THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
SCHOOL OF MEDICINE

HPV Vaccine

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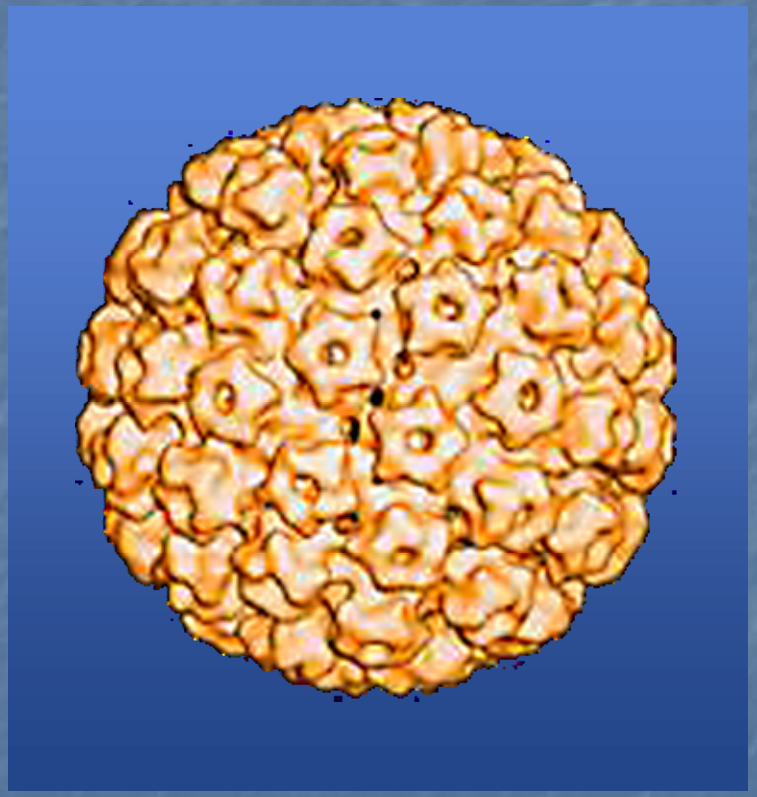
POSITIVE SEXUAL HEALTH
Family Planning

HPV

Nonenveloped double-stranded DNA virus[1]



- >100 types identified[2]
- ~30–40 anogenital[2,3]
  - ~15–20 oncogenic*[,2,3]
    - HPV 16 and HPV 18 types account for the majority of worldwide cervical cancers.[4]
  - Nononcogenic** types
    - HPV 6 and 11 are most often associated with external anogenital warts.[3]

*High risk; ** Low risk

1. Howley PM, Lowy DR. In: Knipe DM, Howley PM, eds. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229.
2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 4. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285.

Oncogenic HPV Types Are an Important Cause of Cervical Cancer

- Infection with oncogenic HPV types is the most significant risk factor in cervical cancer -association discovered 1975
  -found HPV 16 in Cx cancer tissue 1983
- Persistence HPV necessary (but not sufficient) cause of cervical cancer
- Analysis 932 specimens from women in 22 countries indicated prevalence of HPV DNA in Cx Ca worldwide is 99.7%.

HPV Subtypes

Women

HPV 6/11 90% genital warts+10% LSIL

HPV 16/18 25% LSIL

50% HSIL

70% Cx Cancer

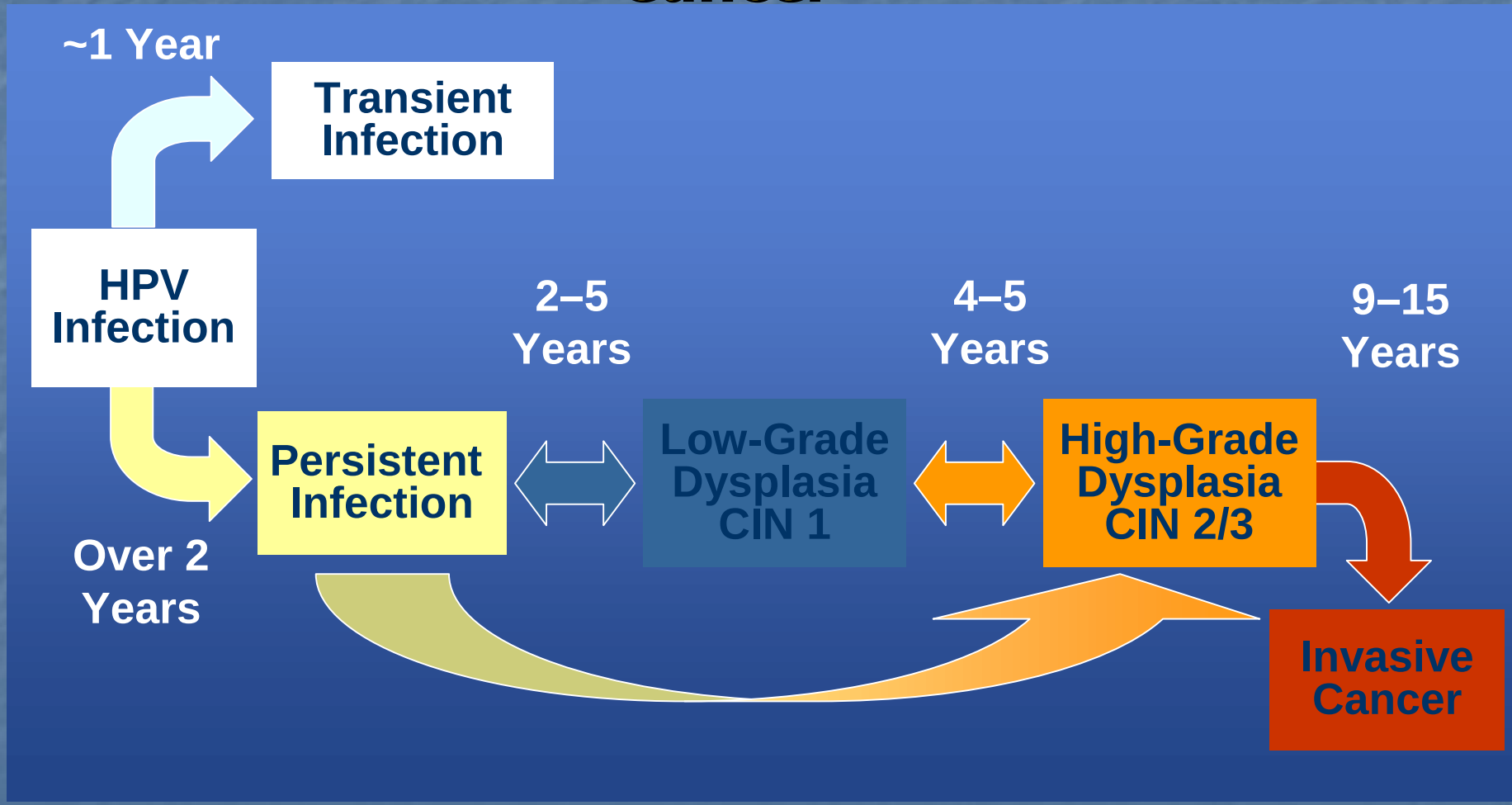
70% of other genital cancers

Men

HPV 6/11 90% genital warts+ transmission to women

HPV 16/18 60% anal cancer+ transmission to women

Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer[1]



1. Adapted from Pagliusi SR, Aguado MT. *Vaccine*. 2004;23:569–578.

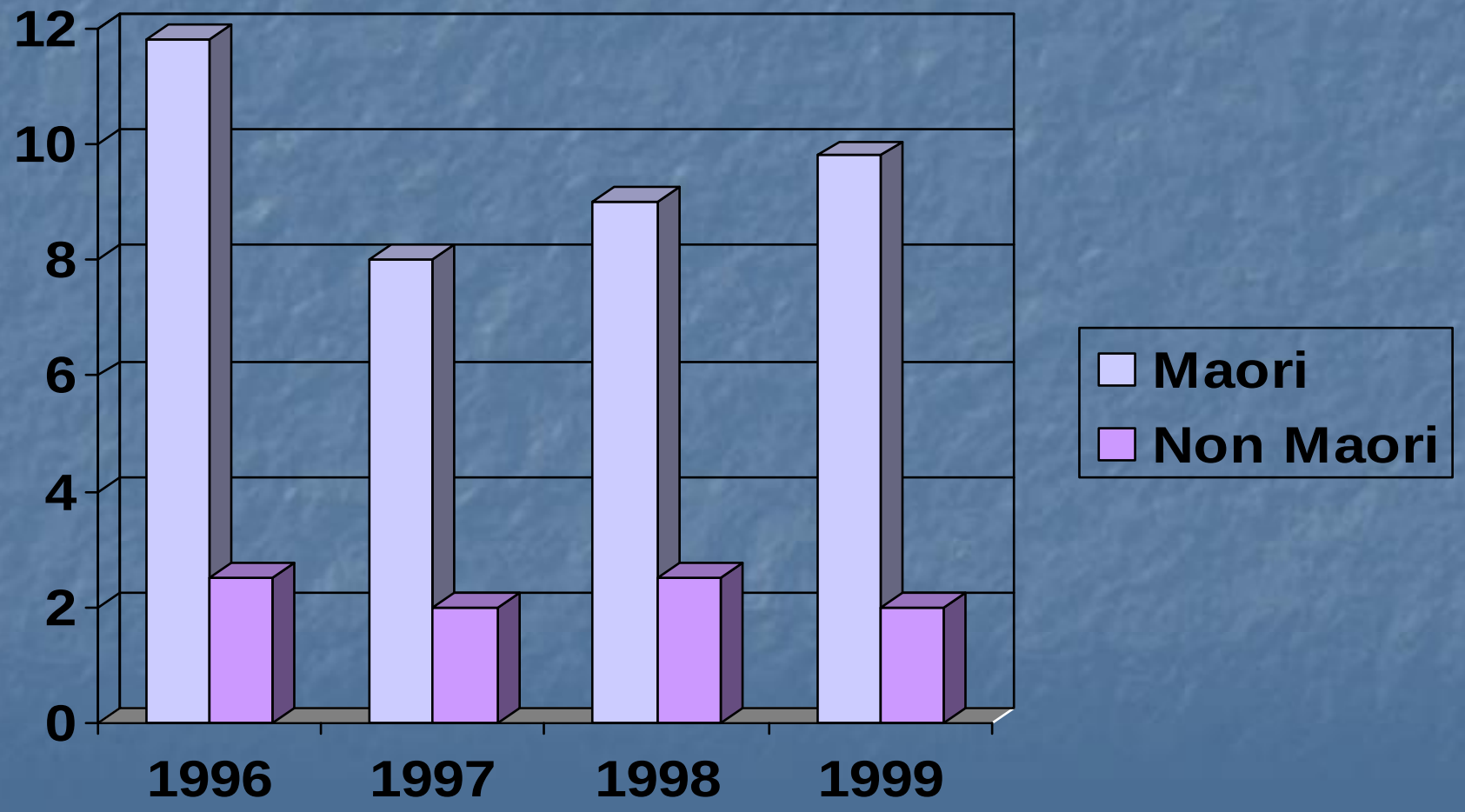
CERVICAL CANCER IN NEW ZEALAND

- Approximately 200 women diagnosed each year
- Approximately 70 die each year

Higher rates for:

- women over 40
- Maori women
- Pacific women

Cervical Cancer Deaths
per 100,000

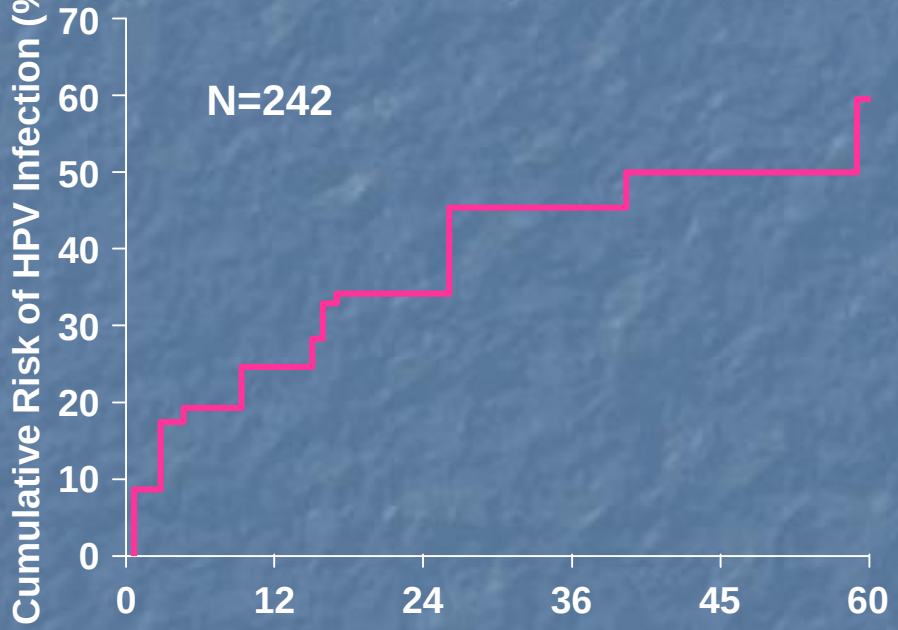


Mechanisms of HPV Transmission and Acquisition

- Sexual contact
  - Through sexual intercourse-**if SI at all can get HPV –even if only one sexual partner**
  - Genital–genital, manual–genital, oral–genital
  - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.
  - Condom use may help reduce the risk, but it is not fully protective.
- Nonsexual routes
  - Mother to newborn (vertical transmission- rare)
  - Fomites (e.g., undergarments, surgical gloves, biopsy forceps-? happens)

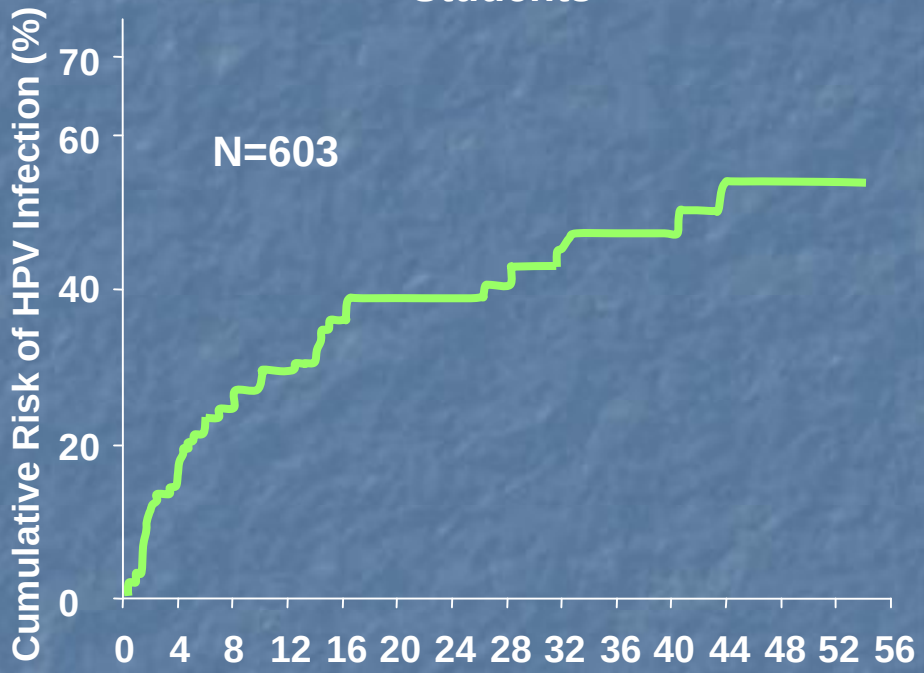
Risk of Acquiring HPV After First Intercourse

Cumulative Risk of Cervical HPV Infection in Female Adolescents With Only 1 Sexual Partner[1]



Adapted from Collins et al.[1]

Study of Female College Students[2]



Adapted from Winer et al.[2]

1. Collins S, Mazloomzadeh S, Winter H, et al. *BJOG*. 2002;109:96–98. 2. Winer RL, Lee S-K, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: Incidence and risk factors in a cohort of female university students. *Am J Epidemiol.* 2003;157:218–226, by permission of Oxford University Press.

HPV acquisition with first male sex partner

- 1 year-28.5%
- 3 year -50%
- Risk

  x3.6 if partner had 2 previous partners

  x8.5 if partner had 3 or more partners

Winer R et al JID 2008;197:279-282

HPV Persistence

- Cx is more vulnerable when immature to the effects of high risk HPV
- 98% HPV disappear with own immune response-2% persistent-? why
- Persistent infection: Detection of same HPV type two or more times over several months to 1 year.
- Persistence in women > 30 years
- If HPV persists though it is not the immune response that is involved in whether get progression to cancer

Average clearance of HPV + smears

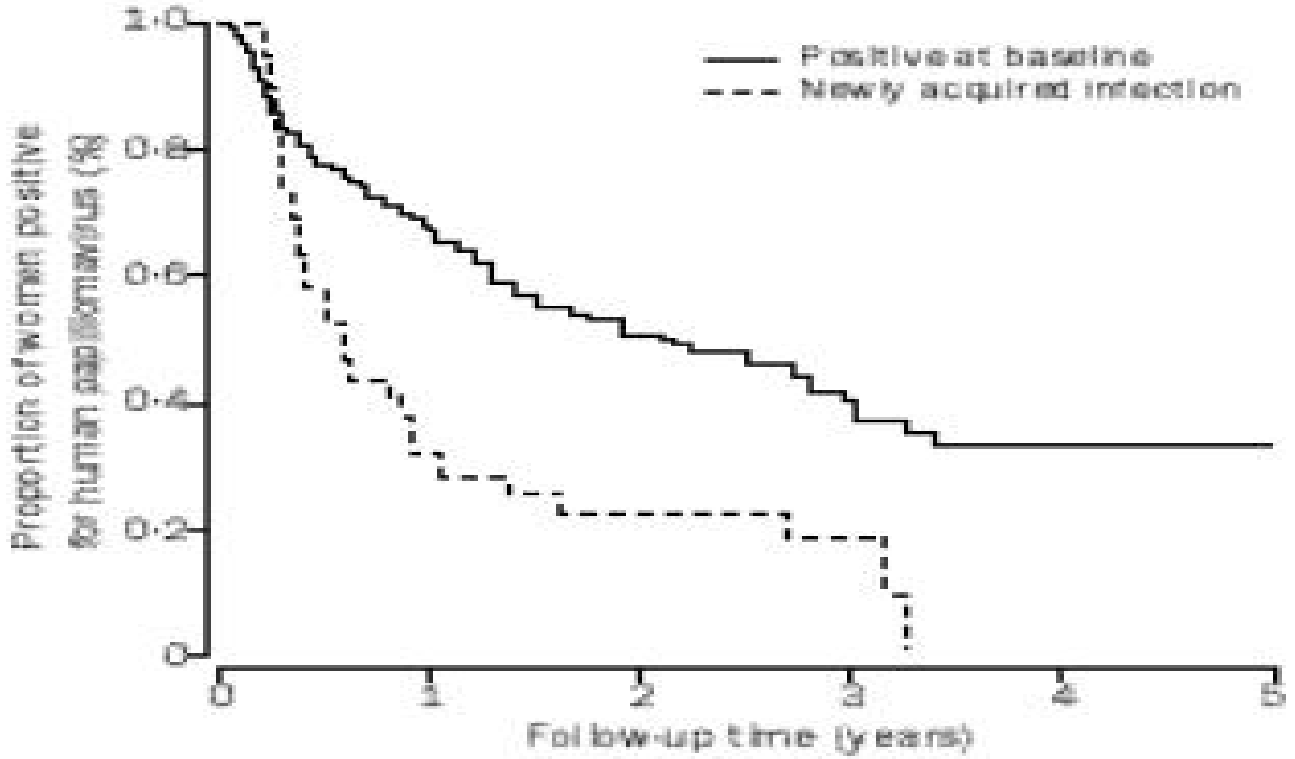


Figure 1: **Clearance of high-risk human papillomavirus in women with cytomorphologically abnormal smears and positive results for high-risk human papillomavirus at baseline**

HPV vaccine

- Made from Virus Like Particles-VLP
- Vaccine makes neutralising antibody to kill virus
- Non infectious and non oncogenic
- Will not cause established lesions to regress
- VLP-highly immunogenic-50 to 100 times more than natural infection
- High antibody levels at 5 years so far

Rationale for a Quadrivalent HPV (Types 6, 11, 16, and 18) L1 VLP Vaccine

- A prophylactic quadrivalent HPV
- Types 6, 11, 16, and 18 vaccine is expected to substantially reduce the burden of HPV-related diseases.
- Prevent 70% of cervical cancers
- This is = effective screening programme
- BUT STILL NEED CX SCREENING- 30% Cx cancers caused by types not in vaccine
- Will take 15 yrs to impact on HSIL and 30 yrs for Cx cancer rates

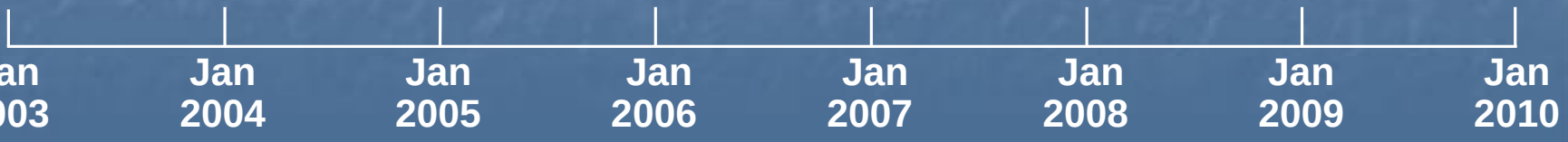
Surrogate end points of vaccine trials

- Not Cx cancer
- Antibody response
- LSIL and HSIL
- Genital warts

GARDASIL™ Clinical Program

- Phase II proof-of-principle
  HPV 16 vaccine
  Women 16–23 years of age
- Phase II GARDASIL
  Women 16–23 years of age
  - Year-5 booster dose evaluation
- GARDASIL Phase III efficacy studies
  Women 16–23 years of age
  - Duration of efficacy registry study
    Nordic region
- GARDASIL Phase III Adolescent Immunogenicity
  Both genders, 9–15 years of age
- Efficacy study in mid-adult women
- Male efficacy study

- ~29,000 subjects enrolled
- Ethnically diverse
- 33 countries



Vaccine Trial Results-Efficacy

Per protocol population

- 100% warts/precursor vulval lesions
- 98% prevention HSIL

Intention to treat-ie had HPV before vaccination or protocol violation

- 73% warts/precursor vulval lesions
- 44% prevention HSIL
- May also be some cross protection for non vaccine subtypes

Vaccine safety

- Gardasil clinical trials 11,000 young women
- Commonest side effect-injection site redness and pain and mild fever
- Licensed for use in more than 100 countries (age 9-26)
- US, UK and Australia have already started

Adverse events with Vaccine

- In February 2007 the Centers for Disease Control and Prevention (CDC) provided an update on adverse experience reports received since licensure of GARADSIL, in the United States.
- The CDC noted that 2.1 million doses of GARDASIL have been distributed in the U.S., and a total of 542 adverse experiences were reported into the VAERS database. The most common adverse experiences were injection site pain, dizziness, syncope (fainting), fever and nausea.

Serious adverse events

- <1% of persons
- Similar in vaccine and placebo groups
- Deaths

  7 placebo

  10 vaccine –none considered vaccine related

	Vaccine	placebo
Motor vehicle	4	3
Overdose Other Rx	3	
Suicide	1	2
VTE	1	1
Asphyxia		1
Cancer arrthymia	1	

Australian school

Following the GARDASIL immunization of 720 girls at Sacred Heart College Oakleigh approximately 25 of them presented to sick bay with headache and other minor symptoms such as nausea and dizziness. Of these 4 (aged 12-17 years) were sent to Monash Medical Centre for further examination.

- *One had chest pain and palpitations; she had a past history of these symptoms. She was discharged the same day.*
- *The second had hyperventilation parasthesiae and was sent home the same day.*
- *The third and fourth had neurological symptoms and were admitted. The fourth girl (17 years old) had reported progressive muscular weakness. Overnight both got better and were seen by the neurologist in the morning who diagnosed non-organic illness.*

What had happened?

- The consensus of the medical experts was that the symptoms experienced by the girls at the hospital were short-lived, and related to anxiety and/or hyperventilation. This was related to the vaccination process, not GARDASIL.
- Reports of fainting, parathesiae and feelings of numbness/tingling are not unusual in mass vaccination campaigns
- Common reactions in mass immunisation sessions, in schools particularly, are anxiety/ fear of needles/fear as a result of watching others being immunised

"The vaccines potential effects on 12 and 13 year old girls were unknown as they were not included in its major trial"

- The clinical trials in the adolescent populations (~2,700 girls and boys, 9 to 15 years) were conducted to assess immunogenicity and safety. In these trials GARDASIL was found to be highly immunogenic and well tolerated (Block et al 2006, Reisinger et al 2007).
- For ethical reasons, immunogenicity studies were conducted to bridge efficacy in females aged 16 to 26 years to the younger populations. To avoid conducting trials requiring genital procedures in boys and girls aged 9 to 15 years, immunogenicity trials were regarded as appropriate by regulatory authorities.

Detectable Serum Antibodies to HPV: Limitations as Marker of Infection or Natural Immunity

- *Antibody responses to natural HPV infection slow and weak*[1]
  - In a study of 588 women with HPV 16, 18, and 6 infections, median time to seroconversion was ~12 months after incident infection.
  - Did not occur in all women
  - Only 54%–69% seroconverted within 18 months of incident infection.
- *Antibody levels are inconsistently found in cervical cancer patients.*[2]
- *Antibody responses vary with HPV type.*[1]

1. Carter JJ, Koutsky LA, Hughes JP, et al. *J Infect Dis*. 2000;181:1911–1999. 2. Carter JJ, Madeleine MM, Shera K, et al. *Cancer Res*. 2001;61:1934–1940.

HPV Test: Inappropriate to Identify Population Eligible for Preventative HPV Vaccination

- HPV test detects ongoing infections, not cleared ones
  - A woman who has cleared infections with all types targeted by a vaccine and may be naturally immune to these types would still be considered eligible for vaccination.
- A woman infected with 1 type could still benefit from a vaccine's protection against other types.

NZ- HPV immunisation programme

- **HPV Vaccine details**
  Official launch day for the new $164 million HPV immunisation programme is Monday, 1 September. The Gardasil vaccine for human papillomavirus will be offered free to all young women aged 12 to 18 years. Stage one is where GPs get involved, with Gardasil being offered from September 1 to older teenagers born in 1990 and 1991 who are no longer at school. School-based vaccination for those aged 12 to 18 follows early in 2009. The vaccine involves three injections over a six-month period. The claiming process for practices would be handled in the same way as for other National Immunisation Schedule vaccines. For practices that didn't get the Ministry of Health fax last Friday, check out the link 'Letter to health care providers' in the backgrounder on the HPV announcement.
  http://www.moh.govt.nz/moh.nsf/indexmh/immunisation-schedule-hpv

MOH- HPV Immunisation website

- Gives overview of the programme
- HPV vaccination questions and answers
- Fact sheets re HPV vaccine

Links to

- Letter to health care providers
- Studies
- Other websites-IMAC and CDC
- Medsafe website has also detailed data sheet on Gardasil
  www.medsafe.govt.nz/profs/datasheet/g/Gardasilinj.htm

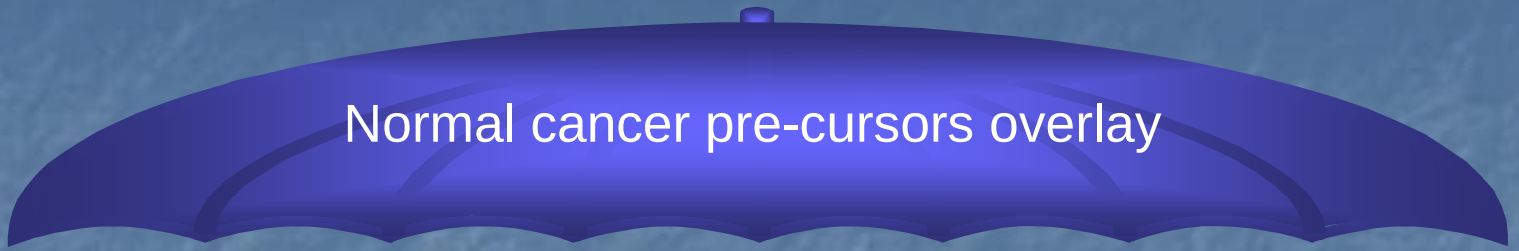
RFPs already out for:-

- Social marketing campaign
- Focus groups of

  54 parents –18 knew re vaccine

  30 young women-3 new re vaccine
- Primary care information/education re vaccine

Cervical cancer - what causes it?



Level of knowledge

Low	Mod	High
▪ Personal hygiene ▪ Endometriosis ▪ History of TOP ▪ Pregnancies/ children ▪ Wall of Cx gets thinner and over time *"gets rubbed away"* ▪ Excess bleeding	▪ Something to do with sexual activity	▪ STD causes warts and cervical cancer ▪ Affects cells in the cervix ▪ Early onset of sexual activity ▪ Multiple sexual partners ▪ Enzymes around the foreskin of a male

Bulk of interviewees

HPV - what is it?

- Overall, very low level of awareness
  - Most never heard of it!
  - Some associations

Level of knowledge

None **Low** **Mod** **High**

- Related to HIV
- Something to do with smears-Human Papa…. virus
- A sexually transmitted disease
- Linked to genital warts
- Linked to cervical cancer
- Virus that causes cervical cancer and genital warts

Bulk of interviewees

RNZCGP submission

- Short time frame
- Need for info to go out to young women
- Will Sept programme by GP for 18,19 year old be opportunistic or need recall
- Clarification if vaccine has to be offered in school first or can be done opportunistically at GP
- Are there enough practice nurses trained ?
- Time of training programmes often difficult for them to attend

The Patient's Point of View: HPV Vaccination Acceptability

- In a survey of 278 participants, parents' willingness to vaccinate their adolescent against sexually transmitted infections depended on severity of disease and vaccine efficacy rather than on sexual transmissibility.[1]
- UK studies 50% parents agreed should be provided without parental consent

1. Zimet GD, Mays RM, Sturm LA, Ravert AA, Perkins SM, Juliar BE. *Arch Pediatr Adolesc Med*. 2005;159:132–137.

Overall the studies opposition associated with:

- Concern may lead to sexual disinhibition
- Viewed their child to be at low risk of infection
- Concern re vaccine safety

Sexual disinhibition

- ? Give false sense of security
- Might initiate earlier sexual behaviour
- Not use condoms
- But still HIV, chlamydia, GC
- School based sex education/condom and ecp distribution-no evidence that these lead to earlier or risky sex

Advisory committee on Immunisation Practices (USA)

- Most effective 11-12 yr old prior to sexual activity
- Catch up 13-26 yr not previously vaccinated
- Dosing schedule 0,2,6 months
- Dose 1 and 2-separate by at least 4 weeks
- Dose 2 and 3-separate by at least 12 weeks
- If dosing schedule interrupted don't restart just give next dose ASAP

Zimet GD et al. Ann Rev Med 2008;59:222-36