Merck Investigator Studies Program (MISP) Protocol

Fall in prevalence of genital HPV infection in males following introduction of universal male HPV vaccination

Section 1: MISP Protocol Identification

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Section 2

2.1: Objective and hypothesis

The aim of this study is to demonstrate a fall in the prevalence of genital HPV infection among teenage males as a result of the implementation of a universal male vaccination program. Our hypothesis is that in a setting where there is already a female vaccination program in place and where herd immunity has resulted in a fall in male HPV prevalence, introduction of a male vaccination program will result in further falls in the prevalence of HPV in males.

2.2 Background

Rationale for study

The provision of HPV vaccination to females through universal vaccination programs has resulted in a fall in prevalence of HPV infection and HPV related lesions among females in countries where this has been introduced. This has been shown in several countries including Australia, which was one of the first countries to roll out free, universal vaccination in females. In Australia studies have shown a significant decline in the prevalence of HPV infection, genital warts and HPV related cervical lesions among females.[1-4]

While such direct benefits have been shown in females, they have not been shown among males as no country to date has rolled out universal, free vaccination of males on a national level. Rather, what has been shown to date are falls in the prevalence of genital warts as a result of herd immunity from female vaccination.[1-2] Mathematical models predict that extending the vaccination program to males will provide incremental benefit.[5] While this is predicted to be occur, there have to date been no data from any countries demonstrating this as no countries have thus far implemented universal vaccination of both males and females.

As the Australian Government has announced that a universal male vaccination program will be introduced in Australia beginning in 2013 we believe we are uniquely placed in Australia to document a fall in HPV prevalence among males that is additional to falls that have already occurred because of female vaccination.

If this study is to be undertaken it is critical that it begins as soon as possible given that vaccination is being rolled out in Australia in 2013. Without this we cannot establish the baseline prevalence of HPV among males prior to male vaccination.

In Victoria the male vaccination program will be provided through:

- An ongoing school based program to boys in year 7 (mainly 12 and 13 year olds with some 11 year olds) with a time limited program for boys in year 9 (mainly 14 and 15 year olds with some 13 year olds) in 2013 and 2014 only.

- An ongoing community based program for boys aged 12 and 13 years together with a time limited program for boys aged 14 and 15 in 2013 and 2014 only.

This means that by 2014, 2015, 2016 and 2017, the oldest cohort of males to have been offered vaccination as part of the Victorian program will be aged 16, 17, 18 and 19 years respectively. The age of boys who will have been offered vaccination by year from 2013 through to 2017 is shown in Table 1. In period 1 (2014-2015), 200 boys will be recruited. The same number, 200, will be recruited in period 2 (2016-2017).

Significance of study outcomes

As Australia is the first country to implement a universal male vaccination program we have the opportunity to be among the first to demonstrate a fall in HPV prevalence among males as a result of male vaccination. While there is

evidence that the prevalence of genital warts among males in Australia has fallen as a result of female only vaccination, falls in the prevalence of HPV infection including high risk HPV types among males in response to universal male vaccination have not thus far been documented in any country but is expected to occur.[5]

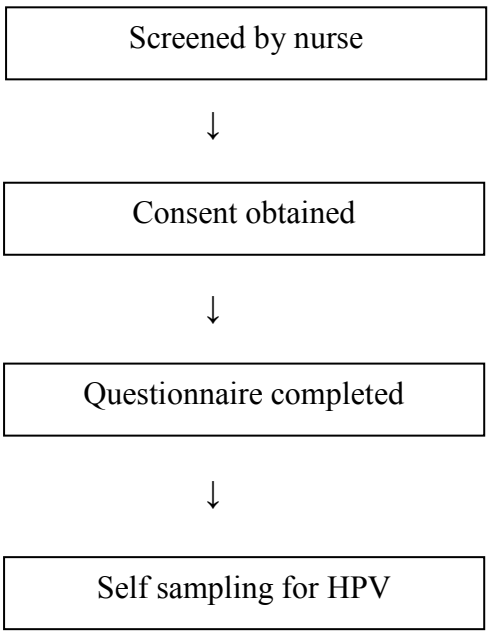
This would provide evidence and argue for the introduction of universal male HPV vaccination programs in countries which have already introduced universal vaccination of females.

2.3 Study design

Study population and sample size

This study will determine the prevalence of genital HPV among males aged 17-19 years using two cross sectional samples, the first obtained over 2014-2015 (period 1) and the second over 2016-2017 (period 2) (Table 1). Given the differing age groups that will have been offered vaccination over the four years, period 1 will provide baseline prevalence among males prior to the vaccination program – a prevalence that reflects herd immunity from pre-existing vaccination of females. In period 1, most 17-19 year old males will not have been offered the vaccine (Table 1). By contrast, in period 2, most 17-19 year old males will have been offered vaccination as part of the male vaccination program (Table 1).

2.4 Study flowchart



2.5 Study procedures

This study will recruit 17 to 19 year old males from universities and other sources including sexual health services. Potential participants will be identified by a nurse or doctor if they present to a health service or if they become aware of the study through advertising will discuss the study with a research nurse.

Eligibility criteria

- Male
- Aged 17 to 19*
- Residing in Australia from 12 years of age[#]
- Able to complete study requirements

Exclusion criteria

- Males who report sex with men in the past 12 months

*Must be aged 17, 18 or 19 years during the four year study period, that is, January 1 2014 through to December 30 2017.

[#]This is to ensure that males included in the study were present in Australia at the time HPV vaccination was offered.

Men who agree to the study will be asked to provide informed, written consent and undertake self-testing for genital HPV and a questionnaire will be obtained. Self-collection of the swab will be completed at the participants convenience using postal specimens that include a self-testing kit that is either given to participants attending services or posted out if recruitment is via advertising.

The questionnaire will capture:

- Demographic information such as age and education level.
- Detailed sexual history including: age at first sex; number and gender of sexual partners over different time periods; sexual practices including oral, anal and vaginal sex; and condom use.
- Relevant medical information such as history of genital warts, circumcision status, and smoking.

- History of previous HPV vaccination

HPV DNA sampling

Each man in the study will be asked to obtain a genital specimen which will be self-collected by participants using a swab on the glans penis, coronal sulcus, foreskin (if uncircumcised), and penis.

Laboratory testing for HPV DNA

Samples will be tested at the Regional HPV Labnet Reference Laboratory, Molecular Microbiology Department, Royal Women's Hospital, Melbourne. Cellular material will be pelleted in 1mL aliquots by centrifugation at 5, 000 ×g and resuspended in 200 µL PBS. Total DNA will be extracted on the MagNA Pure 96 using the MagNA Pure 96 DNA and Viral NA small volume kit (Roche Diagnostics GmbH, Penzberg, Germany).

Extracted DNA will be pre-screened to assess its integrity by quantitative PCR amplification of a 260 base pair product of the human beta-globin gene.[6]

Samples will subsequently be amplified for HPV L1 gene using consensus primers PGMY09-PGMY11[7] and amplicons detected using the PCR ELISA System (Roche Diagnostics GmbH, Penzberg, Germany). A generic probe for detection of the presence of any HPV sequences in the sample using biotin-labelled probes will be used to detect all mucosal HPV types. Samples that are positive by ELISA will be further genotyped by HPV Linear Array genotyping assay (Roche Molecular Systems, Pleasanton, California), involving PCR amplification of target DNA followed by nucleic acid hybridization and detection of 37 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 82v and 89).

Ethical approval

Ethical approval for this study will be obtained from each state in which recruitment is intended to occur. A NEAF will be submitted to the Alfred Hospital Research Ethics Committee, South Eastern Sydney Local health District ethics committee , Far North Queensland Human Research Ethics Committee, Royal Adelaide Hospital Committee, Tasmania Health and Medical Human Research Ethics Committee and South Metropolitan Health Service Human Research Ethics Committee. Site Specific Applications will be made for each site once NEAF approval has been given.

Men will not routinely be informed of their HPV results as HPV testing is not standard clinical practice, HPV is mostly self-limiting, does not cause symptoms and has no treatment if asymptomatic. Accordingly, routine provision of results would be likely to induce more stress among participants that is warranted.

2.6 Study duration

Timelines

This study will require 4 years to complete:

January 2014 – December 2015: approval of study and recruitment in period 1.

January 2016 – December 2017: recruitment during period 2, analysis and reporting.

Feasibility

Our group has a track record of successfully recruiting specific populations that are hard to reach for STI research. We have established strong links with several universities and institutions across Victoria from which 17-19 year old males could be recruited without difficulty and also have a network of clinical sites from which to recruit including the Melbourne Sexual Health Centre.

2.7 Statistical analysis

The primary outcome of interest will be the change in prevalence of quadrivalent vaccine types (6, 11, 16 and 18) among 17-19 year old men in the two time periods. The study will also provide data on the change in prevalence of non-vaccine types.

The required sample size for each year is dependent upon the expected prevalence of genital HPV and affects the precision of the prevalence estimates (95% confidence intervals, CI) in the two cross sectional samples. Different prevalence rates and 95%CI are shown for various sample sizes in Table 1.

Table 1: Estimated 95% confidence intervals for differing HPV prevalent rates and sample sizes

	Sample size (persons)				
HPV prevalence rate (%)	100	200	300	400	500
5	0.0186-0.1183	0.0256-0.0927	0.0293-0.0829	0.0316-0.0774	0.0333-0.0739
10	0.0516-0.1804	0.0637-0.1523	0.0695-0.1411	0.0732-0.1347	0.0758-0.1305

Previous estimates of HPV infection have been determined by investigators in our group for females but are not available for males.[4] A sample size of 200 males in each of the two periods would provide reasonable confidence intervals around expected prevalence rates for individual HPV types. This would require a total of 400 males for the entire four year study.

2.8 Specific Drug Supply Requirements

No study drugs will be used in this study.

2.9 Adverse Experience Reporting

Procedures for reporting will be included in the Study Agreement and be approved by the Alfred Hospital Research Ethics Committee.

2.11 References

1. Donovan *et al.* Quadrivalent Human Papillomavirus vaccination and trends in genital warts in Australia: analysis of national sentinel surveillance data. Lancet Infect Dis 2011; 11(1): 39-44.

2. Fairley CK *et al.* Rapid decline in presentations of genital warts after the implementation of a national quadrivalent Human Papillomavirus vaccination programme for young women. Sex Transm Infect 2009; 85: 499-502.

3. Brotherton *et al.* Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011; 377: 2085-92.

4. Tabrizi SN *et al.* Fall in Human Papillomavirus prevalence following a national vaccination program. JID 2012; 206: 1645-51.

5. Smith MA et al. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. Vaccine 2011; 29: 9112-22.

6. Resnick RM *et al.* Detection and typing of human papillomavirus in archival cervical cancer specimens by DNA amplification with consensus primers. J Natl Cancer Inst. 1990; 82(18): 1477-84.

7. Gravitt PE *et al.* Improved amplification of genital human papillomaviruses. J Clin Microbiol. 2000; 38(1): 357-61.

2.12 Publication Plan

The findings from this research will be presented at relevant international conferences and published in scientific peer reviewed medical journals.

2.13 CV of PI and Investigator group

A CV for PI Marcus Chen is provided.

2.13 Protocol Submission

This protocol has been submitted to MSD Australia.

Table 1: Age of boys who will be offered HPV vaccination via schools and community based programs by year, Victoria 2013-2017.*

Age	11	12	13	14	15	16	17	18	19	20	
2013											
2014											Period 1#
2015											
2016											Period 2#
2017											

*Dark grey squares indicate that boys within these age groups are currently being offered vaccination in the calendar year shown in the row. Light grey squares indicate the age of boys who have previously been offered vaccination for HPV in previous calendar years. Time limited vaccination of year 9 students and those aged 14 and 15 will occur in 2013 and 2014 only whereas ongoing vaccination will be offered to those in year 7 (which may include some 11 year olds) and those aged 12 and 13 years.

#The boxes with hatched lines indicate the age range of boys who will be recruited in Period 1 (2014-2015, n=200) and Period 2 (2016-2017, n=200).