Professor Margaret Stanley
University of Cambridge
Professor Margaret Stanley  
University of Cambridge

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margaret Stanley</td>
<td>Has acted as a consultant for SPMSD Lyon France, GSK Biologicals Rixensart Belgium and MSD Whitehouse Station USA</td>
</tr>
<tr>
<td>Date</td>
<td>April 2013</td>
</tr>
</tbody>
</table>
'Where to next with HPV vaccination? New strategies, new vaccines'.

Margaret Stanley
Department of Pathology
University of Cambridge
UK
HPV

- Non enveloped dsDNA virus, simple capsid of 2 proteins L1 and L2
- Common virus with >100 types identified
- Infects cutaneous and mucosal epithelia
- 30-40 infect the mucosal epithelia of women and men
  - 2 groups
    - low risk types causing warts
      - HPV 6,11
    - 13 high risk types causing cancer
      - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68
      - HPV 16,18 – most important
Estimated annual global burden of HPV associated disease in men and women

<table>
<thead>
<tr>
<th>Disease</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penile cancer</td>
<td>1,050</td>
<td></td>
</tr>
<tr>
<td>Vulvar &amp; vaginal cancer</td>
<td>19,960</td>
<td>19,960</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>13,000</td>
<td>14,300</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>42,000</td>
<td>18,000</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>529,800</td>
<td></td>
</tr>
<tr>
<td>Genital warts</td>
<td>17,600,000</td>
<td>14,400,000</td>
</tr>
</tbody>
</table>
### Vaccine profiles

<table>
<thead>
<tr>
<th></th>
<th>HPV 16/18 vaccine</th>
<th>HPV 6/11/16/18 vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>GlaxoSmithKline</td>
<td>MSD</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>Per dose 0.5 mL</td>
<td>Per dose 0.5 mL</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AS04: Al(OH)$_3$</td>
<td>Aluminium sulphate®</td>
</tr>
<tr>
<td></td>
<td>*MPL®</td>
<td>500 µg 225 µg</td>
</tr>
<tr>
<td></td>
<td>50 µg</td>
<td></td>
</tr>
<tr>
<td><strong>Antigens</strong></td>
<td>L1 HPV 16 20 µg</td>
<td>L1 HPV 6 20 µg</td>
</tr>
<tr>
<td></td>
<td>L1 HPV 18 20 µg</td>
<td>L1 HPV 11 40 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1 HPV 16 40 µg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1 HPV 18 20 µg</td>
</tr>
<tr>
<td><strong>Expression system</strong></td>
<td>Hi-5 Baculovirus</td>
<td>Yeast</td>
</tr>
<tr>
<td><strong>Schedule</strong></td>
<td>Intramuscular 0, 1, 6 mths</td>
<td>Intramuscular 0, 2, 6 mths</td>
</tr>
</tbody>
</table>

**Bivalent**

**Quadrivalent**

*MPL 3-O-deacylated-4’-monophosphoryl lipid A*
Prophylactic HPV vaccines

Efficacy

Effectiveness
## Phase III Randomised Control Trials (RCTs)

### End of Study: Per Protocol Efficacy Populations

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Quadrivalent</th>
<th>Bivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WOMEN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mean Follow up</em></td>
<td>42 months</td>
<td>42 months</td>
</tr>
<tr>
<td><em>Prophylactic Efficacy</em></td>
<td>% 95%CI</td>
<td>% 95%CI</td>
</tr>
<tr>
<td>HPV16/18 CIN2</td>
<td>100 (95,100)</td>
<td>95 (88,98)</td>
</tr>
<tr>
<td>HPV16/18 CIN3</td>
<td>97 (88,100)</td>
<td>92 (67,91)</td>
</tr>
<tr>
<td>HPV16/18 AIS</td>
<td>100 (31,100)</td>
<td>100 (-8,100)</td>
</tr>
<tr>
<td>HPV 16/18 VIN3/VaIN3</td>
<td>100 (83,100)</td>
<td>Not reported</td>
</tr>
<tr>
<td>HPV6/11/16/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIN1/VaIN1</td>
<td>100 (86,100)</td>
<td>Not a target</td>
</tr>
<tr>
<td>EGL</td>
<td>99 (97,100)</td>
<td>Not a target</td>
</tr>
<tr>
<td><strong>WOMEN 25–45 yrs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/11/16/18 PI/CIN/VIN/VaIN</td>
<td>89 (78,95)</td>
<td></td>
</tr>
<tr>
<td><strong>MEN 16–23 yrs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16/18/6/11 EGL (MSW)</td>
<td>90 (69,98)</td>
<td>No studies</td>
</tr>
<tr>
<td>HPV 16/18/6/11AIN (MSM)</td>
<td>78* (40,93)</td>
<td>No studies</td>
</tr>
<tr>
<td></td>
<td>91+ (64,99)</td>
<td>*pre-specified +post hoc analysis</td>
</tr>
</tbody>
</table>

**DATA FROM**
- Lehtinen Lancet Oncol 2012 13:89
- Dillner et al 2010, BMJ 341:3493
- Guiliano 2011 NEJM364:401
- Palefsky 2011 365:401
Australia: Near disappearance of genital warts after commencement of national HPV program

Almost 90% decline in new cases of genital warts in both men and women < 21 yrs old

1. Read et.al., Sex Transm Infect 2011; 87:544e547. doi:10.1136/sextrans-2011-050234
A relative reduction of ~50% of high grade abnormalities (HGA) was observed in women <18 years, post vaccination vs. pre vaccination, less than 3 years after the introduction and the trend continues. Similar early trends have been observed in the US.

Differences in human papillomavirus (HPV) genoprevalence between prevaccine and postvaccine populations. *P < .05 for difference in percentages between groups.

Current issues

• Alternative immunisation schedules

• Gender neutral vaccination

• Next generation prophylactic vaccines
Why consider alternative dosing regimens?

Cost Reduction
   administrative costs
   vaccine costs

Difficulty of delivering 3 doses over 6 months

Immunogenicity in young adolescents
**Quadrivalent HPV Vaccine Phase III Adolescent Immunogenicity Study**

*Neutralizing Anti-HPV GMTs* at Month 7

- Anti-HPV 6 (HPV 6 mMU/mL)
  - Females 10–15 Years of Age
  - Males 10–15 Years of Age
  - Females 16–23 Years of Age
- Anti-HPV 11 (HPV 11 mMU/mL)
- Anti-HPV 16 (HPV 16 mMU/mL)
- Anti-HPV 18 (HPV 18 mMU/mL)

*GMT = geometric mean titers*

Age Specific Neutralizing HPV-6 Antibodies 1 Month Post-Vaccination

PPE population*
Neutralizing anti-HPV 6 GMTs at month 7

*Inclusive of five study protocols; all GMTs measured using cLIA
**2 versus 3 dose HPV vaccine study**  
Phase II post licensure randomised control multicentre study (NCT00501137)  
3 Canadian provinces PI Dr Simon Dobson BC

### Trial design

- **Sample Size**  
  N=825

- **Study group 1**  
  9-13 year olds females  
  N=260
  - Study arm, Gardasil™ 0 and 6 months

- **Study group 2**  
  9-13 year old females  
  N=260
  - Control arms, Gardasil™ 0, 2 and 6 months

- **Study group 3**  
  16-26 year olds females  
  N=305
  - Primary outcome: Anti-HPV 16 and 18 GMT, t = 7 months
GMTs
Group 1
2D 9-13yrs
Group 2
3D 9-13yrs
Group 3
3D 16-26yrs
<table>
<thead>
<tr>
<th>Month</th>
<th>HPV type</th>
<th>Age yrs</th>
<th>Dose</th>
<th>GMT 95% CI</th>
<th>GMT ratio 3:2 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>HPV 16</td>
<td>15-25</td>
<td>3 dose n=111</td>
<td>10322, 8329, 12792</td>
<td>0.93, 0.68-1.28</td>
</tr>
<tr>
<td>7</td>
<td>HPV 18</td>
<td>15-25</td>
<td>3 dose n=114</td>
<td>4262, 3572, 5084</td>
<td>0.77, 0.59-1.01</td>
</tr>
<tr>
<td>24</td>
<td>HPV 16</td>
<td>15-25</td>
<td>3 dose n=101</td>
<td>1865, 1505, 2311</td>
<td>1.10, 0.81, 1.49</td>
</tr>
<tr>
<td>24</td>
<td>HPV 18</td>
<td>15-25</td>
<td>3 dose n=103</td>
<td>728, 588,900, 702</td>
<td>1.04, 0.75, 1.43</td>
</tr>
<tr>
<td>24</td>
<td>HPV 16</td>
<td>9-14</td>
<td>2 dose n=65</td>
<td>11067, 9190, 13328</td>
<td>0.93, 0.68-1.28</td>
</tr>
<tr>
<td>24</td>
<td>HPV 18</td>
<td>9-14</td>
<td>2 dose n=64</td>
<td>5510, 4646, 6535</td>
<td>0.77, 0.59-1.01</td>
</tr>
<tr>
<td>24</td>
<td>HPV 16</td>
<td>9-14</td>
<td>2 dose n=64</td>
<td>1702, 1416, 2045</td>
<td>1.10, 0.81, 1.49</td>
</tr>
<tr>
<td>24</td>
<td>HPV 18</td>
<td>9-14</td>
<td>2 dose n=63</td>
<td>728, 588,900, 702</td>
<td>1.04, 0.75, 1.43</td>
</tr>
</tbody>
</table>
Unresolved issues

Duration of protection: only data on duration comes from 3 dose regimens

No immune correlate

Kinetics of antibody response in 2dose versus 3 dose poorly known

Rudimentary data on antibody affinity and avidity maturation
HPV vaccination in men
HPV is a Potent Carcinogen causing Multiple Related Cancers in Men and Women

Annual number of new cancer cases calculated based on crude incidence rates from IARC database (1998-2002) and population estimate Eurostat 2008; estimate Globocan 2008 for cervical cancer; published HPV prevalence rates were applied (for Europe, when available) Genital warts estimates based on incidence rates in UK, HPA 2007
Increasing Incidence of Penile Cancer and High-Grade PIN in Denmark

Age-standardized incidence rates of penile cancer (all histologies), 1978-2008.

CI=confidence interval; PIN=penile intraepithelial neoplasia.
Increasing Incidence of Anal Cancer: Example of Scotland and England

- Since the 1970s, the incidence of anal cancer in Scotland has more than doubled in both sexes.
- Incidence rates in England from 1986 to 2003 also nearly doubled in both men and women.

Age-standardized incidence rates of squamous cell carcinoma of the anus by year of diagnosis (5-year moving averages) and sex; Scotland, 1975–2002.

Increasing Incidence of HPV-Related Tonsillar Cancer in Sweden

Study of all patients (N=120) diagnosed with tonsillar SCC in the County of Stockholm, Sweden, during 2003–2007

Estimated Standardized Incidence Rate

Calendar Years

## Estimated Cost Per QALY Gained of Male Vaccination

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Female Coverage (3-dose)</th>
<th>20-45%</th>
<th>50%</th>
<th>70- 75%</th>
<th>80- 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Taira, 2004</td>
<td>$41,000</td>
<td>-</td>
<td>$442,000</td>
<td>-</td>
</tr>
<tr>
<td>Cervical + Genital warts (M/F)</td>
<td>Elbasha, 2007</td>
<td>-</td>
<td>$24,000</td>
<td>$42,000</td>
<td>$128,000</td>
</tr>
<tr>
<td>Jit (UK), 2008</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$1,000,000</td>
</tr>
<tr>
<td>Cervical + Genital warts (M/F) + Non-cervical cancers (M/F) RRP (M/F)</td>
<td>Kim, 2009</td>
<td>-</td>
<td>$62,000</td>
<td>$91,000</td>
<td>-</td>
</tr>
<tr>
<td>Elbasha, 2010</td>
<td>$24,000</td>
<td>$27,000</td>
<td>-</td>
<td>$39,000</td>
<td></td>
</tr>
<tr>
<td>Chesson, Preliminary</td>
<td>$24,000</td>
<td>$43,000</td>
<td>$84,000</td>
<td>$192,000</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Chesson H. Presented at the Advisory Committee on Immunization Practices Meeting. February 24, 2011.
Cost Per QALY Gained Vaccinating 12-Yr-Old Boys, All HPV Outcomes—USA CDC Model

Cost effective

Coverage assumptions: refer to 3-dose coverage of females by age 26

Coverage ≈50%
Coverage ≈70%

Current cost per dose:
Public: $109
Private: $130

Error bars show the 5th and 95th percentiles of cost per QALY estimates over hundreds of model runs when varying numerous model parameter values simultaneously

Vaccine cost per dose (excluding administrative costs)

CDC=Centers for Disease Control and Prevention; QALY=quality-adjusted life year.


Adapted from Chesson H. Presented at the Advisory Committee on Immunization Practices Meeting. February 24, 2011.
The burden of HPV associated disease in men is equivalent to that in women in industrialised countries.

High vaccine coverage (>70%) in women should give herd immunity for MSW. This makes male vaccination not cost effective if vaccine cost per dose is high.

MSM are not protected in this scenario but targeting MSM for vaccination is likely to be ineffective, stigmatising, discriminatory. May threaten vaccine uptake in females.
Next generation vaccines
broad protection
cheap
Polyvalent HPV VLP vaccines

MSD Merck is conducting phase III clinical trials of an nonavalent vaccine comprising L1 VLPs of types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Advantages: Proven technology; potential for decreasing Cx Ca risk by 90% vs 70% for Garadsil.

Issues: Increased cost of production. Large efficacy trials to demonstrate increased efficacy.
Many Other 2nd Generation Candidates Are Being Developed

Protein:
• Alternative VLP production systems: E. coli, Pichia, Hansenula, Plants
• L1 pentameric subunits
• L2-polypeptides - many variations

Vectored:
• L1 recombinant AAV
• L1 recombinant Salmonella vaccine
• L1 recombinant Measles vaccine
• L1 AcHERV
Thank you
Using vaccine efficacy against persistent infection with data generated in the qHPV vaccine clinical trial in Australia

- models predict female-only vaccination will reduce HPV 6 incidence by:
  - 92\%\textsuperscript{1} and 80\% in females and males, respectively
  - 97\% and 95\% under female-plus-male vaccination

- Female-only vaccination is predicted to reduce HPV 16 incidence by:
  - 74\%\textsuperscript{2} and 42\% in females and males, respectively
  - compared to 81\% and 73\% under female-plus-male vaccination.

\textsuperscript{1} Donovan et al Lancet Inf Dis 2011
\textsuperscript{2} Tabrizi et al JID 2012
The 8 most common HPV types in CaCx

Courtesy Dr X Castellsague ICO
HPV 16/18 Prevalence By Age: Pre- vs. Post-immunisation Amongst Those Testing HR HPV Positive (England)

Estimated vaccination coverage

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pre-immunisation</th>
<th>Post-immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-18 years</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>19-21 years</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>22-24 years</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

HC2 positive tested by Linear Array (Howell-Jones et al, Vaccine, 2012). Luminex-based genotyping system.

British HIV Association
BHIVA

19th Annual Conference of the British HIV Association (BHIVA)

16–19 April 2013

Manchester Central Convention Complex