New prevention strategies vs Rotavirus and Human Papilloma Virus
Vaccination in the prevention of Rotavirus infection
Overview

- Features of natural infection with Rotavirus
- Vaccine development: choices and challenges
- Rotarix: clinical research results
- Conclusions
Estimated European incidence of rotavirus gastroenteritis (25 EU countries)

An estimated 3.6 million rotavirus episodes per annum occur amongst the 23.6 million children under 5 years in the EU, making gastroenteritis caused by rotavirus the single most frequent vaccine-preventable illness among young children in the EU.

Risk of event

- 1:14,000
- 1:54
- 1:7
- 1:1

End-point

- 231 deaths
- 87,000 hospitalisations
- 700,000 outpatient visits
- 2.8 million episodes at home

Transmission

• Faecal-oral route predominant mode of transmission\textsuperscript{1,2,3}
  – up to one trillion viral particles shed in faeces
  – shedding begins before symptoms and persists after illness
  – fomites on contaminated objects (e.g. toys) retain infectivity for several days

• Transmission still occurs despite improved sanitation\textsuperscript{4}

\textsuperscript{1} Fischer et al Vaccine\textsuperscript{2004; 22S:S49-S54},
\textsuperscript{2} Dennehy Pediatr Infect Dis J, 2000;19:S103–5;
\textsuperscript{3} Linhares and Breeee, Pan Am J Public Health 2000;8(5):305–330;
Epidemiology

Peak incidence of RV disease among children 6–24 months of age

US, Washington:
January 1974–July 1982

England and Wales:
January 1990–December 1994

Brandt et al, J Clin Micro 1983 18 71--78
Ryan et al, J Infect Dis 1996 174 S12--S18
Reoviridae

Family

Group (Seven)

Sub-group (Two)

Serotype

VP7

VP4

VP6

G (1-14)

P (1-8)


Modified from Parashar et al, Emerg Infect Dis 1998 4(4) 561–570
Four most common strains responsible for gastroenteritis (>93%):

- G1P[8]
- G2P[4]
- G3P[8]
- G4P[8]

Emerging strain:
- G9P[8]

European distribution of human group A rotaviruses

Pathogenesis

Rotaviruses adhere to the GI tract epithelia (jejunal mucosa)
- Atrophy of the villi of the gut
- Loss of absorptive area
- Flux of water and electrolytes
- NSP4 viral enterotoxin
- Enteric nervous system activation

**Immunity after infection**

- Natural rotavirus infection attenuates the severity of subsequent infections\(^1\)-\(^3\)
  - Infants become immune after 1–3 infections
  - Immunity leads to accelerated recovery from infection
  - Does not protect against re-infection or mild disease\(^5\)

- **Type of immunity**
  - Systemic - mucosal
  - Humoral - cellular

- **Serum IgA may be the best correlate of protection\(^4\)**

---

Development of rotavirus vaccines began in 1970’s
First rotavirus vaccine licensed in the US in 1998:
- Rotashield®
- Rhesus-based tetravalent human reassortant vaccine (RRV-TV)
- Withdrawn in 1999 due to causal link with intussusception (IS)

What is Intussusception?

• Bowel obstruction:
  – One segment of intestine folds inside the other
  – Intestine wall swells and bleeds

• Most common cause of intestinal obstruction in children less than 2 years old:
  – 90% unknown cause (idiopathic)
  – 10% related to intestinal mass
  – Male infants aged 3–9 months most at risk
  – Death rare if access to treatment prompt

Rotavirus Seasonal Hospitalization and IS cases in New York State

Seasonal distribution of hospitalizations for rotavirus diarrhea and IS among children aged 3–23 months, during 1993–1995

Rennels et al, Pediatr Infect Dis J 1998 17 924–925
Rotavirus Seasonal Incidence and IS cases in US

Seasonal distribution of rotavirus diarrhea and IS in children <3 years old

- Proportion of Cases (%)
- Month
- Rotavirus
- Intussusception

Chang et al Pediatr Infect Dis J 2002 21 97–102 (Southern California Kaiser Permanente Health Care Plan)
Vaccine development: choices and challenges

- Choice of the Rotavirus type
  - Inactivated or life attenuated virus
  - Human or animal/human

- Choice of the vaccine type
  - Oral or injection

- The safety challenge
  - Intussusception

- Complexity of the vaccination schedule
  - Di – Te – Per – HiB – HB – Polio (2-3-4 M)
  - Prevenar (2-3-4 M)

G1P8 (human – attenuated)

Oral

N = 63 000!

Co-ad studies
89-12 strain G1P[8] isolated from stools of a 15-month old boy in Cincinnati

Passaged 26 times in Primary African Green Monkey Kidney (AGMK)

Further Passaged in Approved AGMK

Further Passaged in Vero Cell Line & Cloning steps

Further passaged in Vero cell line

RIX 4414 vaccine lot

J Gamble Inst. Med. Research, Cincinnati

AVANT DynCorporation

GSK Bio

RIX4414 master seed
Goals of rotavirus vaccination

- Provide early protection, comparable to that conferred by natural rotavirus infection
- Protect against moderate/severe RVGE
- Prevent hospitalisation due to RVGE
- Reduce morbidity and socioeconomic burden
- Reduce any RV infection independant of the severity!
- Reduce the global incidence of rotavirus mortality
Rotarix: Phase I – II – III Studies

... a worldwide development
**Rota-023 - Safety Study Aims**

- Placebo-controlled, randomized double blind study (63,000)
- Randomisation : 1 : 1

**Primary Endpoint**
- Safety of RIX4414 with respect to definite IS occurring within 0 - 30 days after each of two vaccine doses

**Secondary Endpoint**
- Safety of RIX4414 with respect to definite IS from Day 0 to 2-3 months post dose 2

Ref: Vesikari T et al ESPID 2005, Abstract 31
Rotarix: no increased intussusception risk after vaccination

- Phase III trial involving over 60,000 subjects showed no increased risk of IS between Rotarix & placebo

<table>
<thead>
<tr>
<th>Timing of IS</th>
<th>Rotarix n ~ 31,000</th>
<th>Placebo n ~ 31,000</th>
<th>Relative risk IS Rotarix vs Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS cases within 31-day window</td>
<td>6</td>
<td>7</td>
<td>0.85 (0.30;2.42)</td>
</tr>
<tr>
<td>IS cases between dose 1 and 30-90 days post dose 2</td>
<td>9</td>
<td>16</td>
<td>0.56 (0.25;1.24)</td>
</tr>
</tbody>
</table>

- Overall safety vaccine: similar to placebo

Ruiz-Palacios et al NEJM 2006 (354(1)): 11-21
Rotarix tolerance evaluation (US – Canada)

- Placebo controlled randomised (1 : 1) study (N = 529)
- Tolerance : similar to placebo

Dennehy PH et al. Vaccine, 2006,24,3780-3781
Rotarix European efficacy study
(ESPID 2006, T Vesikari et al.)

• Espid – May 2006

Total cohort N=3,994
Rotarix European efficacy study (-036)  
(Vaccine : placebo 2:1 randomization)

Visit 1  
month 0

Visit 2  
month 1–2

Visit 3  
month 2–4

Visit 4  
month 15–16

Visit 5  
month 15–16

Visit 6  
month 21–22

September 04  
N = 3,994

Dose 1  
Dose 2

IA immuno/reacto  
Year 1 efficacy analysis

Year 2 efficacy analysis

Vesikari T et al. ESPID, May 3-5, 2006. Abstract 75 – oral presentation
## Efficacy results: European study (-036)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation RV GE</td>
<td>100 %</td>
</tr>
<tr>
<td>Severe RV GE</td>
<td>95.8 %</td>
</tr>
<tr>
<td>Any RV GE</td>
<td>87.1 %</td>
</tr>
<tr>
<td>RV GE medical interventions</td>
<td>92 %</td>
</tr>
</tbody>
</table>

Vesikari T et al. ESPID, May 3-5, 2006. Abstract 75 – oral presentation
**Efficacy results: long term protection (2Y) Latina (-023)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalisation RV GE</td>
<td>83 %</td>
</tr>
<tr>
<td>Severe RV GE</td>
<td>80.5 %</td>
</tr>
<tr>
<td>Hospitalisation Any GE</td>
<td>39.3 %</td>
</tr>
</tbody>
</table>

Velazquez et al. ICAAC Sep 2006.
Rotarix safety when co-administered

Solicited symptoms reported within 15 days post-vaccination, DTPa-IPV, Hib, PnC co-administered (N= 529)

- Fever ≥ 38 °C
- Cough
- Diarrhea
- Vomiting
- Irritability
- Loss of appetite
Immunogenicity of concomitant DTPa-IPV/Hib one month post-dose 3 (HBV given at 0, 1, 5 months)

HRV N ≈ 450
Placebo N ≈ 150

% seropositivity/seroprotection

D T PT FHA PRN HBV Hib Polio 1 Polio 2 Polio 3
Conclusions

• Rotarix has shown excellent protective efficacy results
  • 100 % vs RV GE hospitalisation
  • 95.8 % vs severe RV GE

• Rotarix has a good safety profile
  • Safety similar to placebo

• Rotarix is a live attenuated human rotavirus vaccine to be given orally, in 2 doses:
  • As of the age of 6 w
  • Minimum 4 weeks interval between the 2 doses
  • Vaccination completed by age of 6M

• Rotarix can be given with the classically administered pediatric vaccines
Cervical Cancer prevention: a new paradigm
Overview

• Cervical cancer: a viral cause

• Epidemiology of Cervical cancer

• Development of HPV vaccine

• Cervical cancer prevention: present and future
Cervical cancer - HPV : a long story !

- 1842 : absence of cervical cancer (CC) in nuns suggests role of sexual activity
- 1907 : experimental human transmission of cutaneous warts through cell free preparation
- 1974 : suggestion of role of HPV in CC
- 1983 : isolation of HPV type 16 from cervical pre-cancerous lesions and CC
- 1985 : detection of specific active viral genes in CC
- 1999 : confirmation of the “100 %” association of HPV and CC *

Human papillomavirus

- There are more than 200 types of HPV
- Small DNA-virus containing two strands of DNA within a spherical shell (capsid)
- +/- 30 types target genital mucosa
- 15 are “so called” high risk or oncogenic
- Low risk types cause benign genital warts

HPV capsids, approximately 55 nm in diameter

Image source: Dr Linda Stannard, UCT/Science Photo Library
Papillomavirus – phylogenetics

Target: skin

Genus
Alpha-papillomavirus

18, 39, 45
51, 56, 59
68, 82

Target: mucosa

16, 31, 33
35, 58, 73

HPV types in cervical cancer

Cervical cancer cases attributed to the most frequent HPV genotypes (%)

- HPV genotype 16: 53.5% (53.5)
- HPV genotype 18: 70.7% (17.2)
- HPV genotype 45: 77.4% (6.7)
- HPV genotype 31: 80.3% (2.9)
- HPV genotype 33: 82.9% (2.6)
- HPV genotype 52: 85.2% (2.3)
- HPV genotype 58: 87.4% (2.2)
- HPV genotype 35: 88.8% (1.4)
- HPV genotype 59: 1.3
- HPV genotype 56: 1.2
- HPV genotype 51: 1.0
- HPV genotype 39: 0.7
- HPV genotype 68: 0.6
- HPV genotype 73: 0.5
- HPV genotype 82: 0.3
- Other: 1.2
- X: 4.4

Genetics and structure of HPV

- The HPV genome is a single molecule of double-stranded, circular DNA

- **E6**: oncogene – inactivates p53 (tumour suppressor/DNA repair)

- **E7**: oncogene – binds to pRb (gene transcription inhibitor)

- **L1**: major viral capsid protein – immunogenic

- **L2**: minor viral capsid protein – immunogenic

Natural history of HPV infection

HPV infection

6, 11, other low-risk types
- Anogenital warts
  - Regression
  - Therapy

16, 18, other high-risk types
- Transient infection
  - CIN I/CIN II
- Persistent infection
  - CIN II/CIN III
  - Cancer
  - Regression

CIN = cervical intraepithelial neoplasia
Cytology of the cervix
squamocolumnar junction

The columnar and squamous cells

Uterus

Tall columnar cells

Flat squamous cells

Vagina

Squamocolumnar junction
Cytology of the cervix
transformation zone
Disease progression

Time Months Years

Normal epithelium
HPV infection; koilocytosis
CIN I
CIN II
CIN III
Carcinoma

Screening
Treatment

Persistent HPV infection

CIN = Cervical intraepithelial neoplasia
Protective immunological mechanisms

• Natural exposure to viruses usually results in:
  – cell-mediated responses and/or
  – production of specific antibodies

• But: oncogenic HPV types down-regulate production of cytokines essential for immune response\(^1,2\)

• Prior infection with an oncogenic HPV type does not automatically induce immunity against subsequent infection or reduce the risk of a HPV infection becoming persistent\(^3-5\)
  – The level of protection offered by natural exposure is variable

• After natural infection serum Ig can develop vs VLP\(^1\)

\(^2\)Stanley M. Vaccine 2006;24S1:S1/16–22;
\(^3\)Viscidi RP et al. Cancer Epidemiology, Biomarkers & Prevention 2004; 13: 324–7;
\(^4\)Thomas KK et al. J Infect Dis 2000; 182: 1097-102;
Overview

• Cervical cancer: a viral cause

• Epidemiology of Cervical cancer

• Development of HPV vaccine

• Cervical cancer prevention: present and future
New cases per year: ~ 500,000
Deaths per year: ~ 270,000

Region-specific mortality rates

Mortality from Cervix uteri cancer: ASR (World) (age 15-65+)

- W Europe: 3.4*
- USA: 2.3*
- SE Asia: 10.2*
- E Africa: 34.6*
- S America: 12.9*
- Australia: 1.7*

*Rate per 100,000 population (all ages).

CC incidence / mortality in Be Flanders

Belgium (data 2002)
- 667 new cases per year
- 326 deaths

Overview

- Cervical cancer: a viral cause
- Epidemiology of Cervical cancer
- Development of HPV vaccine
- Cervical cancer prevention: present and future
Composition of most vaccines

- Vaccine
  - Antigen
  - Adjuvant
GSK’s HPV 16/18 Candidate Vaccine

Antigen
20 µg HPV 16 L1 VLP
20 µg HPV 18 L1 VLP

Adjuvant System 04 (AS04)

Immunostimulant
50 µg MPL

Carrier
500 µg Al(OH)₃

Recombinant L1 protein
Self-assemble into virus-like particles
Resemble intact viruses
Non-infectious
AS04 : a new adjuvant?

- Included in Fendrix® : licensed
  - Hep B vaccine for renal dialysis patients

- In total : +/- 28 000 subjects received +/- 43 000 doses ASO4 containing vaccines up till now
AS04 induces high and persistent neutralising antibody levels

3 doses of vaccine administered at 0, 1 and 6 months

Statistically significant ($p<0.05$)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>GMT (EU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>700</td>
</tr>
<tr>
<td>12</td>
<td>600</td>
</tr>
<tr>
<td>24</td>
<td>500</td>
</tr>
<tr>
<td>36</td>
<td>400</td>
</tr>
<tr>
<td>48</td>
<td>300</td>
</tr>
</tbody>
</table>

- HPV 16/18 L1 candidate vaccine with AS04
- HPV 16/18 L1 candidate vaccine with alum

Anti-V5 (HPV 16)

Anti-J4 (HPV 18)

HPV 001 initial HPV efficacy study

- Double-blind, randomised, controlled trial
- Brazil, Canada and USA
- Women 15–25 years of age with ≤6 lifetime partners
  - Seronegative for HPV 16/18
  - DNA negative for high-risk types
- Vaccination schedule: 0, 1 and 6 months
- Follow-up: 18 months (extension phase up to 27 months)

HPV 001 study design

HPV 16/18 L1 Vaccine (AS04 adjuvant) | Placebo Al(OH)₃
---|---
Enrolled (N=1,113) | 
N=560 Intention-to-Treat Cohort (ITT) | N=553 Intention-to-Treat Cohort (ITT)

HPV 16 and HPV 18 efficacy endpoints
- Incident infection
- Persistent infection (6 months)
- Abnormal cytology and CIN lesions

GSK studies HPV 001 and HPV 007: Sustained protection up to 4.5 years

**Figure based on Harper DM et al. Lancet 2004; 364:1757–65.**

GSK studies 001 & 007 up to 4.5 years: First evidence of cross protection vs types 45 & 31

Incident infection with most common oncogenic types beyond 16 & 18

| HPV Type | Vaccine | | Placebo | | | Vaccine Efficacy |
| --- | --- | Event rate (rate per 100) (95% CI) | Event rate (rate per 100) (95% CI) | | % (95% CI) |
| | N | n | Rate | N | n | Rate | |
| HPV-45 | 528 | 1 | 0.1 (0.0-0.4) | 518 | 17 | 1.2 (0.7-1.9) | 94.2 (63.3-99.9) |
| HPV-31 | 528 | 14 | 0.9 (0.5-1.6) | 516 | 30 | 2.1 (1.4-3.0) | 54.5 (11.5-77.7) |
| HPV-33 | 529 | 12 | 0.8 (0.4-1.4) | 519 | 13 | 0.9 (0.5-1.5) | 8.6 (-117.3-61.9) |
| HPV-52 | 524 | 40 | 2.8 (2.0-3.8) | 515 | 48 | 3.5 (2.6-4.6) | 18.6 (-26.5-47.8) |
| HPV-58 | 529 | 14 | 0.9 (0.5-1.6) | 517 | 16 | 1.1 (0.6-1.8) | 14.0 (-87.9-61.1) |

Study not powered to evaluate cross protection against all individual types

Combined initial efficacy and extended follow up studies
### HPV types in cervical cancer

<table>
<thead>
<tr>
<th>HPV genotype</th>
<th>Vaccine types</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>53.5%</td>
</tr>
<tr>
<td>18</td>
<td>70.7%</td>
</tr>
<tr>
<td>45</td>
<td>77.4%</td>
</tr>
<tr>
<td>31</td>
<td>80.3%</td>
</tr>
<tr>
<td>33</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
</tr>
<tr>
<td>58</td>
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<td>35</td>
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<td>56</td>
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<td>39</td>
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<td>68</td>
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<tr>
<td>73</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Cancer cases attributed to the most frequent HPV genotypes (%)

GSK study HPV-007: Safety profile during extended follow up

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Vaccine N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with at least 1 adverse event reported</td>
<td>54 (15.4%)</td>
<td>81 (23.5%)</td>
</tr>
<tr>
<td>Adverse events reported</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td>New Onset Chronic Disease (NOCD)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with at least 1 NOCD event reported</td>
<td>10 (2.9%)</td>
<td>18 (5.2%)</td>
</tr>
<tr>
<td>NOCD events reported</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with at least 1 SAE reported</td>
<td>16 (4.6%)</td>
<td>19 (5.5%)</td>
</tr>
<tr>
<td>SAEs reported</td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

*Including auto immune diseases


ATP Safety analysis
Vaccination of older women?
**HPV acquisition and clearance rates over 3 years**

<table>
<thead>
<tr>
<th>Age (baseline)</th>
<th>Women initially HPV-</th>
<th>Women initially HPV+</th>
<th>Acquisition rate (%)</th>
<th>Clearance rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPV-</td>
<td>HPV+</td>
<td>HPV-</td>
<td>HPV+</td>
</tr>
<tr>
<td>21</td>
<td>56</td>
<td>10</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>31</td>
<td>73</td>
<td>12</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>41</td>
<td>72</td>
<td>11</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>51</td>
<td>262</td>
<td>71</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>463</td>
<td>104</td>
<td>70</td>
<td>19</td>
</tr>
</tbody>
</table>

Risk of persistent infection by age

% persistent HPV 16

Adapted from Castle P et al, JID 2005;191: 1808 -16
GSK study HPV-014: Immunogenicity in Women 15-55 years of age

- Open, age-stratified trial in Germany and Poland (N=666)

- Study objectives
  - **Primary objective:** To demonstrate non-inferiority of seroconversion rates to the HPV-16/18 vaccine
    - 26-45 (26-35 and 36-45) years (N=220) compared to 15-25 years (N=220)
  - **Secondary objective:** To demonstrate non-inferiority of seroconversion rates to the HPV-16/18 vaccine
    - 46-55 years (N=220) compared to 15-25 years

- 3 doses of HPV-16/18 vaccine at months 0, 1 and 6

- Study will continue up to 48 months; results presented are up to 12 months
Antibody levels in 15-25 year olds comparable to those observed in efficacy study

Antibody levels in 26-35 year olds comparable to those observed in efficacy study

Antibody levels in 36-45 year olds comparable to those observed in efficacy study

Antibody levels in 46-55 year olds comparable to those observed in efficacy study

Antibody levels substantially higher than those observed with natural infection

HPV-16 GMC EU/ml

Schwarz et al. ASCO 2006: Abstract 1008
Antibody levels in all ages comparable to those observed in efficacy study

**HPV-18**

- **Efficacy study**
- **15-25y**
- **26-35y**
- **36-45y**
- **46-55y**

Schwarz et al. ASCO 2006 : Abstract 1008
GSK study HPV-014: Antibody concentrations in initially seronegative and seropositive women

HPV-16

seronegative women
- 15-25 years
- 26-35 years
- 36-45 years
- 46-55 years

HPV-18

seropositive women
- 15-25 years
- 26-35 years
- 36-45 years
- 46-55 years

Month 7

Schwarz et al. ASCO 2006 : Abstract 1008
Immuno-bridging study in adolescents 10-14y vs 15-25y of age (HPV 012)

Dubin G et al. ICAAC 2005.
Overview

- Cervical cancer: a viral cause
- Epidemiology of Cervical cancer
- Development of HPV vaccine
- Cervical cancer prevention: present and future
Actual CC-screening

- Recommendations in terms of frequency and follow-up differ from country to country

- Be:
  - Start: 25 Y
  - Every 3 Y
  - Until: 60 Y if no new sex partner and nl test at 60

- Standard
  - Cytology is the standard for screening:
    - Classic cytology
    - Liquid based
  - HPV-testing used in case of abnormal cytology for further triage
Impact of screening on CC:
Age-specific incidence: Brazil vs UK

Age-specific incidence rates of cervical cancer in Brazil and the UK

Potential impact of the HPV 16/18 candidate vaccine

Potential reduction

- ICC (Invasive cervical cancer): 67–71%
- HSIL (High-grade squamous intraepithelial lesion): 52–60%
- LSIL (Low-grade squamous intraepithelial lesion): 14–25%
- ASC-US (Atypical squamous cells of undetermined significance): ~20%

ASC-US: Atypical squamous cells of undetermined significance;
L/HSIL: Low/high grade squamous intraepithelial lesion; ICC: Invasive cervical cancer
Future CC prevention strategies

**ACIP recommendation (www.CDC.gov. : 29-6-2006)**

- Vaccinate girls 11-12 Y
- Catch-up vaccination for 13-26 Y recommended
- Screening remains the same

**Considerations**

- Vaccination of older women:
  - HPV – acquisition rate remains high in older women
- CC Screening algorhythm:
  - frequency
  - HPV-test or cytology as screening tool
Thank You !