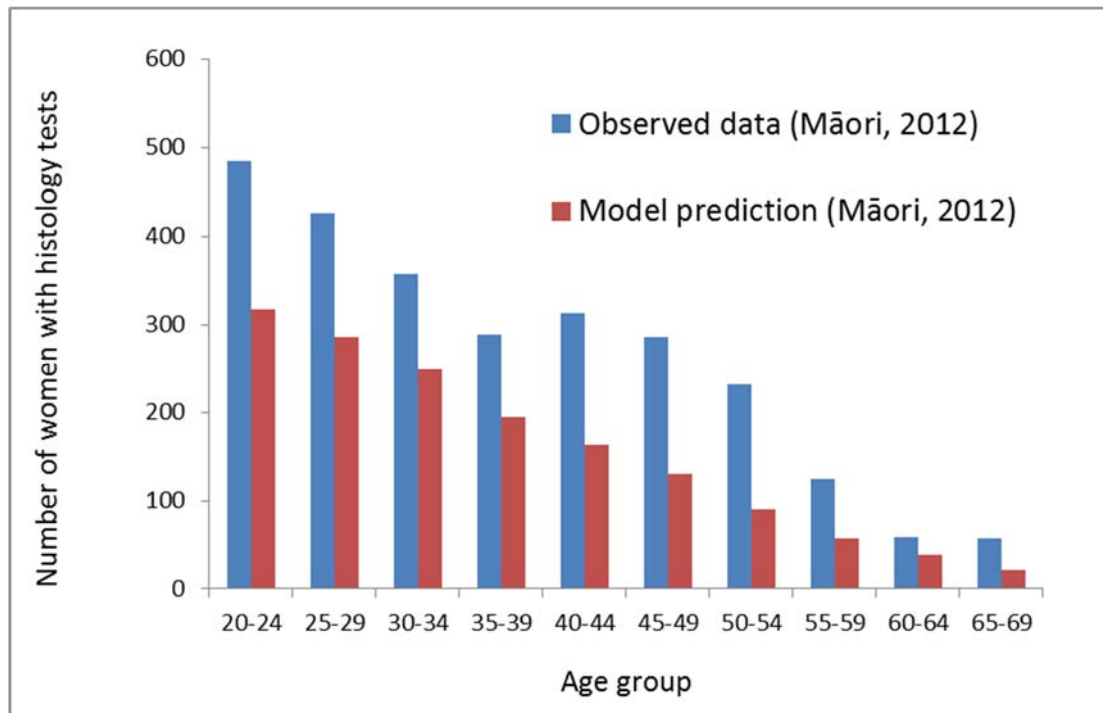
In addition to histology volumes, we calibrated to HPV prevalence among histologically-detected CIN2/3, for HPV type 16, types 16 and/or 18 and high risk types not 16 and/or 18.
Model predictions compare well to the observed data for age-specific HPV 16 prevalence in CIN2/3. However for the younger age group (20-29 years), model predictions do not compare well for HPV 16 and/or 18 and high risk HPV not 16 and/or 18 prevalence among CIN2/3. This is illustrated below in Figure 6.

Figure 6 Prevalence of (a) HPV16 only, (b) HPV16 and/or 18, and (c) other HPV types (not 16 and/or 18) in Māori women with histologically-detected CIN 2/3: model prediction vs observed New Zealand data
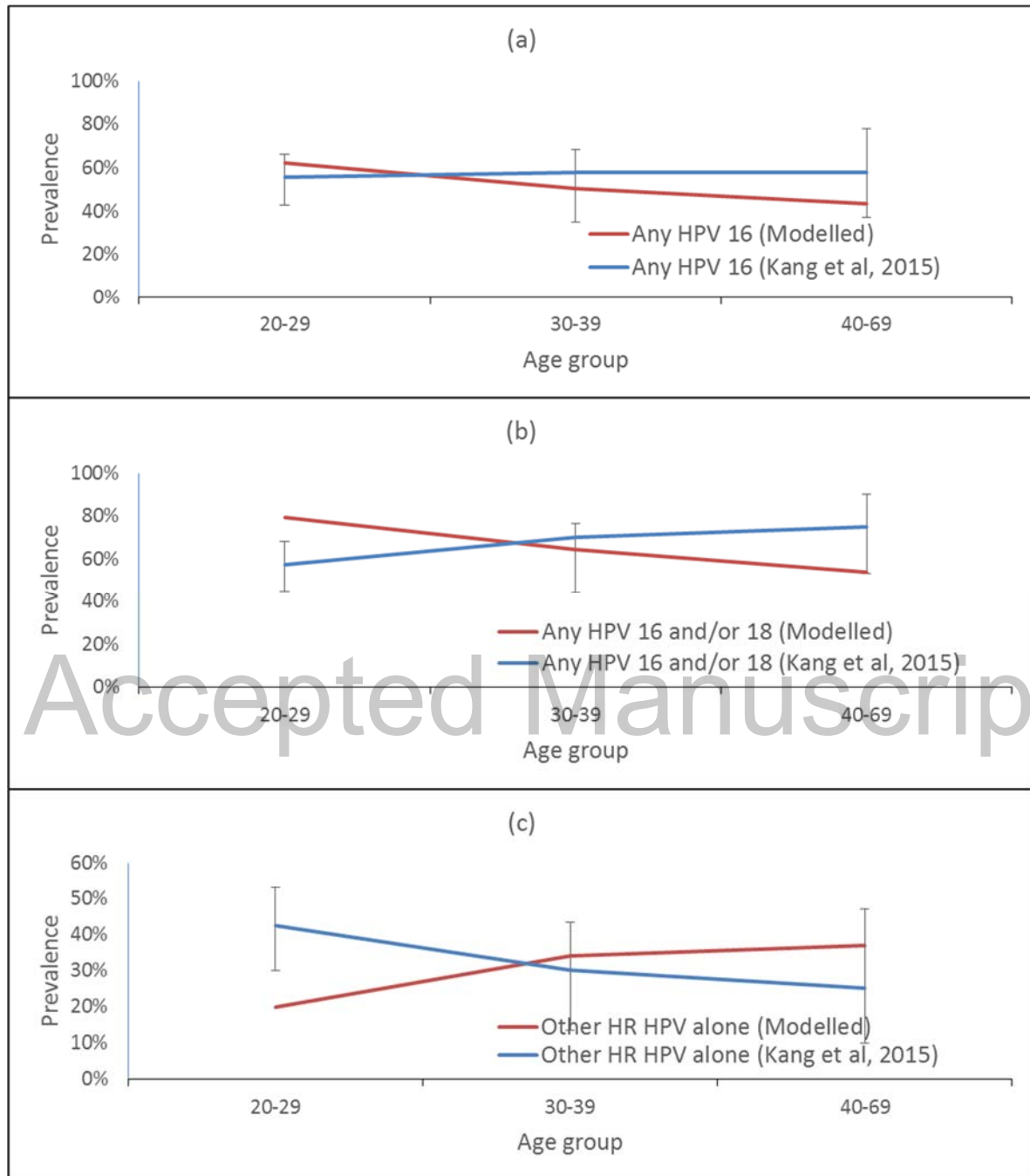
Observed data from Aug 2009 – Jun 2012 (extended recruiting period for Māori women) (7)

1.4   Cervical cancer incidence and mortality

The model is calibrated to the average cervical cancer rate observed in 2008-2012 and average cervical cancer mortality rate observed in 2006-2010 in New Zealand(2). Figure 7 and Figure 8 show the model-predicted incidence and mortality rates are in close agreement with the observed data. The estimated

age-standardised rate of cervical cancer incidence and cervical cancer mortality are also consistent with the data observed in New Zealand(2) (Table 2).

Figure 7 Age-specific cervical cancer incidence per 100,000 Maori women: model prediction vs observed New Zealand data (2008-2012)
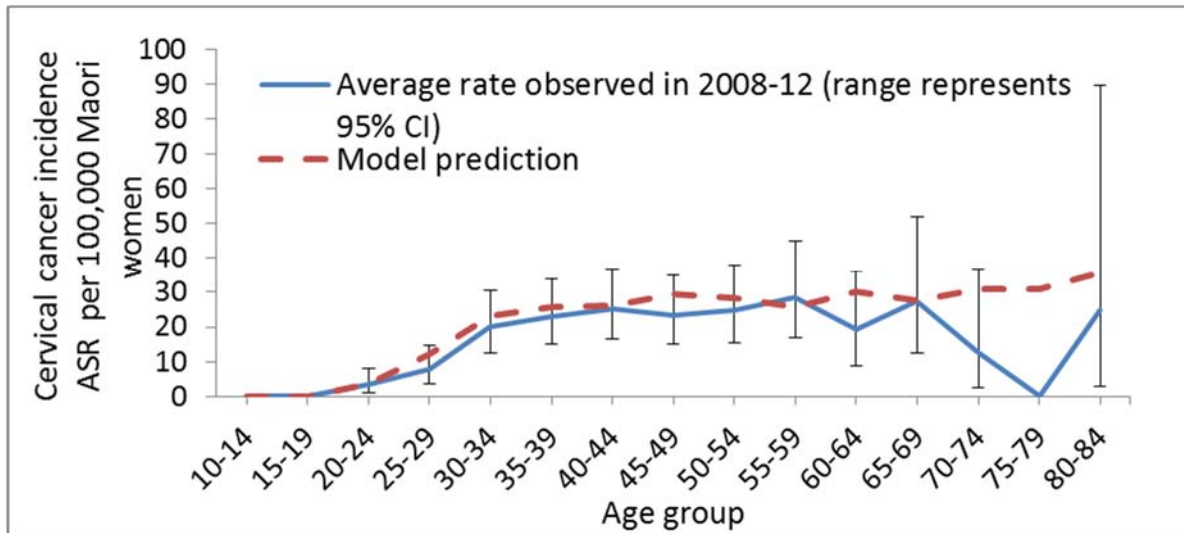
Observed data shows mean and range during the period 2008-2012(2)

Figure 8 Age-specific cervical cancer mortality per 100,000 Maori women: model prediction vs observed New Zealand data (2006-2012)
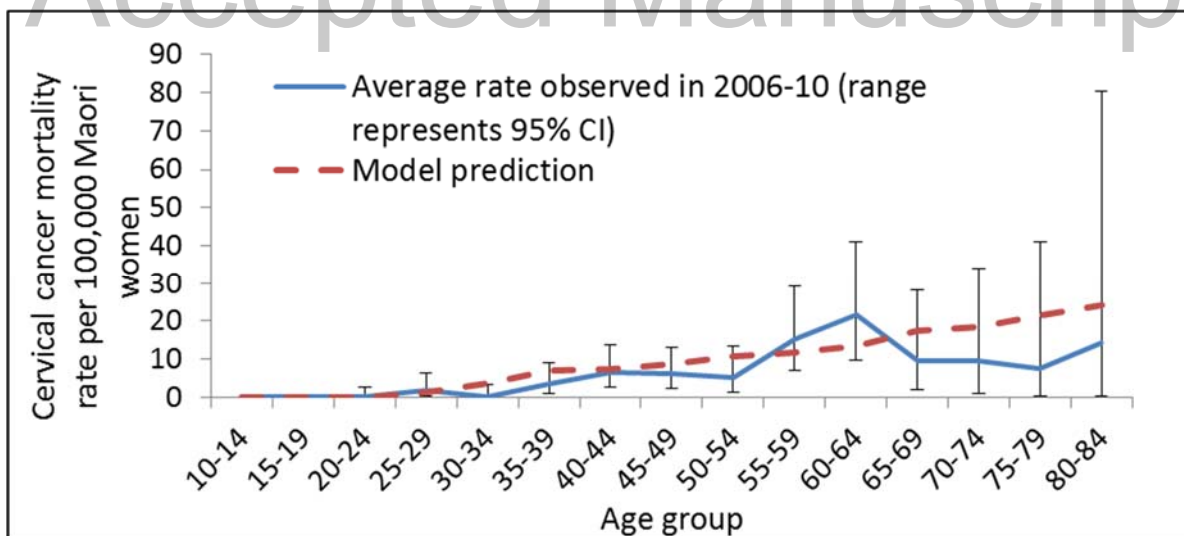
Observed data for 2006-2010(2)

Table 2 Cervical cancer incidence and mortality among Māori women: model prediction vs observed New Zealand data

Category	Cervical cancer incidence		Cervical cancer mortality	
	ASR	Cases	ASR	Deaths
Observed data	12.0 (range: 10.5-13.4) [a]	35.2 (range: 29-40)[a]	4.0 (range: 3.2-4.8) [b]	10 (range: 8-12) [b]
Model prediction	14.5	42.7[c]	4.7	12.2[d]

ASR – Age-standardised rate (per 100,000 women), using WHO standard population (8)

a Mean and range observed over 2008-2012(2)   b Mean and range observed over 2006-2010(2)   c Assuming 2010 Maori population (ages 0-84 years only) (6)   d Assuming 2008 Maori population (ages 0-84 years only) (6)

1.5 Cervical cancer stage distribution at diagnosis

The model-predicted cervical cancer stage distribution among newly diagnosed cervical cancer cases is calibrated to the stage distribution analysed from the cervical cancer cases with a known cancer stage diagnosed in 2001-2008 recorded by the New Zealand Cancer Registry(3) . Figure 9 below shows the model prediction is in good agreement with the observed data.
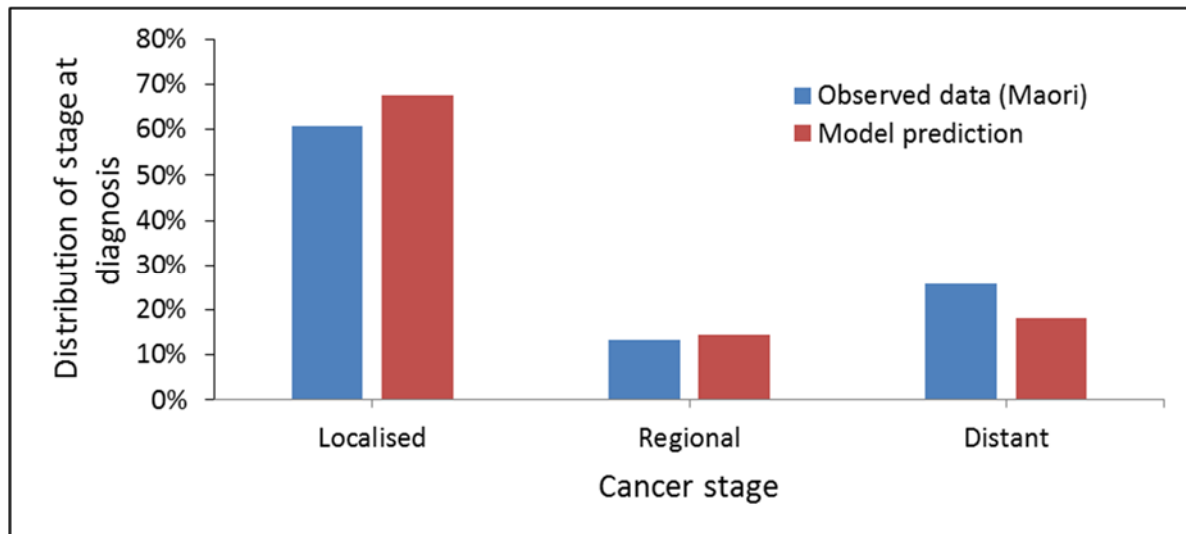
Figure 9 Distribution of cancer stage among newly diagnosed cervical cancer cases in Māori women: model prediction vs observed New Zealand data
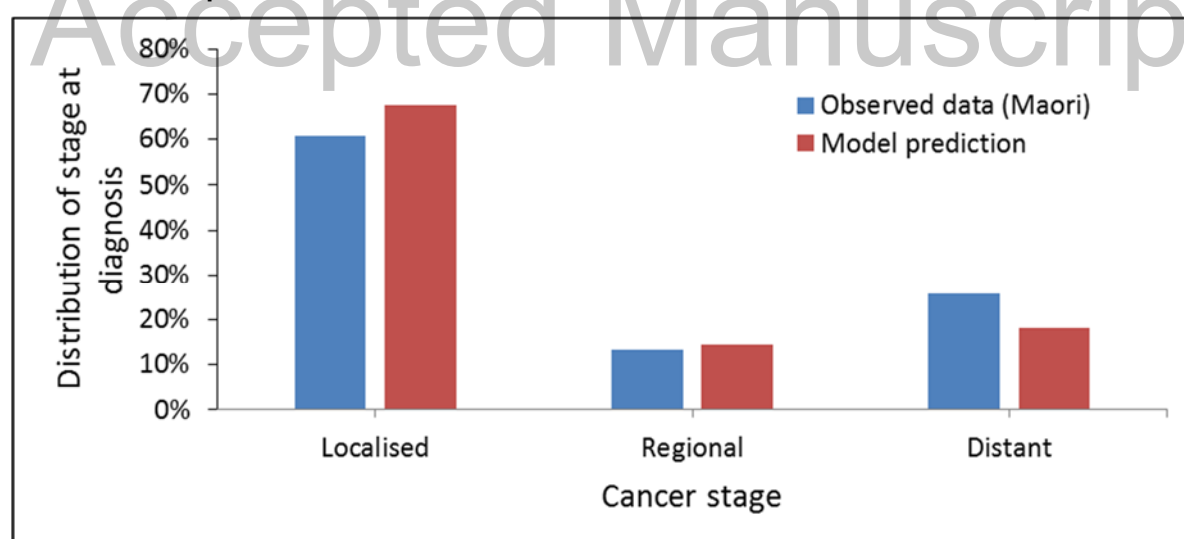
1.6 HPV type distribution in cervical cancers

The predicted proportion of newly diagnosed cervical cancer with HPV 16 and HPV 18 infections are calibrated to findings Sykes e.t al. 2014(4) among the 29 cases with high-risk HPV infections diagnosed in Maori women. Figure 10 below shows the model prediction is in good agreement with the calibration target.

Figure 10 HPV type distribution among newly diagnosed cervical cancer cases in Maori women: model prediction vs observed New Zealand data

2 European/Other women

2.1 Summary

The output of the European/Other-specific natural history and cervical screening model were calibrated to the following data observed in New Zealand:

- The early-rescreening rate observed in European/other ethnicity women in 2014.(1)
- Age-specific three- and five- year coverage rates observed in European/other ethnicity women from 2012-2014. (2)
- Histologically-confirmed abnormalities rate observed in European/other women in 2012. (2)
- Age-specific histologically-confirmed CIN2/3 rates observed in European/other ethnicity women in 2012 (based on an analysis of NCSP Register data).
- The age-specific and age-standardised rate of cervical cancer rate observed in 2008-2012 and cervical cancer mortality rate observed in 2006-2010. (2)
- Cervical cancer stage distribution in non-Maori women analysed from New Zealand Cancer Registry data. (3)
- Proportion of HPV 16 and HPV 18 infections among cervical cancer cases diagnosed in non-Maori women in New Zealand, based on observed data from Sykes et al 2014. (4)

2.2 Screening participation

We modified screening and follow-up re-attendance rate assumptions given a women's last test result to calibrate the model-predicted early-rescreening rate and three- and five-year screening coverage rates with data observed in European/other ethnicity women (1, 2). For a detailed description of model input parameters relating to screening uptake and participation, please refer to Appendix 1. The predicted early-re-screening rate (Figure 11) and age-specific 3- and 5- years screening coverage rates (Figure 12) in European/other women compare well with the observed data.

Figure 11 Proportion of European/Other women re-screened within 30 months: modelled vs observed New Zealand data
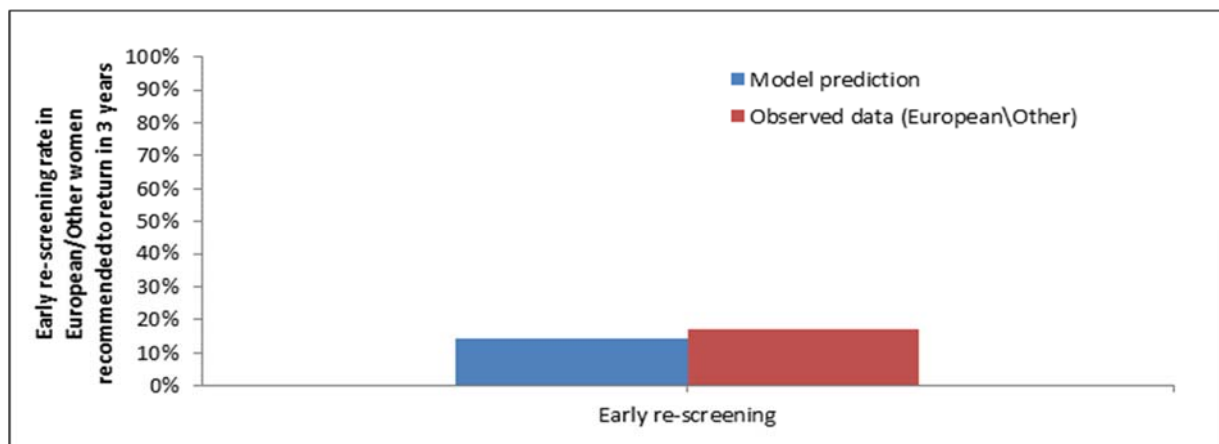
Observed data for the proportion of women with an index test recommendation in 2011 to return at the routine interval of 3 years who are re-screened early (within 30 months) of their index screening test (1).

Figure 12 Age-specific proportion of European/Other women screened in the preceding (a) three and (b) five years: model predictions vs observed New Zealand data
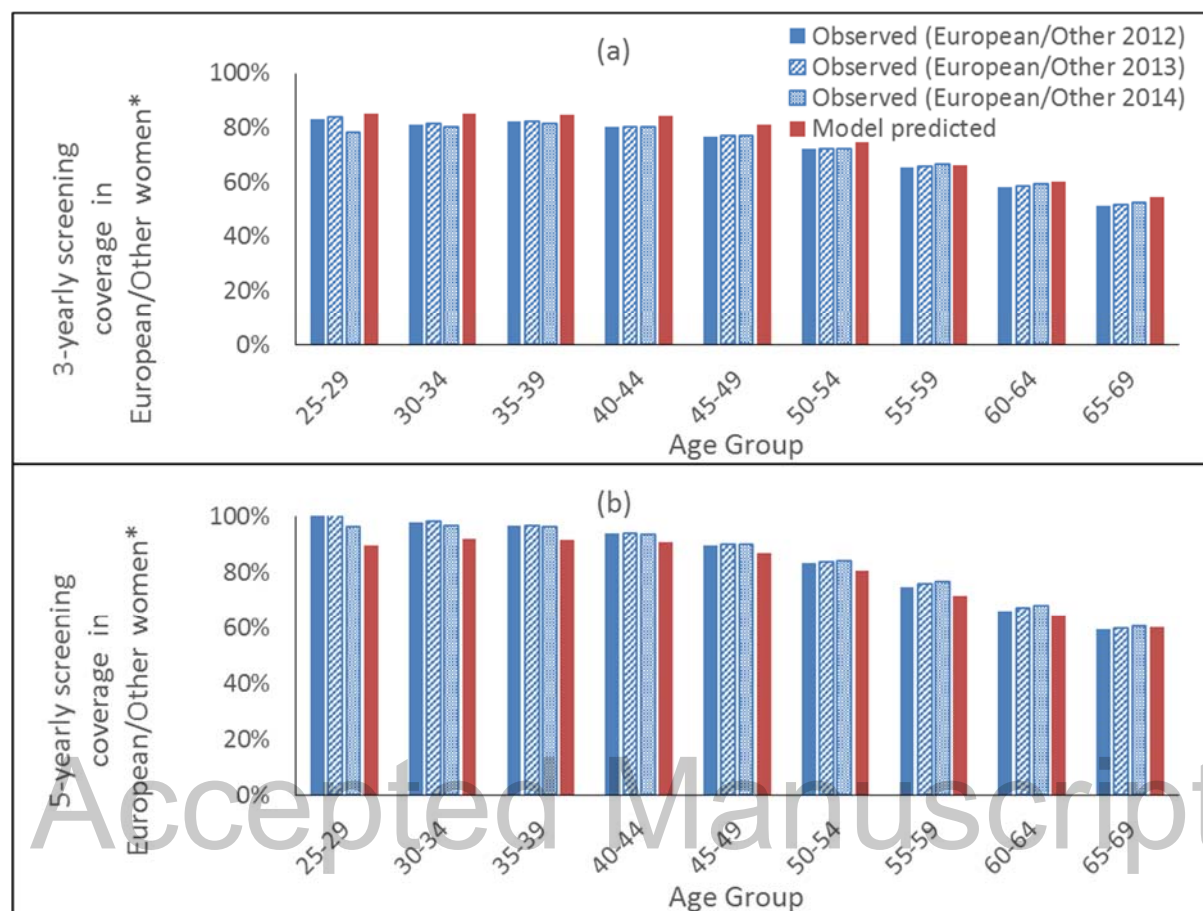
Observed data for women screened in the 3-year periods ending 2012, 2013, 2014, as a proportion of the hysterectomy-adjusted female population [1, 2].

2.3 Histology outcomes

Model-predicted histologically-confirmed abnormalities rates among European/other ethnicity women are calibrated to data observed in the New Zealand National Cervical Screening Program in 2012. [2] Figure 13 compares the model-predicted histologically-confirmed negative/HPV, CIN1 and CIN2/3 per 1,000 European/other ethnicity women screened with the observed data. The predicted rate of histologically-confirmed negative/HPV and CIN1 are lower compared to what was observed in NCSP, whereas CIN2/3 histology rates are in close agreement with the observed data. As noted when discussing the results for Māori women in section 1.3, the differences in rates of negative/HPV histology are likely due to the broader range of samples captured in the observed data from the NCSP Register.

Figure 13 Histology outcomes per 1,000 European/ Other women screened (age 20-69 years): model prediction vs observed New Zealand data
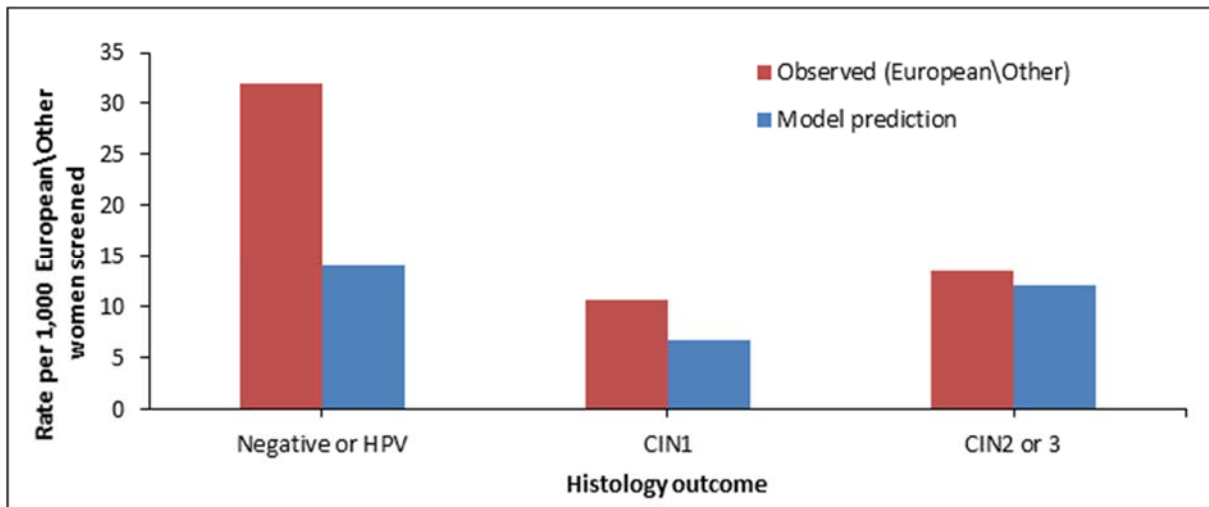
Observed data in 2012(2)

Model-predicted histologically-confirmed CIN2/3 rates among European/other ethnicity women are further calibrated by five-year age group to observed data (based on an analysis of data from the NCSP Register). Figure 14 compares the model-predicted histologically confirmed CIN2/3 age-specific rates per 1,000 European/other ethnicity women screened with these observed data. Model-predicted histologically-confirmed CIN2/3 rates are broadly consistent with the observed data (Figure 14).

Figure 14 Age-specific rates of histologically-confirmed CIN2/3 per 1,000 European/Other women screened: model prediction vs observed New Zealand data
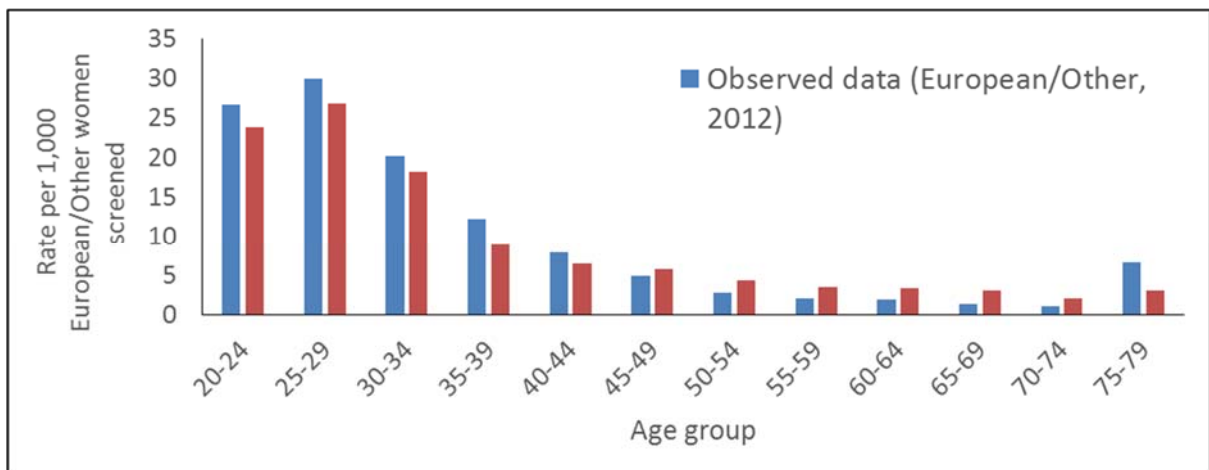

Table 3 compares the model estimated number of women undergoing histology evaluation with data observed in 2012. (2) As for Māori women discrepancies between the model predictions and observed data are large for this target. As many other predicted outcomes compare well with observed targets for New Zealand, it is possible that factors other than model or parameterisation error contribute to the target number of women with histology (and particularly women with negative/HPV histology) being higher than model predictions. The observed data from the NCSP Register includes all histology with a

cervical component, including benign hysterectomy samples, not all of which are related to the screening program (whereas only program-related histology samples are captured in the model). More recent monitoring reports show that approximately 35% of the negative/ benign histology recorded on the NCSP Register data originate from benign hysterectomy samples (5). Additionally, more women with low-grade cytology outcome underwent colposcopy and histology evaluation in the observed data than what was modelled.

Table 3 Histology results in European/Other women aged 20-69 years: model prediction vs observed New Zealand data (2012)

	Negative/ HPV	CIN1	CIN2/3	Cancer	Other	Total
Observed data(2)	10,008	2,901	3,547 [a]	141 [b]	108 [c]	16,705
Model prediction[d]	3,290	1,278	2,170	81	n/a	6,737

a Includes women with the following histology outcomes: CIN2, CIN3 and HSIL not otherwise specified b Includes women with the following histology outcomes: microinvasive, invasive SCC, invasive adenocarcinoma, adenosquamous carcinoma and other cancer c Includes women with the following histology outcomes: glandular dysplasia, adenocarcinoma in situ d Assuming 2012 European/Other population (ages 20-69 years)(6)

This result is consistent with results presented in Figure 15, which displays age-specific model-predicted number of histology tests performed in 2012 on European/Other ethnicity women, against data observed in 2012 (based on an analysis of data from the NCSP Register).

Figure 15 Age-specific number of European/Other women with histology tests: model prediction vs observed New Zealand data
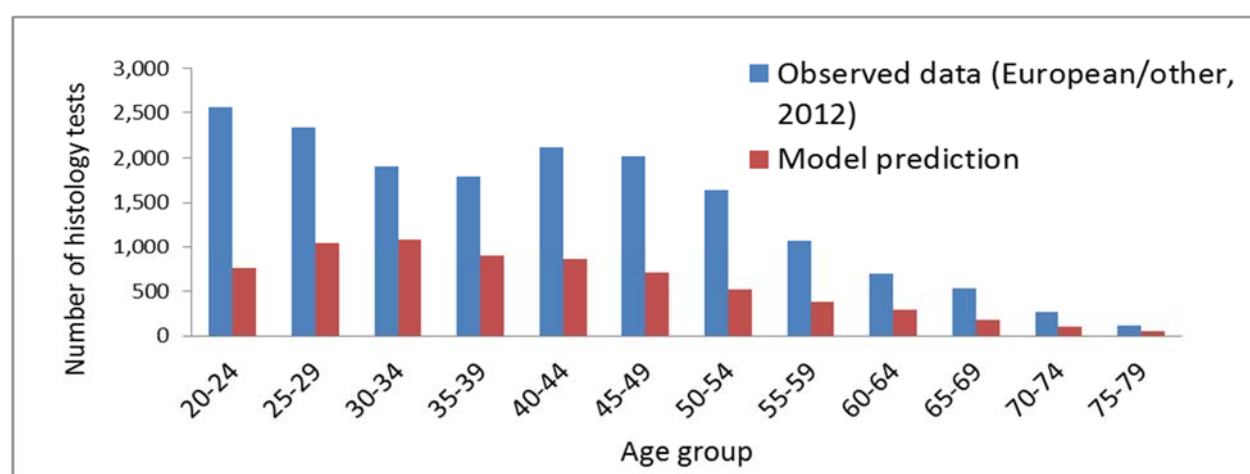

In addition to histology volumes, we calibrated to HPV prevalence among histologically-detected CIN2/3, for HPV type 16, types 16 and/or 18 and high risk types not 16 and/or 18.

Model predictions compare well to the observed data for age-specific HPV 16, HPV 18, and HPV 16 and/or 18 prevalence in CIN2/3. However for the younger age group (20-29 years), model predictions do

not compare as well for high risk HPV (not 16 or 18) prevalence among CIN2/3. This is illustrated below in Figure 16.

Figure 16 Prevalence of (a) HPV16 only, (b) HPV16 and/or 18, and (c) other HPV types (not 16 and/or 18) in European/ Other women with histologically-detected CIN 2/3: model prediction vs observed New Zealand data
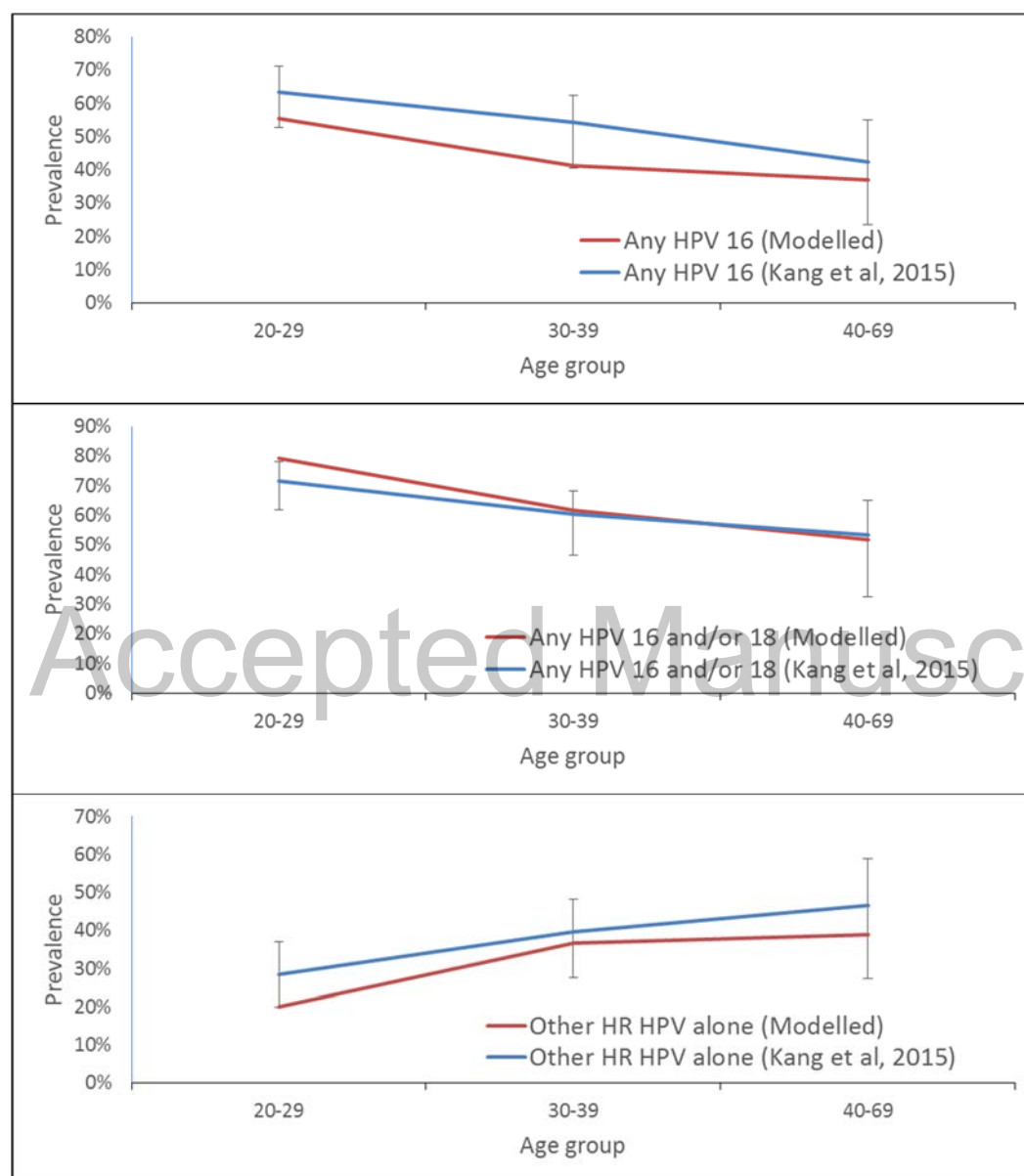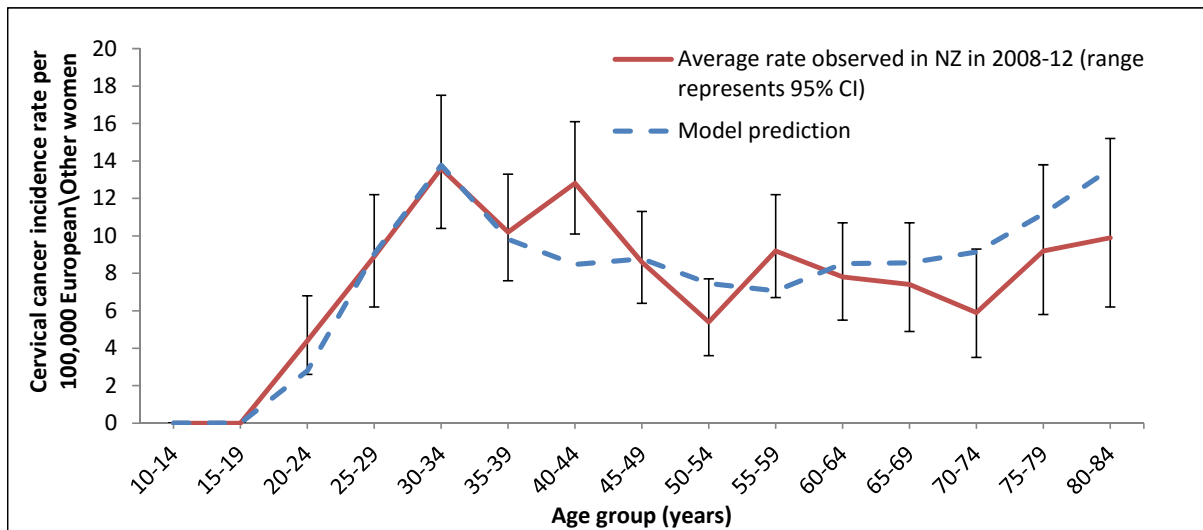

Observed data from Aug 2009- Feb 2011 (7)
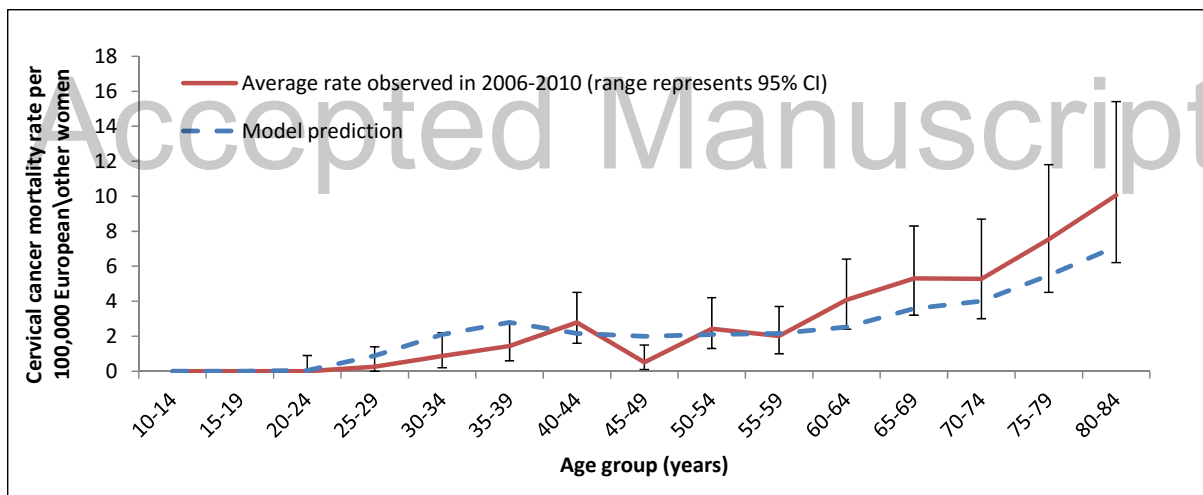
2.4 Cervical cancer incidence and mortality

The model-predicted age-specific cervical cancer incidence rate and cervical cancer mortality rate are calibrated to the cervical cancer rate observed in 2008-2012 and cancer mortality rate observed in 2006-2010 in New Zealand (2) (Figure 17 and Figure 18). The model predictions and the calibration target are in close agreement.

Figure 17 Age-specific cervical cancer incidence per 100,000 European/Other women: model prediction vs observed New Zealand data (2008-2012)

Observed data shows mean and range during the period 2008-2012(2)

Figure 18 Age-specific cervical cancer mortality per 100,000 European/Other women: model prediction vs observed New Zealand data (2006-2012)

Observed data for 2006-2010(2)

Table 4 shows that the model-predicted age-standardised rates and case numbers of incident cervical cancer and cervical cancer deaths are in close agreement with data observed in New Zealand.

Table 4 Cervical cancer incidence and mortality among European/ Other women: model prediction vs observed New Zealand data

| Category	Cervical cancer incidence		Cervical cancer mortality	
	ASR	Cases	ASR	Deaths
Observed data(2)	5.8 (range: 4.6-6.6) [a]	103.8 (range: 87-112)[a]	1.3 (range: 1.0-1.7) [b]	35.4 (range: 29-42) [b]
Model prediction	5.6	98.5[c]	1.4	29.4[d]

ASR – Age-standardised rate (per 100,000 women), using WHO standard population (8)

a Mean and range observed over 2008-2012(2)   b Mean and range observed over 2006-2010(2)   c Assuming 2010 European/ Other population (ages 10-84 only)   d Assuming 2008 European/ Other population (ages 10-84 only)

2.5   Cervical cancer stage distribution at diagnosis

The model-predicted cervical cancer stage distribution among newly diagnosed cervical cancer cases is calibrated to the stage distribution analysed from the cervical cancer cases with a known cancer stage diagnosed in 2001-2008 recorded by the New Zealand Cancer Registry (3) . Figure 19 below shows the model prediction is in good agreement with the observed data.

Figure 19 Distribution of cancer stage among newly diagnosed cervical cancer cases in European/ Other women: model prediction vs observed New Zealand data
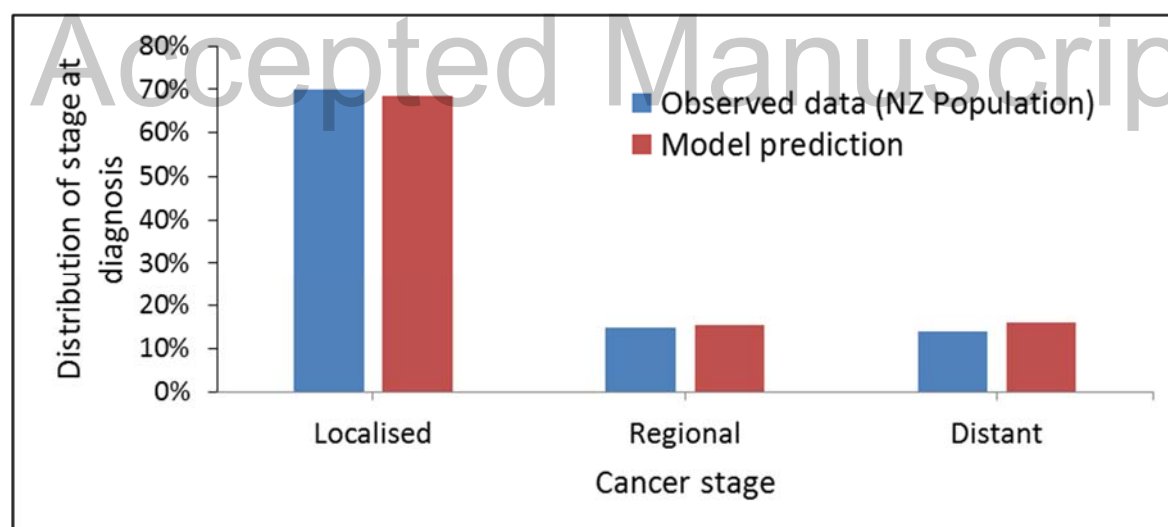
2.6   HPV type distribution in cervical cancers

The predicted proportion of newly diagnosed cervical cancer with HPV 16 and HPV 18 infections are calibrated to findings Sykes e.t al. 2014 (4) among the 169 cases with high-risk HPV infections diagnosed in non-Maori women. Figure 10 below shows the model prediction for European/Other women is in good agreement with the calibration target.

Figure 20 HPV type distribution among newly diagnosed cervical cancer cases: model prediction for European/ Other women vs observed New Zealand data for non-Māori women
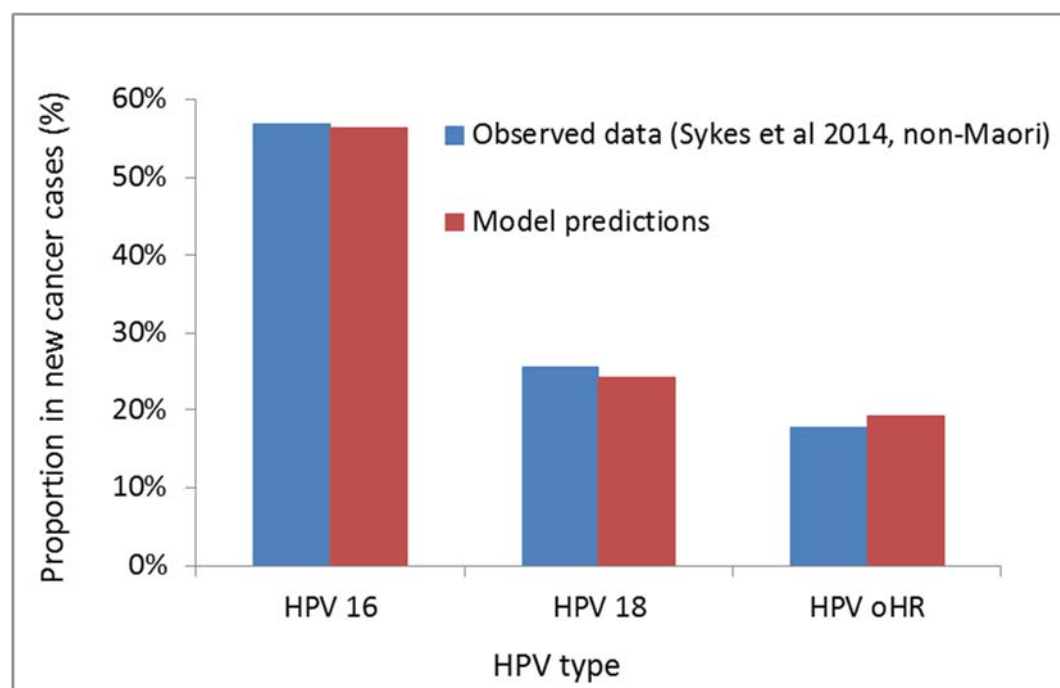
Observed data for non-Māori women from Sykes et al. 2014(4)

3 References

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