Nouveautés vaccinales

Dr Yves VAN LAETHEM
Service des Maladies Infectieuses
CHU Saint-Pierre, Bruxelles
Human Papillomaviruses

- Circular double stranded DNA viruses
  - 7000 - 8000 base pairs
  - Non-enveloped capsid consisting of 72 pentavalent capsomeres
- Up to 200 different genotypes

Classified according to:
- Tropism: Cutaneous or Mucosal
  - ≈30–40 genotypes infect anogenital mucosa
- Risk of neoplasia: Low risk or High risk
  - ≈20 genotypes cause cervical cancer

## Clearly defined pathogenic HPV types and related diseases

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples Types</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>1, 2, 3, 10, 27</td>
<td>Plantar and cutaneous warts</td>
</tr>
<tr>
<td>High Risk</td>
<td>5, 8</td>
<td>Epidermodysplasia verruciformis</td>
</tr>
<tr>
<td><strong>Mucosal</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Low Risk       | 6, 11, 42, 43, 44, 55 \*(common types)* | Condyloma acuminata  
Recurrent Respiratory (Laryngeal) Papillomatosis (JORRP)  
6-11 = 90% of genital warts\(^2\)  
Cervical lesions CIN 1 (4 to 25%)\(^3,5\) |
| High Risk      | 16, 18, 31, 33, 45, 35, 39, 51, 52, 55, 56, 59, 66 | Flat warts, Bowen's disease  
Cervical dysplasia and carcinoma  
16-18 = 70% of cervical cancer\(^6\)  
Carcinoma of penis, vulva, vagina, anus |

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5. Koutsy L *The American Journal of Medicine* 102,3-8, 1997;  
Mechanisms of HPV transmission and acquisition

- **Sexual contact**
  - Through sexual intercourse
  - 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 (eg, undergarments, surgical gloves, biopsy forceps)
    - Hypothesized but not well documented

- **Very variable progression**
  - Not possible to determine who will develop disease
  - 70% of sexually active women will get a Papillomavirus infection during their lifetime
  - May take many years to appear
  - Number of co-factors, identified and non-identified
  - Cervical Cancer: rare and late complication of HPV infection

70% of people will get a HPV infection during lifetime

Estimated prevalence of genital PapillomaVirus infection in a US population of men and women aged 15-49 years

An estimated 70% of sexually active people will be exposed to the virus at some point during their life.\(^{1,2,3}\)

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3. Syrjänen K et al. Sex Transm Dis 1990
4. n=11,851 cervical smears of Danish women (15-93 yrs), Sanofi Pasteur MSD, data on file
HPV and cervical mucosa – Normal Epithelium

Schematic Representation of Normal Stratified Squamous Epithelium

- Superficial zone
- Intermediate zone
- Basal zone
- Basement membrane
- Epidermis
- Dermis
Normal Cervix

HPV enters through a break in the epithelium
HPV infection

CIN 1
Cervical Cancer

CIN 3
CIN 1 – 2/3

CIN 1
Image courtesy of the family of Dr Renso Barrasso (deceased)

CIN 3
Image courtesy of Prof J Monsonego
Cervical cancer – Definition

Cervical cancer results from malignant transformation of the cells which make up the lining of the uterine cervix.

Malignant change most often occurs at the transformation zone.

Malignant changes to the cells lining the uterine cervix produce:

- Squamous epithelium
  - Squamous cell carcinoma (SCC)

- Columnar epithelium
  - Adenocarcinoma
  - Adenosquamous carcinoma
Place du cancer du col dans le monde

- 500.000 cancers par an
  \[ \Rightarrow 250.000 \text{ morts/an} \]

- Lié à des virus hautement prévalents dans la majorité des populations sexuellement actives dans le monde
Cervical cancer is the second most common cause of death from cancer among young women in Europe*

High mortality despite screening for early detection

- 33,500 women diagnosed with Cervical Cancer each year in Europe* , ¹
- 15,000 die (~45%) ¹ equivalent of 40/day or nearly 2/hour

* European Union (25 member states) plus Iceland, Norway and Switzerland
** Skin melanoma (7.5), Ovary (5.4), Thyroid (4.9), Colon/Rectum (4.4), Non-Hodgkin lymphoma (3.2), Hodgkin lymphoma (2.7), Lung (2.6), Corpus uteri (2.5), Brain-CNS (2.4), Leukaemia (2.3), Stomach (1.7), Kidney (1.3), Oral Cavity (0.7), Bladder (0.7), Pancreas (0.6), Liver (0.4), Other Pharynx (0.4), Multiple Myeloma (0.3), Larynx (0.2), Nasopharynx (0.2), Oesophagus (0.2)

Cervical Cancer Incidence – Belgium

Globocan 2002 – Belgium: 667 cases invasive cancer – 326 deaths
(http://www-dep.iarc.fr)

Cervix uteri (invasive and in situ), corpus uteri and ovary:
age-specific incidence in 2000-2001

Fig. 2. Age-specific incidence rates of cervical cancer in five European
countries. (With permission from: Bosch FX, de Sanjosé S. Chapter 1: Human
Cancer Inst Monogr 2003;31:3–14).
**HPV: Necessary cause for cervical cancer**

- **Papillomavirus is necessary to develop cervical cancer**
  - Virtually 100% attributable to Papillomavirus
    - Primary research Bosch (JNCI 1995): prevalence 93% HPV DNA (>1000 biopsies from 22 countries)
    - Re-analysis Walboomers (J Pathol 1999): HPV DNA in 99.7%
    - Delvenne (Vaccine 2001) HPV causes cancer in organotypic culture models
  - Environmental and other co-factors

- **HPV Infection and Cancer Risk**

<table>
<thead>
<tr>
<th>RR</th>
<th>HPV 18 &amp; adenocarcinoma</th>
<th>HPV 16 &amp; cervical cancer</th>
<th>HPV &amp; cervical cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hepatitis B & liver cancer (South-East Asia)
- Hepatitis B & liver cancer (Greece)
- Hepatitis C & liver cancer (Italy)
- Cigarettes & lung cancer

CIN - Current model of genital carcinogenic HPV on disease progression

- High grade dysplasia - CIN 2/3
- Low grade dysplasia - CIN 1
- Transient infection
- Variable can occur in <1 year
- Variable period ~2 years
- Invasive cervical cancer

Endpoint recommended by WHO** & FDA***

Normal cytology

* CIN = Cervical intraepithelial neoplasia
** Food and Drug Administration US
*** World Health Organisation

Human Papillomavirus types 6,11,16,18 are the 4 most common types affecting person’s health

### Short term

**HPV type Infection**

- **Types 16,18**
  - CIN 1 34%
  - VIN 1³
  - ValN 1³
- **Types 6,11**
  - Genital warts 90%

### Medium

- CIN 2/3, AIS 50–70%
- VIN 2/3, ValN 2/3³

### Long

- Invasive cervical cancer 70%
- Vulvar & vaginal cancers³

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Distribution HPV - Invasive Cervical cancer

Clifford G et al. Vaccine 2006
Proportion of cancers associated with HPV types

Munoz N et al. Int J Cancer 2004
## High variability screening Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Age range (years)</th>
<th>Interval (years)</th>
<th>% regularly screened</th>
<th>Cervical cancer Mortality/100,000$^4$ (0-64 yrs)</th>
<th>Cervical cancer Incidence/100,000$^4$ (0-64 yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium$^1$</td>
<td>25–64</td>
<td>3</td>
<td>59</td>
<td>2.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Denmark$^2$</td>
<td>23–59</td>
<td>3</td>
<td>75</td>
<td>3.3</td>
<td>11.4</td>
</tr>
<tr>
<td>England$^2$</td>
<td>25–64</td>
<td>3 to 5</td>
<td>83</td>
<td>2.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Finland$^2$</td>
<td>30–60</td>
<td>5</td>
<td>93</td>
<td>1.2</td>
<td>3.6</td>
</tr>
<tr>
<td>France$^2$</td>
<td>25–65</td>
<td>3</td>
<td>69</td>
<td>2.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Germany$^2$</td>
<td>20–85</td>
<td>1</td>
<td>50</td>
<td>2.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Italy$^2$</td>
<td>25–64</td>
<td>3</td>
<td>53 -74</td>
<td>1.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Netherlands$^2$</td>
<td>30–60</td>
<td>5</td>
<td>77</td>
<td>1.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Spain$^{2,3}$</td>
<td>20–64</td>
<td>3 to 5</td>
<td>49.6</td>
<td>1.6</td>
<td>6.9</td>
</tr>
<tr>
<td>Sweden$^2$</td>
<td>23–60</td>
<td>3</td>
<td>83</td>
<td>2.2</td>
<td>7.4</td>
</tr>
</tbody>
</table>

### Maximum impact of screening limited:
- Never reach 100% coverage
- Need high compliance throughout adulthood
- Hi sensitivity = lo specificity and vice versa

Globocan 2002

BELGIUM

incidence 667 cases

mortality 326 cases

Genital warts – Epidermal changes

- Koilocyte
- Superficial zone
- Intermediate zone
- Basal zone
- Basement membrane
- Capillaries
- Hyperplasia
Progression from Papillomavirus Infection to Genital Warts

Within 20 months*

Initial HPV infection (mainly types 6, 11) → Continuing infection → Genital warts

CIN 1 LSIL

Cleared HPV infection

High incidence (1% adults 15–49 years)*

Distress, anxiety
Difficult to treat

Wart-causing HPV types found in up to 25% of LSIL/CIN**

Genital Warts - examples
Rising Incidence of genital warts

Male incidence x 8
Female incidence x 11

30 % of diagnoses among females under 20 years
Higher rates in males in age group 20-24 years

## Genital warts – Treatment options

### Treatment options for genital warts, with associated clearance and recurrence rates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type</th>
<th>Clearance rate (%)</th>
<th>Recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>End of first treatment course</td>
<td>After 3 months</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td><strong>Type</strong></td>
<td><strong>End of first treatment course</strong></td>
<td><strong>After 3 months</strong></td>
</tr>
<tr>
<td>Cryotherapy$^1$</td>
<td>Ablative</td>
<td>63–88</td>
<td>63–92</td>
</tr>
<tr>
<td>Electrocautery$^1$</td>
<td>Ablative</td>
<td>93–94</td>
<td>78–91</td>
</tr>
<tr>
<td>Imiquimod$^2$</td>
<td>Immune response modifier (IRM)</td>
<td>50–62</td>
<td>50–62</td>
</tr>
<tr>
<td>Interferon$^1$</td>
<td>IRM</td>
<td>19–62</td>
<td>36–62</td>
</tr>
<tr>
<td></td>
<td>Intralesional</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser therapy$^1$</td>
<td>Ablative</td>
<td>27–89</td>
<td>39–86</td>
</tr>
<tr>
<td>LEEP$^1$</td>
<td>Surgical</td>
<td>&lt;90</td>
<td></td>
</tr>
<tr>
<td>Podophyllin$^1$</td>
<td>Cytotoxic</td>
<td>32–79</td>
<td>22–73</td>
</tr>
<tr>
<td>Podophyllotoxin$^1$</td>
<td>Cytotoxic</td>
<td>42–88</td>
<td>34–77</td>
</tr>
<tr>
<td>Surgery/scissor excision$^1$</td>
<td>Surgical</td>
<td>89–93</td>
<td>36</td>
</tr>
<tr>
<td>Trichloroacetic acid$^1$</td>
<td>Ablative</td>
<td>50–81</td>
<td>70</td>
</tr>
</tbody>
</table>

In addition to causing cervical cancer and CIN, human papillomavirus infection is also associated with cancers of the vulva and vagina, VIN and VaIN.

The predominant HPV types associated with these diseases are HPV 6, 11, 16 and 18.

Data on the incidence of vulvar and vaginal cancers are not readily available for Europe.

Each year hundreds of women die from cancer of the vagina and vulva in the US.

If the disease is diagnosed early the patient has a better prognosis, however, the treatment options available can have considerable emotional and physical consequences.

In addition to causing cervical cancer,\(^1\) human papillomaviruses are also associated with many other malignant (cancerous) and benign (non cancerous) lesions including:

- Anal cancer and anal intraepithelial neoplasia (AIN)\(^3\)
- Penile cancer and penile intraepithelial neoplasia (PIN)\(^3\)
- Juvenile onset recurrent respiratory papillomatosis (JORRP)\(^4\)
- Some cases of more rare cancers such as oesophageal cancer and conjunctival cancer\(^3\)

Each year there are too many deaths from these human papillomavirus-related diseases\(^5\)

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Human Papillomavirus diseases start before and go beyond Cervical Cancer (estimated numbers of cases in women / year in Europe*)

- **2,000** Vulvar-vaginal cancers
- **~30,000** Pre-cancerous vulvar-vaginal lesions
- **~250,000** Genital warts

**Infection without detectable abnormalities**

- **33,400** Invasive Cervical cancer
- **163,000** Pre-cancerous cervical lesions (CIN\(^{1,2,3}\))
- **554,000** Potentially pre-cancerous cervical lesions (CIN\(^{1}\))

* 25 EU member states + Iceland, Norway & Switzerland  
** CIN = Cervical intraepithelial neoplasia  
*** Juvenile recurrent respiratory papillomatosis

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6. Daling et al. Gynecol Oncol 2002  
8. Dodge et al. Gynecol Oncol 2001  
12. UK Health Protection Agency. CDR Weekly. 2003  
5. Abramson AL et al. Laryngoscope 1987

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*~450 per day

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*~1,500 per day

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*~450 per day
### Types 6, 11, 16, 18 cause the vast majority of genital HPV diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases/year in Europe*</th>
<th>Estimated proportion 6, 11, 16, 18 related disease among HPV disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16,18</td>
<td>6,11</td>
</tr>
<tr>
<td>Cervical Cancer</td>
<td>~ 25,000 (^1,2)</td>
<td>~ 200,000 (^3,5)</td>
</tr>
<tr>
<td>Pre-Cancerous Cervical Lesions</td>
<td>~ 112,000 (^2,4)</td>
<td>~ 80,000 (^3,5)</td>
</tr>
<tr>
<td>Pot. Pre-cancerous Cervical Lesions</td>
<td>~ 200,000 (^3,5)</td>
<td></td>
</tr>
<tr>
<td>Vulvar-Vaginal Cancer</td>
<td>~ 1,900 (^6-8)</td>
<td>yet to be determined</td>
</tr>
<tr>
<td>Pre-Cancerous Vulvar-Vaginal Lesions</td>
<td>~ 24,000 (^7,9-12)</td>
<td>~ 1,500 (^13)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>&gt;225,000 (^14-16)</td>
<td></td>
</tr>
</tbody>
</table>

* 25 EU member states plus Iceland, Norway and Switzerland

** CIN = Cervical Intraepithelial Neoplasia

European Union endorsed the breakthrough in the prevention of Cervical Cancer on 20 sept 2006

Fast approval of Gardasil® (9 months of review)

Strong indications for Gardasil®

- Prevention of Cervical Cancer
- Prevention of Pre-cancerous Cervical Lesions (CIN*2/3)
- Prevention of Pre-cancerous Vulvar Lesions (VIN**2/3)
- Prevention of Genital Warts

Additional properties

- Efficacious against Potentially Pre-canc. Cervical Lesions (CIN*1)
- Reduction of Pre-cancerous Vaginal Lesions (VaIN***2/3)

[1] Indication of Gardasil in the European Union: Prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. Section 4.1 (Therapeutic Indications) of Summary of Product Characteristics, SPC

- Cervical intraepithelial neoplasia
- Vulvar intraepithelial neoplasia
- Vaginal intraepithelial neoplasia
Gardasil® Human Papillomavirus Vaccine (types 6,11,16,18)

Production

HPV virus:
L1 = external protein
L2 = internal protein

Production in yeast
(HPV L1 gene integrated in genome)
Saccharomyces cerevisiae

GARDASIL®
0.5 ml injected in 3 doses 0, 2, 6 months
Gardasil® combines innovation and experience to optimally balance efficacy, safety and supply

Innovation through a new principle in vaccination

➔ Virus-Like Particles (VLP)* mimic the virus and induce strong and persistent immune response
➔ AAHS** adjuvant further focuses the response and directs it to produce specific antibodies
➔ Clinically proven strong induction of immune memory¹

Experience drawn from millions of doses of well accepted vaccines

➔ Vaccines with AAHS adjuvant have proven high efficacy and good safety profile

* Empty shells made of viral protein but without any genetic material of the virus. They closely resemble the Human Papillomavirus but cannot cause disease.
** Amorphous Aluminium Hydroxyphosphate Sulfate, 225 μg of Aluminium

Up to 100% sustained efficacy – good safety profile – generally well tolerated in large clinical trials²,³

Need for an appropriate efficacy end-point (event that is counted as a case of the disease) to evaluate the difference between vaccinees and placebo recipients.

- Unethical and impossible to use invasive Cervical Cancer as an endpoint.
- FDA/EMEA and WHO agree that pre-cancerous Cervical Lesions are the preferred endpoint.

CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology).

Gardasil® Human Papillomavirus Vaccine (types 6,11,16,18) Study

Endpoints

<table>
<thead>
<tr>
<th>Short</th>
<th>Medium</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 years</td>
<td>4-5 years</td>
<td>10-20 years</td>
</tr>
</tbody>
</table>

- Persistent infection
- Low Grade Cervical Lesions
- Pre-cancerous Cervical Lesions
- Cervical Cancer

Recommended Endpoint
Stepwise development of Gardasil® to meet public health priorities


* United States' Centers for Diseases Control and Prevention's Advisory Committee on Immunization Practices
** for sexually active people
### HPV 16 Vaccine Proof-of-Principle 4 Year Follow-up Results

**Per-Protocol Efficacy Cohort**
**Median 48 Months After Completion of the Vaccination Regimen**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo Cases</th>
<th>HPV 16 Vaccine Cases</th>
<th>Vaccine Efficacy</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed persistant infection</td>
<td>92</td>
<td>0</td>
<td>100%</td>
<td>96-100</td>
</tr>
<tr>
<td>CIN 1</td>
<td>14</td>
<td>0</td>
<td>100%</td>
<td>71-100</td>
</tr>
<tr>
<td>CIN 2/3</td>
<td>12</td>
<td>0</td>
<td>100%</td>
<td>65-100</td>
</tr>
</tbody>
</table>

High efficacy against Cervical Cancer and other HPV diseases before and beyond Cervical Cancer in studies with ~25,000 women

<table>
<thead>
<tr>
<th>Disease related to types 6, 11, 16, 18 (primary endpoint)</th>
<th>Gardasil® per protocol efficacy analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical Cancer</strong> (CIN*2/3 and AIS**)</td>
<td>100% 95% CI [93,100](^1)</td>
</tr>
<tr>
<td>Pre-cancerous (CIN<em>2/3) &amp; Potentially pre-cancerous cervical lesions (CIN</em>1)</td>
<td>100% 97.5% CI [87,100](^2)†</td>
</tr>
<tr>
<td>Pre-cancerous vulvar lesions</td>
<td>100% 95% CI [41.4,100](^2)†</td>
</tr>
<tr>
<td>Pre-cancerous vaginal lesions</td>
<td>No cases in vaccine group(^6)</td>
</tr>
<tr>
<td>Genital warts</td>
<td>100% 95% CI [78.5,100](^2)†</td>
</tr>
</tbody>
</table>

In women exposed to one or more vaccine virus types, Gardasil® was still up to 100% efficacious against disease caused by the remaining types to which the women had not been exposed\(^3\)

* Cervical Intraepithelial Neoplasia  ** Adenoma Carcinoma in Situ

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\(^1\) Ault K, Abstract, European Cancer Conference (ECCO) November 2nd, 2005, Paris France
\(^2\) Sanofi Pasteur MSD, data on file, 2005
\(^3\) Ferris, D. Abstract, EUROGIN meeting, Paris, France, 26 April 2006
\(^4\) 95.2% (95% CI [87.2,98.7]) in the combined analysis of several clinical studies
\(^5\) 98.9% (95% CI [93.7,100]) in the combined analysis of several clinical studies
\(^6\) Current observation of 0 cases in the vaccine group vs. 5 cases in the placebo group suggesting 100% efficacy, not yet statistically significant
Protection induite par vaccin

- **Par production Ac**
  - IgG : à des taux > 100 fois les taux sur infection naturelle chez toutes les vaccinées
  - → pas utilité contrôler ces taux
  - IgM et A : taux et durée moindres

- **Immunité cellulaire : rôle (important) probable**
  - cf. pas de protection par infection naturelle
  - ou : rôle taux Ac ++ ?
  - Durée de la protection: au moins 5 ans

- ! Screening reste nécessaire !
Gardasil®: 5 year results confirm high and sustained efficacy

Antibody titre and clinical efficacy of Gardasil® over time

GMT (mMU/mL)

Neutralising antibodies (HPV type 16)

10,000

1000

100

10

0

7

12

18

24

30

36

54

60

1st

2nd

3rd

Dose

months

5 years

100% Clinical efficacy

100% Clinical efficacy

100% Clinical efficacy

* against infection, CIN (Cervical intraepithelial neoplasia) and genital warts due to HPV types 6, 11, 18; 5 yrs follow up (after dose 1) of a subset (241 women, vaccine & placebo) from a phase III efficacy study

Villa LL – Costa RL – Br J Cancer 2006
Sanofi Pasteur MSD, data on file, 2006
Quid de la protection des femmes déjà infectées?

- **Gardasil :**
  - HPV+/Ac+ : pas de protection démontrée
  - HPV+/Ac - : trend, avec 27 % protection < CIN1/3 et adénoC
  - HPV-/Ac+ : effet booster, avec $\uparrow$ Ac de 12 à 26 X à J 60

- **Si HPV+/Ac+ pour un des sérotypes :**
  n’empêche pas immunogénicité pour autres sérotypes vaccinaux
In clinical with ~25,000 women, Gardasil® has shown a very good safety profile and was very well tolerated.

- The most commonly reported adverse events were injection site reactions and fever.

- Fever >38.9°C (oral temperature) within 5 days post-vaccination visit was reported in 1.5% of the GARDASIL®-vaccinated population (n=6,040) compared to 1.1% in the placebo group (n=3,981).
Immunogenicity Bridge

Number of Subjects Evaluable (n)

<table>
<thead>
<tr>
<th>Age</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>68</td>
<td>129</td>
<td>166</td>
<td>141</td>
<td>166</td>
<td>148</td>
<td>109</td>
<td>85</td>
<td>137</td>
<td>440</td>
<td>511</td>
<td>624</td>
<td>576</td>
<td>564</td>
<td>400</td>
</tr>
</tbody>
</table>

Serum cLIA GMT with 95% CI, mMU/mL

Efficacy Program

Children - adolescents higher immune response than adults

Human Papillomavirus vaccination should start with those who would benefit most (comparable to the US CDC’s ACIP recommendation + recent VVOG guidelines).

- **Routine**: 9-12 years
- **Catch up**: 13-26 years
- **Could be considered later on**: 27-45 years

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Proportion of females harbouring Human Papillomavirus (any type) [%] against Age (years)

- **Pre-exposure**: Cannot screen adolescents
- **Peak exposure**: 15-18 years

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* United States’ Centers for Diseases Control and Prevention’s Advisory Committee on Immunization Practices
*** Vlaamse Vereniging Obstetric Gynaecologie
** for sexually active people
Long Term Follow-Up Study Through Nordic Registries

Denmark  Finland  Sweden  Norway  Iceland

Phase III Study Registry-Based Follow-Up

Study population
- 3.5 yr
- 6 yr
- 8 yr
- 10 yr

New subjects
- 2 yr
- 4 yr
- 6 yr

Timeline:
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
Cervarix (GSK)

- Vaccin bivalent 16-18, sur culture cellulaire d’insecte
- Adjuvant différent :
  - Sanofi: Hydroxyde d’aluminium
  - GSK: idem + ASO4
- Revendique taux Ac plus élevé/plus longtemps,
  - MAIS techniques ELISA différentes …

⇒ étude comparative des 2 vaccins va commencer

< immunogénicité sur 18-26 ans (+ autres sous groupes)
Protection croisée (sur PCR des sérotypes) après 6 mois montrée pour type 45 (95 %) et 31 (54 %) et 52

Données en attente chez Sanofi

Efficacité sur prévention infection persistante et prévention des lésions précancéreuses provoquées par 16 et 18 : 100 %
(si on prend en compte virus dans lésion et échantillons antérieurs)
ou 90% si
sur >18.000 femmes de 15 à 25 ans de 14 pays de 4 continents

Lancet juin 2007

NB: Recul de plus de 5 ans aussi quant au maintien efficacité
Meilleure immunogénicité chez 10-14 ans aussi (taux x2)
Papillomavirus vaccination and screening: A strong interaction in the future

Vaccination: little impact on pap smears for first 5–10 years

- Long natural history of disease

Vaccine recipients still need screening

- Vaccines targeted to cover 70% oncogenic HPV infections
- Screening = opportunity for vaccination

Screening target population will benefit from introduction of vaccination

- Increased HPV-cancer awareness \(\Rightarrow\) \(\uparrow\) screening
- Screening not 100% effective (coverage, sensitivity)
Risque « virologique »?

- Shift possible vers sérotypes cancérigènes non vaccinaux
  MAIS : 16 et 18 induisent le plus haut risque de dysplasie
  (suivi de 10 ans)

- ! Screening reste nécessaire !
Rotavirus

Prévention de la gastroentérite à rotavirus des petits enfants
Rotavirus

- Agents les plus fréquents de gastroentérite aigue (GE) de par le monde chez nourrisson et jeune enfant
- Chaque année : 125.105 cas et 500.000 décès (> 80 % dans PVD)
- Chez nous : léthalité très faible mais cause 15-50 % des GE → 1ère cause hospit et 2ème consultation chez les < 5 ans

- Rotavirus : virus ARN avec triple enveloppe protéique réassortiment assurant diversité++ des virus circulant
  MAIS 4 génotypes prédominants (> 90 % des hospit.)
  G1, G2, G3, G4, et émergence du G9 récente
Incidence sous estimée

? 15.200/100.000 enfants de < 5 ans en Europe
Mortalité 1/54.000

! Aspect infection nosocomiale USA : ¼ des diagnostics !

cf. étude européenne : 90% GE nosoco sont virales

transmission par personnel à partir

environnement (dose infectante faible/

excrétion virale++)

Belgique : 6-7.000 hospit/an
Essentiellement entre 6 et 24 mois

- 95% infectés > 1 fois à l’âge de 5 ans
- avant 3 mois: asymptomatique car Ac maternels / allaitement / immaturité intestinale
- infection symptomatique très rares après 5 ans car immunité s’accroît à chaque épisode

Avec impact essentiellement sur qualité de vie des enfants / parents
**Paediatric Rotavirus Gastroenteritis can lead to severe consequences**

- Hits when infants are particularly vulnerable (6-24 months)\(^1\)
- No known risk factors\(^1\)
- Unpredictable evolution of symptoms & severity\(^{1,2,3}\)
  - Overnight, a seemingly mild PRG can become life-threatening
- >20 diarrhoea or vomiting episodes in 24 h not uncommon\(^3\)
- Severe dehydration may require hospitalisation

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[1] Raebel MS, Ou BS, Pharmacotherapy, 1999
Rotavirus is a leading cause of infant hospitalisation

Virtually all children will be infected at least once by the age of 2 to 3

In Europe* per year in children <5 yrs

- 231 deaths
- 87,000 hospitalisations
- 700,000 office visits
- 2,800,000 domiciliary episodes

Rotavirus represents 50-60% of emergency room visits & hospitalisations for paediatric gastroenteritis

Cases of Acute Gastroenteritis

- Hospital
  - RV+ 28%
  - RV- 61%
- Emergency room
  - RV+ 49%
- Office visits
  - RV+ 28%

REVEAL study 2004/2005, Epidemiology in seven European regions*

* European Union (25)

** in Belgium, England, France, Germany, Italy, Spain, Sweden

RV+ = Rotavirus positive
RV- = Rotavirus negative

References:
Paediatric Rotavirus Gastroenteritis (PRG) peaks in winter and leads to similar numbers of hospitalisation as RSV

PRG can overload hospitals at a time when they are already busy with RSV infections & bronchiolitis

Monthly distribution of RSV and rotavirus during 5 outbreak seasons in a Parisian hospital

Number of hospitalisations per year in Germany, France and the United Kingdom

* Respiratory Syncitial Virus

http://www.grog.org/cgi-files/db.cgi?action=bulletin_vrs;
who.int/vaccines-diseases/diseases/rotavirusdisease.shtml;
Sanofi Pasteur MSD, REVEAL**, final report 2006

** Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society, prospective multicentre, observational study in 7 EU regions, Oct 2004 to Sept 2006
There are several different rotavirus types that circulate in unpredictable proportions: from country to country...

Geographic distribution of rotavirus serotypes collected in selected European countries


Proportion of G-serotypes (%) per month in the seven REVEAL* study areas

Santos N, Hoshino Y, Rev Med Virol, 2005

* Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society
P van Damme, Oral presentation, 7th International Rotavirus Symposium, Lisbon, 12th June 2006 REVEAL
Prospective multicentre, observational study in 7 EU regions, Oct 2004 to Sept 2005
It is unpredictable which rotavirus type will infect a given child at a given time in a given region…

Variation in the distribution of rotavirus types in Europe¹

<table>
<thead>
<tr>
<th>Rotavirus type</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1P[8]</td>
<td>0%</td>
</tr>
<tr>
<td>G2P[4]</td>
<td>~50%</td>
</tr>
<tr>
<td>G3P[8]</td>
<td>100%</td>
</tr>
<tr>
<td>G4P[8]</td>
<td></td>
</tr>
<tr>
<td>G9P[8]</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of rotavirus serotypes (in %) as:
- collected in several European countries²
- observed in the 7 REVEAL* study areas³

... but 5 rotavirus types are responsible for ~98% of rotavirus disease


* Rotavirus gastroenteritis Epidemiology and Viral types in Europe Accounting for Losses in Public Health & Society
Efficacité des vaccins

- **Première génération (fin années ’70)**
  - souche non humaine, par voie orale : résultats faibles / variables
  - vaccin tétravalent (1998) : RotaShield
  - OK, mais retiré après 1 an car risque faible/démontré d’invagination intestinale : 1/38-58.000, ↑↑ si après 6 mois d’âge…

- **Deuxième génération (2006)**
  - Rota Teq : pentavalent réassortant
  - Rotarix : monovalent humain
Rota Teq

- Vaccin pentavalent basé sur G1, G2, G3, G4, G6
- Vivant atténué par voie orale, sur réassortant virus bovin / virus humain
- Trois doses à 4 sem. intervalle, entre 6 ème et 26 ème sem.
- Efficacité : globale 74 %
  sur formes sévères : 98 %
- Pas augmentation risque invagination
- Pas interférence avec vaccin hexavalent
RotaTeq® vaccination starts early and is completed before peak infection

Proportion of cases of Paediatric Rotavirus Gastroenteritis (%) per month of age

- Vaccination can start from 6 weeks
- Vaccination completed

P. van Damme, Oral presentation, 7th International Rotavirus Symposium, Lisbon, 12th June 2006 REVEAL Prospective multicentre, observational study in 7 EU regions, October 2004 to September 2005
RotaTeq®’s indication covers the 5 predominant disease-causing rotavirus

<table>
<thead>
<tr>
<th>Composition</th>
<th>5-type (pentavalent) G1, G2, G3, G4, P1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Covering the 5 predominant disease-causing rotavirus types</td>
</tr>
<tr>
<td>Efficacy</td>
<td>High &amp; consistent</td>
</tr>
<tr>
<td>Safety / tolerability</td>
<td>Good safety profile &amp; well tolerated</td>
</tr>
<tr>
<td>Use</td>
<td>Oral Fully liquid, ready-to-use</td>
</tr>
<tr>
<td></td>
<td>3 doses, ≥ 4 weeks apart</td>
</tr>
</tbody>
</table>

- from the age of 6 weeks
- G1, G2, G3, G4 & G9

- 98%* - 100%** prevention of severe disease
- 96%† - 100%†† reduction of hospitalisation

Efficacy & Safety studied in 70,000 infants

- One of the largest studies in vaccine history (REST#)
- Stringent protocol with high quality level

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* 95% CI [88.3, 100]
** 95% CI [95, 100]
† 95% CI [90.5, 98.2]
†† 95% CI [87.4, 100]

§ due to the serotypes G1, G2, G3, G4
$ due to the serotypes G1, G2, G3, G4, G9

# Rotavirus Efficacy and Safety Trial

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[3] Block SL et al. CDC, 2005
Rotarix

- Basé sur souche G1
- Vivant atténué; 2 doses à > 4 semaines, entre 6ème et 24ème sem.
- Pic excrétion virale à J7, sans maladie dans contacts

Plusieurs études montrent :

> 70% contre toutes formes
> 85% contre formes sévères et +/- 90% contre formes nécessitant hospitalisation

Protection croisée contre G3, G4, G9

Pas d’augmentation invagination

- Étude RDB en cours dans 6 pays européens;
  résultats préliminaires : >96 % protection sur formes sévères
Cout des infections à Rotavirus

- Dans une étude d’un des producteurs de vaccin :
  - coût pour l’Europe : 91.000.000 euros / an en hospitalisation

- Études coût/efficacité indépendantes en attente
Prévention du réveil localisé d’une infection à Herpès zoster
Zona

- Plus de 50% ont plus de 60 ans
- Complication la plus fréquente: neuropathie post zostérienne
dont la fréquence augmente avec l'âge
qui peut durer des années
pas (bien) prévenu par traitement antiviral (au contraire sympt. aigus)

- Lié à diminution immunité cellulaire spécifique avec l'âge
- Zona suscite booster naturel: rares récidives si immunocompétents
Zostavax (Sanofi Pasteur)

- Vaccin vivant atténué; 14 fois plus puissant que vaccin Varicelle
  
  Etude RDB sur 38.500 patients de > 60 ans (NEJM 2005)
  
  Sur suivi médian de 3,1 ans:
  - Zona: 315 versus 642 (-51%)
  - Névralgies post zoster: 27 versus 80 (-66%)

- Effets secondaires plus fréquents dans groupe vaccin, mais
  mineurs à modérés

  Pas en Belgique avant 2ème moitié de 2008
Vaccin méningo conjugué A/C/Y/W135

- Cf. vaccin conjugué C
  - vaccination large dans nombreux pays européens, dont Belgique.
  - diminution drastique du nombre de cas / modif. épidémiologiques.
    (49% cas en 2001, 10% en 2005)

- Cf. vaccin polysaccharidique A/C/Y/W135:
  - inadéquat chez nous car:
    - seul C réellement présent
    - protection limitée dans temps (3 ans) et âge (> 2 ans) cf.polysacch.
      impliquant revaccination/ diminution (significative?) taux Ac induit

Employé (presque) uniquement, en Europe, pour vaccination :
  voyageurs dans ceinture des méningites / pèlerins Hajj-Omrah
Menactra (Sanofi Pasteur)

- Vaccin conjugué quadrivalant (conjuguaision à toxoide diphtérique)
- Induit immunité long cours (plus de 8 ans au moins)
- Evite portage
- Recommandé en routine depuis 2005 aux USA par ACIP, pour 11-12 ans, puis 11-18 ans, ainsi que de 19 à 55 ans si risque accru.
  (cf.depuis ’97-2000: 1/3 cas sont Y et 1/3 C)
- Associé à syndrôme de Guillain Barré (risque?)
- Intérêt en Belgique?

  Souches Y et W135 : 2 et 4% du total, stables en nombre absolu
  (↑en nombre relatif)
Vaccin antipneumococcique conjugué 10 ou 13 valents

Cf. activité du vaccin 7 valents clairement montrée:

- diminution des infections invasives de enfant ET des adultes (protection de groupe)
- diminution des souches R aux AB

MAIS: - shift vers souches NON vaccinales
- adéquation insuffisante pour épidémio adulte

Les deux nouveaux vaccins (GSK et Wyeth):

- étendent souches couvertes pour enfants
- couvrent de 75 à 85% des souches invasives de l’adulte

Phases 3 en cours/programmées
Et le futur plus lointain…

- Vaccin S. pyogenes
- Vaccin S. aureus, P. aeruginosa, C. difficile…
- Vaccins CMV, EBV, … (HIV…)
  Désillusion récente pour HCV…
- Vaccin P. falciparum: existe (Malarix), à améliorer
  < % protection, groupes d’âge,…
- Vaccin M. tuberculosis (autre que BCG…)
- MAIS aussi vaccins avec « nouveaux « adjuvants/techniques (ADN,…)
  à application muqueuse (le 1er: Influenza)
  thérapeutiques (HIV,…)
  oncologiques