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The advantages and disadvantages of introducing a funded HPV vaccine for boys aged between 9 – 20 years

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Abstract

Human Papillomavirus (HPV) vaccine has been internationally recognised to decrease the prevalence of HPV related diseases. Introduced to New Zealand with a female focus in 2008, the researcher of this study wanted to explore the advantages and disadvantages of providing a funded vaccination programme to males aged between the ages of 9-20 years.

Through the use of a systematic literature review, six articles were used for data extraction, synthesis and analysis to determine the advantages and disadvantages of introducing a funded vaccine for males.

Four emerging results were determined through the use of data extraction, analysis and synthesis. These were then presented in a narrative form to establish both advantages and disadvantages of introducing a funded vaccine programme for males. With discussion focused on the main findings and how that could fit to a New Zealand immunisation programme.

Good evidence was found to support that the HPV vaccine decreased HPV viruses (vaccinated types), however results also showed that extending vaccination to males could not, at this stage, be considered cost effective. Further evidence regarding the health benefits and cost effectiveness of providing a full funded vaccination to New Zealand males is required.
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Whilst the front page contains only my name there are a number of other special people who came on the journey with me – and some of them even managed to see it to the conclusion.

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1 Introduction

The following dissertation is an integrative literature review investigating the advantages and disadvantages of vaccinating males aged between nine to twenty years with the Human Papillomavirus (HPV) vaccine. The review was performed using a systematic approach utilising a framework provided by Joanna Briggs Institute (JBI). The topic is close to the author’s interest having worked for over ten years in primary health care in rural Southland as an independent vaccinator and practice nurse. This interest has increased with the introduction of vaccination against HPV for New Zealand females aged between nine and twenty years. Of particular interest is the decision to restrict vaccination to females in New Zealand, when Australia’s HPV vaccination programme includes males. On a personal note, the author has two sons adding to her professional interest in exploring the advantages and/or disadvantages to vaccinating boys. Recently after the introduction of the HPV vaccine for females the author attended a course leading to a certificate of proficiency in reproductive and sexual health, cementing her interest in the current regulations surrounding the HPV vaccine and its delivery to particular demographic groups. It is this history that has led her to complete her dissertation on the current topic.
2 Background

This chapter will focus on the introduction of vaccination in New Zealand and the evolution of vaccination programmes within New Zealand. It will outline the introduction of the HPV vaccine to the New Zealand immunisation schedule and the development and rationale for its inclusion onto the schedule. Information regarding the HPV disease itself and the advantages of vaccination will be considered with reference to other similar immunisation programmes worldwide. Vaccination with the HPV vaccine for males will be discussed using an evidence based practice approach, extending to universal vaccination and herd immunity.

Vaccination within New Zealand has been undertaken for nearly a century and was first documented in 1926 with the introduction of vaccination for diphtheria at a small number of orphanages and schools at the request of local medical officers (MOH, 2011). The diphtheria vaccination programme was further developed, and was first offered in 1941 to all children aged seven years, delivered through the Plunket Society and medical services. This was the initiation of a whole population vaccination programme in New Zealand and was motivated by recurrent diphtheria epidemics. The period 1940-1948 saw the introduction of tetanus, pertussis and later the BCG vaccine, extended mainly to nurses as the recipients, with all vaccination being voluntary at the time (MOH, 2011). In 1961, New Zealand's first national immunisation policy was developed, and included diphtheria, tetanus and pertussis vaccines to be provided free of charge to children (MOH, 2011; Richardson, 2013). Since the initiation of New Zealand's National Immunisation Schedule (NIS), the programme now consists of over thirteen different vaccinations, some of which are combined into a single vaccination for ease of delivery.

In 2004 the Ministry of Health introduced New Zealand's National Immunisation Register (NIR). It was initially implemented district by district and monitored the delivery of vaccines. It is now used to monitor vaccine coverage nationally. All individuals are registered with their own personal health index number, which is used to report any infectious diseases to the Ministry of Health. The introduction of the NIR has been revolutionary in the monitoring of disease progression and vaccine coverage. As a result, the Ministry is now able to identify uptake rates and also determine the efficacy of a vaccine that has been implemented (MOH, 2011, as cited in Richardson, 2013).
New Zealand has a funded immunisation schedule, which allows access to vaccines for free for selected groups as determined by need. In 2012, parliament passed legislation that allowed New Zealand’s Pharmaceutical Management Agency (PHARMAC) to control the purchasing and management of all New Zealand’s vaccines. The MOH, however, remains responsible for the National Immunisation Schedule (MOH, 2011). For a vaccine or pharmaceutical to be placed on the New Zealand National Immunisation Schedule, Medsafe must first approve it for use, and then a submission must be presented before PHARMAC for consideration to be included as a funded vaccine. PHARMAC will then determine a funding proposal with a supplier for the cost of a vaccine and then seek input from various health sources, including the Ministry of Health on need, capacity and possible implementation of the vaccine. Once a decision has been made to add a vaccine to the National Immunisation Schedule it then becomes each District Health Board’s (DHB) responsibility to use their funding for vaccines, medicines and other health services implemented (MOH, 2011, as cited in Richardson, 2013). Once it is decided which vaccines are safe and to be funded these are added to what is known as the National Immunisation Schedule. The current immunisation schedule covers free childhood immunisations for diphtheria, tetanus, acellular pertussis, inactivated polio, haemophilus influenza type b, hepatitis B, 13-valent pneumococcal conjugate, rotavirus, measles, mumps and rubella until aged 11 years. HPV vaccine is offered for girls 12 years of age, through a series of three vaccines. The schedule also offers funded vaccines for diphtheria and tetanus for adults at age 45 years and 65 years. Influenza vaccine is offered for over 65 years and high risk groups that are identified by disease and health status.

The selection of vaccines for the national schedule does cause some controversy, particularly for the introduction of a new vaccine. This is mainly due to the debate from different specialities as to which diseases need to be decreased or are having the most impact on an already stretched healthcare system as determined by different specialties. PHARMAC funding models are competitive in nature and this aids to the debate of which vaccines are a priority to include within an already full and stretched schedule. Evolution of the schedule is constant and parameters for inclusion continually change. Examples of these could be either rubella, HPV, or the push to have varicella included to the schedule, however many factors such as cost, implementation, efficacy and delivery of the vaccines must be considered (Richardson, 2013).

The history of vaccines in New Zealand continues to evolve. A case in point would be the introduction of Rubella in 1970, which included all 4 year olds and a catch-up offered to 5 to
9 year olds through school. Due to poor uptake, it was re-structured within the schedule in 1979 to include 11-year-old girls only, similarly in terms of age to the current HPV vaccine. In 1990, a single composite vaccination was introduced to include rubella along with measles and mumps and was extended to all 12 to 15 month old children, with a booster vaccine recommended at four years of age (MOH, 2011).

In 2008 the Human Papillomavirus (HPV) was introduced to New Zealand’s immunisation schedule as a quadrivalent vaccine, and was extended to 12-year-old girls only, with a catch-up schedule implemented to include all females born post 1990 (MOH, 2011). In 2013 this was extended to include males less than twenty-six years of age with a confirmed diagnosis of HIV. A year later, this was also extended further to include females with a confirmed diagnosis of HIV (MOH, 2014).

In 2007 the New Zealand HPV Project was developed by a group of professionals dedicated to improving education and management of HPV within New Zealand for both the public and health professionals. The project disseminated important information about potential benefits of HPV vaccination (Gardasil TM) in preventing the spread of the HPV virus consequently avoiding genital manifestations of HPV in both females and males. HPV vaccination in females prevents genital warts, cervical, vaginal and vulval pre-cancerous lesions, and their progression. If given before exposure to the virus, HPV vaccination in males offers an effective method of avoiding genital pre-cancerous lesions, anal cancer and other associated cancers in males, provided they were not previously exposed (New Zealand HPV project, 2015).

2.1 AETIOLOGY OF DISEASE

The Human Papillomavirus (HPV) was discovered over a century ago and was first thought to be responsible for all types of human warts. However, it is now known to have over one hundred different serotypes and is responsible for multiple diseases and clinical manifestations (CDC, 2015). Three decades of research and investigation has led to the discovery that HPV is responsible for both cervical cancers and cancers of the anal, penile, head and neck regions (CDC, 2015). This discovery has resulted in the development of HPV vaccines and realisation of the need for more vaccine programmes for both genders worldwide.
Although one hundred different serotypes exist, they can be categorised into two different groups. First, mucosa/genital types of which there are over forty serotypes and second, non-mucosal/cutaneous types of which there are over sixty serotypes. The mucosal/genital types are known as high-risk types of HPV. It is these that can lead to changes ranging from low-grade dysplasia of the cervical cells, cancer precursors and ano-genital cancers, to genital warts and laryngeal papilloma's. Non-mucosal types are less serious and responsible for warts of the hands and feet (CDC, 2015; New Zealand HPV Project, 2015). Considering the multiple serotypes of HPV, it is possible for a person to contract more than one serotype. Each serotype is distinguished by a genetic sequence found via its protein L1 on the outer capsid (CDC, 2015).
2.2 TRANSMISSION

Transmission occurs, via direct contact when the virus infiltrates through the squamous epithelial layer of skin to reach the deeper basal epithelial cells. Once access is gained through small micro-abrasions the virus uses the skin’s healing process to promote the attachment of virions to squamous epithelial cells (Immunisation Handbook, 2014). Disease progression occurs post initial infection, highlighting the importance of vaccination pre-exposure to the HPV virus.

Considered as one of the most common sexually transmitted diseases in the world, much focus surrounds HPV being contracted sexually. However, skin on skin contact alone can be responsible for contraction of the disease (CDC, 2015; New Zealand HPV Project, 2015; Immunisation Advisory Centre, 2015). Condoms are widely promoted as the best protection against transmission, but protection is not guaranteed using condoms alone.

Chances of contracting HPV are increased with unprotected sexual intercourse and multiple partners. It is also widely known that gender, ethnicity or demographics appear to play no specific role in increase or reduction in contracting the disease. There is evidence to suggest that in individuals who have sexual intercourse with an HPV infected partner, approximately two thirds of them will develop genital warts (Arima et al., 2010). Many HPV infections typically clear spontaneously through cytotoxic lymphocytosis, a natural immunological response. However, the re-infection or persistent infection with high-risk HPV strains of the virus is considered a risk factor for the aforementioned cancers, with persistent infection leading to abnormal precancerous cell changes, posing a risk for both females and males (CDC, 2015; National Screening Unit, 2015). Unfortunately, a high percentage of those who contract HPV will be asymptomatic and will have no clinical manifestation, which aids the spread of the disease, and is not a reflection of the destructive and devastating character of the virus or sequelae of infection that it may cause (CDC, 2015; Immunisation Advisory Centre, 2015; New Zealand HPV project, 2015).

Although HPV is thought to play a major part in the development of multiple diseases, environmental and social risk factors are also known to be contributors in the development of sequelae of HPV infection. Factors such as tobacco use, pregnancy, ultraviolet radiation, folate deficiency and immune suppression are thought to be contributors of disease progression (Medscape, 2015).
2.3 Vaccines and Vaccination

Three HPV vaccines exist and these were developed using the HPV virus. HPV has microscopic capsid proteins, which interact with α6β4 integrin, an enzyme of wound repair, allowing for cell entry and replication. These microscopic capsid proteins are used to make the antigen for the HPV vaccines that have been developed. These inactivated vaccines are recommended for the prevention of several different types of HPV (CDC, 2015).

Of the two vaccines approved in New Zealand, Gardasil™ is promoted as it gives immunity to four (16, 18, 6, & 11) serotypes to prevent vulval, cervical and anal cancers. It is also promoted for the prevention of pre-cancerous lesions or abnormality to these regions, to prevent genital warts and specifically the high-risk serotypes of the HPV infection itself (Best Practice Advocacy Centre New Zealand (Bpac), 2012). The vaccine has proven safety, with data demonstrating that after five years and nearly 404,500 people vaccinated the chance of an adverse reaction is less than 0.01%, indicating that the chance of a severe reaction is low (MOH, 2014). The publicly funded vaccine for girls is said to cost approximately $500 for three doses of Gardasil™ (New Zealand HPV Project, 2015). The cost of the alternative vaccine, Cervarix™, is approximately $154 per dose with three doses equalling approximately $462 for a full three-dose course, however Cervarix™ only vaccinates against two serotypes 16 and 11 which give coverage to genital warts but not high risk serotypes that can lead to cancers (New Zealand HPV Project, 2015).

A variety of treatments are available for genital warts ranging from solutions for a person to apply to the genital area (for example, condyline™, Aldara™, and Trichloroacetic acid™), or either cryotherapy or laser removal which is performed by a health professional (New Zealand HPV Project, 2015). Treatment for genital warts is invasive as the treatment must be applied to the genital region. There is also a financial cost which both males and females incur if they seek treatment through primary health care services. However treatment for some age groups is funded, an example of this is the under 25 year age group who are funded for free sexual health or contraceptive consultations at a District Health Board level, depending on that boards decisions regarding funding distribution (WellSouth, 2015). Funded consults might also apply to people over 25 years of age, but this is need dependant. The treating nurse or doctor has to evaluate whether or not the individual fits the criteria for their District Health Board’s funding. When available the funding can be claimed through general practices or sexual health clinics with the intention to increase accessibility towards better sexual health (WellSouth, 2015).
As noted previously the New Zealand HPV programme was developed in 2008, with vaccination, first offered to women born in 1990 or later. The Ministry of Health at this time assessed overseas HPV programmes that were already being implemented and instigated its own HPV programme, which was adapted to suit New Zealand. These adaptations included only funding the HPV vaccine for girls instead of both genders, and, in most regions, offering a school based delivery system, which was thought to enable accessibility (New Zealand HPV Project, 2015).

The scheduled vaccines are delivered to the majority of girls through a school-based programme. Although the vaccine is approved for use in females aged between 9 to 45 years and males between 9 to 15 years, government funding currently only covers vaccination cost for girls aged nine to twenty years. Non-funded, but approved vaccines can be delivered in primary care practice with recommendation from a general practitioner (MOH, 2014; Best Practice Advocacy Centre New Zealand, 2012).

2.4 Efficacy and Effectiveness

A decrease in the contraction of HPV in women through vaccination could have an immense beneficial effect by reducing the rates of cervical cancer, other cancers and HPV related diseases (WHO, 2015). This could also have an impact on the male population by reducing HPV transmission and acquisition, even in the absence of male vaccination.

Worldwide it is thought that 40 countries have implemented vaccination programmes for HPV (WHO, 2015). However, a number of countries also have barriers to the implementation of a robust HPV vaccine delivery system, especially in developing countries. A number of countries that are still in the early stages of implementing health initiatives such as de-worming, visual screening, nutrition and other earlier initiatives would struggle with HPV implementation as these require amenities and skilled health workers that the other initiatives do not. For example, a cold chain accreditation is required to ensure the safe delivery of vaccines and appropriate storage of vaccines, making the implementation and storage of HPV vaccinations complicated for those developing countries (WHO, 2015). A number of countries fund HPV vaccination for women in the same age group as in New Zealand (WHO, 2015). Many of these programmes are in the early years of implementation and no empirical data is yet available making it difficult to gauge the full effects of the programme and the full impact it will have on cancers, including cervical cancers.
There is increasing evidence of effectiveness of the currently implemented programmes (mainly for females), although longer term disease prevention is not yet demonstrable (Tabrizi et al., 2012) due to the time it takes to assess the disease progression to the cancerous stages. An assessment of Australia’s national HPV vaccination programme reviewed the initial effect that the programme had on HPV infections in women who were attending Family Planning clinics (Tabrizi et al., 2012). The records of women between 18-24 years, before and after the commencement of the vaccination programme were reviewed. Inconsistencies in data collection were reduced through using the same clinics, age groups, strategies and collection methods. The findings noted that the frequency of HPV genotypes in the post vaccination group of women was 28% lower than the pre-vaccination group (Tabrizi et al., 2012). This study suggested that the vaccine, while in the earlier stages of initiation, is contributing to a decrease in the occurrence and spread of the HPV (Tabrizi et al., 2012).

Early evidence from New Zealand also suggests effectiveness from the HPV vaccine despite being in the early stages of initiation. Between 2009 and 2012, the number of people presenting to sexual health clinics with genital warts decreased by 32% post vaccination programme initiation (MOH, 2014). Family planning clinics also noted a decrease in genital wart presentations by a massive 52% (Ministry of Health, 2014). The decrease was noted across all ethnicities and was predominantly in women from the 15- to 19-year-old age bracket, the group first offered the vaccination through the HPV vaccination programme. Although in its early stages of implementation, this data suggests the effectiveness that the HPV vaccination programme is already having for women in New Zealand (Immunisation Handbook, 2014).

Some vaccinations have been found to have a decline in effect over time. For example, Diphtheria antitoxin levels decrease after the initial three doses given and have been shown to provide a waning immunity, causing careful consideration of long-term coverage (Immunisation Handbook, 2014). The New Zealand HPV vaccination programme has now been running for just over seven years and the results show no indication of declining immunity. However, it is possible that in the future a booster could be needed yet it will be a while longer before this is known (Immunisation Handbook, 2014).
2.5 COST EFFECTIVENESS

As indicated above, cost effectiveness is an important consideration when introducing a new vaccine. After recognising that HPV is a universal disease that affects both men and women and can lead to further disease development for both a number of studies have attempted to evaluate the worth of including males in HPV vaccination programmes worldwide (CDC, 2015; New Zealand HPV Project, 2015; WHO, 2015). Overall, the findings are controversial. A study carried out by Elbasha and Dasbach (2010) assessed the value of vaccinating males against HPV in America. In their study they evaluated the monetary worth of vaccination versus the likely health impact of vaccination of the male population, in protecting against HPV types of cancer or genital warts. Figures from publicly available health data were applied to models that projected the cost of treatment for both genital warts and for cancers that might be contracted from HPV strains 6/11/16/18. These costs were then used as a comparison against the vaccination costs of the male population between ages 9 and 26 years. It was found that by vaccinating this demographic and age group, the health benefits to males were widespread and financially a viable option. It also looked at longevity and quality of life, concluding a considerable health and financial benefit to both (Elbasha & Dasbach, 2010).

Chesson, Ekwueme, Saraiya, Dunne, & Markowitz (2011) also estimated cost-effectiveness for vaccinating the male population in America by using models that evaluate the reduction of economic and health burden that is related to HPV associated diseases. The study used a simplified model to establish the cost of the vaccine then the cost of acquiring, detecting, and treating HPV associated diseases. The authors concluded that it became economical to vaccinate against HPV for males only when the uptake of vaccination was low in females. Much discussion was provided on whether it would be better financially to achieve a higher uptake of female vaccination, which would also provide some protection for males through herd immunity. The authors determined that if vaccination coverage for females were greater, it would reduce the overall problem of HPV over the entire population (Chesson, Ekwueme, Saraiya, Dunne, & Markowitz, 2011).

A study performed by de Kok, Habbema, Rosmalen, and Ballegooijen (2011) clearly portrays a financial and economic benefit for vaccinating against all HPV associated diseases. The authors studied the estimated potential of the maximum effect of HPV vaccination on non-cervical HPV cancers. Using a mathematical equation they estimated the impact HPV vaccination could have on reducing cancers other than cervical. They focused instead on penile, oral cavity, oropharynx, anal, vaginal and vulval cancers. Using simulation that
related to these other cancers they took into account the life years earned, savings and cost
effectiveness of the vaccine which lead to a 18% increase in savings, and made vaccination
13% more cost effective. The authors concluded that if HPV vaccination was to completely
prevent all of the non-cervical cancers caused by HPV, then there would be a substantial
increase in the cost effectiveness of vaccinating not only the female population, but the male
population too (de Kok, Habbema, Rosmalen, & Ballegooijen, 2011).

Estimating cost of vaccination versus the burden of disease triggered by HPV is hard to
comprehend as a majority of studies have used frameworks to establish costs. The
frameworks have been used to estimate the cost of vaccine versus the perceived cause of
disease and its progression. However few studies have evidence based research, or if they do
this is often based on early programme implementation and includes evaluation of genital
warts rather than HPV related cancers. This estimation and framework use creates room for
debate with regard to the actual cost of HPV vaccination programmes and the savings that
could transpire. However, the literature certainly raises questions as to whether there could be
health benefits for extending the vaccination programmes to include males.

2.6 HERD IMMUNITY

Immunity is considered to be the body’s biological state where individuals are capable of
defending themselves against a particular disease. This occurs through complex mechanisms
that identify and remove an infection or disease from the body before it can become harmful
(Immunisation Handbook, 2014). Immunity can be acquired in three different forms; active
immunity, where an individual has acquired the disease themselves and the body has
produced antibodies during the initial eradication of the disease and would recognise these
should they acquire it again, or through vaccination where an individual is administered the
disease antigen or a small amount of live vaccine, such as MMR, for the body to build its own
antibodies to fight the disease. It can also be acquired passively which often occurs in utero
or through the breast milk via the host, or by vaccination with serum that includes antibodies

In addition to the immunity an individual can acquire, another type of immunity is known as
herd immunity, which occurs when a high number of individuals have been administered a
vaccine for disease protection, therefore lowering the incidence, creating a population-wide
reduction of the disease and subsequently reducing the spread of the disease. When levels of a
disease are low it is said that people are protected by herd immunity, whereby most of the herd are immune and, therefore, the remainder of the herd’s chances of meeting or being surrounded by infected people is reduced (Immunisation Handbook, 2014).

A lot of controversy surrounds the topic of herd immunity, with some research determining that herd immunity is as good as vaccination once disease prevalence is low and other research determining that people should be able to access health care themselves to ensure that they have direct immunity to the disease rather than relying on herd immunity from the greater community.

The New Zealand Immunisation handbook (MOH, 2014) noted a decrease in the prevalence of HPV that has been seen in unvaccinated young men in Australia since the initiation of their National HPV vaccination programme which targets women and girls in the same age group similarly to New Zealand’s HPV programme. Australian investigators have concluded that this reduction in the prevalence of HPV (vaccinated types) in unvaccinated heterosexual young men was linked to herd immunity (MOH, 2014). It was also noted in one Australian clinic that there was a virtual elimination of genital warts not only in young women but also in young heterosexual men at the same time, in the same age bracket. It also noted that there was no decrease in genital warts presentation in women over the vaccinated age bracket or amongst men who have sex with men demographic, further supporting the hypothesis this reduction was likely to be from vaccination (MOH, 2014).

The New Zealand immunisation handbook also discusses the possibility of cross-protection that has been seen for non-vaccinated HPV types. Non-vaccinated HPV types are responsible for approximately one third of cervical cancers. There is said to be a small reduction in these cancers for the immunised groups (Immunisation Handbook, 2014).

2.7 ISSUES OF TARGETED VACCINATION

Currently in New Zealand vaccination is funded for females between the ages of 9 to 20 years. The omission of males brings to question the literature that has exposed HPV as a health issue for males as much as it is for females. Although the full effect of HPV and its relationship specifically with cancer is yet to be fully understood, there are notable links (Immunisation Handbook, 2014). Literature also suggests that male vaccination is founded
on many assumptions or factors to debate whether it is a financially viable option for immunisation programmes (Cifu & Davis, 2014). Literature also shows that immunisation of females in New Zealand is likely to provide some herd immunity for males; this has yet to be verified or statistically validated (Immunisation handbook, (2014). It could be argued that by vaccinating boys and men, it will in fact offer some immunity to women and girls.

Men are also responsible for transmitting the infection to women, therefore when immunising girls only, other demographics and genders are left unprotected, leaving girls only with certainty of protection. This leaves a percentage of New Zealand’s population unprotected (for example, men having sex with men), leaving them at a higher risk of contracting HPV. Today’s youth are very transient in nature, this is supported by migration numbers from statistics New Zealand, with an increase of travellers in the year 2000 of 3,873,000 travellers venturing overseas to 4,554,600 in 2014, showing vast increase in travel (Statistics New Zealand, 2015). Such mobility should be considered when weighing up whether to offer immunisation to females alone. By offering males the vaccine we would also be providing a wider and more thorough base for herd immunity.

Consideration of the international context is necessary, as over the last two decades travel has changed significantly with the introduction of more overseas flights at cheaper rates and an increase in tourism worldwide. As noted earlier, many countries are said to lack resources to offer immunisation for HPV thus providing a new dimension to analyse (WHO, 2015). For worldwide herd immunity to occur there would need to be a reasonable uptake of HPV vaccination at a global level. However with some countries lacking resources to implement HPV vaccination it is going to take time for all countries to establish these immunisation practices. For a country, such as New Zealand, the frequency of travel beyond the geographical border means that it will be difficult to establish herd immunity. In addition to the countries that simply cannot afford an HPV vaccination programme, uptake in the countries providing HPV vaccination isn’t proven to be high. As a result, there remains a huge population that are potential carriers and from whom New Zealand males might contract HPV infection. Ministry of Health, (2014) suggests that over 70% uptake of the vaccine needs to be obtained to give good herd immunity against HPV and this target has yet to be reached in New Zealand. As HPV vaccination is funded for women, it appears that a case might also be made for it to be funded for boys or adolescent men, especially when these are both high-risk groups for other sexually transmitted diseases.
Nyitray et al. (2011) sum up the status quo regarding inclusion of males in the vaccination programme by stating that vaccines can prevent infection and disease among both women and men, vaccine programmes have primarily targeted women, in part, due to a greater burden of disease among women, and also due to limited availability of HPV data for men (Nyitray et al., 2011).

However significant data and literature exists that supports the recommendation of vaccination of males, but the progression of implementing this into existing immunisation programmes has been slow (NZ HPV Project, 2014; MOH, 2014; CDC, 2015).

2.8 Current Regime

New Zealand currently offers a funded HPV vaccine for girls from year 8-13. This is a series of three state funded injections delivered through either participating schools who are visited by their district health boards HPV team or through general practices. Other included individuals for a funded vaccine are individuals aged below 26 years of age with HIV infections or those immunocompromised. Transplant patients and men who have sex with men are also funded for a series of 3 HPV vaccines according to New Zealands immunisation schedule (MOH, 2014).

2.9 Universal Vaccination or Optional Vaccination

Vaccine coverage is a widely debated topic. The first question often asked is, how do we reach or meet our target population? Tabrizi et al. (2012) discussed the benefits of the implementation of the school-based delivery system in the Australian HPV vaccination programme. This programme has stated to have a 55% uptake of women enrolling to have the vaccine. It was not compulsory to register whether or not you were participating, so it is thought that the uptake was actually higher than 55% (Tabrizi et al., 2012).

New Zealand currently has a school-based delivery system that could be easily adapted to include both females and males. This would provide a strong framework on which to campaign for higher uptake in our younger citizens by enlisting them in this part of the immunisation programme. Education for parents about the risk that HPV poses to boys could see the current vaccination programme challenged. If parents were educated that their boys were at a high risk of contracting HPV, at equal risk as their daughters, there is a possibility that they would heavily question why funded vaccines were not being offered to both males
and females. Particularly in light of HPV being a male and female disease that can lead to a variety of destructive outcomes, whether it is genital warts or an even more destructive health issue like cancer, later in life.

2.10 MALE VACCINATION

In addition to the harms of HPV infection for women, there is a wide range of literature to suggest that it also causes a burden of disease among men. Elbasha and Dasbach (2010) suggest that males are most likely to acquire the HPV swiftly after sexual debut and it remains a threat at any time throughout adolescence and adult life. HPV can cause a range of serious diseases affecting men, for example penile, anal, respiratory papillomatous, head/neck cancers and also genital warts. Whilst vaccination of females provides some protection to males through the principles of herd immunity, men who have sex with other men are not benefitting. A comparative study of the prevalence of HPV virus in men concluded that men were more at risk of contracting HPV if they were having sex with men than if they were having sex with women (Nyitray et al., 2011).

To date, much of the literature on vaccination of males has focused on cost effectiveness. One American study found that the health benefits to males were extensive and that financially it was a viable option (Elbasha & Dasbach, 2010). However, another American study concluded that it became economical to vaccinate against HPV for males only when uptake of vaccination was low in females (Chesson et al., 2011). In their opinion, working to ensure females were vaccinated was the better goal. Focused more specifically on the benefits of vaccination for the non-cervical cancers, de Kok et al. (2011) concluded that if HPV vaccination was to completely prevent all of the non-cervical cancers caused by HPV, then there would be a substantial increase in the cost effectiveness of vaccinating not only the female population, but the male population as well.

Initial exploration of the literature has indicated that there is debate as to the benefits and costs of HPV vaccination programmes being extended to males. However, at a personal level there are clearly health benefits for those who have been vaccinated. There is evidence of an effective vaccine that has the ability to seroconvert, with a decline in the contracting of HPV for those vaccinated. Although some countries, such as America, are now vaccinating males against HPV, in New Zealand the scheduled vaccination programme provides only women with access to free funded vaccine against HPV, whereas men can access the vaccine if they
are willing to pay. For years affordability and access have been major factors in all health care systems, and these factors have created barriers in equity to healthcare.

Given that there is some evidence the HPV vaccination might prevent a range of other HPV-related cancers in addition to cervical and that a wider vaccination programme is likely to benefit herd immunity and thus protect women further, the topic for this review focuses on the advantages and disadvantages of HPV vaccination for boys. It will be achieved through a systematic integrative review of the current literature dating back to 2009. It is presently becoming a topic of discussion within our health care system as to whether or not males should also receive funded immunisation for HPV (MOH, 2014).

In conclusion, although it has taken over a century for science to establish not only a strong link to cervical cancer but to other cancers, we need to entertain the idea that in the future HPV could be responsible for a range or variety of other health issues. There is currently substantial evidence to demonstrate that HPV not only affects women but men also. There is extensive evidence that the HPV vaccine is an effective vaccine that has the ability to sero-convert those who have been immunised. There is literature supporting a decline in the contraction of HPV for those vaccinated. It appears, however, that although some countries such as America are now vaccinating males against the HPV, New Zealand has taken a ‘wait and see’ approach to consider the uptake of a funded HPV vaccination programme that includes males. The evidence to date would suggest further consideration should be given to including males in the funded immunisation programme.
3 Methodology and Methods

3.1 INTRODUCTION
Within this chapter discussion will be focused on the method of an integrative review that explores the advantages and disadvantages of HPV vaccination for males aged between 9 to 20 years using a systematic approach. The initial literature search included both qualitative and quantitative research and other relevant sources that were deemed appropriate to the study. This integrative review used a rigorous and extensive search strategy, inclusion and exclusion criteria, and literature which was critically appraised to establish results for analysis to conclude whether it would be advantageous or a disadvantage to introduce the vaccination of boys with the HPV vaccine.

3.2 METHODOLOGY
Research has been a pivotal component to the advancement of health care worldwide (Polit & Beck, 2012). Existing literature has often been utilised as the basis of a study or to examine a specific research question. Where previously primary research has been undertaken, a reviewer may evaluate existing data that has already been published through the process of a literature search, to establish their own body of research or to summarise quantities of literature to establish a conclusion (Cook, Mulrow & Haynes, 1997).

The following integrative literature review used a systematic approach; these have taken on increasing importance within the healthcare system and are increasingly used for the basis of clinical guidelines (Polit & Beck, 2012). A systematic approach allows for the reviewer to implement a strategy for data collection, synthesis and conclusions in a manner that reduces bias and enables the reviewer to look at large volumes of relevant literature, but condense this into a topic specific manageable amount for synthesis and analysis by using scientific tools or strategies to ascertain the most relevant literature (Cook, Mulrow & Haynes, 1997). This research used a systematic approach to integrate widespread research data for the purpose of extraction, analysis and synthesis.

Meta-analysis is the most robust form of systematic review and considered the gold standard method for use when undertaking a review of literature for the purpose of clinical guideline.
It uses the process of integrating quantitative studies into statistical findings. However these studies need to be very similar or virtually identical in topic and nature for meta-analyses to work or be combined into one unit for the purpose of analyses (Polit & Beck, 2012). Whilst meta-analysis is the most robust form of review and offers objectivity, it is always focused from a quantitative perspective and inevitably the criteria and scope has to be very narrow (Polit & Beck, 2012). For this reason a meta-analysis was not the appropriate method for this review as the studies identified did not provide data that could be aggregated.

An integrative review is the broadest type of review, as it can include numerous methodologies, including studies using both quantitative and qualitative data, which are more commonly found within nursing research (JBI, 2014; Whittemore & Knafl, 2005). Whittemore and Knafl (2005) argue that a literature review allows a researcher to take both theoretical literature and empirical literature to establish a clearer view or understanding of a particular healthcare issue that the researcher may wish to explore. The integrative review method can also play an important role in integrating evidence-based initiatives into a practical framework, or explore a rationale for any healthcare initiative (Whittemore & Knafl, 2005). The reviewer used this method in order to be able to incorporate both qualitative and quantitative studies and establish a clear conclusion about the advantages and disadvantages of the introduction of HPV vaccination for boys.

3.3 **Method**

Initially the integrative review was to include research from both a qualitative and quantitative review. Throughout the review however, no qualitative literature was found that met the inclusion and exclusion criteria and this led to the review only including quantitative literature. The quantitative literature for the review was not similar enough to warrant using meta-analysis. An integrative review was selected to explore the question: What are the advantages and disadvantages of HPV vaccine for boys aged between 9-20 years?

Recent literature was used to establish what data was currently available on HPV programmes already implemented, this was achieved through a systematic literature search for data that was then collected, reviewed, and synthesised.
Numerous websites were reviewed prior to the initial start of the review to establish the viability of the study. National and worldwide websites that discussed the vaccination of males as well as those that did not were searched. Brief initial searches were also completed on the Joanna Briggs Institute (JBI) systematic reviews, Ovid-MEDLINE and the Cochrane databases to verify that no previous study had been completed. Colleagues and other health professionals including the Southern District Health Board immunisation team were also involved through discussion at the outset of the study to establish if anyone was currently working on a similar study.

The Joanna Briggs Institute (JBI, 2011) promotes the use of PICO (Population, Intervention, Comparison, and Outcome) to assist the researcher in setting parameters around literature that is to be included in the review. The use of PICO assists in the construction of a clear and precise question for the researcher when performing a systematic integrative review (JBI, 2011). The researcher used the JBI PICO tool as a basis to establish the parameters that would define inclusion and exclusion criteria.

The following (Table 3.1) illustrates the use of PICO when choosing key words to base the initial database search on. This enabled the researcher to have defined guidelines when searching the databases and websites.

### Table 3.1. Criteria considered for the Review will include

<table>
<thead>
<tr>
<th>Population</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenomena of interest</td>
<td>HPV vaccination programmes</td>
</tr>
<tr>
<td>Context</td>
<td>HPV vaccination programmes/ boys/men/ or implementation in NZ</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Advantages/disadvantages of introducing a vaccine programme for males from school age</td>
</tr>
<tr>
<td>Studies</td>
<td>Qualitative/quantitative</td>
</tr>
</tbody>
</table>

### 3.4 INCLUSION AND EXCLUSION CRITERIA

**Articles included during the review:**

- Published post 2009 until April 2015
- In the English language
- Qualitative and quantitative studies
- Primary research, not reviews of previous studies.
• Discuss the advantages/disadvantages or benefits or harms of HPV
• Studies had to be centred on HPV vaccination of males

Articles excluded during the review:
• Studies that were predominantly about females/girls.
• Studies predominantly about men over 20 years old.
• Studies that were not about HPV vaccination in males

An initial search was conducted to consider all research and literature that was based around HPV, its vaccine and implementation of programmes at a worldwide level regardless of methodology, giving as broader range of perspectives and findings to later be synthesised. It included both qualitative and quantitative literature that was accessed via Otago University library user's website to access multiple databases.

3.5 SEARCH STRATEGY
A three-staged approach was undertaken for the literature search, as recommended by Joanna Briggs Institute; with the first stage identifying key words to guide the search (JBI, 2014).

3.5.1 Keywords
The initial search of keywords was broken down into four different concepts that were then merged with truncation, phase searching and variations of AND and OR as well as against the four concepts the researcher checked for synonyms and related terms. The researcher at various points checked that the words being used covered all variations of the word and when a word of similar meaning was found to be covered by this particular word it was also added to the concept that it was consistent with. Once the initial search was complete the keywords from articles that appeared to be suitable to the author were also checked for further keywords that may have been missed at the time of initial searching to ensure all terms or definitions were included in the search.

The concepts developed throughout the search phase and those used for the final search were as follows:
Table 3.2. Search concepts

| Concept One                  | Papillomavirus infection, papillomavirus, HPV, human papillomavirus |
| Concept Two                  | Vaccines, vaccinate, vaccinated, vaccination, papillomavirus vaccines, immunise, immunisation programmes, HPV Vaccine, vaccine acceptability |
| Concept Three                | Primary prevention, patient, acceptance of healthcare, health knowledge and attitudes, practice, advantages, benefits, disadvantages, pros, cons |
| Concept Four                 | Males, boys and universal |

Access was obtained through University of Otago Library article databases. The following databases were searched, CINAHL, EMBASE, Ovid MEDLINE, Web of Science, JBI, Cochrane reviews and Scopus. The searching using Scopus produced large amounts of literature and there was an inability to define search terms adequately, and was later excluded as a result.

3.5.2 Searching of other resources

Many other resources were utilised to obtain background research on the topic for a fuller understanding. The researcher accessed numerous websites for information regarding the disease, its progression, and current HPV programmes for women and males. These were accessed via internet and included the following: Google, Ministry of Health website, Centre for controlled diseases website (CDC), New Zealand HPV programme, Best Practice Guidelines, NICE guidelines, Up-to-date website and Google Scholar. Some sites were deemed unsuitable for the actual database search of the integrative review because the researcher could not impose limitations on or could not narrow the search to within the inclusion and exclusion criteria.

The aim of a three-stage search strategy is to ensure that all relevant literature is retrieved via a systematic approach that will ensure a full and comprehensive set of results (JBI, 2011). The first stage of the literature search involved defining the key concepts, with the first two concepts run through all databases to establish a body of literature. The second stage began with a more comprehensive search using the four concepts together to establish that all variations of keywords were implemented in the review. The final results were then reviewed with the first stage of searching.
The third stage comprised of checking all the reference lists of the chosen articles to ensure no other articles had been missed that would be beneficial or crucial to the review. All articles were reviewed to establish whether they would contribute to answering the proposed dissertation question.

3.6 SELECTION OF STUDIES

The search strategy resulted in the identification of a total of 1620 articles found via the initial search strategy and two additional articles provided by the Southland/Otago Immunisation Co-ordinator. These articles included some or all of the four differing concepts shown in Tables 3.1 and 3.2. Duplications were removed and one was excluded due to having no author leaving a total of 1611 articles. Initial screening was achieved with the researcher reviewing all titles and excluding further articles that would not address the intended research aims. These articles were mostly excluded on the grounds of being found to have a female focus or mainly cervical cancer, but had referred to males at some stage. In addition, some were literature reviews and these were excluded because the intention of the review was to source primary data. Some were found to be outside of the inclusion criteria, for example publication prior to 2009. Following this process 1261 articles were removed from consideration leaving 350 articles for more robust reviewing. The abstracts of the remaining 350 articles were then reviewed. Where it was not clear that inclusion criteria were met most of the article was read to establish suitability for the study. A total of 154 articles were then read in full to establish whether they answered the research question and met the final inclusion criteria. The exclusion of 145 articles occurred mainly due to articles being male focused but having an age parameter that went to 26 years rather than 20 years or were focused on both genders. At this point nine articles remained.

The search strategy was documented using PRISMA flow charts to track the search strategy process. PRISMA (2009) is a researching database that develops a wide range of tools to aid the researcher in ensuring that there is clear transparency of a search strategy. In particular they provide checklists and flow diagrams that enable the researcher to clearly show how their search strategy has been undertaken; for the purpose of clarity this research has used PRISMA's flow chart to illustrate the search process, refer to Figure 3.1.
The author and one supervisor then critically appraised the nine articles, resulting in three articles being excluded from the study for a variety of reasons. One study was determined unlikely to answer the proposed aim of the study, and another article was excluded because it was a literature review rather than original research. Six papers were concluded to have met with all inclusion criteria. These were critically appraised by the researcher and one supervisor to determine that they met 70% of critical appraisal criteria.
Potential literature articles identified through search of databases: =1620
CINAHL, Ovid (Medline), Web of Science, EMBASE, Scopus

Additional records identified through other sources (n =2)

Records after duplicates removed = 1,611

Records screened = 1,611

Records excluded following evaluation of titles and abstracts = 1,261

Full-text articles excluded, with reasons = 197

Articles excluded due to not fitting criteria of review or able to answer research = 144

Articles excluded due to not meeting critical appraisal or researchers criteria = 3

Studies retrieved for full literature review = 154

Studies evaluated for methodological appraisal and reference list check = 9

Final number of articles that passed critical appraisal for the literature review: = 6

Figure 3.1. Flow diagram of search strategy
3.7 ASSESSMENT OF METHODOLOGICAL QUALITY

A critical step for integrative reviews is to evaluate the literature for its quality (JBI, 2014). This is often completed through a critique of methodological quality for each proposed article. For this study each article was reviewed for methodological quality and validity by both the primary reviewer and her supervisors.

JBI assessment and review instruments guided assessment of methodological quality. As the review is based on quantitative studies, including some that used economic impact, the tools selected were relevant to these methods. The three articles that reported research using quantitative methods were reviewed, guided by the tool from Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MASTARI). The three papers that had a cost effectiveness or economical component were reviewed, guided by the Joanna Briggs Institute Analysis of Cost, Technology and Utilisation Assessment and Review Instrument (JBI- ACTUARI) (JBI, 2014).

Three assessors, individually assessed each of the six papers, and then consulted with each other to determine which papers would be included in the study. All three assessors were broadly consistent in their assessments adding congruity to the methodological quality of the study.

3.8 DATA EXTRACTION

Due to the nature of the articles found from the initial search strategy, with three having an economic focus and three being of a quantitative nature, the decision was made not to use JBI extraction tools for two reasons. The first of these was that due to the varying nature of articles it was deemed by the reviewer to be diversifying too much, and secondly the tools were to be accessed online, but access difficulties hindered the process. Therefore the reviewer used tabulation as a form of extraction with the data of all six articles being tabled in two ways, firstly they were tabled with each study’s information which included author, year of publication, country of origin. The type of research that the study was and the method that was used in each study. Included were characteristics of the study, limitations and inclusions and lastly the study outcomes (see Table 4.1). For the reviewer to get a clearer idea of each study's results, a second table was used to extract the main ideas (see appendix A).
3.9 **DATA ANALYSIS**

Data analysis is a pivotal part of the literature review process as it allows the researcher to synthesise emerging findings from the literature and group them into categories for analysis (JBI, 2011). Analysis for this review required the combination of literature from quantitative paradigms, with half of these including economic analyses. Tables 4.1 for the study and the table in Appendix A provided initial guidance in synthesising a final set of findings. Each of the studies was read multiple times to understand the key points of each article. Ultimately four main categories were identified as representing the findings from all six studies reviewed. These are narrated in the results section of the study.

In conclusion, JBI (2014) was used to guide the process of identifying studies for the systematic review. The extraction process was based on extraction processes used by examining and tabling the findings for analysis. The reviewer was left with four main findings from the integrative review process, it is these that formed the results of the dissertation and which the discussion for the review is based around. These main findings can be found narrated in the results section, followed by a discussion that focuses on a summary of findings, future research and implications for practice.
4 Results

4.1 INTRODUCTION

This chapter presents a summary of the findings from the six studies that resulted from the integrative literature review process. The six studies that were ultimately included for further analysis include two published in the United Kingdom (UK), one in France, one in New Zealand, one in the United States of America (USA) and one in Australia.

Initially the author read through all six studies and summarised findings from each of the results sections and synthesised findings into four main categories and in some cases further expanded these with sub-categories. All six studies were ultimately selected as best answering the integrative review research question: What are the advantages and disadvantages for vaccinating males under 20 years with the HPV vaccine?

4.2 RESULTS

An important finding from the literature review process was that there were no primary research, interventional or observational studies of successive cohorts addressing the review question. Instead the six articles included in the review relied on modelling to estimate the advantages and disadvantages of vaccinating males between the ages of 9-20 years with the HPV vaccine. These articles did meet the inclusion criteria, and were critically appraised by the reviewer and two supervisors.

All six studies reviewed used simulated models and two of these developed mathematical programmes to predict efficacy (Brisson, van de Velde, Franco, Drolet, & Boily, 2011; Brown & White, 2010). One further study used a mathematical model to predict results utilising a previously developed model (Burger, Sy, Nygard, Kristiansen, & Kim, 2014). Pearson et al. (2014) used a markov macro-simulation model which is a model that allows for simulation of changing health states over a period of time, allowing for different variables to be imputed to establish a set of results, in this case a macro simulation model was used allowing for probabilities to be entered to reflect an entire cohort or large number. Smith and Canfell (2014) used a dynamic model that simulated two cohorts, and Marty, Roze, Bresse, Largeron, and Smith-Palmer (2013) used a Microsoft spreadsheet that was used for inputting data based on earlier developed models.
Four studies used comparable cohorts on which to base their model with one further study using a simulated model to calculate how different variables such as vaccine cost, vaccinating boys and girls and the health outcomes that these would have on including males to an existing programme. One further study used a markov-macro-simulated model to predict the quality of life years that would be gained and to what economic value this would be at, it was dependant on a variety of variables for example; herd immunity and future health statistics (Pearson et al., 2014).

All six studies were reviewed and displayed using a table format for comparison; see Table 4.1.
## Table 4.1. Details of six included studies

<table>
<thead>
<tr>
<th>Study (Year) Title</th>
<th>Type of Study/Method</th>
<th>Characteristics of Model</th>
<th>Outcomes</th>
<th>Notes / limitations / inclusions etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown, V., and White, K.A.J. (2010). United Kingdom. The HPV vaccination strategy: could male vaccination have a significant impact?</td>
<td>Quantitative</td>
<td>Has developed a model that can allow for introduction of different variables. Using mathematical model to check for efficacy</td>
<td>Results show that waning immunity plays a large factor in allowing infection to persist. Concludes that infection reservoir occurs through males.</td>
<td>It is a mathematical equation and possibly requires more data variables inputted and outputted and for answers to be studied in “real word”</td>
</tr>
<tr>
<td>Brisson, M., van de Velde, N., Franco, E., Drolet, M., and Boily, M. (2011). United Kingdom. Incremental Impact of Adding Boys to Current Human Papillomavirus Vaccination Programmes: Role of Herd Immunity.</td>
<td>Quantitative</td>
<td>Both males and females with HPV vaccination. Developed a mathematical model to predict cost efficacy of vaccination in both males and females.</td>
<td>Vaccinating males showed reduction in HPV incidence over 70 years. However showed that the benefit of vaccinating males decreased with an increased uptake of females having vaccinations.</td>
<td>Weakness: Makes key assumptions of different values when using a variety of variables that are entered into model.</td>
</tr>
<tr>
<td>Burger, E., Sy, S., Nygard, M., Kristensen, I. and Kim, J. (2014). USA. Prevention of HPV-Related Cancers in Norway: Cost-Effectiveness of Expanding the HPV Vaccination Program to Include Pre-Adolescent Boys.</td>
<td>Quantitative</td>
<td>Uses many variables to calculate the health outcomes and costs of different vaccination scenarios, including female and male vaccination with the HPV vaccine. Uses previously developed mathematical models.</td>
<td>Results showed that vaccine pricing contributed to whether or not vaccination for both males and females would be cost effective. Results conclude that males should only be added to the vaccination programme if vaccine is less costly.</td>
<td>Study is based on assumptions and actuals and also model is developed to fit Norway’s systems/cost structure. Assumption can vary depending on study.</td>
</tr>
<tr>
<td>Source</td>
<td>Methodology</td>
<td>Analysis</td>
<td>Conclusion</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Marty, R., Roze, S., Largeron, N., and Smith-Palmer, J. (2013). France.</td>
<td>Quantitative</td>
<td>Both males and females. Includes all diseases related to HPV.</td>
<td>Screening of girls alone had an 80% decrease in carcinomas, vaccinating boys a 61% decrease and together both sexes concluded a 90% reduction in disease.</td>
<td></td>
</tr>
<tr>
<td>Pearson, A., Kvizhinadze, G., Wilson, N., Smith, M., Canfell, K., and Blakely, T. (2014). New Zealand.</td>
<td>Macro-simulation model.</td>
<td>Vaccination of boys was not found to be cost-effective if including them in a girls only HPV vaccination program in NZ. For cost effectiveness vaccine would need to be cheaper.</td>
<td>Assumes certain parameters, which then extrapolates the data to determine disease reduction.</td>
<td></td>
</tr>
<tr>
<td>Smith, M., and Canfell, K. (2014). Incremental Benefits of Male Vaccination Accounting for Inequality in Population Uptake</td>
<td>Quantitative</td>
<td>Two cohort groups using simulated model to determine if differing factors affected vaccine uptake.</td>
<td>Results showed the population incremental impact of adding males was lower if vaccine uptake was correlated.</td>
<td>Simulated theory. Based on many variables. Can be limitation depending on realism of simulation.</td>
</tr>
</tbody>
</table>

Qualitative
- Uses models that have been developed earlier to input data.
- Uses Microsoft excel spreadsheet for inputting data.

Quantitative
- Uses models that have been developed earlier to input data.
- Uses Microsoft excel spreadsheet for inputting data.
- A Markov macro-simulation model was used which made adjustments for herd immunity, future health statistics incl: cervical cancer, pre-cancer etc., was based on 12yr old boys scenario.

Dynamic model simulated vaccination of two cohorts.

Comparable Cohort/Case Control Studies.

Health sector costs, simulated.
- Quality-adjusted life-years (QALYs).
- Based on New Zealand health system.

Based on New Zealand health system.

Results can only be as accurate as the assumptions that they make about some of the unknown variables.
4.3 ANALYSIS OF RESULTS – MODELLING HPV VACCINATION FOR BOYS

4.3.1 Category One: Decrease in HPV

All six vaccination modelling studies predicted a decrease in HPV infection as a result of HPV vaccination of males. The decrease was attributed to various reasons including vaccination (Brisson et al., 2011; Brown & White, 2010; Burger et al., 2014; Marty, Roze, Bresse, Largeron, & Smith-Palmer, 2013; Pearson et al., 2014; Smith & Canfell, 2014), vaccination coverage (Brown & White, 2010; Marty et al., 2013; Smith & Canfell, 2014) and social factors (Smith & Canfell, 2014). Each of these reasons contributed to the main finding of predicted decrease in HPV. Furthermore all six studies predicted that vaccination of males would lower HPV vaccinated diseases.

Whilst female vaccination alone was shown to result in substantially decreased HPV infection and disease (including cancer) in both males and females (Brisson et al., 2011; Brown & White, 2010; Burger et al., 2014; Marty et al., 2013; Smith & Canfell, 2014). Male vaccination in addition to female vaccination was predicted to further reduce HPV. Brisson, van de Velde, Franco, Drolet, and Boily (2011) showed adding male vaccination to female vaccination resulted in a further 20% reduction in HPV. In comparison Smith and Canfell (2014) found the effect to be slightly less at around a further 10% reduction. However, all articles did conclude that there would be increased benefit clinically if males were to be added to HPV vaccination programmes. Brisson et al. (2011) used their model to predict that vaccinating 12-year-old girls showed a rapid reduction in HPV by 65% for females and 62% reduction for males. Brisson et al. (2011) further used their model to include boys at the same age and circumstance, predicting a further reduction to 85% for females and 88% for males, calculating that there would be reduction with female vaccination but this was in fact reduced significantly more with the inclusion of males. This was supported further by Smith and Canfell (2014) who considered that the vaccination of males decreased the likelihood of HPV in all sub-groups or varieties of HPV related cancers and drew attention to a large decrease in HPV 16 which is often associated with genital warts (Smith & Canfell, 2014). Brown and White (2010) used modelling to depict the reduction of HPV but further showed that the eradication of HPV was not possible unless there was an inclusion of males in vaccination programmes (Brown & White, 2010).
4.3.2 Category Two: Disease outcomes

Four studies (Brisson et al., 2011; Burger et al., 2014; Marty et al., 2013; Pearson et al., 2014) showed findings that contributed to HPV disease related illnesses. These were broken down into two different sub-categories genital warts and HPV related cancers.

4.3.2.1 Genital Warts

Reduction in genital warts was a primary focus for the cost/benefit evaluations and was described in all of the studies reviewed as a main finding. However only three studies discussed genital warts in depth, with two studies describing a significant reduction in genital warts with female vaccination alone and suggested this was reduced significantly more when male vaccination was introduced for both males and females (Burger et al., 2014; Marty et al., 2013; Pearson et al., 2014).

Three studies determined throughout their modelling that the effectiveness of HPV vaccination was better for HPV 6/11 that was the main contributor of genital warts (Burger et al., 2014; Marty et al., 2013; Pearson et al., 2014). Three studies concluded that male vaccination helped reduce genital warts for both females and males (Brisson et al., 2011; Brown & White, 2010; Smith & Canfell, 2014), with another author determining that by including male vaccination genital warts would decrease by 89% for males and 91% for females (Marty et al., 2013).

Burger, Sy, Nygard, Kristiansen, and Kim (2014) also support this theory through the use of a simulated model by considering gender-neutral vaccination with a decrease in genital warts by 85% for females and 84% for males. Marty et al. (2013) also allude to some cross protection of non vaccinated HPV diseases through HPV vaccination determining that there would be a 58% decrease for females and 71% decrease for males of non vaccinated variants of HPV by including male vaccination.

4.3.2.2 HPV related cancers

HPV related cancers referred to cervical, head, neck, penile, anal and all other related cancers caused by HPV infection. Marty et al. (2013) found that female only vaccination programmes reduced cervical cancer by up to 85% and that by including male HPV vaccination it would increase this to 96% providing further protection. Marty et al. (2013) further discussed findings related to other cancers that were determined to be caused by HPV infection.
It discussed and compared female vaccination, male vaccination and compared these with screening rates. Results suggested that there was an 84% decrease for females and a 61% decrease for males with female only vaccination and that HPV related cancers reduced by 86% in males when vaccinated compared with screening results alone (Marty et al., 2013). The study postulated how extending vaccination to males had the ability to decrease HPV related cancers by 65% (Marty et al., 2013). Marty et al. (2013) concluded that the greatest impact seen by vaccinating males as well as female was head and neck cancers decreased by 88% as opposed to 65% when only vaccinating females.

Two studies discussed the impact that male vaccination would have on penile and anal cancers concluding that the inclusion of males with the HPV vaccine would reduce penile cancer from 68% to 18%. Furthermore anal cancer reduced by 63% for female HPV vaccination only contrasting with an 86% reduction for both female and male vaccination programmes (Burger et al., 2014; Marty et al., 2013).

4.3.3 Category Three: Results of cost benefit analysis

Three articles used cost benefit analysis through modelling simulation to consider whether or not to vaccinate males (Brisson et al., 2011; Burger et al., 2014; Pearson et al., 2014). Cost benefit analysis was determined as both the financial cost involved in vaccinating an individual with the HPV vaccine versus the cost of a person contracting HPV disease itself or the progression of HPV to other disease states. The three studies further evaluated that this was based on many factors. These three studies used simulated theories that included benchmarking the cost of giving the HPV vaccine across a population of males against the life years that would be saved if they didn’t contract HPV disease or disease states caused from HPV progression these were referred to as quality of life years (QALYs). These QALYs were used to aid in the conclusion of cost effectiveness of a vaccination programme for males. There were distinct advantages and disadvantages and several factors that were determined to contribute towards cost. Cost was evaluated throughout the studies in a variety of ways with articles evaluating the cost of HPV vaccination that established parameters around HPV vaccination and used different variables and values to help establish at which point it would be useful to vaccinate males with the HPV vaccine. This category was broken up into three small sub-categories: advantages, disadvantages and factors contributing to cost.
4.3.3.1 Disadvantages

Three studies used modelling to predict the quality of life years (QALY) achieved and the cost of these for both male and female vaccination with HPV vaccine. Burger et al. (2014) and Pearson et al. (2014) in particular focused on the incremental value that male vaccination would give to HPV vaccination. Pearson et al.’s (2014) model predicted that when increasing coverage of both females and males the cost of the intervention’s used (eg., an increase in vaccine, time and associated costs, compared with the QALYs gained) would not be beneficial, and that with the increase in coverage the expense also increased. Pearson et al. (2014) also concluded that adding males to an already established female vaccination programme offered a similar number of QALYs, but with greater cost. This cost for male vaccination was also increased if the current female programme was an existing intensified programme as the males would have already had some coverage from herd immunity when the existing programme was intensified. The study by Burger et al. (2014) supported this by determining that expanding vaccination of HPV to boys with an already existing girls programme was not cost effective or considered good value for money (Burger et al., 2014).

Brisson et al.’s (2011) dynamic model showed that the vaccination programme returns on girls was higher than that of males. This was thought to be due to herd immunity that is acquired by males through the vaccination of females. When males are added to the programme then the cost benefit effect of this begins to lessen as the cost of each individual vaccine must be accounted for. This finding was also supported by Burger et al. (2014) who concluded that it would not be value for money (Brisson et al., 2011; Burger et al., 2014; Pearson et al., 2014).

4.3.3.2 Advantages

When considering cost, some benefits from additional male vaccination were found, but these were focused on the health benefits as opposed to it being value for money. Two of the selected studies, Brisson et al. (2011) and Burger et al. (2014), determined that there were health benefits to be gained by including males, while Pearson et al. (2014) concluded that it would be more cost effective to intensify a girls only programme to establish those health benefits at a more cost effective rate. Pearson et al. (2014) concluded that if boys were to be vaccinated at the current rate girls were, it would cost approx $117,000 per Quality of Life Year(QALY) gained from vaccination, compared with $83,000 for female vaccination, concluding that this would not be the most economical threshold.
4.3.3.3 Factors contributing to Cost

Three studies described vaccination costs as being critical to whether male vaccination would be beneficial (Brisson et al., 2011; Burger et al., 2014; Pearson et al., 2014). Pearson et al. (2014) concluded through modelling that even with low vaccination costs it would not be cost effective to vaccinate males. This contrasted with two studies which concluded that if vaccine and administration costs were low enough then simulated models demonstrated that it would be cost effective to vaccinate males. Burger et al. (2014) and Pearson et al. (2014) concluded that when considering cost and QALY, several factors changed value depending on whether the model used included only cervical cancer outcomes, or if including all HPV related cancers. Burger et al. (2014) considered that when a dose of vaccine was valued at $75, the QALY varied from between $20,600 for cervical cancer HPV disease consideration, or $5,000 if also including all cancers and genital manifestations. This study also concluded that the vaccine cost was key to a male vaccination becoming cost effective.

4.3.4 Category Four: Variables considered in the studies

The results of the six studies had multiple assumed variables used to predict results. Pearson et al. (2014) argued that the overall uncertainty of HPV reduction was the main sensitivity and created extreme uncertainty when establishing the effect and value of adding males to a female vaccination programme (Pearson et al., 2014).

Another variable was vaccine efficacy that each study assumed when using their simulated theories. In four of the studies, a vaccine efficacy of 99%-100% was assumed. One study used vaccine efficacy as a variable in different scenarios (Brown & White, 2010), and another study did not state what vaccine efficacy was used (Brisson et al., 2011; Burger et al., 2014; Marty et al., 2013; Pearson et al., 2014). Vaccine efficacy was a variable that both Brisson et al. (2011) and Brown and White (2010) used or discussed with both studies concluding that if efficacy increased then HPV decreased. Brisson et al. (2011), showed that this was less beneficial for males when vaccine efficacy was decreased, and further determined an HPV disease increase, showing that under this scenario it would be beneficial to vaccinate boys.
Vaccine pricing was another issue that several authors discussed as being an integral factor in cost effectiveness of introducing the HPV vaccine to males, with general consensus that the lower the vaccine price the more economical vaccinating became (Burger et al., 2014; Pearson et al., 2014).

4.3.4.1 Vaccine Coverage

Assumed vaccine coverage was considered as a variable by all of the six studies reviewed. Vaccine coverage is the term used to describe the total proportion of people within a population that are vaccinated, and this is often demonstrated or discussed as a percentage.

Vaccine coverage was specifically considered in four of the modelling studies, concluding that the inclusion of male vaccination substantially increased population coverage (Brisson et al., 2011; Brown & White, 2010; Marty et al., 2013; Smith & Canfell, 2014). Vaccination coverage was estimated using scenarios where there was 50% (Smith & Canfell, 2014) or 70% variations in coverage (Brown & White, 2010; Marty et al., 2013) to simulate disease reduction. Coverage was predicted at the same level when simulating male vaccination or the inclusion of male vaccination as was used for female prediction prior to male vaccination being added to model. Results concluded that when vaccination coverage is poor or low, it influenced the prevalence of HPV disease (Brisson et al., 2011; Brown & White, 2010; Burger et al., 2014; Pearson et al., 2014; Smith & Canfell, 2014). Brown and White (2010) demonstrated with a mathematical equation model that males form a reservoir for HPV to remain active and that HPV eradication would only be possible if male vaccination was to be included. Brown and White's study (2010) also considered the effect of waning immunity over time within its simulated model and postulated what part this could play in HPV persistence.

4.3.4.2 Herd Immunity

The effect of herd immunity was well documented in most articles and for narration was broken into three different sub categories, males, females, and both females and males, to make it easy to define similarities. Pearson et al. (2014) found that males benefitted from strong herd immunity when female coverage was high.
One study showed that when female coverage is low, herd immunity is very low. It further concluded that when female coverage was high there was very small benefit to be gained for herd immunity with vaccinating males (Smith & Canfell, 2014).

Marty et al. (2013) discussed the impact on herd immunity when vaccinating both males and females. The study concluded that by vaccinating both males and females with HPV vaccine the overall prevalence of genital warts would decrease by 71% as opposed to 58% if only females were to be vaccinated (Marty et al., 2013). In the study it found that the vaccination of both boys and girls would give additional disease protection through herd immunity to both males and females (Marty et al., 2013).

4.3.4.3 Social Factors

A number of other co-related factors were also considered in Smith and Canfell’s study. These included the nature and behaviour of social groups, and inequalities that could affect vaccine coverage, uptake or rate of contraction of HPV. Smith and Canfell’s (2014) study was the only study to consider this relationship of correlated factors. Smith and Canfell (2014) concluded that female only vaccination programmes showed a decrease in HPV disease by 56% however this was reduced to 49% for those that had certain correlated factors. Groups that had correlated factors had less of a long term reduction, showing that correlated factors have an impact on HPV reduction. Smith and Canfell (2014) found that including male vaccination increased both vaccination coverage of females and males. However, they also found it increased coverage for groups that had correlated factors and resulted in lower HPV prevalence of HPV of 60-61% across all diversities. They also predicted through modelling that if there were no correlated factors to consider that including male vaccination would incur a decrease of HPV of 79% amongst males and females (Smith & Canfell, 2014).

In conclusion, the results from analysis of six modelling studies clearly showed three specific main points. Firstly, in all six studies, vaccination with the HPV vaccine postulated decreased HPV infection, this was further decreased with the inclusion of males in vaccination programmes. The second main point related to changes in disease outcomes with vaccination, with all studies showing a decrease in genital warts and other HPV related diseases, considered to decrease further when males were included.
Thirdly, three of the studies concluded that it was not a cost effective exercise to additionally vaccinate males for HPV under current circumstances. However this was based on modelling and perceived variants including duration and efficacy of the vaccine itself. In general it appears that male vaccination is worthwhile but that cost could be a constraint towards this happening.
5 Discussion

5.1 INTRODUCTION
This chapter will consider the main findings and identify limitations from the literature review. It will examine the significance of these findings and how they relate to wider literature and discuss the implications for practice and further research. The key purpose of this literature review was to evaluate the advantages and disadvantages of vaccinating males with the HPV vaccine at a population level, and its implications.

5.2 FINDINGS OF LITERATURE REVIEW
It is widely accepted that HPV is the cause of numerous diseases (CDC, 2015; HPV Project, 2015; WHO, 2015) and is as much a health issue for men as it is for women. It has taken over a century to recognise the full impact that HPV can have on an individual and establish the links that it has to cancers. Much focus has been on the vaccination of women due to the early links that HPV has with cervical cancer. However, it is now widely established that for men there are also links to a variety of cancers. It is further accepted that there are three vaccines that can stop the contraction and spread of some HPV sero-types through the use of Cervarix™, Gardasil quadrivalent™ and Gardasil 9vHPV™. One of the main findings from this integrative review was that vaccination programmes using these vaccines do in fact decrease HPV. The second main finding was the impact they have on HPV disease itself and its progression. The third main finding was that including males in any vaccination programme at current costs was generally not cost effective. There were a variety of other factors when considering vaccination programmes for HPV that were raised, with the main ones being efficacy of the vaccination, coverage and the impact that social factors can have on uptake of vaccination.

5.3 LIMITATIONS
All studies included in the initial scope of the literature review were confined to the English language and it is possible that other relevant studies have been reported in other languages. No articles prior to 2009 were included in order to keep the literature review current and up to date.
Earlier studies may have included earlier theories, frameworks or literature that could have been relevant, to the review, however it could possibly be that these would be based only on modelling. There is a chance that through year limitation primary research or observational studies could have been overlooked.

Another limitation was that no primary research, interventional or observational studies met the final inclusion criteria for further review. All six articles finally included were based on simulated models. It will take a number of years for ‘real life’ data to become available as the first HPV vaccination programme only begun upon its licensing in 2006 (MOH, 2015). Another main limitation of the study was that all the studies reviewed had multiple and different variables, in which their study was based on. However these variables were hypothetical in nature leaving doubt as to how they would actually stack up in ‘real life’.

No studies were found that compared the different types of HPV vaccine and the focus instead was on females versus universal or male vaccination. By diversifying a simulated model to see how different types of HPV vaccines compared, it could show different options for any future developments, and possibly show the most cost effective way to giving full population vaccination.

5.4 AREAS FOR FURTHER RESEARCH

The first and foremost area for future research is to gain data from primary research, interventional or observational studies in order to establish both the short term and long term effects that HPV vaccination will have on a population. Currently there is only a limited amount of ‘real life’ data related to HPV vaccine efficacy and it is centred on the decrease of genital warts within a small population of family planning clinics and sexual health clinics based in New Zealand between 2009-2012 (MOH, 2014).

All six articles reviewed identified that a high percentage of the targeted population needed to be vaccinated in order to benefit from herd immunity and decrease the prevalence of HPV infection. Currently, New Zealand has HPV vaccination rates of approximately 47% (Blakely et al., 2013). This is well short of the 80% that Fine, Eames, and Heymann (2011) identified as necessary to achieve herd immunity for a vaccine preventable disease, however they do note that by selectively targeting highly transmitting groups the rate could be lower (Fine, Eames, & Heymann, 2011). New Zealand currently targets the most at risk groups aiming to vaccinate females before they are sexually active by introducing HPV vaccination at 12 years of age.
However, it is controversial that they offer this only for females when the at risk group would extend to males too. Doing so creates a reservoir for HPV to transmit through and males without access to a funded vaccine. For future research, it could be beneficial to increase New Zealand's vaccination rates to establish both individual immunity for women, helping to create herd immunity that could extend to the male population. For this to occur New Zealand needs to reassess how to educate and reach the target population and look at strategies that would educate, and promote this vaccine to lift national levels. Vaccination rates are always of concern in a current or developing programme.Currently, HPV vaccination rates in New Zealand are not considered high even though most of the delivery is through a school based system, with specialised teams attending to prospective vaccinee's at school. Further research is needed to understand why New Zealand's delivery of the HPV vaccine is not resulting in an 80% vaccination rate, especially when the delivery is based around ease of access for people who work and possibly a reliable way to get education through to individuals and to parents.

Only one of the studies included in the present review considered social factors in relation to vaccination and herd immunity (Smith & Canfell, 2014). Vaccination is often considered as an essential measure of herd immunity. Smith and Canfell, 2014 offer a new dimension to this by discussing correlated factors that contribute to the success of vaccination. An area for further research could be to consider the social impacts on HPV vaccination and an essential measure could be a decrease in HPV or HPV related diseases, however this would once again take some primary research to prove. Given that the HPV programme has only been running in New Zealand since 2008, New Zealand has not yet achieved a high proportion of the population vaccinated (New Zealand HPV Project, 2015). There is a future need to increase New Zealand's immunisation uptake rates to help establish some herd immunity against HPV.

Two studies argued that the most cost effective way of protecting both sexes from HPV would be to increase vaccination rates of females (Burger et al. 2014; Pearson et al, 2014). However, it has been argued that by including males there is an increased chance of creating herd immunity, which is known to improve the chances of stopping outbreaks of any vaccinated disease (Salathe, 2015). It could be argued that by allowing universal vaccination to be funded for both sexes, coverage across the whole population would offer protection to those unvaccinated and would cover the entire highly transmitting demographic rather than just females, and aid in achieving an 80% vaccination rate.
There are also potential benefits to populations like men who have sex with men, who under the current regime would not be funded for vaccination against HPV. The area of herd immunity needs further research in terms of the HPV vaccine in order to determine which populations are better targeted for any vaccination programme in order to achieve herd immunity. Future research around this topic would be useful if extending to men who have sex with men.

As discussed in the background chapter a large amount of literature indicates the success that Gardasil™ (MOH, 2014), has been having on genital warts for both females and males, therefore, possibly securing its place as a preferred vaccine for HPV related diseases. However in February 2015, the Advisory Committee on Immunisation Practices (ACIP) promoted a new vaccine for the prevention of HPV disease. This vaccine was a form of Gardasil™ which contained protection against a further five strains of HPV. The vaccine known as 9vHPV™, contains all serotypes covered by the Gardasil quadrivalent™, and further included protection against serotypes 31, 33, 45, 52 and 58. These strains are known to be responsible for a higher proportion of HPV related cancers (CDC, 2015). The addition of 9vHPV™ now allows for three different vaccines that can vaccinate against HPV disease. This exposes a new dimension to explore when considering factors surrounding both HPV vaccination of females and universal vaccination programmes.

Gardasil’s 9vHPV™ costs an extra $13 per dose more than that of Gardasil quadrivalent™. It is noted on the Centre for Disease Control and Prevention (CDC) website that this new vaccine is more cost effective than other HPV vaccines. CDC (2015) discusses when considering quality of life years (QALY) that 9vHPV™ was never more than $25,000 with any given scenario.

With this information it could be argued that males would become cost effective to vaccinate with this new vaccine. However literature on 9vHPV™ vaccine itself states that this vaccine’s five extra serotypes are responsible for only 10% of HPV attributed cancers (CDC, 2015). Gardasil quadrivalent™ contains serotypes 16 & 18 and these have been identified as responsible for 64% of HPV attributed cancers (CDC, 2015).
Whilst there could very well be merit in the use of 9vHPV™ vaccine due to the extra protection for HPV related diseases, it is also said that the five extra serotypes that are covered account for a larger proportion of female related cancers so could actually make it more cost effective for females as opposed to males. Using simulated theories may actually indicate that it is still only cost effective for females as those five extra serotypes are the cause of cervical pre cancers, meaning that 9vHPV™ could possibly benefit females more than males (CDC, 2015), however for future research it is an avenue worth exploring.

The use of only two options for HPV vaccination, Gardasil™ or Cervarix™, has been considered (WHO, 2015). However throughout the literature review no studies considered the cost effectiveness of using only two doses for males and the effect that this could have on disease reduction or the benefit that could be given for males. The World Health Organisation (2015) raised the possibility of a vaccination schedule that would include two doses with the HPV vaccination, or the schedule for vaccination having longer intervals for delivery. This could decrease the cost of the HPV vaccine overall, and could increase access and convenience for parents, individuals or health providers delivering vaccines. If using less vaccine, for example two doses, were a feasible option to giving immunity against HPV then it could make the vaccine a more affordable option for all countries, and individuals and could in turn help increase vaccination coverage at a community level or even a global level.

The World Health Organisation (2015) does concede that the studies on HPV are small when it comes to delivery of the two dose method and lengthening of intervals between each individual dose. At present the reliability or effectiveness of long term protection is not known. Further research is needed and could be key towards justifying cost effectiveness of the vaccine if proven to provide immunity or health benefits against HPV and for a duration of time. In the future, consideration could be given to a universal two dose scenario for both females and males, making the cost of female vaccination less and covering males as well to ensure equality.

Another factor often predicted in the simulated theories is the impact that the HPV vaccine itself has on the spread of HPV related diseases. There is some literature to suggest that HPV vaccine, which includes serotypes 6 & 11, is very effective against the development of genital warts. However, there is very little current research that can definitively state that Cervarix, Gardasil, or 9vHPV are going to decrease or eradicate HPV related cancers in those who are vaccinated fully.
Simulated factors such as waning immunity or the longevity of immunity, pattern of spread, and the effectiveness of HPV vaccine, could be major factors in real life scenarios in future. Further research is needed on these contributing factors to ensure more accurate data in which to make appropriate changes to vaccination programmes.

None of the six articles discussed vaccination in relation to education and since this area was overlooked by all the studies it would be an avenue for future research, as education is pivotal towards increasing vaccination rates and awareness about HPV and its related diseases.

5.5 IMPLICATIONS FOR FUTURE PRACTICE

Ethical issues surrounding all aspects of health are controversial, and this is expected due to individuals offering different opinions, usually formed around competing values associated with health, public funding that is available, access or the health benefits proven from specific health initiatives. The focus of this literature review was to establish the advantages and disadvantages of vaccinating males with the HPV vaccine. Throughout this study much focus has been on the vaccination of males in addition to females, and the cost effectiveness of this, versus health benefits to be gained. All six studies included in the final review predicted that HPV vaccination reduces the incidence of HPV related diseases, but that this is at a substantial cost. This cost versus benefit is predicted to increase significantly for males in particular. However when considering future practices it could show that we should be trying to significantly increase our female vaccination rates to try and establish some herd immunity for males. As primary research is developed we may find that it becomes very clear to vaccinate males especially if the long term effects of HPV vaccination are proven better with a significant decrease in HPV related diseases.

With each HPV vaccine given there is always a risk to be considered. CDC (2015) noted some local reactions can occur with vaccination including redness, pain or swelling at injection site. More serious side effects to the vaccine can include nausea, headaches, fever or muscle and joint pain, or more seriously anaphylaxis. The risk for these is considered minimal (CDC, 2015; Immunisation Handbook, 2015). The literature reviewed did not consider wider issues, such as whether women are being asked to bear the risks of vaccination, while males might benefit through herd immunity.

It could be argued that females get the health benefits associated with this risk, but should equal rights not be considered when it comes to both health benefits and the risks associated with these by offering a funded vaccine for both females and males.
It will be interesting for future research to establish whether or not the financial benefits that are expected in the reduction in cancers (especially cervical) are as high as is hoped. If it were found that the impact on cancer is not as considerable as the simulated models show, this could lead to a review of the vaccine for females. There has been some evidence of cross protection between the vaccine preventable HPV and other serotypes that there currently is not a vaccine for. It will take time before the results towards these HPV diseases are seen. If they did occur, or if there are distinct links in the future between throat, head and neck cancers, especially for females with vaccination, it would be an immensely positive unintended consequence of the vaccination. However such findings would possibly cause controversy, and raise questions as to why the males in the population were not funded for this with research clearly indicating at this stage it can give immunity to a number of different cancers for both genders. The implication for this in future practice should be focusing on educating people on an individual level to ensure they can make an informed choice for a funded vaccine or to purchase a vaccine if not funded (Immunisation Handbook, 2014).

As demonstrated in the background chapter, justification for vaccinating females only is due to HPVs link with cervical cancer. However it is also well documented in literature that HPV serotypes 6 and 11 are the main cause of genital warts (CDC, 2015; Immunisation Handbook, 2014; New Zealand HPV Project, 2015). In other words it is not only cervical cancer that women will be protected against, should they opt to have the funded vaccine, but also genital warts. Vaccinating women is thus seen as a means to decrease cervical cancers as well as genital warts, with the latter expected to have an impact on their incidence amongst heterosexual men. Understandably, although not potentially life threatening, genital warts can cause embarrassment and stress to an individual, and be difficult to adequately treat. If males and females were to both be offered a funded vaccine then it is sensible to recognise that treatment for this particular STI would not be needed providing a person is vaccinated, however that would not include other STIs. If a free and funded vaccination was to be offered to both sexes, then this would be a more ethical approach to this physical health concern and it would also save all individuals from what could be considered an invasive treatment both mentally and physically. I would suggest the cost argument, is more about health budget spending as opposed to health benefit gains.

All six studies included in the literature review discussed the cost of HPV vaccination which they evaluated as playing a fundamental part in whether vaccination was cost effective.
Vaccine price threshold was explored on numerous occasions and a fundamental theme that became apparent is that vaccine price contributed to cost effectiveness hugely. Throughout time, vaccines have often become more cost effective and if at present vaccination of males is not cost effective, it may be a point to revisit in the future, especially if the cost of vaccine reduces.

All six articles included in the literature review were based on simulated models that were used to either assess the cost effectiveness of the HPV vaccine for males or to determine how a variety of factors influenced the spread of HPV disease. Some models were more robust than other models due to clarity of variables used. With the use of simulated models many factors were considered by the author to be omitted such as the value on immunity. For example, when a simulated model used immunity of over 20 years, it was a simulated theory. Presently there is very little proof that the HPV vaccine does not have waning immunity and it could be found that HPV requires a booster in years to come. This is a point that health practitioners should be aware of as there could be occurrences of genital warts for the vaccinated populations, or an increase in HPV related diseases later, the implications for this would need to be providing this feedback to practitioners, in order to be vigilant around early recognition of any HPV related diseases in vaccinated individuals. Reporting of any occurrences in disease could be made by health professionals through the Centre for Adverse Reactions Monitoring (CARM).

Vaccine coverage correlates to the success of vaccine programmes and herd immunity. The literature review has shown that whilst HPV programmes are known to decrease HPV, the most cost effective scenario for coverage is herd immunity which is provided by a high coverage of vaccinated females. In New Zealand vaccine coverage is currently at approximately 47% (Blakely et al., 2013; MOH, 2015) for females only. For herd immunity to occur vaccine coverage would need to be over 70% to have an impact on males. For an increase in HPV vaccine coverage to occur there would need to be a nationwide drive. Currently, programmes are run through schools, and for unknown reasons coverage is still low. Health promotion would need to be considered for this to be lifted to increase vaccination rates. Social media is a huge factor in the promotion of HPV vaccination and there is recent literature that discourages the vaccination against HPV and wrongly insinuates the harmfulness that the vaccine can cause. Although reputable websites like CDC discuss these issues or insinuations, many people would not know which sites they need to view to get non-biased information, or access to evidence based research, avoiding bloggers and non-
professional opinions. Education surrounding the safety and disease progression of HPV would be needed to combat some of the negativity that can be found via websites.

A health promotion consideration could be to utilise more social media for promotion and to dispel myths surrounding the risks of not being vaccinated. This may help negate some of the current literature available that is opinion rather than research based that is discouraging HPV vaccination.

An intensified programme that included both females and males would help increase vaccination rates and extend to a community level with a raised awareness of HPV as a health issue. New Zealand Best Practice Guidelines (BPAC, 2012), are often used as a source in decision making not only at a national level but at a primary care level and it would be good to see these developed more to see support for a funded HPV vaccine for males given the disease burden that it can cause. However, another scenario that could be considered is for the vaccine to be offered universally in the hope of attaining at least 50% coverage across all entities. By vaccinating males as well as females it could equate to larger numbers being vaccinated giving some extra herd immunity benefits and with the inclusion of males it could offer some herd immunity to the female demographic who aren’t vaccinated.

The integrative review has highlighted that Gardasil™ vaccine is effective in lowering the incidence of HPV disease. However it has also determined that the cost effectiveness for male vaccination is not cost effective therefore making it look unlikely that a funded HPV vaccine will be added to New Zealand’s schedule anytime soon. This presents insight into future practices, or implications for practice. As a practice nurse with this knowledge it has highlighted the need to educate and promote female vaccination that is available on the New Zealand immunisation schedule to try and increase female vaccination rates to give the best protection we can through herd immunity for males within the New Zealand setting.

Currently, awareness of the HPV vaccine is driven and centred on female vaccination. If male vaccination were included in the immunisation schedule, it would be an opportunity to educate parents of both males and females about HPV disease burden, regardless of their child’s gender and this would lead to increased awareness of HPV and its role in causing disease and cancers, should the body’s own immune system not provide adequate antibodies. It could also lead to more education surrounding HPV and its diseases and increase rates of vaccination to combat this. This view is consistent with Salathe (2015) who argued that while
there are communities that harbour strong opposition to vaccination, there will always be outbreaks of vaccine preventable diseases, which leaves a reservoir for these diseases to be transmitted through. Salathe (2015) argued that this would still occur even if herd immunity levels are achieved, lending weight for the need for education surrounding vaccination not only for HPV but for vaccination in general. It also lends weight for an argument for males to be offered a funded HPV vaccination to help achieve both personal gains against HPV and towards community focused immunity for both females and males.

5.6 CONCLUSION

Three of the studies focused on the cost of vaccination for males and this makes it hard to determine that the perceived high cost of providing a female and male vaccination programme is a strong enough argument against doing so, given that there are clear health benefits for males obtained from HPV vaccination. It could be considered unethical to offer a funded vaccination on the basis of sex alone when clear links have established the role of HPV in male cancers and genital warts. On the flip side of this it could be offered that it is unethical to spend considerable amount of money on HPV vaccination for males when a large amount of variables are unproven, given the current price is deemed not cost effective.

Through the last decade, there is much literature to prove the effectiveness of HPV for females and males, making the non-vaccination of males very controversial. An argument for the vaccination of males could lie in the statistics of HPV related disease treatments that is used on the male demographic including those of cancer. As the intensive treatment of HPV related diseases is known to be very costly even if for one individual alone, it could be argued that it would be cheaper to vaccinate against HPV than to try and later cure an HPV caused disease. In other words, prevention is better than cure.

Despite the equivocal results the reviewer recommends that a funded vaccine for HPV should be universally available within New Zealand. The literature review itself has presented that HPV vaccine can help reduce the incidence of HPV related diseases, however possibly not with cost effectiveness.
Often health care is overshadowed by financial constraints and it appears that although HPV vaccine for females is well justified and funded, it may be some time before male vaccination is available in a funded form due to financial restrictions or restrictions on many variables that are at present unproven such as prevention of cancers or duration of efficacy.

In concluding, it is clear that HPV affects males and females, concluding that HPV vaccination should be made available for males in a funded form as it has been for females. Several disadvantages were highlighted throughout the literature review with the main theme being cost effectiveness. From a Ministry of Health perspective, cost effectiveness is a clear disadvantage, however whether this is a rationale for not funding males for an HPV vaccine when the risks of contracting such a destructive disease are so high, is hard to evaluate.

It could be a considered view that it is biased and unethical that a funded HPV vaccine programme not be initiated to include males within the New Zealand setting given that a programme at a school-based level already exists.
References


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### Appendices

#### Appendix A: Articles included in Systematic Literature review first stage initial data extraction

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Vaccine efficacy</th>
<th>Duration of protection</th>
<th>Assumed vaccine coverage</th>
<th>Reduction in HPV</th>
<th>Reduction of HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith, M., and Canfell, K. (2014).</td>
<td>High 100%</td>
<td>Long lasting</td>
<td>71%</td>
<td>56-79% correlated and unrelated</td>
<td>Decrease by up to 85%</td>
</tr>
<tr>
<td>Brisson, M., van de Velde, N., Franco, E., Drolet, M., and Boily, M. (2011).</td>
<td>100%</td>
<td>20-70 years</td>
<td>50%</td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>Marty, R., Roze, S., Largeron, N., and Smith-Palmer, J. (2013).</td>
<td>100%</td>
<td>50-100 years</td>
<td>70%</td>
<td>71%</td>
<td>91%</td>
</tr>
</tbody>
</table>

- **Vaccine efficacy**: 99%
- **Duration of protection**: 20 years
- **Assumed vaccine coverage**: 73%
- **Reduction in HPV**:
  - **Girls**: Increased
  - **Boys**: Yes but at a cost of NZ$117,500/QALY
- **Reduction of HPV**:
  - **Genital Warts**: Reduced in all sub groups
  - **Cancers**: General reduction in HPV overall with no specific mention of any particular disease
  - **Anal Cancer**: 33-88%
  - **Penile Cancer**: 29-47%
<table>
<thead>
<tr>
<th>Vaccine Coverage</th>
<th>Increase</th>
<th>Increased cost resulted in increased QALY</th>
<th>Improved outcomes overall</th>
<th>Reduced HPV further</th>
<th>Increased vaccination characteristics</th>
<th>HPV decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Decrease in reduction of HPV</td>
<td>Decreased outcomes</td>
<td>HPV increased</td>
<td>Increased boys only</td>
<td>HPV increased</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccine Efficacy</th>
<th>Increase</th>
<th>Boys less beneficial</th>
<th>HPV decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decrease</td>
<td>Boys cost effective</td>
<td>HPV increased</td>
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</table>

<table>
<thead>
<tr>
<th>Cost effectiveness</th>
<th>Girls</th>
<th>NZ$10,332/QALY dependant on vaccine cost</th>
<th>Not cost effective at NZ$83,000/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boys</td>
<td>NZ$21,157/QALY dependant on vaccine cost</td>
<td>Dependant on vaccine cost</td>
</tr>
</tbody>
</table>

**Female only vaccinations** | **Males added to female only vaccinations**

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