Vaccination against Herpes viruses

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Vaccination against Herpes viruses

• In clinical use:
  - Varicella Zoster Virus

• In development:
  - Cytomegalovirus
  - Herpes Simplex Virus
  - Epstein-Barr Virus
Vaccination against Herpes viruses

• In clinical use:
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Some issues in the development of vaccines against Herpes viruses

• Wide spectrum clinical manifestations and pathogenic mechanism

Development of a vaccine has to be tailored to the objective of the intervention (prevention of infection, transmission, disease, complication...
The objectives of vaccination against the different Herpes viruses vary:

- **Varicella Zoster Virus:**
  - Prevention of primary infection: varicella
  - Prevention of reactivation: zoster

- **Cytomegalovirus:**
  - Prevention of transmission: congenital infection
  - Prevention of illness in immunocompromised individuals

- **Herpes Simplex Virus:**
  - Prevention of primary infection: genital herpes
  - Prevention of reactivation: genital herpes

- **Epstein-Barr Virus**
  - Prevention primary infection: IM and PTLD
  - Therapeutic vaccines against EBV-associated malignancies
Some issues in the development of vaccines against herpes viruses

- Role of antibodies as well as cell mediated immunity in the defenses against Herpes viruses

Live attenuated vaccines
Adjuvant systems inducing strong antibody as well as CMI responses
Some issues in the development of vaccines against herpes viruses

• All Herpes viruses have the ability to establish lifelong latency in the host

  - Development of a vaccine can not simply be based upon determining the dominant immune response to natural infection
  - Live attenuated vaccines can establish latency
  - Changes in epidemiology resulting from vaccination can impact on the risk of reactivation
Varicella zoster virus vaccines
Varicella Zoster virus

- Transmission by virions aerosolized from skin lesions and from respiratory tract: contamination of about 90% of non-immune.
- Latency by migration of the virus to the dorsal root and trigeminal ganglia.
- Clinical manifestations:
  - Varicella (primary infection)
  - Zoster (recurrence)
Varicella: complications

- 6% of the cases
  - Viral pneumonia
  - Bacterial superinfection: cutaneous, deep tissue (arthritis, necrotizing fasciitis), pneumonia
  - CNS involvement (1/1400): cerebellitis/encephalitis
  - Reye syndrome
  - Varicella at the beginning of pregnancy: <2% congenital varicella
  - Varicella within 5 d before and 2 d after delivery
The burden of varicella in Belgium

• Incidence:
  - 1000 to 1500 cases/100,000 population per year, in the absence of vaccination

• Number of clinic visits for varicella
  - between 300 and 500 / 100,000 population per year

• Incidence of hospitalizations
  - 6/100,000 population all ages included per year
  - 105/100,000 in children < 1 year

ISP-réseau des médecins vigies
Données RCM
Monovalent varicella vaccines

- Live attenuated vaccine (Oka strain) developed in Japan in the 1970s, marketed in Europe in the 1990s: Varilrix™ (2,000 PFU, GSK) et Provarivax™ (1,400 PFU, Sanofi-Pasteur MSD)
- Co-administrable with hexavalent vaccines and MMR
- Well tolerated
- Varicella-like rash in 3 to 4% of children <13 ans, and in 5 to 10% of adolescents or adults
- Risk of zoster < wild type infection
Monovalent varicella vaccines

• Immunogenicity
  - 12 months to 12 years: 75 à 100% seroconversion
  - >12 years: 75 à 94% after 1 dose, 97 à 100% after 2 doses

• Vaccination schedule recommended before 2007
  - 1 dose between 12 months and 12 years
  - 2 doses at 4 to 8 weeks interval after 12 years
Monovalent varicella vaccines

• **Efficacy**
  - Duration of protection: estimated to vary between 10 to 20 years in the 1990s, in situations of wild type virus circulation

• **Inclusion in vaccination programs:**
  - USA 1995
  - Sicily 2003, Germany 2004
  - Canada, Australia 2005
  - Greece 2007
Impact of vaccination on the epidemiology of varicella in the USA

Reported varicella cases and vaccination coverage* by year -- Varicella Active Surveillance Project, 1995-2005

Monovalent varicella vaccines

- **Effectiveness**
  - In the situations where wild type virus circulation is limited by a high vaccination coverage (88% in the USA in 2005), effectiveness after 1 dose: 75%
  - Recommendation to administer a 2nd dose, whatever the age (USA, 2007): seroconversion >99%, GMT Ac x 20
Vaccination against varicella in Belgium: recommendations of the CSS/HGR (2005)

• Systematic vaccination not recommended
  - Risk of insufficient vaccine coverage, causing age shift
  - Questions regarding the magnitude and the duration of protection
  - Risk of transient increase in zoster incidence (reduction in virus circulation)

• Vaccination of high risk individuals (non immune young adults, close contacts of immune deficient individuals)

• Recommendations updated when quadrivalents MMR-V vaccines available
Combined MMR-V vaccines

MMR + VZV → MMR-V

Priorix-Tetra™ (GSK)
ProQuad™ (Sanofi-Merck)
# ProQuad™ (Sanofi)

<table>
<thead>
<tr>
<th>VIRUS STRAIN</th>
<th>Median Cell Culture Infective Dose</th>
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### Priorix-Tetra™ (GSK)

<table>
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<tr>
<th>Virus strain</th>
<th>Median Cell Culture Infective Dose</th>
<th>Control vaccines</th>
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<tr>
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<td><em>Priorix-Tetra™</em></td>
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<tr>
<td><strong>Varicella</strong> Oka</td>
<td>&gt; 10&lt;sup&gt;3.3&lt;/sup&gt;</td>
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Combined MMR-V vaccine

- Immunogenicity: combination resulted in interferences in the antibodies GMT
  - ↑ for measles,
  - ↓ for mumps in GSK vaccine,
    - Reformulated x 5
  - ↓ for VZV in Merck-Sanofi vaccine,
    - Reformulated x 20
- Vaccination schedule: 2 doses at 3 months interval
Fever after dose 1

Priorix-Tetra™ vs Priorix+Varilrix

(Study MeMuRu-OKA 044) Grade 3 fever ≥ 39.4 °C (rectal temperature)
Combined MMR-V vaccine

- ProQuad™ licensed in the USA in 2005
- Balance to be evaluated between:
  - Opportunity for an rapid high VZV coverage
  - High rate of fever > 39°C ~8th day, higher rate of febrile seizures (RR 2.3 in the 12 days after vaccination, CI 0.6-9)
    Possible impact on adhesion?

- ACIP preference for tetravalent vaccination in 2007, but not anymore in 2008, because of the increased risk of febrile seizures
Combined MMR-V vaccine

- License of ProQuad™ and Priorix-Tetra™ granted by EMEA
- Priorix-Tetra™ available in Belgium
- Recommendations of the CSS/HGR under review
Zoster (shingles)

- Reactivation of latent VZV causing a localized generally painfull rash

Lifelong risk of occurrence: 10 to 20%

Complications:
- Posherpetic neuralgia
- Zoster ophtalmicus
- Peripheral facial nerve palsy
Incidence of zoster according to age

Pellissier and Brisson
In: Vaccines, 2008
Age-related cellular immune response to VZV

Burke et al, 1982
A vaccine to prevent Herpes zoster and postherpetic neuralgia in older adults

• Rationale:
  - Decrease in cell mediated immunity with age plays a substantial role in the pathogenesis of zoster
  - Exposure to varicella decreases the risk of zoster
  - Boosting cell mediated immunity with a vaccine might protect against zoster
A vaccine to prevent Herpes zoster and postherpetic neuralgia in older adults

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• Live attenuated Oka/Merk VZV vaccine

• Minimum potency: 19,400 PFU (4.29 log₁₀)

• Evaluated in a double blind placebo controlled trial involving 38,546 adults older than 60 years

Oxman et al NEJM 2005
Effect of zoster vaccine on the cumulative incidence of zoster

Oxman et al NEJM 2005
Effect of zoster vaccine on the cumulative incidence of post herpetic neuralgia

No. at Risk

<table>
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<tr>
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<td>19254</td>
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<td>4</td>
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Oxman et al NEJM
2005
Efficacy of zoster vaccine by age stratum

<table>
<thead>
<tr>
<th>Measure</th>
<th>Overall</th>
<th>60–69</th>
<th>≥70</th>
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</thead>
<tbody>
<tr>
<td>$V_{E_{B01}}$ (%)</td>
<td>61.1 (51–69)</td>
<td>65.5 (52–69)</td>
<td>55.4 (40–70)</td>
</tr>
<tr>
<td>$V_{E_{PHN}}$ (%)</td>
<td>66.5 (48–79)</td>
<td>65.7 (20–87)</td>
<td>66.8 (43–81)</td>
</tr>
<tr>
<td>$V_{E_{HZ}}$ (%)</td>
<td>51.3 (44–58)</td>
<td>63.9 (55–71)</td>
<td>37.6 (25–49)</td>
</tr>
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A vaccine to prevent Herpes zoster and postherpetic neuralgia in older adults

- Live attenuated Oka/Merk VZV vaccine
- Minimum potency: 19,400 PFU (4.29 log₁₀)
- Evaluated in a double blind placebo controlled trial involving 38,546 adults older than 60 years

Oxman et al NEJM 2005

- Licensed by FDA and EMEA
- Recommended in the USA by ACIP for all adults older than 60 years
Cytomegalovirus vaccines
Human Cytomegalovirus

- Transmission:
  - Horizontal by close contact with body fluids, transfusion/transplantation
  - Vertical
- Latency established in myelomonocytes, endothelial cells..
- Clinical manifestations
  - mononucleosis syndrome
  - congenital disease
  - severe infections in immunodepressed subjects
Objectives of CMV vaccination

- To prevent primary infections in women during pregnancy
- To convert susceptible patients to an immune status before exposure to the risk of CMV under conditions of immune suppression
CMV vertical transmission as a result of primary infection during pregnancy

1-4% Primary infection

30-40% Vertical transmission

10-15% symptomatic

10% Normal development

90% Will develop sequelae

85-90% asymptomatic

5-15% Will develop sequelae

85-95% Normal development
Risk of congenital CMV in infants born to mothers with preexisting immunity

- Reactivation or reinfection
- Much lower risk of vertical transmission than after primary infection (0.5 – 2%)
- Most infected newborn asymptomatic at birth
- 10 – 15% risk of developing hearing impairment

Natural immunity reduces the risk and severity of congenital infection, but does not suppress it
Objective of a CMV vaccine to prevent congenital infection

- To establish conditions under which women enter pregnancy with preexisting immunity, as natural immunity
  - reduces the rate of vertical transmission
  - protects against the development of severe disease in the fetus
- Neutralizing antibodies necessary
- Cell mediated immunity probably necessary
Approaches for the development of a CMV vaccine

- live attenuated vaccine: « pasteurian » approach

- recombinant protein + adjuvant: « modern » approach
Live attenuated vaccine « Towne »

- evaluated since the 1970s, administered to >1000 patients/volunteers
- well tolerated, induces Ab and CMI
- reduces severity of infection in renal transplants and subcutaneously challenged healthy volunteers
- does not prevent natural infection in exposed mothers
Recombinant glycoprotein B vaccine

- **gB**: target of neutralizing antibodies and CD4 lymphocytes, protects animals against in utero transmission
  - Sanofi-Pasteur: gB + MF59
    - MF59: emulsion water/lipid (squalene)
    - well tolerated, induces Ab and modest CMI
    - recently published phase 2 study
  - GSK Bio: gB (+fragment gD HSV) + AS01
    - AS01: QS21 (saponin) + monophosphory-lipid A
    - Well tolerated, induces Ab and substantial CMI
    - Phase 1 study ongoing
• Double blind placebo controlled trial in 234 women of childbearing age seronegative for CMV
• Vaccine: CMV gB + MF59 or placebo
• Minimum of 1 year follow up
• Endpoint: CMV infection in vaccinees
Figure 2. Kaplan–Meier Estimates of Probability of Remaining Free of CMV Infection.

Up to 42 months after study enrollment, subjects in the vaccine group were more likely to remain free of CMV infection than were subjects in the placebo group (P=0.02). In the vaccine group, 18 subjects were found to have CMV infection, as compared with 31 in the placebo group.
Main contribution of this study: proof of concept that a vaccine can prevent natural CMV infection

Remaining challenge: to demonstrate that vaccine induced immunity can impact on rate and severity of congenital infections
Challenges in evaluating a CMV vaccine in a phase 3 efficacy trial

- If the rate of congenital infection is the primary endpoint, assuming a vaccine 50% effective, enrollment of
  - 3400 susceptible women if transmission in placebo group is 3%
  - 10000 susceptible women if transmission in placebo group is 1%
- If protection from symptomatic congenital infection is the endpoint, assuming a vaccine 50% effective, enrollment of more than 50000 women required

need to identify virologic or immunologic predictors of transmission
HSV vaccine
• GpD adjuvanted with Alum/MPL (ASO4)
• 2 Double bind placebo controlled trial including respectively 268 and 1867 young healthy adults
• No efficacy preventing genital herpes in man
• Efficacy in women seronegative for HSV 1 and HSV2, but no efficacy for those seropositive for HSV 1 before vaccination
Time of occurrence of genital herpes in women who were seronegative for HSV 1 and HSV2 at the time of vaccination
EBV vaccine
Recombinant gp350 Vaccine for Infectious Mononucleosis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of an Epstein-Barr Virus Vaccine in Healthy Young Adults

Etienne M. Sokal,1 Karel Hoppenbrouwers,2 Corinne Vandermeulen,1 Michel Moutschen,1 Philippe Léonard,4 Andre Moreels,2 Michèle Haumont,2 Alex Bollen,5 Françoise Smets,1 and Martine Denis6

1Université Catholique de Louvain, Cliniques Universitaires St-Luc, and 2Vrije Universiteit Brussel, Campus Erasme, Brussels, 3Department of Youth Health Care, Katholieke Universiteit Leuven, Leuven, 4Laboratory of Pathology, University of Liège, Liège, 5Henogen, Gosselies, and 6GlaxoSmithKline Biologicals, Rixensart, Belgium

- Gp350 adjuvanted with Alum/MPL (ASO4)
- Double bind placebo controlled trial including 181 young healthy adults
- No efficacy in preventing asymptomatic EBV infection
- Demonstrable efficacy in the development of infectious mononucleosis (78%, 95% CI: 1-96%)
Timing of occurrence of infectious mononucleosis in vaccine and placebo recipient
Conclusions

• Because of the complexity of the pathogenesis of Herpes viruses infection, development of vaccines is a major challenge

• Vaccines against varicella and zoster are effective and well tolerated. Their place in the vaccination program is under debate in Belgium

• Adjuvanted recombinant glycoproteins show some promise for the development of vaccines against CMV, HSV and EBV