THE QUADRIVALENT HPV VACCINE IN MANITOBA, CANADA: FROM PROGRAM IMPLEMENTATION TO REAL-WORLD EFFECTIVENESS

By

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Chapter 1

Introduction

The human papillomavirus (HPV) is the most common sexually transmitted infection, affecting 550 000 Canadians annually.[1] For sexually active women, the lifetime risk of HPV infection is approximately 75%.[2] The highest prevalence is in women under twenty years of age.[1]

We now know that persistent infection with a high-risk HPV type is the necessary cause of virtually all cervical cancers.[3] High-risk HPV types also cause cancers of the vulva, vagina, urethra, anus, penis and, head and neck.[1] In 2008, it was estimated that HPV was the cause of approximately 5% of all incident human cancers.[4] The quadrivalent HPV vaccine (QHPV) first became available in 2006, followed by the bivalent vaccine (BHPV) in 2007, and the 9-valent vaccine (9vHPV) in 2014.[5,6] As of October 2014, 64 countries had implemented national HPV vaccination programs.[7] The primary goal of these vaccination programs is to reduce HPV-related cancer and their precursors. The HPV vaccine is now listed on the World Health Organization's List of Essential Medicines.[8]

In Canada, HPV vaccines are recommended for all females and males ages 9 to 26.[9] In March 2007, the federal government committed $300 million over three years to develop provincially run, publicly funded vaccination programs against HPV.[10] In Canada, a 3-dose QHPV vaccination program aimed at 12 year-old girls, with 70% coverage is predicted to prevent 1.9 million cases of anogenital warts (AGWs), over

500,000 cases of high grade cervical dysplasia, and over 20,000 cases of invasive cervical cancer over a 70 year period.[11] As of 2010, all provinces and territories had instituted school-based vaccination programs for girls, varying from grade 4 to 8 depending on jurisdiction.[12]

Vaccines, in general, have been hailed as one of the greatest medical advances of modern times.[13] Despite this, there has been a very public and impassioned debate over the implementation of widespread HPV vaccination programs. Parents, policy makers, clinicians, industry and media have all weighed in on issues ranging from the medical merits of the vaccine to the ethical, political and social implications of such programs. The safety and efficacy of HPV vaccines against intermediate clinical endpoints, including cervical dysplasia and AGWs, was initially established through several large randomized controlled trials.[14-19] The results of these trials provided the basis for which widespread vaccination programs were developed. However, randomized controlled trials tend to recruit highly selected populations and employ strict protocols such that they may not be applicable to real world populations.[20] Therefore, it is important to use well-designed population-based observational studies to measure vaccine effectiveness in the general population following the implementation of any new vaccination program.

Since September 2008 in Manitoba, the QHPV has been used to vaccinate more than 25,000 grade six girls (born on or after January 1st 1997) as part of the provincial publicly funded school-based vaccination program. The relatively early introduction of the QHPV in Manitoba and the availability of well-established, population-based health

administrative databases, including immunization, cervical screening, physician billing and hospital databases, provide a unique opportunity to perform ongoing evaluation of our publicly funded HPV vaccination program.

To date, several questions still remain as to the optimal use of the HPV vaccine in order to maximize the potential public-health benefit. It is my goal to address some of these questions here.

Thesis summary and organization

This document is presented as a manuscript-style thesis. The work presented here is divided into six chapters. Chapter 2 provides a background literature search, including the pathogenesis and epidemiology of HPV infection and the burden of AGWs. I briefly review the randomized evidence for HPV vaccination, which provided the basis for HPV immunization programs worldwide and discuss the challenges in applying randomized evidence to the real-world setting. Chapter 3 provides background information on the development and rationale for the current HPV vaccination program in Manitoba, Canada. In chapter 4, we present a systematic review and meta-analysis on the efficacy and safety of a 2-dose versus 3-dose HPV vaccination schedule. In chapter 5, we present a historical matched cohort study to assess the effectiveness of the QHPV program in Manitoba in reducing the incidence of medically-attended AGWs. We use population-wide, individual-level data to assess whether vaccine effectiveness depends on age at vaccination, evidence of prior sexual activity, and number of administered vaccine doses. The work in chapters 4 and 5 are presented as they were submitted for consideration for

peer-reviewed publication. Chapter 6 provides a summary of key research findings, as well as discussion around policy implications of these findings. I discuss current gaps in knowledge and possible directions for future work.

Chapter 2

Background Literature Review

In chapter 2, we briefly review the natural history and pathogenesis of HPV infection. We review the prevalence of HPV infection and AGWs, with a focus on the available data from Manitoba. Background information on the HPV vaccine is provided, including initial evidence from randomized trials that have lead to widespread HPV immunization programs worldwide. We also discuss the challenges that exist in assessing HPV vaccine efficacy and translating this into real world application of the vaccine. This background provides a rationale for the systematic review and cohort study presented in chapters 4 and 5, respectively.

Natural history and pathogenesis of HPV infection

The papillomavirus is a double stranded DNA virus that infects the squamous epithelium of its host.[21] German virologist Harald zur Hausen was the first to postulate the role of HPV in cervical cancer in the late 1970s.[22] Since that time, more than 200 papillomavirus genotypes have been characterized, with upwards of 40 types shown to infect the human genital and oropharyngeal tracts.[1] These are divided into high-risk and low-risk types, depending on their oncogenic potential. Persistent infection with a high-risk HPV types (e.g. HPV-16, -18, -31, -33, -45, -52, -58) is the necessary (but not sufficient) cause of cervical cancers and their precursors, high-grade cervical intraepithelial neoplasias (CIN 2/3).[1] High-risk HPV types can also cause cancers of the vulva, vagina, urethra, anus, penis and, head and neck.[1] Infection with low-risk HPV types (e.g. HPV-6, -11) can cause AGWs, as well as low-grade intraepithelial neoplasias.[1]

HPV can be transmitted by any intimate touch, including non-sexual skin-to-skin contact.[1] Compared to other sexually transmitted infections, HPV is highly transmissible. Among discordant couples practicing vaginal intercourse without a condom, the risk of HPV transmission over 6 months is approximately 20%.[23] To put this in perspective, the 6-month risk of transmission of HIV in discordant couples (without using condoms and not on retroviral therapy) is 0.8%.[24]

Once transmitted, high-risk HPV types may induce carcinogenesis through the integration of the HPV genome into host chromosomes.[21] The HPV genome is approximately 8kpb, encoding genes for 8 distinct proteins of which E6 and E7 are responsible for cellular transformation.[25] These E6 and E7 oncoproteins interact with tumour suppressor genes p53 and pRB, respectively, to prevent programed cell death and induce unregulated cellular proliferation.[1] If left unchecked, this can ultimately result in malignant transformation of the cell.[25] For low-risk types, the HPV genome resides extrachromosomally in the host nucleus; this results in benign hyperproliferative lesions, including AGWs.[26]

HPV has the ability to evade the host immune response. It produces no significant viremia, and minimal inflammatory response, both features normally induced to alert the human immune system.[27] Despite this, it is estimated that approximately 80% of HPV infections are cleared by the host through cell-mediated immunity among people

with intact immune systems.[1] As a result, HPV-related disease is, ultimately, a rare consequence of a very common infection.[1]

Prevalence of HPV infection

HPV is not a reportable infection in Canada.[2] Therefore, estimates of HPV prevalence prior to vaccine availability are based on opportunistic sampling of select populations, including patients in routine cervical screening clinics, family planning clinics, prenatal clinics, and STI/HIV clinics.[2,12] Estimates on the overall prevalence of HPV (any type) among females in Canada range from 10.8% to 29%.[28] The largest Canadian population-based sample to date, published in 2009, included 4821 women aged 13 to 86 years participating in a cervical cancer screening program in British Columbia.[29] The prevalence of HPV types 6, 11, 16, and 18 were 4.0%, 0.2%, 10.7% and 3.5%, respectively.[29] Overall prevalence was highest in women under 20 years of age, which is in keeping with other North American and European studies.[30-32]

In Manitoba, a study conducted in 2008 on an opportunistic sample of 592 women attending Papanicolaou (Pap) screening clinics found an overall prevalence of HPV (any type) to be 19.4%.[33] Of these, 7.4% tested positive for low-risk HPV types, including HPV-6 and -11.[33] Age less than 30 years was a significant predictor of HPV positivity.[33]

Prevalence of AGWs

Like HPV infection, AGWs are not a reportable disease in Canada.[33] Estimates on incidence and prevalence are limited. Where available, these estimates are often based on algorithms used to identify medically-attended cases of AGWs through administrative health databases.

In 2009, Kliewer et al. were the first to use linkage of hospital and physician claims databases to estimate the baseline incidence and prevalence of AGWs in Manitoba. Between 1984 and 2004 (i.e. prior to the availability of the HPV vaccine), approximately 25,000 Manitobans were diagnosed with AGWs.[34] Incidence and prevalence rates for both sexes peaked in 1992 (170.8 cases per 100,000 females; 149.9 cases per 100,000 males).[34] The rates decreased thereafter, until the early 2000s when they began to rise again. In 2000 the incidence and prevalence of AGWs in men surpassed those in women. Among women, the highest incidence was seen in those aged 20 to 24.[34] For men, the highest incidence was seen in the 20 to 29 year age group.[34]

An updated analysis by Thompson et al. used similar algorithms to assess AGW incidence rates in Manitoba from 1990 to 2011 (i.e. before and after introduction of the HPV vaccine).[35] They compared incidence rates of AGW by sex, age group, and place of residence (urban versus rural). Consistent with the findings of Kliewer et al., they found that prior to 2000 the age-standardized incidence of AGWs was higher in females compared to males. Subsequently, since 2000, incidence rates of AGWs have been consistently higher among males. For females, the incidence rates did not change significantly between 2000 and 2011; for males, age standardized incidence rates of

AGWs increased by 31% from 2001 to 2010, widening the male to female incidence rate ratio steadily over this time period. AGW incidence was higher in urban compared to rural areas for both males and females, which may be attributable to differences in access to care, although this was not assessed in this study.

Possible explanations for these patterns over time include changes in sexual behaviour, such as increasing number of sexual partners and an increase in the number of males who have sex with males, coupled with an increase in riskier sexual practices.[34] However, these explanations remain speculative, as no studies to our knowledge have examined trends in risk factors for AGWs in Canada.[34]

HPV vaccine

The development of prophylactic HPV vaccines was the result of international collaboration, which began in the 1980s and early 1990s shortly after zur Hausen proposed the role of HPV in the pathogenesis of cervical cancer. Prophylactic HPV vaccines are classified as subunit vaccines; they rely on virus-like particles (VLPs) to evoke an immune response in the host.[36] Specifically, they contain the L1 capsid proteins of each HPV type contained in the vaccine.[36] These VLPs self-assemble using host machinery and are then recognized by the host immune system to elicit an antibody-mediated immune response.[36] Importantly, prophylactic HPV vaccines do not contain viral DNA, and therefore, cannot cause HPV infection. In theory, these 'inactivated' vaccines require multiple doses to provide protection, as one dose alone is not sufficient

to produce a protective immune response, but instead 'primes' the immune system to mount a more robust response to subsequent doses.[37]

There are currently three different prophylactic HPV vaccine formulations approved for use. The BHPV (Cervarix®) protects against two high-risk types- HPV-16 and -18, which cause approximately 70% of cervical cancers.[12] It does not, however, protect against low-risk types, which can cause low-grade intraepithelial neoplasias and AGWs. The QHPV (Gardasil®) also protects against high-risk HPV-16 and -18, as well as two additional low-risk types- HPV-6 and -11, which cause over 90% of AGWs.[12] More recently, a 9-valent HPV vaccine (9vHPV; Gardasil-9®) has been approved, which protects against the same four HPV types as QHPV, as well as 5 additional high-risk types- HPV-31, -33, -45, -52, -58; this brings the overall protection against cervical cancer from 70% up to 90%.[6]

Prophylactic HPV vaccines are intended for primary prevention of HPV infection. Therefore, for maximum vaccine effectiveness, these vaccines are ideally administered prior to the initiation of sexual activity. The average age of sexual debut differs between countries, and local HPV vaccination policies should reflect these differences.[38] While co-infection with multiple HPV types is possible, it is conceivable that some women with a pre-existing HPV infection may still benefit from vaccination with polyvalent HPV vaccines i.e. may still receive protection from types to which they have not previously been exposed. This idea lends support to the approval of prophylactic HPV vaccines in women who are already sexually active. However, at the population level, the benefit of

HPV vaccination of sexually active adult females is questionable. This is discussed further in Chapter 5.

HPV vaccine efficacy

Evidence for the efficacy and subsequent widespread approval of HPV vaccines for males and females over the age of 15 were based on the results of several large phase III randomized trials. Efficacies against clinical endpoints from these trials are summarized in Table 1-1. In each of these trials, results are presented for both According to Protocol (ATP) and Intention-to-treat (ITT) cohorts. The ATP cohorts are restricted to trial subjects who received all three doses at the specified intervals; they must have no evidence of prior HPV infection, as assessed by PCR DNA or serology.[39] They are considered the 'best case scenario' for the effectiveness of the vaccine. The ITT cohort approximates the effectiveness of the vaccine among individuals of similar demographic and risk profiles.[39] They include all individuals who are randomized and receive at least one dose of vaccine; they include subjects with evidence of prior HPV exposure and current infection or clinical evidence of HPV-related disease.[39]

Table 1-1. Summary of landmark trials of HPV vaccine efficacy against clinical endpoints related to HPV vaccine-types.

	% Efficacy (95% CI)	
	ATP cohort	**ITT cohort**
QHPV		
Females age 15-26[16,15]		
CIN2	100 (94.7-100)	54.8 (40.8-65.7)
CIN3	96.8 (88.1-99.6)	45.1 (29.8-57.3)
AIS	100 (30.9- 100)	60.0 (<0-87.3)
VIN 2/3 or VaIN 2/3+	100 (82.6- 100)	78.5 (55.2- 90.8)
AGWs	-	79.5 (73.0- 84.6)
Females age 24-45[40]		
Persistent (>6mos) infection	89.6 (79.3- 95.4)	49.0 (35.5- 59.9)
CIN (any grade)	94.1 (62.5- 99.9)	47.5 (16.3- 67.7)
CIN 2/3	83.3 (37.6- 99.6)	22.4 (42.5- 58.3)
External genital lesions	100 (30.8- 100)	8.5 (<0- 63.4)
Males age 16-26[41]		
External genital lesions	90.4 (69.2- 98.1)	65.5 (45.8- 78.6)
Persistent (>6mos) genital infection	85.6 (73.4- 92.9)	27.1 (16.6- 36.3)
AIN (any grade)	77.5 (39.6- 93.3)	50.3 (25.7- 67.2)
Persistent (>6mos) anal infection	94.9 (80.4- 99.4)	59.4 (43.0- 71.4)
BHPV		
Females age 15-25[17]		
CIN 2+	94.9 (87.7- 98.4)	60.7 (49.6- 69.5)
CIN 3+	91.7 (66.6- 99.1)	45.7 (22.9- 62.2)
AIS	100 (<0- 1000	70 (<0- 94.7)
Females age 18-25[42]		
Persistent (>12mos) infection	90.9 (82.0- 95.9)	49.0 (38.1- 58.1)

ATP: according to protocol; ITT: intention to treat; QHPV: quadrivalent HPV vaccine; BHPV: bivalent HPV vaccine; CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AGWs: anogenital warts; AIN: anal intraepithelial neoplasia

Several challenges exist in assessing HPV vaccine efficacy and translating this into real world application. Although the prevention of invasive cancer is the ultimate goal of HPV vaccination, cancer develops slowly, over years to decades. Because pre-malignant lesions are treated immediately, cancer as an end-point for vaccine efficacy trials is both unfeasible and unethical. Therefore, approvals to date are based largely on intermediate clinical endpoints of infection. The use of pre-invasive clinical endpoints present some challenges. Although a diagnosis of CIN2/3 increases the risk of progression to invasive cancer, it is a cytologically imprecise diagnosis, and is often due to co-infection with multiple vaccine and non-vaccine HPV types. [18,43]

It is important to note that trials that looked at the 15-26 year old age group, excluded subjects with more than five lifetime sexual partners. Prior exposure to HPV should be minimal among the target age group for primary immunoprevention-adolescents age 10-14. For this group, we would expect that with adherence to the recommended vaccination schedule, vaccine effectiveness in the real world to be closer to the efficacy seen in the ATP cohorts. However, those who initiate vaccination at an older age are more likely to have engaged in sexual activity prior to vaccine receipt and may have already come into contact with the virus. In the PATRICIA trial of BHPV, 6-7% of women were positive for HPV-16 or -18 on cervical specimen at the time of enrollment.[17] In the FUTURE I/II analyses, 26.8% of women were positive for vaccine-type HPV types on either the cervix or by serology.[39] Unsurprisingly, the efficacy of HPV vaccine for clinical endpoints was lower among the ITT cohorts (i.e. those with evidence of prior HPV exposure) in all trials, and particularly among females age 24 to

45, where there was no exclusion based on number of lifetime sexual partners.[40] These results have implications for the implementation of catch-up vaccination programs for people initiating vaccination at an older age.

For approval of use in the 10 to 14 year old age group, the use of intermediate clinical endpoints (HPV infection, cytological abnormalities) in trials is not feasible, as a large proportion of this group is unlikely to have been exposed to HPV. Furthermore, invasive gynecological exams are not justified in this group. Therefore, approvals for use in the target group for primary prevention are based on immunologic non-inferiority compared to groups where clinical efficacy has been shown (i.e. older adolescents and adults). Both the International Agency for Research on Cancer (IARC) and the United States National Cancer Institute (NCI) agree that immunologic non-inferiority is a valid end-point for licensure of novel HPV vaccine dosing schedules in different age groups.[44] However, at present there is no known immune correlate for clinical protection from HPV infection.[44] Also, the non-inferiority margin used for these immunobridging trials seems arbitrary. A systematic review on the use of non-inferiority margins in vaccine trials by Donken *et al*., found that most trials use a mean geometric antibody concentration (GMC) ratio of 1.5 or 2, but none of the 136 eligible immunogenicity trials provided a clear explanation as to their choice of margin used.[45]

Ultimately, while the results of these trials were promising, randomized trials tend to recruit highly selected populations and employ strict protocols such that they may not be applicable to real world populations.[20] Also, vaccine effectiveness at the population level is highly influenced by policy decisions and successful implementation of a

vaccination program.[20] Therefore ongoing evaluation of vaccine effectiveness in the general population is needed.

Chapter 3

The Manitoba Context

Preface

Integration of a new vaccine into a publicly funded immunization program is the responsibility of provinces and territories, and each must determine the optimal conditions of use of the vaccine in the epidemiological context of that jurisdiction.[46] The QHPV became available in Manitoba in August 2006 for females aged 9-26 years, and was subsequently introduced into the routine provincial immunization schedule for all girls in grade 6 in the fall of 2008. Since that time, recommendations have been extended to include females up to the age of 45, as well as males aged 9 to 26. However, challenges exist in identifying those in the population who stand to benefit the most from this public health intervention, particularly within the context of a publicly funded health care system. In this chapter we discuss the introduction of the HPV vaccine in Manitoba, Canada, with particular attention to HPV vaccine uptake before and after introduction of the publicly funded school based program.

Introduction of the HPV vaccine in Manitoba

In July 2006, Merck's QHPV vaccine, *Gardasil®,* was licensed and approved for use in Canada.[2] This was the first vaccine on the Canadian market to offer protection against HPV. In February of 2007, the National Advisory Committee on Immunization (NACI) put forward recommendations, supported by the Public Health Agency of Canada, for the use of QHPV for females aged 9 to 26 years.[28] Shortly thereafter, in the

spring of 2007, the federal government committed $300 million in funding to the provinces and territories to support a national HPV immunization program.[10] The goals of this program include:

1. *"To reduce cervical cancer precursors (cervical intraepithelial neoplasias grade 2 and 3) by 60% within the first 20 years of the HPV immunization program;*
2. *To reduce the morbidity and mortality of HPV-related cancers and their precursors through combined primary prevention (immunization) and secondary prevention (screening);*
3. *To implement school-based HPV immunization programs in all provinces and territories. These programs would cover females only at this time."*

It is important to note that these goals and subsequent recommendations for HPV vaccination in Canada are based on several assumptions. Firstly, the targeted reduction in cervical cancer precursors is based on a vaccine efficacy of 95%, as well as vaccination coverage of 85% for all girls aged 11, 80% for girls aged 14, and 75% girls aged 17.[10] Ten years post-introduction, uptake of HPV vaccine in most provinces and territories in Canada falls short of these goals.[47] Secondly, these numbers are based on the assumption that the vaccine provides life-long immunity, the data for which remains yet to be seen.[10] In terms of the reduction of mortality due to cervical cancer, it is recognized that there is a lag time between diagnosis and death, and the assumption lies in that the outcome of active treatment (surgical, chemotherapy, radiation) is known by five years after

diagnosis.[10] It is stressed that the development of an HPV immunization program should not replace the need for organized cervical cancer screening programs.[10]

Between September 2007 and June 2008, the *Human Papillomavirus Immunization Program (HPVIP) Advisory Group* and the *HPVIP Working Group* were convened to identify issues related to developing an HPV immunization program in Manitoba.[2] In March of 2008, these groups put forth a formal recommendation to the Manitoba Minster of Healthy Living recommending the first cohort of HPV vaccination for females in grade six, to commence in the 2008/09 school year. This cohort would receive a three-dose vaccine schedule, administered by a public health nurse, in the school setting. This recommendation was based on the fact that, as primary prevention, the QHPV is ideally administered to girls prior to the onset of sexual activity. Approximately 20% of Canadian 15-year-olds have had a sexual encounter.[10] Studies have shown that the risk of acquiring an HPV infection peaks within the first 5 to 10 years after onset of sexual activity.[17] Also, school attendance is better in middle years compared to senior years, which supports the completion of a 3-dose HPV vaccination series.[2] In Manitoba, information on reproductive health is introduced into the school curriculum in grade five.[2] Although concerns have been raised that vaccination of adolescents could lead to altered risk perceptions and an increase in risky sexual behaviours, several studies have suggested these fears are unfounded.[48-53] Furthermore, immunization within the school setting has been found to be cost-effective and at that time, programs already existed in Manitoba for hepatitis B in grade four and tetanus, diphtheria and pertussis in grade eight/nine.[2]

In February of 2010, indications for use of the QHPV in Canada were expanded to include males aged 9 to 26 years for the prevention of anal intraepithelial neoplasia, anal cancer and AGWs, although not through the publicly funded, school-based program.[9] Since that time, the efficacy of QHPV in preventing external genital lesions and persistent HPV infection in males has been shown.[41] As of September 2016, boys were eligible for QHPV vaccination as part of the school-based program in Manitoba.

In April 2011, use of the QHPV was approved for women up to age forty five.[2] An updated NACI statement in 2012 suggested that these women would still benefit from HPV vaccination even if they were sexually active or had evidence of prior HPV infection.[12] It was thought that the most cost-effective way to reduce HPV-related disease in the population was to increase overall coverage in females, as opposed to vaccinating males. In light of these recommendations, in November 2012, the Public Health Branch of Manitoba Health expanded it's eligibility criteria for publicly funded HPV vaccination to include females aged 9 to 26 years outside of the school-program who were deemed by their healthcare provider to be at increased risk of HPV infection. Eligibility for this high-risk catch-up program was at the discretion of the care provider but could include: early onset of sexual activity, multiple sex partners, history of STI, adolescent pregnancy, immune compromise, history of abnormal Pap, family history of HPV-associated cancers.[54] However, due to emerging evidence demonstrating lower vaccine effectiveness in older, sexually active females, as well as low uptake through this program, the high-risk catch up program was terminated in March of 2014. While the

vaccine remains approved for women up to the age of 45 in Canada, the out-of-pocket cost of the 3-dose HPV vaccine schedule is approximately $400-$500[55], making it inaccessible to many.

In early 2014, based on the available evidence, the World Health Organization's Strategic Advisory Group of Experts (SAGE) suggested that a 2-dose schedule could be considered for primary vaccination in 9 to 14 year olds.[56] As a result, many jurisdictions have moved to a 2-dose HPV vaccination schedule for healthy, immunocompetent adolescents. This was implemented in Manitoba in September 2015. However, these recommendations are based on immunological outcomes, and long-term data on clinical outcomes and the potential need for a booster dose are still needed. This is discussed further in Chapter 4.

Currently in Manitoba, a two dose QHPV vaccination schedule is recommended and offered through the publicly funded school based program for all healthy males and females who initiate vaccination before the age of 15.[57] For those who missed the school based program, a three dose schedule is recommended, unless the first dose was administered before the age of 15.[57] For males born after January 1, 2002, there is currently a publicly funded 3-year catch up program for school based vaccination in grade 6 as well as grade 8 or 9.[57] Females born between 1986 and 1996 who initiated the vaccination series prior to March 31, 2014 through the high risk catch up program are still eligible for a publicly funded 3-dose schedule.[57] Immunocompromised females (born after 1997) and males (born after 2001) are also eligible for the 3-dose schedule.[57]

Uptake of HPV vaccine in Manitoba

Since 2008, Manitoba Health and CancerCare Manitoba has conducted evaluation of the provincial HPV immunization program.[2] A major component of this evaluation is vaccine uptake, both through the public and private systems. Highly accurate data on uptake of HPV vaccine in Manitoba is possible due in part to the Manitoba Immunization Monitoring System (MIMS), a unique population-based immunization registry that includes all publicly funded vaccinations administered in the province since 1986.[58] Kliewer *et al*. have presented this data in a series of reports through CancerCare Manitoba. More recent data is provided by Manitoba Health. A summary of the pertinent findings of these reports is presented below.

Between August 2006 (when the vaccine first became available in Manitoba), and September 2008 (when the publicly funded, school-based program was initiated), only 1.47% of eligible females age 9 to 26 received at least one dose of HPV vaccine.[59] The highest age-specific uptake was among females aged 17.[59]

In the first year of the school-based program, 52.7% of eligible grade 6 girls (the 1997 cohort) received at least one dose of the vaccine.[60] Allowing for catch-up doses, the 2014 Manitoba Annual Immunization Surveillance Report found that by the time they reached age 17, 57.6% of the 1997 cohort had received 3 doses of the vaccine (considered 'complete' with respect to the recommendations at the time).[61] Published data on completeness by the age of 17 is not yet available for subsequent birth cohorts in

Manitoba. However, an unpublished analysis by Manitoba Health shows that as of July 20, 2015, 60.5% of the 1997 cohort had completed a 3-dose vaccination schedule.[62]

Prior to the implementation of the school based program, age standardized vaccination rates were highest in Winnipeg, compared to the rest of the province.[59] The lowest rates were seen in the northern health regions.[59] For both urban and rural residents, vaccination rates were positively correlated with income quintile, which suggests that cost through the private system may be a barrier to uptake.[59] Alternatively, there could be underlying differences in healthcare seeking behaviours based on income that explain this finding. During the first year of the school based program, publicly funded vaccination rates of eligible 11 year old females was similar between rural and urban residents overall (44.6% and 46.1%, respectively).[60] However, there was still significant geographic variation in uptake, with lowest rates in the northern regions of the province.[60] In the same report, Kliewer *et al*. showed that these same regions had among the lowest rates of cervical screening uptake, and highest rates of abnormal cervical cytology and invasive cervical cancer in the province.[60] However, more recently, uptake rates in the Northern Health Region seem to be improving, with 63.1% of the 1997 birth cohort residing in that region having completed a 3 dose schedule, compared to 57.6% in Manitoba overall.[61]

Chapter 4

The efficacy and safety of a two- versus three-dose human papillomavirus vaccine schedule: A systematic review and meta-analysis

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Preface

Many jurisdictions have moved towards a 2-dose HPV vaccination schedule for vaccination of young adolescents. While it is hoped that this schedule will increase uptake and improve cost-effectiveness of a vaccination program, the recommendation for a 2-dose schedule is based on little clinical data. No randomized studies to date report clinical outcomes of a 2-dose vaccination schedule in any age group. Existing immunologic data from immune-bridging trials are based on a somewhat arbitrary non-inferiority criterion, and do not provide any clinical correlate of protection. Evidence from observational studies is just now beginning to emerge.

We conducted a systematic review and meta-analysis, according to the Methodological Expectations of Cochrane Intervention Review, to synthesize and critically appraise the most long-term data available on the comparative efficacy, safety and duration of protection of a 2-dose vs. 3-dose HPV vaccine schedule.

Throughout the manuscript, we discuss the lack of clinical efficacy data among the 9-14 year age group. We acknowledge that, in this population, licensing of the 3-dose, and subsequent 2-dose vaccination schedules were based on bridging immunogenicity data alone. However, we feel it is important, nonetheless, to highlight the lack of clinical efficacy among the target population for primary vaccination. We do this, not to call into question the efficacy of the vaccine in this age group, but rather to emphasize the need

for ongoing evaluation and peer-reviewed publication of real-world effectiveness of both the 3-dose and 2-dose schedules among this group, particularly as they reach the age of sexual debut.

Ultimately, several questions about a 2-dose schedule still remain. Ongoing post-licensure observational data is required to assess the population level impact and herd effects of a 2-dose HPV vaccination schedule. Further research is needed to link health policy decisions related to licensing and use of the HPV vaccine to clinically relevant, patient-centered outcomes.

The following manuscript is presented as it was submitted to *Papillomavirus Research* January 2017.

Abstract

Background: The HPV vaccine was initially licensed to be given as three separate doses over a 6-month period. Based on available evidence, several agencies are now recommending a 2-dose schedule for adolescents.

Objective: To synthesize and critically appraise the available on the comparative efficacy, safety and duration of protection of a 2- vs. 3-dose HPV vaccine schedule.

Methods: We included randomized trials from MEDLINE, EMBASE, CENTRAL, WHO's International Clinical Trials Registry Platform, Merck and GlaxoSmithKline Clinical Trials Registries, and conference proceedings. Primary clinical outcomes, secondary immunogenicity outcomes and safety outcomes were considered.

Results: All included trials reported immunogenicity outcomes; none reported clinical outcomes. Two doses of both bivalent and quadrivalent HPV vaccines in girls (age 9-14) was non-inferior to 3-doses in women (age 15-26). However, when compared within the same age group, the non-inferiority of the 2-dose schedule in girls is violated within the first 1-2 years of vaccine administration for both the bivalent and quadrivalent vaccines compared with the 3-dose schedule.

Conclusions: Few randomized trials have compared the 2- versus 3- doses of HPV vaccine. Existing evidence for a 2-dose schedule in girls is based on immunogenicity data, and not on established clinical efficacy in this age group.

Introduction

The human papillomavirus (HPV) is the most common sexually transmitted infection.[1] For sexually active women, the lifetime risk of HPV infection is 50-80%.[1] Since 2007, 52 countries worldwide have implemented HPV vaccination programs.[63] The primary goal of these vaccination programs is to reduce HPV-related cancers and their precursors.

HPV vaccines were initially licensed to be given as three separate doses over a 6-month period. Both bivalent (BHPV) and quadrivalent (QHPV) vaccines have demonstrated almost complete protection of the 3-dose schedule against infection and cervical dysplasia caused by HPV vaccine-types at 10 years follow-up in women aged 15 to 26 in several large, randomized trials. [18,64-67]

Currently available prophylactic HPV vaccines are directed against the L1 capsid protein of the viral particle itself, prior to cellular infection [68]. Therefore, the target group for primary vaccination against HPV is in youth, before possible exposure to the virus via sexual activity [69]. As it is not feasible to observe sequelae of HPV infection in this population, approval for vaccine use in this age group was established via immunobridging non-inferiority trials [70]. For HPV vaccine licensure, non-inferiority is inferred if the lower bound of the 95% confidence interval for geometric mean antibody concentration (GMC) ratios (2-doses/ 3-doses) does not fall below 0.5. In other words, if the trial population attains antibody levels that are at least half as high as the group where clinical efficacy has been established, non-inferiority can be inferred [71].

Proof-of-principle of a 2-dose HPV vaccine schedule was shown in post-hoc analysis of a large non-randomized clinical efficacy trial in women aged 18-25 [72]. Since then, several trials have assessed the immunologic non-inferiority of a 2-dose schedule in girls (aged 9-14) versus a 3-dose schedule in women (age 15-26) [73-76].

In early 2014, based on the available evidence, the World Health Organization's Strategic Advisory Group of Experts (SAGE) suggested that a 2-dose schedule could be considered in adolescents aged 9-14 [56]. Several agencies have subsequently licensed a 2-dose schedule in this population. However, data on clinical efficacy of a 2-dose vaccination schedule is lacking and the duration of protection remains uncertain.

The goal of this systematic review and meta-analysis was to identify, critically appraise and summarize the most long-term data available on the efficacy, safety, and duration of protection of a 2-dose versus 3-dose HPV vaccine schedule.

Materials and Methods

We conducted a systematic review according to the Methodological Expectations of Cochrane Intervention Review [77] and reported using the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria [78]. Ethical approval was not required for this review as no individual patient data was used.

Populations, interventions, comparators, outcome measures (PICOs)

We posed the question "In females aged 9-26 years old receiving the HPV vaccine, what is the comparative efficacy and safety of a 2- versus 3-dose administration schedule?" To be eligible, a trial had to report on females receiving 2- versus 3-doses of either the BHPV or QHPV, with an interval of 6 months between first and last dose. Primary clinical outcomes were incident and persistent HPV-16/18 infection, incident cervical intraepithelial neoplasia grade 2 and higher (CIN2+), and incident anogenital warts. Secondary immunogenicity outcomes were, GMC ratios (2-dose/3-dose) and seropositivity rates at longest follow-up. Immunogenicity outcomes were assessed separately for both HPV-16 and -18. Duration of follow-up was measured in months post first vaccination. Secondary safety outcomes included serious adverse events following immunization at longest follow-up.

We included two-arm randomized trials of 2- versus 3-dose administration schedules, as well as multi-arm immunobridging non-inferiority trials that included both randomized younger females and an additional non-randomized comparator group of older females. Although the latter include analyses based on non-randomized allocations of treatment arms, we felt it necessary to include them, as these trials were the basis of licensure of HPV vaccines among adolescents age 9-15. Therefore, our main analysis was divided into two comparisons: *Comparaison 1* assessed randomized 2-dose versus a 3-dose schedule comparisons in girls (age 9-14). *Comparaison 2* assessed non-randomized immunobridging comparisons of a 2-dose schedule in girls (age 9-14) versus a 3-dose schedule in women (age 15-26).

Search strategy for identification of studies

We searched PubMed (NLM), MEDLINE (Ovid), EMBASE (Ovid), and the Cochrane Library (CENTRAL - Wiley) from inception to August 2015 for relevant citations of published randomized trials using individualized search strategies prepared for each database. See Appendix A for the search strategy for MEDLINE. To identify ongoing, planned or unpublished trials, we searched the World Health Organization's International Clinical Trials Registry Platform, Merck Clinical Trials Registry, and GlaxoSmithKline Clinical Trials Registry. We also searched OpenGrey.eu for grey literature from Europe.

In addition to electronic searching, we searched relevant abstracts and conference proceedings for the European Research Organization on Genital Infection and Neoplasia (EUROGIN) and the International Papillomavirus Society from 2012 - 2015. All searches were supplemented by hand searching the bibliographies of key papers for relevant citations. Where available, extended follow up analyses of included trials that became available during the data analysis period were also included.

Study selection, data abstraction, and data management

We used a two-step process for trial screening and selection. Two reviewers (KW and AC) independently screened the titles and abstracts (where available) of search results to determine if a trial met the general inclusion criteria. The full text of all potentially relevant reports were retrieved for formal review and independently assessed

by the two reviewers using a standardized, pre-piloted form. Disagreements were resolved by consensus. Reference management was performed using EndNote X7 (Thomson Reuters).

Data synthesis

We analyzed data from included studies using Review Manager (RevMan version 5.3.1) . Using random-effects models, we expressed immunogenicity outcomes as mean GMC ratios (GMC in the 2-dose group divided by GMC in the 3-dose group) with 95% confidence intervals (CI). Immunologic non-inferiority was violated if the lower bound of the 95% CI fell below 0.5 (the non-inferiority criterion used for HPV vaccine licensure). We presented dichotomous data (seroconversion and safety) as pooled risk ratios (RR) with 95% CI calculated using random-effects models. We quantified statistical heterogeneity using the I-squared test [79].

Subgroup analysis

Due to differences in immune response over time, all GMC ratios were analyzed (where possible) at discrete follow-up times (in months) after first vaccination. Due to differences in immune response based on vaccine formulation, subgroup analysis was performed separately by vaccine valency (BHPV and QHPV).

Assessment of risk of bias

Internal validity of included trials was assessed using the Cochrane Collaboration Risk of Bias tool [77,80].

Results

Trial Characteristics & Study Populations

Table 4-1 shows a summary of the characteristics of included trials. Of the 3,183 records identified from electronic and hand-searches, we included six study reports in our analysis; four unique trial reports [73-75,81], enrolling 3,057 females, and two extended follow up analyses [82,83] (Figure 4-1). Five of the included reports are from peer-reviewed journals [73,74,81-83], and one is from a clinical trial registry [75]. All trials took place between 2007 and 2014. Duration of follow-up post-first dose ranged from 7 to 60 months. All trials took place in middle- and high-income countries. Three of the four trials are industry sponsored [73,75,81]. Three of the four unique trials are assessed as having high risk of bias, mainly due to incomplete outcome data [73-75] (see Appendix B).

Table 4-1. Characteristics of included trials

Study, year	Country	Vaccine	Age (years)	Doses	Schedule	N (randomized)	Longest follow-up
Dobson 2013	Canada	QHPV	9-13 9-13 16-26	2 doses 3 doses 3 doses	M0, 6 M0, 2, 6 M0, 2, 6	259 261 310	36 mos
Leung 2015	France Singapore Sweden Hong Kong	QHPV	9-14 9-14	2 doses 3 doses	M0, 6 M0, 2, 6	358 358	24 mos
Puthanakit 2015	Canada, Germany, Italy, Taiwan, Thailand	BHPV	9-14 15-25	2 doses 3 doses	M0, 6 M0, 1, 6	550 482	36 mos
Romanowski 2011, 2014, 2016	Canada, Germany	BHPV	9-14 9-14 15-25 15-25	2 doses 3 doses 2 doses 3 doses	M0, 6 M0, 1, 6 M0, 6 M0, 1, 6	78 82 162 157	60 mos

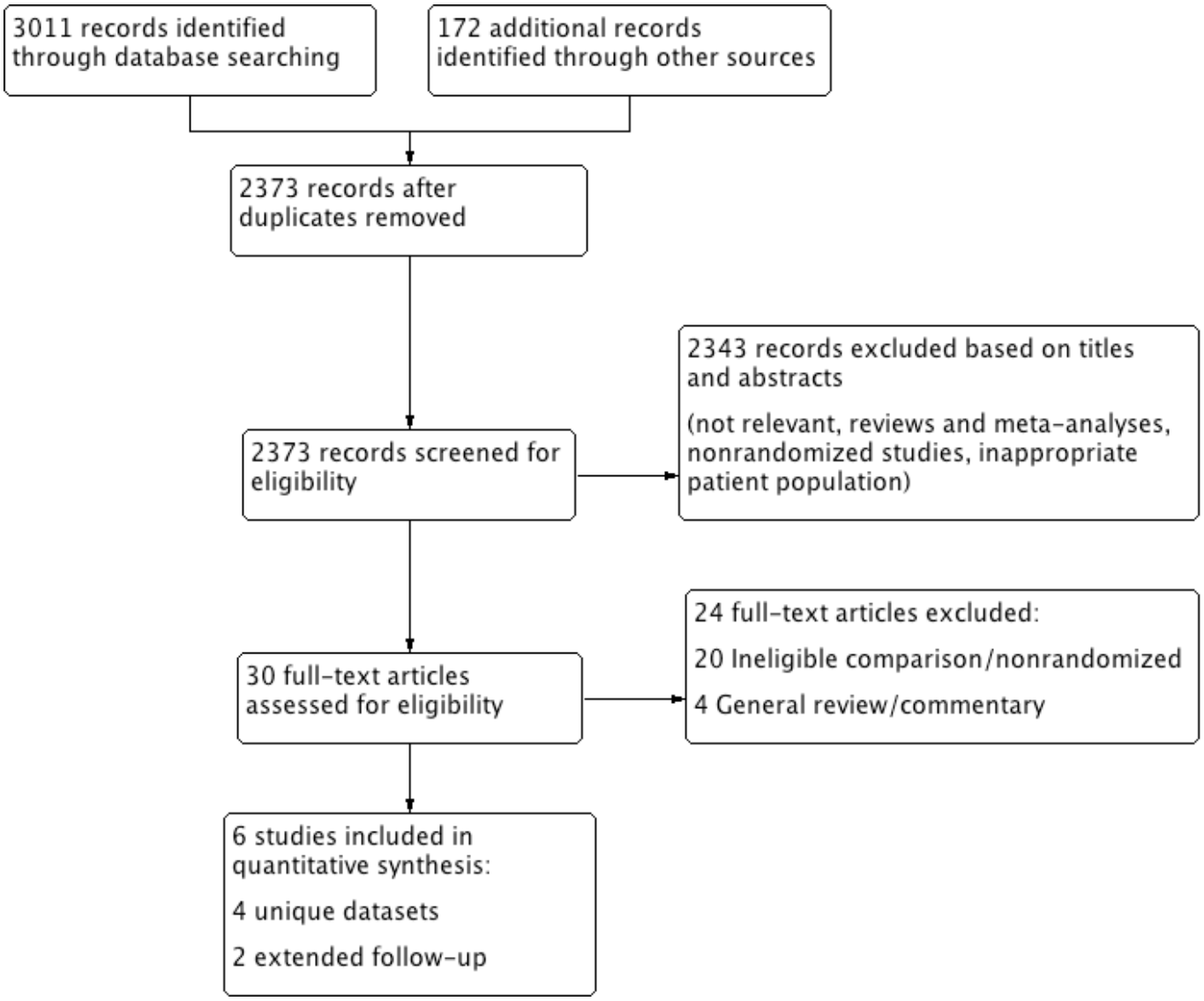

Figure 4-1. PRISMA flow diagram

Two trials assess the BHPV [73,75] and two trials assess the QHPV [74,81] in healthy females. Two of the trials assess *comparaison 1* [74,81]; three of the trials assess *comparaison 2* [73-75]; None of the trials provided information pertaining to sexual activity, prior sexually transmitted infection, or prior cervical screening abnormalities. Immunogenicity data on the intention-to-treat cohort (i.e. the total vaccinated cohort regardless of pre-vaccination sero-status) is only available for two trials [74,81]. Thus, for consistency, all immunogenicity data is analyzed only in females who were seronegative for HPV vaccine-types at baseline (the according-to-protocol cohort).

Primary clinical outcomes

The primary goal of the HPV vaccine is to reduce HPV-related disease including pre-invasive disease and cancer. However, none of the included studies reported on clinical outcomes of interest to this review.

Secondary immunogenicity outcomes

Seropositivity cut-offs vary by trial, and are generally based on the lower limit of detection for the particular assay used. Over 99% of all subjects seroconverted for both HPV-16 and HPV-18 at 7 months' follow-up. All seroconverted females, regardless of vaccine schedule, had GMCs well above the level induced by natural infection [19]. There was no significant difference in pooled seropositivity rates at longest follow-up across all four trials (Appendix C). Significant heterogeneity exists in comparisons where the

Dobson trial [74] carries more weight. This may be explained, in part, by the use of a different immunoassay in this trial (competitive Luminex immunoassay), which uses a less sensitive seropositivity cutoff, compared to the enzyme-linked immunoassay used in other included trials [84]. Krajden et al. formally assessed the Dobson trial, using different immunoassays, and found that seropositivity began to wane beginning at 18 months' post-vaccination for HPV-18 [85].

Comparaison 1

Three unique trials assess immunogenicity of a 2- versus 3-dose HPV vaccine schedule in girls age 9-14 [73,74,81]. Longest follow-up for this comparison was 36 months [74]. For HPV-16, 2 doses appear immunologically non-inferior to 3 doses at all follow-up times (Figure 4-2). For HPV-18, the immunologic non-inferiority criterion is violated at 12 months (GMC ratio 0.55, 95% CI 0.48-0.64), after which point we observe waning immunogenicity to 36 months (GMC ratio 0.44, 95% CI 0.34-0.56) (Figure 4-3). Where pooled estimates are available, heterogeneity ranges from 0-92% for HPV-16, and 0-4% for HPV-18. This may be due, in part, to the use of different immunoassays to define the according-to-protocol cohorts [84], as well as differences in vaccine formulation (BHPV versus QHPV). The latter is explored further in subgroup analyses (below).

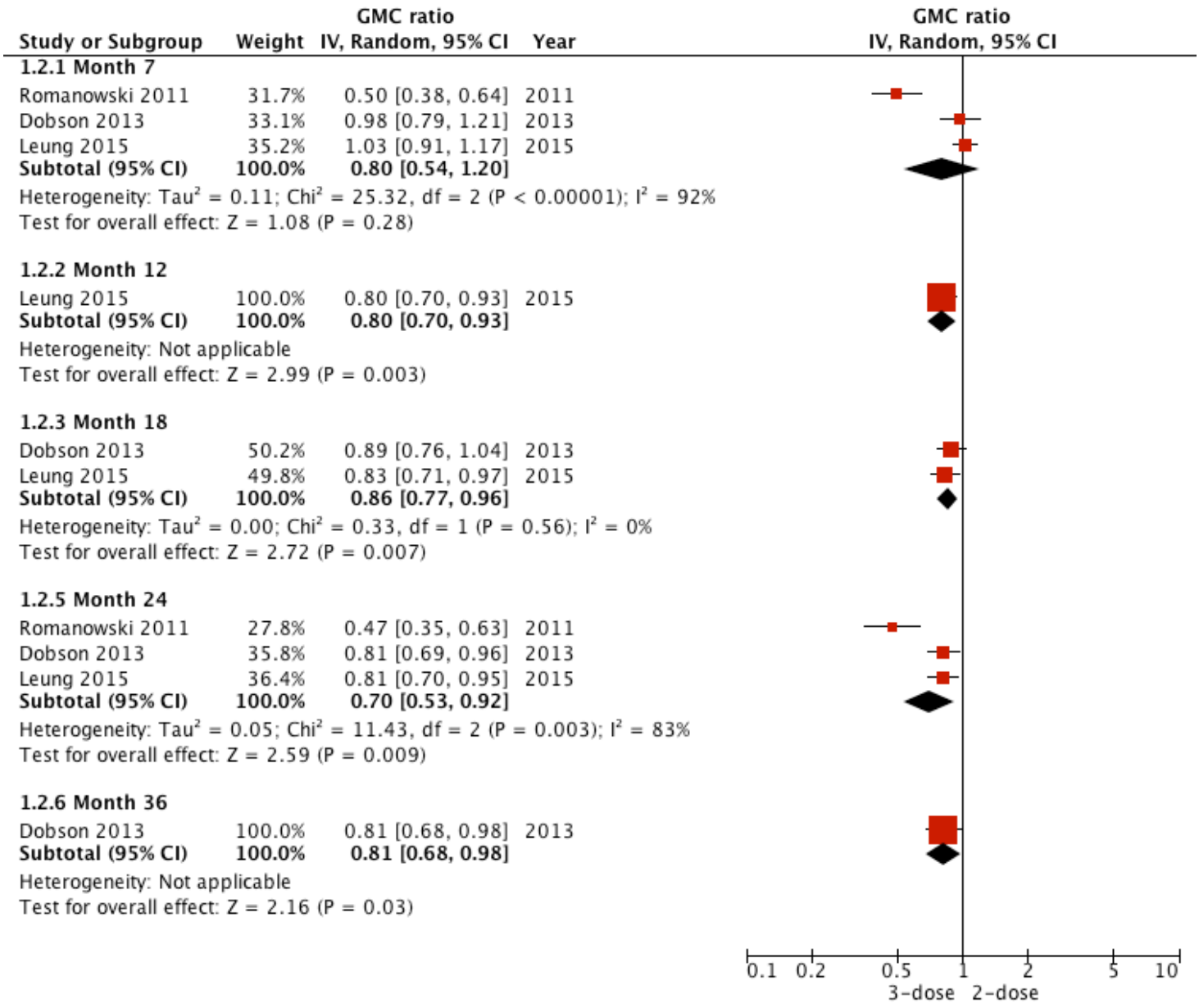

Figure 4-2. HPV-16: Non-inferiority of mean geometric antibody concentrations for 2- versus 3-doses HPV vaccine in girls age 9-14. Boxes and horizontal lines represent point estimates for GMC ratios (2-dose/3-dose), varying in size according to weight, and the 95% confidence intervals. GMC=mean geometric antibody concentration; SE= standard error; CI= confidence interval; IV= inverse variance method; Tau^2=Tau-squared; Chi^2= chi-squared; df= degrees of freedom; I^2= I-squared; Z= Z score.

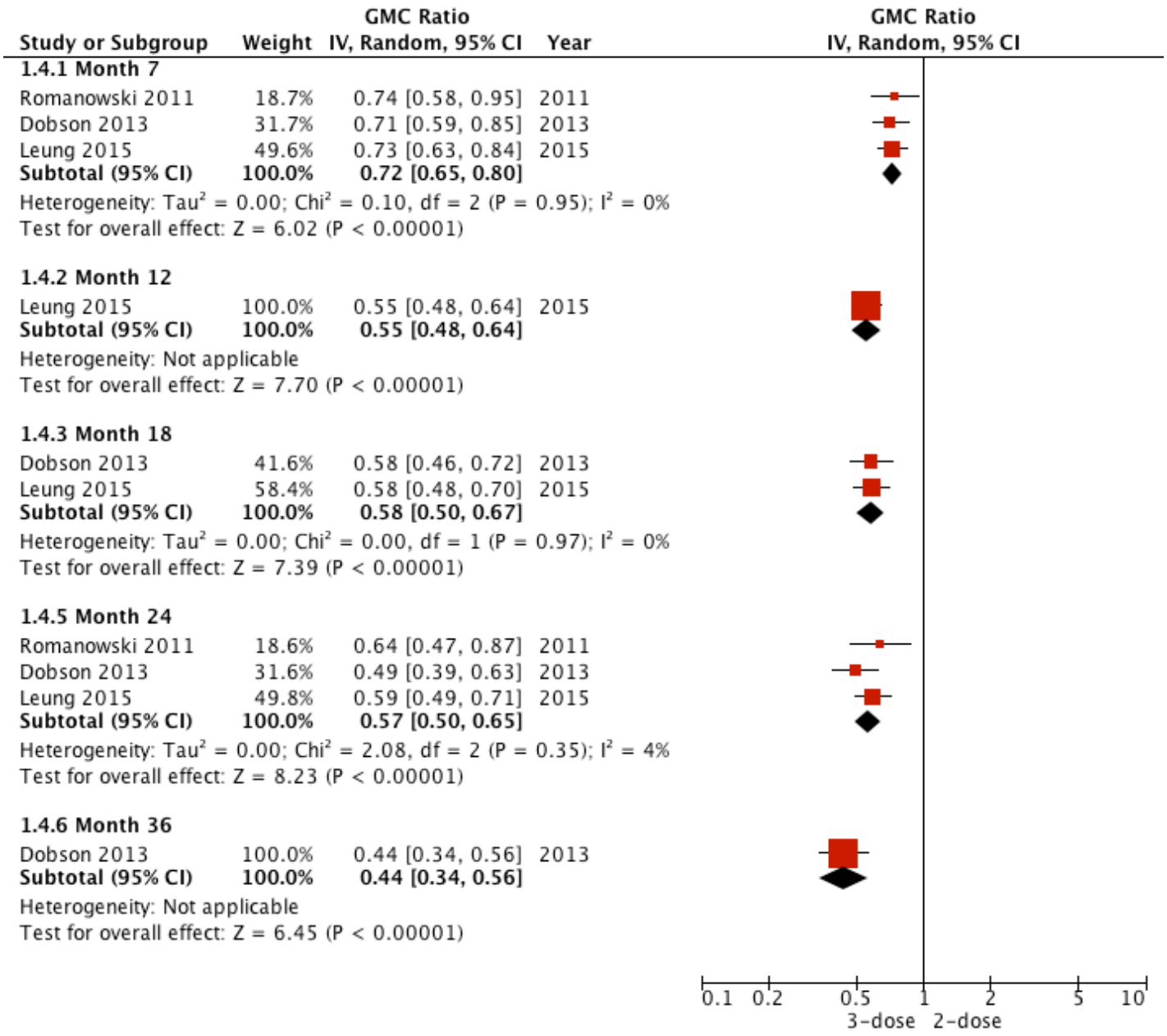

Figure 4-3. HPV 18: Non-inferiority of mean geometric antibody concentrations for 2- versus 3-doses HPV vaccine in girls age 9-14. Boxes and horizontal lines represent point estimates for GMC ratios (2-dose/3-dose), varying in size according to weight, and the 95% confidence intervals. GMC=mean geometric antibody concentration; SE= standard error; CI= confidence interval; IV= inverse variance method; Tau^2=Tau-squared; Chi^2= chi-squared; df= degrees of freedom; I^2= I-squared; Z= Z score.

Comparaison 2

Three unique trials assess immunogenicity of 2 doses in girls versus 3 doses in women [73-75]. Longest follow-up for this comparison was 60 months [83]. For both HPV-16 and -18, non-inferiority of a 2-dose schedule in girls is maintained at all follow-up times (Fig 4-4; 4-5). Where pooled estimates are available, heterogeneity ranges from 0-98% for HPV-16, and 68-95% for HPV-18. This significant heterogeneity can be attributed to the reasons outlined above.

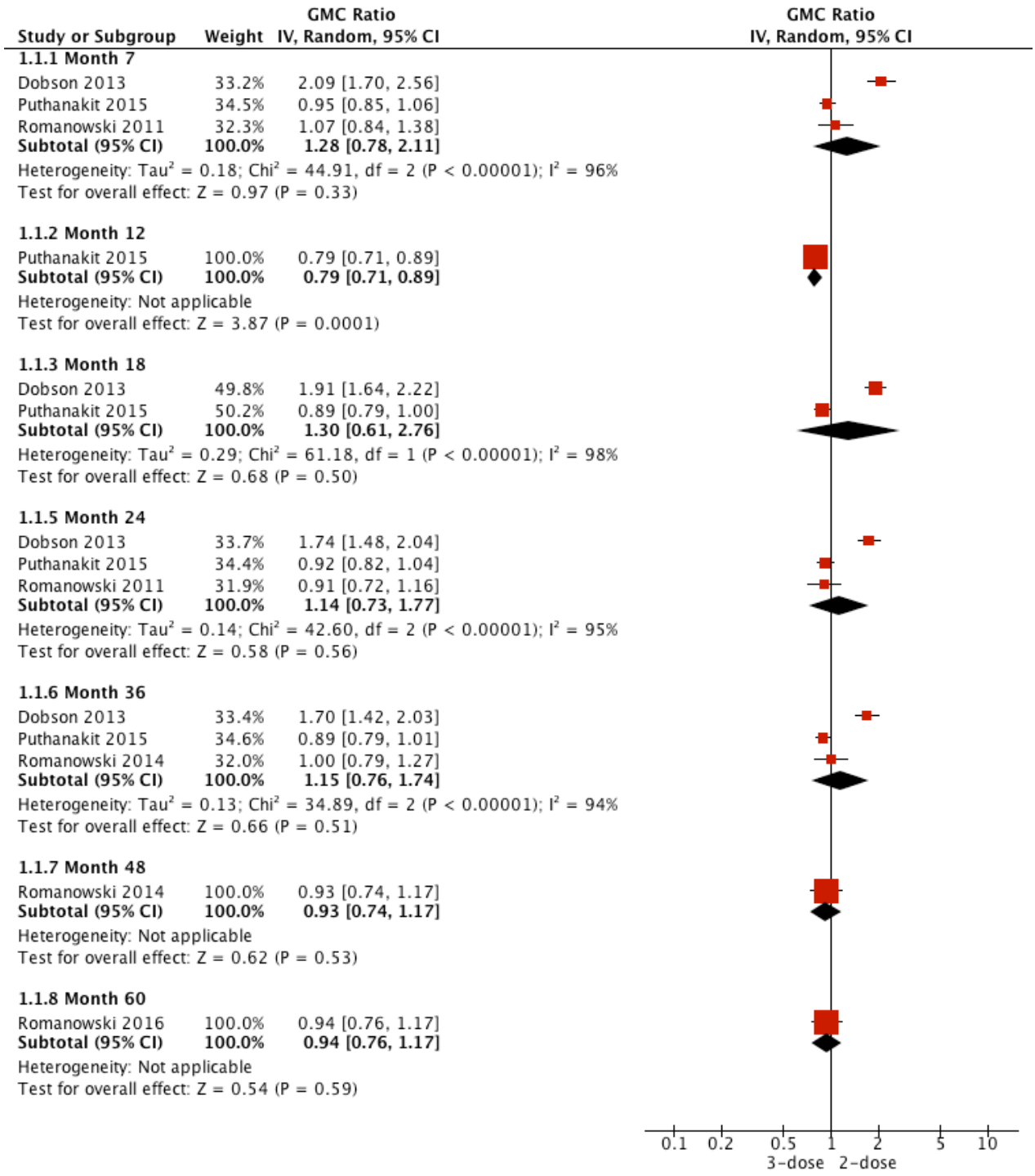

Figure 4-4. HPV-16: Non-inferiority of mean geometric antibody concentrations for 2-doses HPV vaccine in girls (age 9-14) versus 3-doses HPV vaccine in women age 15-26. Boxes and horizontal lines represent point estimates for GMC ratios (2-dose/3-dose), varying in size according to weight, and the 95% confidence intervals. GMC=mean geometric antibody concentration; SE= standard error; CI= confidence interval; IV= inverse variance method; Tau^2=Tau-squared; Chi^2= chi-squared; df= degrees of freedom; I^2= I-squared; Z= Z score.

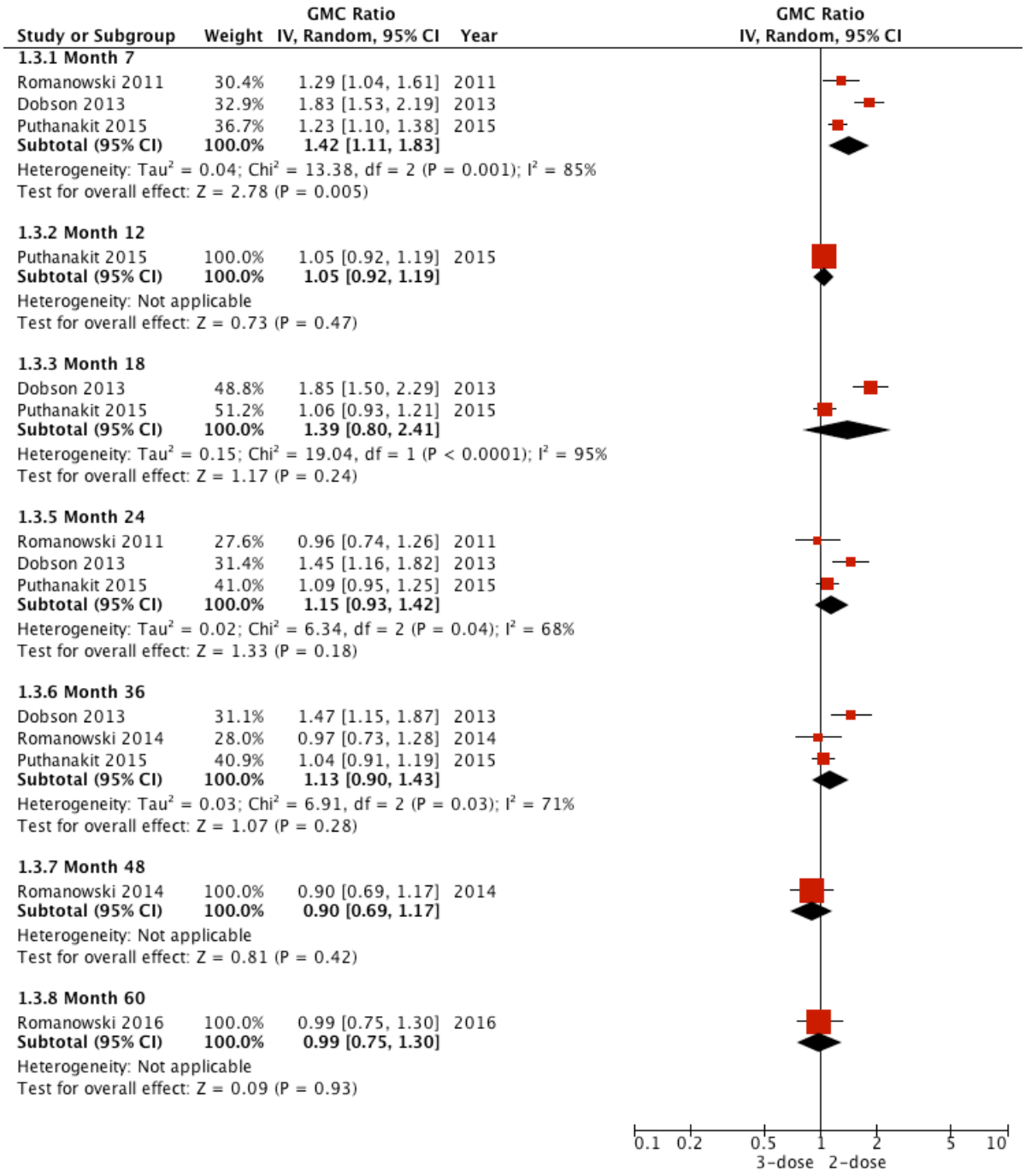

Figure 4-5. HPV-18: Non-inferiority of mean geometric antibody concentrations for 2-doses HPV vaccine in girls (age 9-14) versus 3-doses HPV vaccine in women age 15-26. Boxes and horizontal lines represent point estimates for GMC ratios (2-dose/3-dose), varying in size according to weight, and the 95% confidence intervals.
GMC=mean geometric antibody concentration; SE= standard error; CI= confidence interval; IV= inverse variance method; Tau^2=Tau-squared; Chi^2= chi-squared; df= degrees of freedom; I^2= I-squared; Z= Z score.

Subgroup analyses: Immunogenicity by vaccine valency

Comparaison 1

Among trials that assess immunogenicity of a 2- versus 3-dose schedule in girls age 9-14, non-inferiority of the 2-dose schedule is violated within the first 24 months for both formulations (summarized in Appendix D). For the BHPV, GMC ratio for HPV-16 falls below the non-inferiority criterion at 7 months (GMC ratio 0.50 95%CI 0.38, 0.64) and for HPV-18 at 24 months (GMC ratio 0.64 95%CI 0.47, 0.87). For the QHPV, non-inferiority is maintained to 36 months for HPV-16; however, pooled GMC ratio for HPV-18 falls below the non-inferiority criterion at 12 months (pooled GMC ratio 0.55 95%CI 0.48, 0.64). Where pooled analyses are available, heterogeneity is generally reduced to 0%. Within the QHPV subgroup, residual heterogeneity (I^2 30%) is observed for HPV-18 at 24 months, where the trials being pooled use differing immunoassays.

Comparaison 2

Among trials that assess immunogenicity of 2 doses in girls versus 3 doses in women, non-inferiority of the 2-dose schedule is maintained to the longest available follow-up times for both vaccine formulations (summarized in Appendix D). Where pooled analyses are available, heterogeneity is reduced to 0%.

Secondary safety outcomes

All four unique trials assess serious adverse events at the longest available follow-up, ranging from 24 months [81] to 48 months [82]. There is no significant difference in serious adverse events between 2-dose and 3-dose HPV vaccination schedules (Figure 4-6).

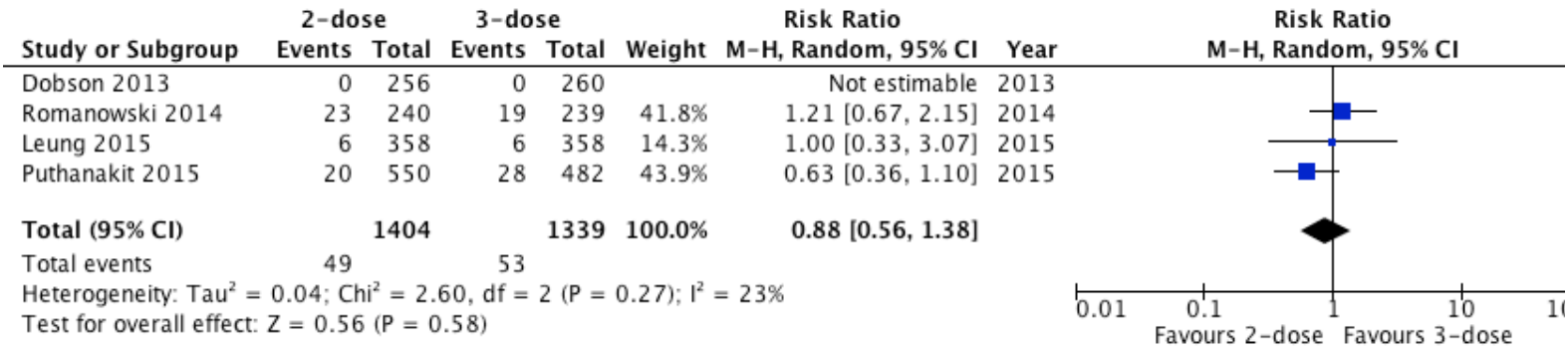

Figure 4-6. Safety outcomes. Number of Serious Adverse Events at longest follow-up, all ages

Discussion

In this systematic review of 2 versus 3 doses of HPV vaccine, we found no trials that reported clinically relevant outcomes, including incident and persistent HPV-16/18 infection, incident CIN2+, and incident anogenital warts. To date, all published trials have reported on immunogenicity outcomes. Based on the non-inferiority criterion used for vaccine licensing in young girls, we found that a 2-dose HPV vaccine schedule in girls (age 9-14) was non-inferior to a 3-dose schedule in women (age 15-26). Specifically, at sixty months follow-up, girls who received 2 doses maintained 94% GMC levels for HPV-16 and 99% GMC levels for HPV-18, compared to women who received 3 doses. When compared within the same age group, non-inferiority of 2 doses was violated within the first 1-2 years of vaccine administration for both the BHPV and QHPV. At longest available follow-up (36 months), girls who received 2 doses maintained 81% GMC levels for HPV-16 and 44% GMC levels for HPV-18, compared to girls who received 3 doses. However, it is important to note that GMC levels at all follow-up times remained well above those induced by natural infection [17]. We observed waning immunogenicity of 2 doses over time in girls age 9-14, and found no data beyond 36 months for this same-age comparison.

Although incidence and mortality from HPV-related cancers are of highest clinical relevance, it is too soon to measure these outcomes given their long latency and the novelty of the vaccine, and because standard of care requires treatment of premalignant lesions [44]. For evaluation involving HPV-naïve young adolescents, the use of intermediate clinical endpoints (HPV infection, cytological abnormalities) is not

feasible because these outcomes don't occur, and invasive gynecological exams are not justified in this population. The biological rationale for the use of immunobridging analyses in HPV vaccine trials is supported by the finding that GMCs among girls age 9-14 are at least twice those seen in women aged 15-25, where sustained clinical efficacy against HPV infection and cervical cytological abnormalities has been observed [86]. As a result, both the International Agency for Research on Cancer (IARC) and the United States National Cancer Institute (NCI) agree that immunologic non-inferiority is a valid end-point for licensure of novel HPV vaccine dosing schedules in different age groups [44].

Proof-of-principle for the efficacy of fewer than three doses of HPV vaccine was initially shown in post hoc analysis of the Costa Rica Vaccine Trial, but this study did not include girls ages 9-14, the target group for primary vaccination [72]. In 2010, Dobson et al. presented encouraging preliminary data showing similar antibody titers among girls who had received 2 or 3 doses of the QHPV at 24 months post-vaccination [87]. However, the relationship between antibody titers and clinical outcomes remains unclear. Few observational studies have examined the clinical effectiveness of a 2-dose schedule of HPV vaccine, using intermediate clinical endpoints. Post-hoc analysis of two large randomized control trials of BHPV vaccine efficacy showed that among a nested cohort of women who broke protocol, vaccine efficacy against incident and persistent HPV-16 and -18 infections was similar irrespective of the number of doses [88]. This study did not include adolescent girls. A prospective cohort study of over 1 million recipients of the QHPV vaccine found that 2 doses in girls aged 10-16 was associated with less protection against incident anogenital warts compared to 3 doses, although the absolute difference

was only 59 prevented cases per 100,000 person-years [89]. Also, this study did not take into account the interval between doses [89]. A population-based study by Blomberg et al. highlighted the importance of dose interval when comparing effectiveness of a 2-dose versus 3-dose schedule. Specifically, they found that for females aged <16 years, the incidence rate ratio for anogenital warts was 2.18 (95%CI 1.86-2.54) in favour of 3-doses over 2-doses.[90] However, when dose interval was taken into account, effectiveness of a 2-dose schedule against anogenital warts approximates that of a 3-dose schedule (IRR 1.03; 95% CI 0.69-1.55) when the two doses are given approximately 6 months apart.[90]

Hypothesized advantages of a 2-dose vaccination schedule include improved acceptability by patients, their parents and healthcare providers, which may lead to improved HPV vaccination coverage. Some evidence also suggests that a 2-dose schedule is likely to be more cost-effective [91]. These are important considerations for clinicians and policy-makers alike. However, these predictions are based on assumed lifetime vaccine protection [11]. It remains to be seen whether girls will require a booster dose, and whether a 2-dose vaccination schedule will increase the likelihood of needing one, particularly in light of the waning immunogenicity over time that we have observed.

In addition to duration of protection, several important questions about a 2-dose vaccine schedule remain unanswered. Clinical efficacy has not been firmly established in any age group. We do not know whether the cross-reactivity for non-vaccine HPV types seen with the 3-dose schedule will be as robust for the 2-dose schedule. Also, to the best of our knowledge, no studies have assessed a 2-dose vaccination schedule in males.

These issues will have important implications for herd immunity and overall effectiveness of a vaccination program.

We feel that the overall risk of bias for the meta-analysis is low. Immunologic outcomes are objective, and are therefore less likely to be affected by selection performance, and detection biases. Safety outcomes, on the other hand, are more subjective. For this review, we focus on serious adverse events following immunization (SAEFI), which are defined as events that are 'life threatening or resulting in death, require hospitalization or prolongation of an existing hospitalization, result in residual disability or cause congenital malformation' [92]. This outcome is more objective, and thus unlikely to be affected by detection bias. All trials adhered to their published protocols. We aimed to avoid publication bias by including unpublished trials, although the total number of trials was too small to carry out formal assessment. Three of the five included trials were industry-funded. However, these trials tended to show non-inferiority of a 2-dose vaccination schedule (i.e. support the administration of fewer doses) and therefore we do not believe sponsorship bias plays a major role here.

This review is limited by a paucity of data. Intention-to-treat immunogenicity data was only available for two of the included trials [74,81]. Although it violates the intention-to-treat principle, the use of the HPV-naïve according-to-protocol cohort in our analyses allows us to estimate the efficacy of HPV vaccination in the target group for primary vaccination: adolescents prior to sexual activity [84]. Subgroup analyses were limited by the small number of primary trials, and are susceptible to type II errors due to relatively small

sample sizes. No trial reported follow-up beyond 60 months. No clinical outcomes were reported for any age group. Although the use of GMC ratios can help standardize immunogenicity measures across age groups and vaccine formulations, interpretation depends very much on an arbitrary non-inferiority criterion. Donken et al. performed a systematic review of non-inferiority margins used in vaccine trials [45] Among 103 trials using non-inferiority margins based on GMC ratios, half used a margin of 0.5, whereas the other half used a margin of 0.67 [45]. Eighty five percent of the trials did not discuss the rationale for using a particular cut-off [45]. Ultimately, immunologic non-inferiority does not directly provide accepted clinical correlates of protection.

In conclusion, few randomized trials to date have addressed the question of efficacy of 2 versus 3 doses of HPV vaccine. Existing evidence for a 2-dose schedule in girls is based on a pre-licensing arbitrary immunologic non-inferiority criterion, and not on established clinical efficacy in this age group. We observed waning immunogenicity over time with a 2-dose schedule and it remains unknown whether this will increase the need for a booster dose. Post-licensure observational data is required to assess the population level impact and herd effects of a 2-dose HPV vaccination schedule. Further research is needed to link health policy decisions related to licensing and use of the HPV vaccine to clinically relevant, patient-centered outcomes.

Acknowledgments

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Author contributions

SMM conceived of the research question and provided content expertise throughout. KW prepared the study protocol. GR and KW devised the search strategy and GR rand the search. KW and AC independently screened the identified records for eligibility and extracted the data. KW performed the statistical analysis with the support of RR. AA and RZ provided methodological support in all aspects of the study. KW drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

Chapter 5

Early evidence of the effectiveness of the human papillomavirus vaccination program against anogenital warts in Manitoba, Canada: A registry cohort study

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Preface

In this manuscript, we describe a record-linkage cohort study we carried out in Manitoba to assess the effectiveness of the QHPV vaccination program in reducing AGWs. The primary objective of this study was to estimate the effectiveness of the QHPV in preventing medically-attended AGWs. As a secondary objective, we assessed whether vaccine effectiveness depends on age at vaccination, medical history suggestive of prior sexual activity, and number of administered vaccine doses. Supplementary information on data sources utilized and definitions of covariates, including ICD and tariff codes used to identify cases of AGWs, can be found in **Appendices E** through **M**. Additional information and results not explicitly presented in this manuscript can also be found in **Appendices N** through **P**.

This study addresses the important public health issue of HPV vaccination program effectiveness in the real world setting. While RCT data has shown the vaccine to be highly effective in selected populations, these findings may not accurately predict vaccine effectiveness in routine practice. To date, few published studies have examined the effectiveness of the quadrivalent HPV vaccine against AGWs using individual-level data, and only one has examined the effectiveness of both routine school-based and temporary "catch-up" programs

This study is the first to compare outcomes among vaccinated versus unvaccinated females using algorithms to identify cases of AGWs based on high quality population based administrative health data. It is also the first to assess the effectiveness

of a catch up HPV vaccination program based on high-risk sexual activity. Our findings that females vaccinated over the age of 18 may be less protected against anogenital AGWs seem credible and can guide public health policy and clinicians and patients' decisions on the optimal use of the QHPV vaccine.

The following manuscript is presented as it was submitted to *Journal of Epidemiology and Community Health* May 2017.

Abstract

Background: We assessed the effectiveness of the quadrivalent HPV (QHPV) vaccination program in Manitoba, Canada in reducing incident anogenital warts (AGWs), and to what extent effectiveness depends on age at vaccination, and number of doses.

Methods: Females ≥ 9 years old who received the QHPV in Manitoba between September 2006 and March 2013 (N=31,464) through the publicly funded school-based program and a high-risk catch-up program were included. They were matched on age and area of residence to unvaccinated females. Information on incident AGWs was obtained from provincial administrative databases using algorithms. Using stratified Cox regression models, we estimate hazard ratios (HR) for the association between QHPV and AGWs.

Results: For females vaccinated at age ≤18 years, receipt of QHPV was associated with a 40% reduction in AGWs risk (HR 0.6; 95%CI 0.4-0.8). Further adjustment for socioeconomic and medical history did not alter this estimate. For females vaccinated aged ≥19 years, there was no evidence of a drop in AGWs incidence, especially among those who were sexually active (HR 2.8; 95%CI 2.1-3.7). Among females vaccinated at age ≤18 years, risk of AGWs was lowest among those who received 3 doses, corresponding to VE of 56% (95%CI 30-70%). For females vaccinated at older age, risk of AGWs remained increased regardless of the number of doses.

Conclusion: Women vaccinated at an older (≥19 years) age, may be less protected against AGWs, particularly if sexually active prior to vaccine administration. Further efforts should be targeted at increasing vaccine uptake among pre-adolescents, prior to the initiation of sexual activity.

Introduction

Since its inception, the quadrivalent human papillomavirus vaccine (QHPV), has been licensed in over 133 countries, and has been introduced into dozens of national vaccination programs.[93] In randomized clinical trials (RCTs), the vaccine was effective in preventing infection with HPV types 16 and 18, which cause 70% of cervical cancers; and 6 and 11, which cause 90% of anogenital warts (AGWs).[9,94] RCTs aim to determine vaccine efficacy, the biological impact of the vaccine in providing a protective immune response when given as directed to a susceptible population. RCTs tend to recruit selected populations and employ strict protocols such that their findings may not accurately predict vaccine effectiveness (VE) in routine practice.[20] VE at the population level is also influenced by policy decisions and implementation details of the vaccination program.[20] In evaluating VE of HPV vaccination programs, age at vaccination is a critical parameter, given that the highest risk for acquiring an HPV infection is within 5-10 years following sexual debut; and since current prophylactic HPV vaccines have no therapeutic effect on pre-existing infections.[95]

AGWs have a significant public health impact due to their prevalence, psychosocial impact, and healthcare cost.[93,96] Changes in incidence of AGWs may serve as a useful early indicator of the effectiveness of QHPV vaccination programs because AGWs have a short latency time, unlike cervical neoplasms, which take years to decades to manifest.[97] A decline in rates of AGWs after the introduction of the QHPV has been reported in several countries;[98-105] such "ecological" studies are susceptible to confounding by contemporary trends, such as changes in management guidelines or

patterns of sexual behaviours.[106] Few published studies have examined QHPV effectiveness against AGWs using individual-level data[53,89,107,108], and only one has explored the effectiveness of both routine school-based and temporary "catch-up" programs.[109]

The QHPV became available in Manitoba in August 2006, and was introduced into the publicly funded school-based program for all girls in grade 6 (11-12 years old) beginning in September 2008.[2] A publicly funded program for females aged 9 to 26 deemed at 'high-risk' for HPV infection by their health care provider was initiated in November 2012, and lasted for 2 years.[110] We conducted a retrospective matched cohort study to estimate the effectiveness of the QHPV in preventing incident medically-attended AGWs in Manitoba, and to assess to what extent VE depends on age at vaccination and number of administered vaccine doses.

Methods

Settings and data sources

We analyzed population-based cohorts by linking Manitoba Health's (MH) vaccine registry with hospital, physician and prescription claim databases, all part of a comprehensive repository of administrative and clinical databases housed at the Manitoba Centre for Health Policy.[111] MH is a government agency that provides publicly funded universal healthcare to virtually all of Manitoba's 1.3 million residents. Insured services include hospital, physician and preventive services including some immunizations. All provided services are recorded in centralized electronic databases that can be linked using

a unique lifetime personal health identification number (PHIN). The Manitoba Population Registry (MPR) tracks addresses and dates of birth, insurance coverage and death for all insured persons. The Manitoba Immunization Monitoring System (MIMS) is a population-based province-wide registry of virtually all vaccines administered to Manitoba residents since 1988.[112] Vaccine type and date of vaccination are captured through direct data entry for vaccines administered by public health staff or using physician claims data for vaccines administered by physicians.[112] Since 1971, the Hospital Abstracts Database recorded all hospital admissions in the province, including diagnoses and treatments coded using the International Classification of Diseases (ICD) and the Canadian Classification of Health Interventions.[111] The Medical Services Database, also in operation since 1971, captures physician services including tariff codes for each service provided and a single ICD-9 diagnosis.[111] The provincial Drug Program Information Network (DPIN) captures all out-of-hospital prescriptions dispensed in Manitoba since 1995.[113]

Eligibility and construction of matched cohorts

Using the MPR, we identified all females age 9 years and older who were registered with MH at any point between September 2006 and March 2013 (the *enrollment period*). To build the *vaccinated cohort* we identified all eligible females who received at least one dose of QHPV during the enrollment period, regardless of whether the vaccine was received through the publicly funded school-based or 'high-risk' programs or from a private provider. The bivalent vaccine was not available in Manitoba during the enrollment period.

The cohort of vaccinated females was linked to the MPR to identify females with no record of receiving the vaccine during the study period (the *unvaccinated cohort*). Each vaccinated female was matched, with replacement, on birthdate and area of residence to three non-vaccinated females (a *matched set*). The index date for a matched set was considered as the date of the first vaccine dose for the vaccinated female in that set. To ensure sufficient length of time to measure important covariates, we excluded females with less than five years of MH insurance coverage prior to the index date.

Study outcome

Information on incident medically-attended AGWs was obtained from hospital, physician and drug prescription databases between August 21, 2001 and March 31, 2013 (the *follow-up period*) using previously described algorithms.[34] Because it is possible for the same individual to have multiple episodes of AGWs, each episode of care had to be separated by 12 months without any related claims to be considered incident. To exclude prevalent AGWs infections, females with a diagnosis of AGWs within 12 months before the index date were excluded.

Other covariates

Socio-economic status was based on postal code of residence and area level income quintile obtained by linking with the 2006 Canadian census data. Information on health services utilization and medical comorbidities prior to the index date was obtained from the same sources using previously validated algorithms.[114] Clinical markers

suggestive of prior sexual activity were determined using a composite measure of pregnancy, sexually transmitted infection (STIs), Pap cytology, or contraceptive drug use. Any female with evidence of any of these outcomes prior to the index date was considered 'sexually-active' for the purpose of this study. Information on STIs was obtained from the MH Communicable Disease Surveillance Database and on Pap cytology from the electronic database of *CervixCheck*, Manitoba's organized cervical cancer screening program.

Statistical Analysis

We used Kaplan-Meier survival analysis to determine the cumulative incidence of AGWs for both the vaccinated and unvaccinated cohorts. The cohort follow-up period (and time-to-event for the purpose of the survival analysis) was measured from the index date to the earliest of the following dates: (i) date of occurrence of the first AGWs episode (ii) date of termination of coverage for any reason (e.g., death or migration) as obtained from the MPR; or (iii) study end date (March 31, 2013).

Using Cox proportional hazard models, with stratification on the matched sets to account for correlation, we estimated hazard ratios (HRs) for AGWs among the vaccinated, compared to the unvaccinated. Analyses were stratified by number of doses, age at first vaccination, and by evidence of sexual activity; the statistical significance of any detected interaction was assessed using a likelihood ratio test. VE was calculated as $(1- HR)\times 100$.

A priori power simulations were performed using average age-stratified annual AGWs incidence rates per 100,000 females between 2004 and 2006 (i.e. prior to availability of QHPV). Among females aged 9-14 years, this study had 100% power (at α=0.05) to detect ≥20% reduction in AGWs risk. Corresponding estimates were 75% and 90% to detect ≥40% risk reduction among females aged 15-17 and ≥18 years, respectively.

Results

During the enrollment period, a total of 31,464 females received ≥1 dose of the QHPV. The majority (87%) of them were 9-18 years old (Table 5-1). Compared to their unvaccinated matches, they were more likely to live in urban areas, and be in the top three income quintiles. Vaccinated females had more physician visits but fewer hospitalizations in the five years prior to index date than their unvaccinated matches. They were also more likely to have clinical markers suggestive of sexual activity prior to index date (Table 5-1).

Among vaccinated females, 68% received 3 doses of the QHPV (the recommended number during the study period), 21% received 2 doses, and 11% received only 1 dose (Table 5-1). Compared to those who completed three doses, females who received 1 or 2 doses tended to be older, and of lower income quintile. They had more physician visits and hospitalizations, and were more likely to have chronic disease, including immunosuppression and autoimmune diseases. Compared to those who completed three doses, females who received only 1 dose were 8 times as likely to have a

history of reported STIs and almost 7 times as likely to have had abnormal cervical cytology (Table 5-1).

Table 5-1. Clinico-demographic characteristics by vaccination status and number of QHPV doses

Characteristics	Vaccinated				Unvaccinated
	1 dose N=3521 %	2 doses N=6666 %	3 doses N=21,277 %	≥1 doses N=31,464 %	N=94,327 %
Age group (years)					
9-18	60.5	88.7	90.9	87.0	87.0
19-24	26.7	7.8	7.0	9.4	9.4
≥ 25	12.8	3.5	2.1	3.6	3.6
Place of residence					
Rural	40.9	41.4	41.4	41.3	42.5
Urban	57.3	57.1	57.6	57.5	56.4
Public Trustee	1.8	1.5	1.0	1.2	1.2
Income Quintiles					
Q1-Q2	41.5	37.6	33.2	35.0	39.0
Q3-Q5	56.1	60.2	65.7	63.4	59.1
Cannot be determined	2.4	2.2	1.2	1.5	1.9
Hospitalizations*					
0	86.7	93.1	94.2	93.2	91.7
1	8.3	5.3	4.6	5.1	5.6
≥ 2	5.1	1.6	1.2	1.7	2.7
Physician visits*					
> Median	66.2	54.0	54.3	55.6	47.3
Chronic diseases					
Any chronic disease	4.4	2.9	3.3	3.3	2.5
Immunosuppression	4.4	2.6	2.2	2.6	2.2
Autoimmune disease	3.3	1.7	1.6	1.8	1.9
Sexually active prior to index date					
Overall‡	45.2	15.4	12.4	16.7	14.2
Any STIs	12.8	3.2	1.6	3.2	3.3
Pelvic inflammatory disease	8.4	3.5	2.5	3.4	2.4
Contraceptive drug use	41.5	12.9	10.5	14.5	11.5
Pregnancy	7.2	1.4	0.5	1.4	3.6
Abnormal Pap cytology	4.0	1.0	0.6	1.1	1.0

*During 5-year period prior to index date

‡ Has evidence of one or more of pregnancy, sexually transmitted infection, pelvic inflammatory disease, abnormal Pap, and/or contraceptive drug use prior to index date

After a median follow up time of 29 months, females vaccinated at age ≤18 years had a lower incidence of AGWs compared to their unvaccinated matches (rate ratio [RR] 0.6; 95%CI 0.4-0.8; Table 5-2). Conversely, females vaccinated at age ≥19 had a higher incidence of AGWs compared to their unvaccinated matches, especially those who had clinical markers of sexual activity prior to vaccination (RR 3.1; 95%CI 2.4-4.0). Those who completed 3 doses had a lower incidence of AGWs compared to those who received <3 doses.

Table 5-2. Incidence rates (per 10,000 person-years) of medically-attended AGWs by stratification group and vaccination status

Group	Person-years	Events	Rate (95%CI)	Rate ratio (95%CI)
9-18 years old				
Unvaccinated	193,054	181	9.4 (8.1-10.9)	1.0
Vaccinated	65,432	35	5.4 (3.8-7.5)	0.6 (0.4-0.8)
1 dose	s	s	14.6 (5.5-38.8)	1.6 (0.6-4.2)
2 doses	s	s	15.3 (7.9-29.3)	1.6 (0.8-3.2)
3 doses	56,788	22	3.9 (2.6-5.9)	0.4 (0.3-0.6)
≥ 19 years and not sexually active				
Unvaccinated	8,095	26	32.1 (21.9-47.2)	1.0
Vaccinated	1,820	8	44.0 (22-87.9)	1.4 (0.6-3.0)
1 dose	s	s	86.0 (21.5-344)	2.7 (0.6-11.3)
2 doses	s	s	N/A	N/A
3 doses	1,336	6	44.9 (20.2-99.9)	1.4 (0.6-3.4)
≥ 19 years and sexually active				
Unvaccinated	21,244	116	54.6 (45.5-65.5)	1.0
Vaccinated	7,849	134	170.7 (144.1-202.2)	3.1 (2.4-4.0)
1 dose	1,287	36	279.7 (201.7-387.7)	5.1 (3.5-7.4)
2 doses	1,196	24	200.7 (134.5-299.4)	3.7 (2.4-5.7)
3 doses	5,365	74	137.9 (109.8-173.2)	2.5 (1.9-3.4)

s= suppressed because of low numbers

For females vaccinated at age ≤18 years, further adjustment for socioeconomic and medical history in multivariate Cox models did not alter the estimate of a 40% reduction in AGWs risk (HR 0.6; 95%CI 0.4-0.8; Table 5-3). For females vaccinated at age ≥19 years, there was no evidence of a reduction in AGWs risk, especially among those with clinical markers suggestive of sexual activity (HR 2.8; 95%CI 2.1-3.7). Among females vaccinated at age ≤18 years, risk of AGWs was lowest among those who received 3 doses of the QHPV, corresponding to VE of 56% (95%CI 30-70%). For females vaccinated at older age, risk of AGWs remained increased regardless of number of doses. However, we note that among females vaccinated at age ≥19 years with clinical markers of sexual activity prior to index date, the risk of AGWs was lower after 3 doses of the QHPV (adj HR 2.5; 95%CI 1.7-3.6) compared to 1 dose (adj HR 3.7; 95%CI 2.1-6.8; Table 5-3).

Table 5-3. Effect of QHPV on incident medically-attended AGWs by stratification group

Group	Crude*		Adjusted‡	
	HR	95%CIs	HR	95%CIs
9-18 years				
Unvaccinated	1.0		1.0	
Vaccinated	0.6	0.4-0.8	0.6	0.4 - 0.8
1 dose	0.7	0.2-1.9	0.6	0.2 - 1.8
2 doses	1.4	0.6-3.3	1.4	0.6 - 3.3
3 doses	0.4	0.3-0.7	0.4	0.3 - 0.7
≥19 years and NOT sexually active				
Unvaccinated	1.0		1.0	
Vaccinated	1.4	0.5-4.2	1.8	0.5 - 5.8
1 dose	3.0	0.3-35.8	3.1	0.2 - 44.9
2 doses	N/A	N/A	N/A	N/A
3 doses	1.8	0.4-7.2	3.1	0.6 - 14.8
≥19 years and sexually active				
Unvaccinated	1.0		1.0	
Vaccinated	3.3	2.5-4.3	2.8	2.1 - 3.7
1 dose	4.4	2.5-7.7	3.7	2.1 - 6.8
2 doses	3.2	1.8-5.9	3.0	1.6 - 5.7
3 doses	2.9	2.0-4.1	2.5	1.7 - 3.6

* Model adjusted for matching variables (birth date [-/+ 30 days], neighborhood of residence).

‡ Model adjusted for matching variables plus previous hospitalization, and previous physician visit.

Discussion

We found that the risk of AGWs was reduced by 40% among females who were vaccinated when they were ≤18 years old. We found no evidence of a reduction in AGWs risk among females vaccinated at an older age, especially among those with clinical markers suggestive of prior sexual activity. We also found that VE was highest after three doses, regardless of age group or sexual history. Among women who were suspected to be sexually active prior to vaccination, three doses of QHPV appears to impart a greater magnitude of protection compared to one dose. Because these women are at a higher risk of HPV infection prior to vaccination, this protection does not translate into a clinically significant reduction in AGWs risk. Non-compliance with the recommended 3-dose regimen could be a marker for higher risk sexual activity, and a consequently higher risk of HPV infection.

The lack of VE among those vaccinated at older age is likely related to the fact that QHPV, and similar vaccines, are generally less effective among those previously infected with HPV.[115,116] Most of these women were likely exposed to HPV particularly among those vaccinated free of charge through the 'high-risk' program. Eligibility for this high-risk catch-up program was at the discretion of the care provider but could include: early onset of sexual activity, multiple sex partners, history of STI, adolescent pregnancy, immune compromise, history of abnormal Pap, family history of HPV-associated cancers. Women who perceived themselves to be at higher risk of HPV (and other STIs) might have been more inclined to seek or consent to HPV vaccination. A previous study found that women aged ≥19 years who were treated for AGWs were three

times more likely to be vaccinated than those who were not.[117] In addition, older women were less likely to receive 3 or even 2 doses, which may have further reduced overall VE in this group. These factors may have conspired to eliminate any measurable benefit of vaccination in this group. It was not possible to identify women vaccinated through the high-risk program in our study, but they likely represented a majority of the ≥19 years of age group with clinical markers suggestive of prior sexual activity.

Our findings among those vaccinated at younger age (≤18) are consistent with the range of VE estimates expected based on evidence from both pre-licensure RCTs and post-marketing observational studies. In the FUTURE I/II RCTs, VE was lower (pooled estimates: 53-57%) in the intention-to-treat analyses than in the per-protocol analyses which were restricted to HPV-naïve women who received all 3 doses.[118] Efficacy against dysplasia was also lower among older women and among women with abnormal baseline cervical cytology; VE was a mere 18.7% in the latter group in one trial.[119] This finding is consistent with that of a previous analysis of women vaccinated in Manitoba outside the school-based program.[20]

Smith *et al.* observed similar VE (RR =0.57 [0.2-1.58]) against AGWs among girls vaccinated at age 9-13 in Ontario's school-based program despite employing a different study design- they used a historical instead of concurrent comparison group.[53] VE among older females was not estimated in their study. VE estimates from two European studies were higher, but showed the same pattern of lower VE among those vaccinated at older age. Leval *et al*., using Swedish health administrative databases,

reported a VE of 76% (95%CI 73-79%) among those who completed a three-dose schedule, with the first dose given before age twenty.[107] Dominiak-Felden *et al.*, using data from a Belgian insurance drug database, reported lower VE estimates, 68.5% (95%CI 1.2-99%), among women who were ≥18 when vaccinated.[108] The higher VE observed in the European studies may reflect differences in sexual behaviour patterns. For instance, the median age of first sexual intercourse for Belgian women was 17.2 years compared to 15 years in Manitoba, where only 48% of sexually active teens reported using condoms on a regular basis.[120] Other possibilities include concurrent changes in clinical management guidelines and practices, particularly that both European studies relied on reimbursement for imiquimod prescriptions as a proxy for AGWs diagnosis, and differences in adherence to vaccine schedules. In our study, women vaccinated at an older age were less likely to complete all three doses, which is consistent with observations made elsewhere.[121]

Although several jurisdictions (e.g., Australia, France, United Kingdom) have implemented temporary age-based catch-up programs targeting women up to 26 years of age,[122] we are not aware of jurisdictions other than Manitoba implementing programs specifically targeted at high-risk women. These programs were justified by data from RCTs showing that older (typically previously infected) women may still benefit from protection against vaccine HPV types that they were not already exposed to.[115,116] Efficacy in these trials was, however, much lower in the intention-to-treat analyses, e.g., 42% against AGWs in one trial.[116] Women in these trials were generally at lower risk of HPV (as indicated by older age at sexual initiation), and most previously infected women

were only exposed to only one vaccine HPV type. It is not clear whether their findings can be applied to high-risk groups. Whereas vaccination might still be beneficial for women known to be at low risk of HPV, our findings suggest that population-based programs that specifically target high-risk groups are unlikely to be effective. The cost-effectiveness of such a program is likely even lower than age-based catch-up programs, which are generally inefficient.[123]

The higher VE observed among pre-adolescent girls suggests that in jurisdictions such as Manitoba, where significant inequity in rates of HPV-related diseases and vaccine uptake exists, programs aimed at increasing uptake among young children from high-risk communities might be a better approach than risk-based or even age-based programs. Rates of initiation and completion of HPV vaccination have been low among indigenous females in the province.[124] This is particularly concerning given that among this population, rates of HPV disease are higher and rates of cervical screening are lower than among non-indigenous populations.[33,125] If these trends continue unabated, it is possible that overall rates of HPV disease in Manitoba may remain at their pre-vaccine levels despite high coverage of the low-risk population.

Strengths and limitations

A major strength of this study is the availability of high quality, population-based health administrative databases in Manitoba. MIMS, the only long-standing immunization registry in Canada, has been validated for the pediatric population, and is used by clinicians as the patient's official immunization record.[112] As such, our study is

less susceptible to exposure misclassification and recall bias than studies relying on self-report or medical records.

By including only medically-attended AGWs cases, we likely underestimated the disease's incidence rates.[34] In cohort studies, disease under-ascertainment does not bias the relative risk estimates unless the resulting misclassification is related to the likelihood of exposure. Because increased detection of AGWs among vaccinated women (especially those vaccinated at older age) cannot be ruled out, we attempted to mitigate bias by adjusting for propensity to seek healthcare (number of encounters with healthcare providers).

The clinical markers used to suggest prior sexual activity are not very sensitive, and are not a perfect indicator of previous HPV exposure, which may have reduced our ability to adjust for the effect of history of HPV infection in our analyses. Another limitation of the study is the relatively short follow-up time (median 2.5 years); VE may have been underestimated, especially among younger women, because vaccine effects may not be observable during the study period because fewer of these women would have been sexually active. Finally, several of our analyses were underpowered to produce precise estimates of VE especially in subgroup analyses.

In conclusion, our findings do not support the effectiveness, at the programmatic level, of HPV vaccination for females over the age of 18 years. We found that women vaccinated at an older age, possibly through the high-risk catch-up program, were less

protected against AGWs. Further efforts should be targeted at increasing vaccine uptake among children, prior to the initiation of sexual activity, especially in communities with historically high HPV disease rates.

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Author contribution

SMM designed the study and supervised the analysis. EK contributed to the conception and design of the study and to the interpretation of the data. KW, SBE, and SMM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KW and SBE analyzed the data. KW and SMM drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

Chapter 6

General Discussion

Summary of key findings

HPV is a highly transmissible sexually transmitted infection that infects the majority of sexually active adults at some point in their lifetime. HPV infection is not reportable in Canada, and most infections go undetected. The majority of these are cleared by an intact host immune system. Nevertheless, it is estimated that high-risk HPV types cause up to 5% of all cases of cancer worldwide.[4] Additionally, non-invasive HPV related disease poses a major economic and psychosocial burden.

In most places in the world, intermediate clinical outcomes of HPV infection, such as intraepithelial neoplasias and AGWs, are not reportable. Therefore, current data on the clinical sequelae of HPV infection are based largely on retrospective analysis using population based health administrative databases. In Manitoba, incidence rates of AGWs are highest among females age 20 to 24 and males age 20 to 29.[34] This is in keeping with national data that suggests the highest risk of acquisition of HPV infection is within 5-10 years of sexual debut.[10] Since 2000, the incidence rate of AGWs among females has remained relatively stable, whereas the rate in males continues to climb. This may be due, in part, to the introduction of the HPV vaccine in the province in 2006, which was targeted mainly at females for the first 4 years, although it is unclear whether other factors related to sexual behaviours also contribute to this gender discrepancy. Since, September 2016, males are included in the school based publicly funded

vaccination program. It is hoped that in time we will see the trend of increasing AGWs in males abate.

As of September 2015, Manitoba moved to a two-dose vaccination schedule for all those initiating HPV vaccination before the age of 14. These recommendations are based on immunobridging trials of mean geometric antibody concentrations following two doses in females age 9-14 compared to three doses in females age 15-26. In theory a two-dose schedule may improve cost-effectiveness and overall vaccination coverage. However, it is important to note that the rationale for the non-inferiority criterion used for licensing in young girls is not well described in the literature. Furthermore, at present, there is no known immunologic correlate of clinical protection from HPV infection. However, given the novelty of the vaccine it is still too soon to observe the clinical outcomes of HPV infection among this target group for primary immunoprevention.

In our systematic review and meta-analysis of two versus three doses of HPV vaccine, we found that based on immunogenicity, a 2-dose HPV vaccine schedule in girls (age 9-14) was non-inferior to a 3-dose schedule in women (age 15-26) up to 60 months follow up. But when compared within the same age group of females age 9-14, immunologic non-inferiority of 2 doses was violated within the first 1-2 years of vaccine administration for both the BHPV and QHPV, and no data are reported beyond 36 months follow up. However, we note that GMC levels after 2 doses at all follow-up times remained well above those induced by natural infection.[17] As of August 2015, we

found no trial that reported clinical outcomes following a 2- versus 3-dose schedule. We are currently in the process of updating this search. Ultimately, ongoing collection of high quality long-term clinical trials and observational data is required to assess the clinical effectiveness of a 2-dose HPV vaccination schedule in young adolescents, whereas further immunologic data may help to determine the need for a booster dose later in life.

We conducted a registry cohort study to estimate the effectiveness of both routine school-based and temporary high-risk catch-up HPV vaccination programs against medically-attended AGWs in the real-world setting. This study was one of the first to use algorithms based on high quality population-wide health administrative databases to identify cases of AGWs at the individual level. Between September 2006 and March 2013, we identified 31,464 females who received at least one dose of QHPV. After matching on birthdate and area of residence to non-vaccinated females, we found that those who received at least one dose of QHPV were more likely to live in urban areas and be in the top three income quintiles. In our study, vaccinated females were also more likely to have clinical markers suggestive of prior sexual activity prior to vaccination. We found that the risk of AGWs was reduced by 40% among females who were vaccinated when they were $\leq$18 years old. However, we found no evidence of a reduction in AGWs risk among females vaccinated at an older age, especially among those with clinical markers suggestive of prior sexual activity. Vaccine effectiveness (VE) among these older females was lower than that seen among the ITT cohort in the FUTURE I/II trials, where VE against AGWs was 79.5% among females aged 15-26 years.[66] There are a few

possible explanations for this. First, in our cohort study, completion of 3-doses of QHPV was significantly lower among females over the age of 18, compared to adolescent females, which may have contributed to lower vaccine effectiveness. Second, the FUTURE trials excluded females with more than five lifetime sexual partners. Given that our study included females vaccinated through a high-risk catch-up program, we suspect that many of our older females would not have been eligible for FUTURE, based on this exclusion criterion. In a trial of females aged 24-45 years, where there was no exclusion based on sexual history, QHPV VE in the ITT cohort was only 8.5% against external genital lesions caused by HPV vaccine types.[40] Prophylactic HPV vaccines have no known therapeutic effect on established infections.[39] Therefore, every effort should be make to vaccinate young adolescents prior to the initiation of sexual activity.

HPV vaccine surveillance and evaluation in Manitoba

For both clinicians and policy makers, ongoing evaluation of population effectiveness is essential for the development of a successful publicly funded vaccination program. This calls for the establishment of a comprehensive and systematic vaccine surveillance and evaluation program to address questions of vaccine safety, uptake, impact, and effectiveness.[126] Manitoba is unique in that the majority of the population is centralized in one major city, Winnipeg, and most specialized clinical and laboratory services are located there. In addition, Manitoba possesses a wealth of well-established and complete administrative health databases that can be linked by a unique personal health identification number. These databases are representative of over 99% of the population, or approximately 1.3 million inhabitants, which is comparable to other large

North American datasets. The Manitoba Immunization Monitoring System (MIMS) is the longest standing registry of publicly funded immunization in the country.[61] The province also maintains a unique cervical cancer screening registry, CervixCheck. This was established in 2000, and reporting of all Pap tests, colposcopy and cervical biopsy results became mandated by law in 2001.[127] In addition, the Public Health Agency of Canada's National Microbiology Lab carries out HPV typing and is actively participating in epidemiological and post vaccine surveillance studies examining prevalence of oncologic and non-oncologic HPV types in the province. For these reasons, Manitoba is well situated to be a leader in HPV vaccine surveillance and evaluation.

To date, Manitoba has trailed behind the other provinces in HPV vaccine uptake. According to results from the 2013 Childhood National Immunization Coverage Survey, estimated HPV vaccine coverage (at least one dose) among females age 12-14 was 65.2% (95%CI 60.9-69.3%) in Manitoba.[128] This was the lowest rate of all provinces (ranging from 89.3% in Newfoundland and Labrador, to 67.5% in British Columbia and Ontario), but higher than the territories (64.3% in Yukon, 52.6% in Nunavut, and 52.4% in Northwest Territories).[128] This study was subject to recall bias, as it relied on telephone interviews. Only 45% of respondents returned completed consent forms to allow researchers to contact their health care providers. Also, minimal socio-demographic data was collected, so it is not clear whether selection bias has occurred.

A study by Demers et al. in 2009 found that among an opportunistic sample of women attending a Pap test clinic, HPV infection was associated with First Nations and

Metis ethnicity and self-described difficult financial situation.[33] For First Nations and Metis women over the age of 30, the risk of HPV infection was over 3-fold higher than in Caucasian women (OR 3.3; 95%CI 1.7-6.4).[33] Women over the age of 30 who described their financial situation as difficult also had a 3-fold increase in risk of HPV infection (OR 3.3; 95%CI 1.2-9.4).[33] In Manitoba, cervical screening rates among First Nations women over the age of 40 was found to be significantly lower than that of other Manitoba women (RR 0.84; 95%CI 0.75-0.93), and this disparity widened as women progressed into their 50s and 60s.[125] This is particularly concerning, given that First Nations women were also more likely than other Manitoba women to have high grade abnormalities on cervical screening (RR 1.88; 95%CI 1.65-2.13).[125] First Nations women also had more than double the rates of invasive cervical cancer, in both the 25-39 year age group (21.9 per 100,000 First Nations women; 10.2 per 100,000 other Manitoba women), and in the 40-69 year age group (24.3 per 100,000 First Nations women; 12.3 per 100,000 other Manitoba women).[125] Early reports on privately funded HPV vaccination show a significant disparity in uptake between First Nations and Non-First Nations females in the province.[124] Although this disparity seems to have improved with the introduction of the publicly funded school based program, Manitoba is still falling below the targets set out by Health Canada, and the differences in uptake between health regions and income quintiles are disconcerting. Ultimately, if we are not reaching those at greatest risk, the potential benefit of a publicly funded vaccination programs is reduced.[129]

Policy implications

Publicly funded HPV vaccination programs in Canada apply a universal approach, whereby eligibility and access are based solely on age. However, what is universal in principle, may not be universal in practice.[130] Instead, we should consider a targeted approach to HPV vaccination which can be applied to a priority subgroup within the broader population.[130] An example of a targeted health intervention already underway in Manitoba is the Prenatal Benefit, which provides mothers who have a net family income of less than $32,000 per year with a monthly subsidy to encourage good nutrition during pregnancy, as well as connection to early prenatal care and community support.[131] Challenges with a targeted approach are that it may address the consequences of health inequity, rather than the cause.[130] There is also the potential for over- or under-inclusion when designing targeted approaches.[130]

The concept of proportionate universalism is a blended approach that employs the idea that programs and policies must include a range of responses for different levels of disadvantage experienced within the population.[130] The goal is to narrow the health inequity gap and improve overall public health in a population. In the context of the HPV vaccine, this means coming up with novel ways to reach those most in need, including improving access, and empowering individuals and local communities by way of education about HPV and its sequalae. For HPV vaccination, these initiatives would need to be targeted towards the parents and guardians of young adolescents, prior to initiation of sexual activity.

Gaps in knowledge and future directions

Due to the novelty of the HPV vaccine, data on vaccine effectiveness against intermediate and long-term outcomes of HPV infection are scarce. This is particularly true among the target age group for HPV vaccination, who may have not yet initiated sexual activity. Programs that support the early introduction of the HPV vaccine argue that the benefits of a vaccine that can potentially prevent cancer are too great to delay its implementation. However, rigorous surveillance and evaluation of vaccine effectiveness, as well as safety, uptake, and impact on screening should be a priority. Manitoba is well equipped to carry out this work. At present, a registry cohort study employing similar methods to the ones used here is underway to assess effectiveness of HPV vaccine against cervical dysplasia in the province since introduction of the publicly funded school based program.

We have found a paucity of data from randomized trials on the relative efficacy of two and three doses of HPV vaccine among pre-adolescents. Given the relatively recent approval of the 9vHPV vaccine, and the inclusion of boys into the publicly funded school based HPV vaccination program, we are currently updating our systematic review to include these parameters. However, there is still no known immunologic correlate of clinical protection, and ultimately, further observational research is needed to link health policy decisions regarding the optimal use of HPV vaccine to clinically relevant, patient centered outcomes.

To our knowledge, there are no validated algorithms using administrative health databases to assess sexual risk taking behaviour. This may be useful in studying predictors of vaccine uptake and effectiveness. It may also help in designing prevention programs and educational interventions related to healthy sexual practices and screening.

We have not identified any studies of risk factors for AGWs in the Manitoba population. So we do not know if gender differences in AGWs incidence rates are related to vaccine uptake or sexual practices. To explore these questions, we are extending our ecological analysis of AGWs incidence rates to compare the rates of other sexually transmitted infections before and after introduction of the HPV vaccine in the province.

In conclusion, challenges exist in identifying those in the population who stand to benefit the most from any preventative health intervention, particularly within the context of a publicly funded health care system. Our systematic review of two versus three doses of HPV vaccine suggests that when compared to three doses among adult women, two doses in adolescent females produces an immunologically non-inferior response. However, immunogenicity does not necessarily translate into clinical effectiveness, as there remains to be no known immune correlate of clinical HPV infection. Ongoing surveillance on clinical outcomes is required as the first cohorts of those vaccinated in early adolescence start to become sexually active. In our cohort study of quadrivalent HPV vaccine effectiveness against AGWs in Manitoba, we found no evidence of a reduction in AGWs risk among females vaccinated at an older age, especially among

those with clinical markers suggestive of prior sexual activity. Accumulated evidence in Manitoba indicates that those at greatest risk of HPV infection also have the lowest rates of cervical screening and vaccine uptake. The proportionate universalism approach may be a way of reducing the sociodemographic disparity seen in the incidence of HPV-related disease in Manitoba. For HPV vaccination, this may be achieved by educational programs aimed at the parents of youth deemed to be at high risk for HPV infection, prior to them becoming sexually activity.

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Appendices and Supporting Documents

Appendix A. PubMed Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Completed: August 17, 2015

Search sequence	Search terms
1	exp human papillomavirus 6/ or human papillomavirus 16/ or human papillomavirus 18/ or human papillomavirus 31/
2	Alphapapillomavirus/
3	HPV$.ti,ab.
4	(qhpv or bhpv).ti,ab.
5	"Papillomavirus Infections"/
6	papillomavirus$.ti,ab.
7	Alphapapillomavirus$.ti,ab.
8	human papilloma$ virus$.ti,ab.
9	(hpv$ adj4 (infection? or cervic$ or cervix or cancer$ or infectious or neoplas$ or uterine)).ab.

10	or/1-9 [HPV]
11	vaccines/ or cancer vaccines/ or viral vaccines/
12	(vaccine? or vaccination?).ti,ab.
13	or/11-12 [Vaccines]
14	10 and 13 [HPV & Vaccine]
15	Papillomavirus Vaccines/
16	((papillomavir$ adj3 vaccin$) or (HPV$ adj3 vaccin?)).ti,ab.
17	(gardasil or Cervarix).ti,ab.
18	or/15-17 [HPV Vaccine]
19	18 not 13 [Illustrates unique citations identified by these terms]
20	Randomized Controlled Trial.pt.
21	Pragmatic Clinical Trial.pt.
22	exp Randomized Controlled Trials as Topic/
23	"Randomized Controlled Trial (topic)"/
24	Randomized Controlled Trial/
25	Randomization/
26	Random allocation/
27	Double-Blind Method/
28	Double Blind Procedure/
29	Double-Blind Studies/
30	Single-Blind Method/
31	Single Blind Procedure/
32	Single-Blind Studies/
33	Placebos/ or placebo/
34	(random* or sham or placebo*).ti,ab,hw.
35	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
36	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

37	or/20-36 [CADTH RCT filter for ML-EM - accessed Feb 2015]
38	meta-analysis.pt.
39	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
40	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
41	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
42	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
43	(data synthes* or data extraction* or data abstraction*).ti,ab.
44	(handsearch* or hand search*).ti,ab.
45	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
46	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
47	(meta regression* or metaregression*).ti,ab.
48	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
49	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
50	(cochrane or (health adj2 technology assessment) or evidence report).jw.
51	(comparative adj3 (efficacy or effectiveness)).ti,ab.
52	(outcomes research or relative effectiveness).ti,ab.
53	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
54	or/38-53 [CADTH Systematic Review/Meta-Analysis/Health Technology Assessment filter - Accessed Feb 15]
55	exp animals/ not humans.sh.
56	37 not 55 [animal studies filter]

57	(14 or 18) and 56 [Trials Results to Export]
58	**((14 or 18) and 54) not 56 [Systematic Review-Meta-analyses to export; trials (line 56) excluded]**
59	57 or 58

Key:
#1-10 HPV
#11-13 vaccines
#14 HPV and vaccines
#15-18 papillomavirus vaccine
#19 papillomavirus vaccine NOT vaccine
#20-37 CADTH RCT filter
#38-54 CADTH Systematic review filter
#55-56 Animal studies filter

Reference

CADTH database search filters. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014.

Appendix B. Risk of bias assessment


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Dobson
Leung
Puthanakit
Romanowski

Appendix C: Seropositivity* rates at longest follow-up

Comparison	HPV type	Number of trials	Risk Ratio [95% CI]	Heterogeneity (I^2)
2-dose girls v. 3-dose girls	HPV-16	2	1.00 [0.99-1.00]	0%
	HPV-18	2	0.94 [0.88-1.00]	70%
2-dose girls v. 3-dose women	HPV-16	3	1.00 [1.00-1.00]	0%
	HPV-18	3	1.02 [0.97-1.07]	97%

* HPV-16 seropositivity cutoffs used include ≥8EU/mL (13, 16), ≥19EU/mL (15), ≥20mMU/mL (14). HPV-18 seropositivity cutoffs used include ≥7EU/mL (13, 16), ≥18EU/mL (15), ≥24mMU/mL (14).

Appendix D. Summary of subgroup analysis of bivalent and quadrivalent HPV vaccine

A. Comparison 1: 2-doses versus 3-doses in girls age 9-14

	Bivalent HPV vaccine (1 trial)	Quadrivalent HPV vaccine (2 trials)
HPV-16	Non-inferiority criterion VIOLATED at 7 mos [GMC ratio 0.50 95%CI 0.38, 0.64] I^2= n/a	Non-inferiority criterion MAINTAINED to 36 mos I^2= 0%
HPV-18	Non-inferiority criterion VIOLATED at 24 mos [GMC ratio 0.64 95%CI 0.47, 0.87] I^2= n/a	Non-inferiority criterion VIOLATED at 12 mos [pooled GMC ratio 0.55 95%CI 0.48, 0.64] I^2= 0%

B. Comparison 2: 2-doses in girls versus 3-doses in women

	Bivalent HPV vaccine (2 trials)	Quadrivalent HPV vaccine (1 trial)
HPV-16	Non-inferiority criterion MAINTAINED to 60 mos I^2= 0%	Non-inferiority criterion MAINTAINED to 36 mos I^2= n/a
HPV-18	Non-inferiority criterion MAINTAINED to 60 mos I^2= 0%	Non-inferiority criterion MAINTAINED to 36 mos I^2= n/a

Appendix E. Identification of HPV vaccination

In MIMS and the Medical Services databases, the tariff (billing) code 8891 has been used since 2008 to specifically refer to the administration of the quadrivalent HPV vaccine. Before that, clinicians used the tariff 8800 (generic code for vaccination) and indicated in a free-text "comment" field that the HPV vaccine was administered. In addition, the DPIN was used to identify females who filled a prescription for the QHV vaccine (DIN 02283190).

Appendix F. Tariff codes used to identify a person with anogenital warts

Code	Description
3372	Anus, condyloma, single or multiple, internal or external, destruction, in hospital
3433	Anus, condyloma, external, electrodessication, initial, per sitting
3434	Anus, condyloma, external, electrodessication, subsequent, per sitting
4120	Penis, penile skin lesion, including warts, local excision or fulguration, per sitting
4412	Vulva, condylomata excision or destruction any method less than 10 warts up to 25% of vulva
4413	Vulva, condylomata excision or destruction any method 10 or more warts more than 25% of vulva
4415	Vagina, condylomata excision or destruction any method less than 5 warts up to 25% of vagina
4416	Vagina, condylomata excision or destruction any method 5 or more warts more than 25% of vagina
4422	Vulva, condyloma accuminata local excision, fulguration, chemical application or injection or other treatment, per sitting
4427	Vulva, condyloma accuminata, extensive removal under general anaesthesia
4430	Vulva, condylomata excision or destruction any method less than 10 warts up to 25% of vulva
4432	Vulva, condylomata excision or destruction any method 10 or more warts more than 25% of vulva
4472	Vagina, condylomata excision or destruction any method less than 10 warts up to 25% of vagina
4475	Vagina, condylomata excision or destruction any method 10 or more warts more than 25% of vagina

Appendix G. Identification of hospitalized cases of anogenital warts

Date	ICD version	Criteria[1]	Number of fields[2]
04/1994-03/2004	9	078.11 diagnosis OR (078.10 / 078.19 diagnosis AND related procedure)	16 diagnosis and 12 procedure
>03/2004	10	A630 diagnosis OR (B07 diagnosis AND related procedure)	25 diagnosis and 20 procedure

[1] See Appendix E and F for related procedures used.
[2] All diagnostic and procedure fields were included.

Appendix H. ICD-9-CM procedure codes

Code	Description
48.82	Excision of perirectal tissue
49.04	Other excision of perianal tissue
49.3	Local excision or destruction of other lesion or tissue of anus
49.31	Endoscopic excision or destruction of lesion or tissue of anus
49.39	Other local excision or destruction of other lesion or tissue of anus
58.3	Excision or destruction of lesion or tissue of urethra
58.31	Endoscopic excision or destruction of lesion or tissue of urethra
58.39	Other local excision or destruction of lesion or tissue of urethra
61.3	Excision or destruction of lesion or tissue of scrotum
64.2	Local excision or destruction of lesion of penis
67.32	Destruction of lesion of cervix by cauterization – electroconization of cervix
67.33	Destruction of lesion of cervix by cryosurgery – cryoconization of cervix
67.39	Other excision or destruction of lesion or tissue of cervix
70.33	Excision or destruction of lesion of vagina
71.3	Local excision or destruction of vulva and perineum

Appendix I. ICD-10 procedure codes

Code	Description
1RS59CAGX	Destruction vagina using per orifice approach and device NEC
1NT59CAGX	Destruction anus using per orifice approach and device NEC
1PQ59LAGX	Destruction urethra using open approach and device NEC
1RW59JAGX	Destruction vulva using external approach and device NEC
1RW59JAX7	Destruction vulva chemocautery agent
1RY87LA	Excision, partial perineum

Appendix J. Tariff codes for treatment of anogenital warts[1]

Code	Description
0253	Excision & simple closure – single lesion, any location
0254	Excision & simple closure – each additional lesion to a maximum of four
0255	Excision & closure – multiple lesions, extensive
0397	Laser vaporization, other than face, one lesion
0398	Laser vaporization, other than face, two lesions
0399	Laser vaporization, other than face, three or more lesions
0400	Cautery (electro, chemo) destruction or simple surgical excision of benign or premalignant lesions
0401	Cautery (electro, chemo, or simple surgical excision, one lesion) elsewhere
0402	Warts & fibrocutanous tags - simple
0404	Cryocautery, etc., of benign lesion of skin, etc., second lesion
0405	Cryocautery, etc., of benign lesion of skin, etc., subsequent lesions (each)
0406	Cryocautery, etc., of benign lesion of skin, etc., complicated lesions
3300	Rectum, villous papilloma of rectum, extensive, local excision
3301	Rectum, unlisted or unusually complicated
3311	Rectum, proctosigmoidoscopy
3315	Rectum, proctosigmoidoscopy with removal of polyp or papilloma, single
3317	Rectum, proctosigmoidoscopy with removal of polyp or papilloma, multiple
3429	Anus, unlisted or unusually complicated
3994	Urethroscopy, therapeutic, polyps, urethral, excision of fulguration with or without urethroscopy
4000	Urethra, urethroscopy, diagnostic, initial or subsequent
4120	Penis, unlisted or unusually complicated
4221	Scrotum, skin lesion, local excision
4229	Scrotum, unlisted or unusually complicated
4611	Cervix, local excision of lesion, cauterization of biopsy, one or more sites
4641	Cryosurgery of the cervix for other conditions
8470	General practice visit – regional gynaecological exam – including cytological smear - cervix
8471	General practice visit – regional gynaecological exam – no cytological smear
8495	Obstetrics / gynaecology visit – complete gynaecological exam – including cytological smear - cervix
8496	Obstetrics / gynaecology visit – regional gynaecological exam – including cytological smear - cervix
8497	Obstetrics / gynaecology visit – regional gynaecological exam – no cytological smear
8498	General practice visit – complete gynaecological exam – including cytological smear - cervix
8499	General practice visit – complete gynaecological exam – no cytological smear
8501	Office visits, regional, history and examination
8502	Office visits, complete or extensive re-examination for same illness
8507	Office visits, subsequent visit
8509	Office visits, regional or subsequent visit or well baby care
8529	Office visits, regional intermediate visit or subsequent visit or well baby care

[1] Only included if the diagnosis was 078 and if it followed within two weeks a claim that had an anogenital wart tariff

Appendix K. Data sources utilized

Data Source	Description
Manitoba Health Population Registry (MPR)	A continuously updated registry that stores basic demographic information (e.g. date of birth and sex) on all insured Manitobans since 1970. This registry gathers information on dates and reasons for the initiation and termination of health care coverage (e.g. birth, migration in or out or province and death), and on changes in address and marital status of the insured individuals.
Manitoba Immunization Monitoring System (MIMS)	A population-based province-wide registry recording all immunizations administered to Manitoba residents since 1988. Information, including vaccine type and date of immunization, is captured through direct data entry for vaccines administered either by public health staff (who administer all vaccines received through the public school-based program) or via the physician billing system (see below).
Hospital Abstracts Database	Records virtually all services provided by hospitals in the province, including admissions and day surgeries, since 1971. Data collected comprise demographic as well as diagnosis and treatment information including primary diagnosis and service or procedure codes. This database uses International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before April 2004, and the Canadian adaptation of the ICD-10 (ICD-10-CA) and the Canadian Classification of Health Interventions (CCI) afterwards.
Medical Services Database	Collects information, based on physician fee-for-service or shadow billing, on services provided by physicians in offices, hospitals and outpatient departments across the province since 1971. Each billing record includes a tariff code and a 3-digit ICD-9 code which identifies the principal diagnosis or main reason for the visit.
Drug Program Information Network Database	An electronic, on-line, point-of-sale prescription drug database that connects Manitoba Health and all pharmacies in Manitoba since 1995. The DPIN system generates complete drug profiles for all out-of-hospital transactions at the point of distribution.
MH Communicable Disease Surveillance Database	Tracks the dates and results of most sexually transmitted and blood borne infection tests performed in Manitoba (excluding HPV).
CervixCheck	Dates and results of all cervical screening tests since 2001 in Manitoba

References

(1) http://www.umanitoba.ca/faculties/medicine/units/mchp/resources/repository/index.html (accessed July 21, 2014)
(2) http://www.gov.mb.ca/health/publichealth/cdc/sti/index.html (accessed July 21, 2014)

Appendix L. Definitions of other covariates used in the analysis

Variable*	Definition
Drugs	
Anti-HIV	Protease inhibitors (J05AE), Nucleoside and nucleotide reverse transcriptase inhibitors (J05AF), Non-nucleoside reverse transcriptase inhibitors (J05AG), Antivirals for treatment of HIV infections, combinations(J05AR)
For treatment of diabetes	Drugs used in diabetes (A10)
Immunosuppressants	Antineoplastic agents (L01), Immunosuppressants (L04A)
Systemic steroids	Corticosteroids for systemic use, plain (H02A), Corticosteroids for systemic use, combinations (H02B)
Contraception	G03A, G02B
Sexual health related covariates	
Ongoing pregnancy	≥ 1 admission (O10-O16, O20-O29, O30-O48, O94-99, Z32-Z36) OR ≥ 2 physician claims (640-649, V22) OR ≥ 1 tariff code for prenatal services. Must be within ± 30 days of the index date
Completion of Pregnancy	≥1 admission (O8, O65-O75, O80-O84, O85-O92, Z37-Z39) OR ≥ 2 physician claims (650-659, 670-676, 670-676, V27) OR ≥ 1 tariff code for delivery, abortion or postnatal services. Must be within 270 days following the index date
HIV/AIDS	≥ 1 admission (B20-B24, R75, Z21) OR ≥ 2 physician claims (042 V08) OR ≥ 1 prescriptions for drugs used in treatment of HIV.
STI	Having a positive test for gonorrhea, chlamydia, hepatitis B or C, HIV, lymphogramuloma venereum, syphilis OR ≥ admission OR ≥ 1 physician code for the above listed and/or chancroid, granuloma inguinale, trichomoniasis.
Sexual activity	Any pregnancy, STI, pelvic inflammatory disease, or prescription for contraception, as defined above.
Medical conditions	
Autoimmune disease	≥ 1 admission (ICD-10 codes) OR ≥ 2 physician claims (ICD-9 codes), as listed in Appendix I
Immunosuppressed	Having an organ transplant or a diagnosis of HIV/AIDS, other immune deficiency disorders or cancer (other than non-melanoma skin cancer), or receiving prescriptions for immunosuppressants or systemic steroids.
Chronic disease	Having a diagnosis of diabetes, chronic cardiovascular disease (excluding hypertension), chronic respiratory disease (excluding asthma), chronic renal failure, or chronic liver disease.

*All diagnoses are considered in the 5 years prior to index/vaccination date.

Appendix M. Administrative codes used to identify autoimmune diseases

Disease	ICD9 codes		ICD10 codes
	Physician claims	Hospital data	
Pernicious anemia	281	281.0	D51.0
Autoimmune hemolytic anemia	283	283.0	D59.1
Idiopathic thrombocytopenic purpura	287	287.32	D69.3
Thyrotoxicosis	242	242	E05
Autoimmune thyroiditis	245	245.2	E06.3
Type 1 diabetes	250 (AND ≥ 1 prescription [ATC: A10A])	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93	E10
Primary adrenocortical insufficiency	255	255.41	E27.1
Guillain–Barre syndrome	357	357.0	G61.0
Iridocyclitis	364	364.0-364.3	H20
Crohn's disease	555	555	K50
Ulcerative colitis	556	556	K51
Autoimmune hepatitis		571.42	K75.4
Primary biliary cirrhosis		571.6	K74.3
Celiac disease	579	579.0	K90.0
Pemphigus	694	694.4	L10
Pemphigoid	694	694.5	L12
Psoriasis vulgaris	696	696.1	L40.4
Alopecia areata		704.1	L63
Vitiligo		709.1	L80
Seropositive rheumatoid arthritis	714	714.0, 714.1, 714.2, 714.8, 714.9	M05–M06
Juvenile arthritis	714	714.3	M08
Waegner's granulomatosis	446	446.4	M31.3

Polymyositis	710	710.4	M33.2
Dermatomyositis	710	710.3	M33.0, M33.1
Polymyalgia rheumatica	725	725	M31.5–6, M35.3
Myasthenia gravis	358	358.0	G70.0
Systemic sclerosis	710	710.1	M34
Systemic lupus erythematosis	710	710.0	M32.1, M32.8,M32.9
Sjogren's syndrome	710	710.2	M35.0
Ankylysing spondyitis	720	720.0	M45

Appendix N. Demographic and clinical features by vaccine completion status

Variables	Complete (3 doses) (n=21277)		Incomplete(1 or 2 doses) (n=10187)		Unvaccinated
	N	%	N	%	%
Age group (years)					
9-18	19336	90.9	8040	78.9	87.0
19-24	1494	7.0	1462	14.4	9.4
25+	447	2.1	685	6.7	3.6
Median age (IQR)	11	11 - 13	12	11 - 18	11 - 15
Locality of residence					
Rural	8803	41.4	4198	41.2	42.5
Urban	12260	57.6	5822	57.2	56.4
Public Trustee	214	1.0	167	1.6	1.2
Manitoba region of residence					
Winnipeg	11373	53.5	5393	52.9	53.3
North	1587	7.5	1179	11.6	8.8
South	8103	38.1	3448	33.8	36.7
Public Trustee	214	1.0	167	1.6	1.2
Winnipeg region of residence					
Northern Suburbs	3813	17.9	1790	17.6	17.8
Inner City	1349	6.3	827	8.1	6.9
Southern Suburbs	6211	29.2	2776	27.3	28.6
Non-Winnipeg/ Public Trustee	9904	46.5	4794	47.1	46.7
Winnipeg community areas					
Assiniboine South	779	3.7	330	3.2	3.5
Downtown	775	3.6	460	4.5	3.9
Fort Garry	1396	6.6	617	6.1	6.4
Inkster	540	2.5	255	2.5	2.5
Non-Winnipeg/ Public Trustee	9904	46.5	4794	47.1	46.7
Point Douglas	574	2.7	367	3.6	3.0
River East	1596	7.5	745	7.3	7.4
River Heights	850	4.0	432	4.2	4.1
Seven Oaks	1018	4.8	473	4.6	4.7
St. Boniface	1065	5.0	458	4.5	4.8
St. James - Assiniboia	905	4.3	436	4.3	4.3
St. Vital	1216	5.7	503	4.9	5.5
Transcona	659	3.1	317	3.1	3.1
Regional Health Authorities					
Interlake-Eastern	2279	10.7	1084	10.6	10.7
Northern	1580	7.4	1173	11.5	8.8
Prairie Mountain	2949	13.9	1269	12.5	13.4
Public Trustee	214	1.0	167	1.6	1.2
Southern	2875	13.5	1095	10.7	12.6
Winnipeg	11380	53.5	5399	53.0	53.3
Income Quintile categories					
Cannot be calculated	253	1.2	230	2.3	1.9

Q1-Q2	7055	33.2	3971	39.0	39.0
Q3-Q5	13969	65.7	5986	58.8	59.1
Hospitalizations*					
0	20051	94.2	9259	90.9	91.7
1	973	4.6	642	6.3	5.6
2+	253	1.2	286	2.8	2.7
Median hospital admission (IQR)*	0	0 - 0	0	0 - 0	0 - 0
Median physician visits (IQR)*	14	8 - 23	15	8 - 25	6 - 22
Immunosuppressed**					
Yes	472	2.2	331	3.2	2.2
Autoimmune diseases**					
Yes	350	1.6	229	2.2	1.9
Any chronic diseases**					
Yes	694	3.3	346	3.4	2.5
Sexually active before index date***					
Yes	2638	12.4	2619	25.7	14.2
Any STIs**					
Yes	330	1.6	662	6.5	3.3
Pelvic inflammatory disease**					
Yes	536	2.5	526	5.2	2.4
Contraceptive drug use**					
Yes	2231	10.5	2321	22.8	11.5
Pregnancy**					
Yes	111	0.5	344	3.4	3.6
Median follow up time (months)	34	22 - 51	5	4 - 17	11 - 42

*During 5-year period prior to index date

** See appendices H and I for administrative codes used for identification

*** Composite of any pregnancy, sexually transmitted infection, pelvic inflammatory disease, and/or contraceptive drug use prior to index date

Appendix O. Cumulative percentage of AGW by demographic and clinical features

Variables	AGW (%)	
	YES	NO
Age group (years)		
9-18	0.2	99.8
19-24	1.8	98.2
25+	1.5	98.5
Median age (IQR)	17 - 23	11 - 15
Locality of residence		
Rural	s	s
Urban	0.6	99.4
Public Trustee	s	s
Manitoba region of residence		
Winnipeg	0.6	99.4
North	s	s
South	0.3	99.7
Public Trustee	s	s
Winnipeg region of residence		
Northern Suburbs	0.4	99.6
Inner City	0.3	99.7
Southern Suburbs	0.8	99.2
Non-Winnipeg/ Public Trustee	0.2	99.8
Winnipeg community areas		
Assiniboine South	0.6	99.4
Downtown	s	s
Fort Garry	1.1	98.9
Inkster	s	s
Non-Winnipeg/ Public Trustee	0.2	99.8
Point Douglas	0.3	99.7
River East	0.4	99.6
River Heights	0.8	99.2
Seven Oaks	0.2	99.8
St. Boniface	0.7	99.3
St. James - Assiniboia	0.6	99.4
St. Vital	0.7	99.3
Transcona	0.5	99.5
Regional Health Authorities		
Interlake-Eastern	0.3	99.7
Northern	s	s
Prairie Mountain	0.3	99.7
Public Trustee	s	s

Southern	0.2	99.8
Winnipeg	0.6	99.4
Income Quintile categories		
Cannot be calculated	0.4	99.6
Q1-Q2	0.4	99.6
Q3-Q5	0.4	99.6
Hospitalizations*		
0	0.4	99.6
1	0.3	99.7
2+	0.7	99.3
>=11 physician visits*		
Yes	0.6	99.4
Immunosuppressed**		
Yes	1.0	99.0
Autoimmune diseases**		
Yes	1.0	99.0
Any chronic diseases**		
Yes	0.6	99.4
Sexually active prior to index date***		
Yes	1.9	98.1
Any STIs**		
Yes	2.2	97.8
Pelvic inflammatory disease**		
Yes	1.9	98.1
Contraceptive drug use**		
Yes	2.1	97.9
Pregnancy**		
Yes	1.0	99.0

*During 5-year period prior to index date

** See appendices H and I for administrative codes used for identification

*** Composite of any pregnancy, sexually transmitted infection, pelvic inflammatory disease, and/or contraceptive drug use prior to index date

Appendix P. Cumulative percentage of AGW by vaccination status

Variables	AGW (%)	
	YES	NO
Exposure status		
Vaccinated (at least 1 dose)	0.6	99.4
Unvaccinated	0.3	99.7
Completion status		
Complete (3 doses)	0.5	99.5
Incomplete (1 or 2 doses)	0.7	99.3
Unvaccinated	0.3	99.7
Number of doses		
1 dose	1.2	98.8
2 doses	0.5	99.5
3 doses	0.5	99.5
Unvaccinated	0.3	99.7