Vaccination against Herpes viruses

Jack Levy
Head, Dept pediatrics, CHU Saint-pierre
Director, Clinical Investigation Unit, ImmumeHealth

Vaccination against Herpes viruses

- In clinical use:
  - Varicella Zoster Virus
- In development:
  - Cytomegalovirus
  - Herpes Simplex Virus
  - Epstein-Barr Virus

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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 ractivation: 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

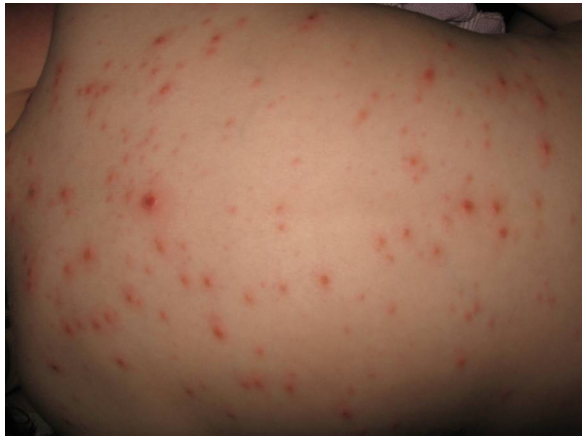
- All Herpes viruses have the ability to establish lifelong latency in the host

→ -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, necrotizig fasciitis), pneumonia
  - CNS involvment (1/1400): cerebellitis /encephalitis
  - Reye syndrome
  - Varicella at the beginning of pregnancy : <2% congenital varicella
  - Varicella whithin 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

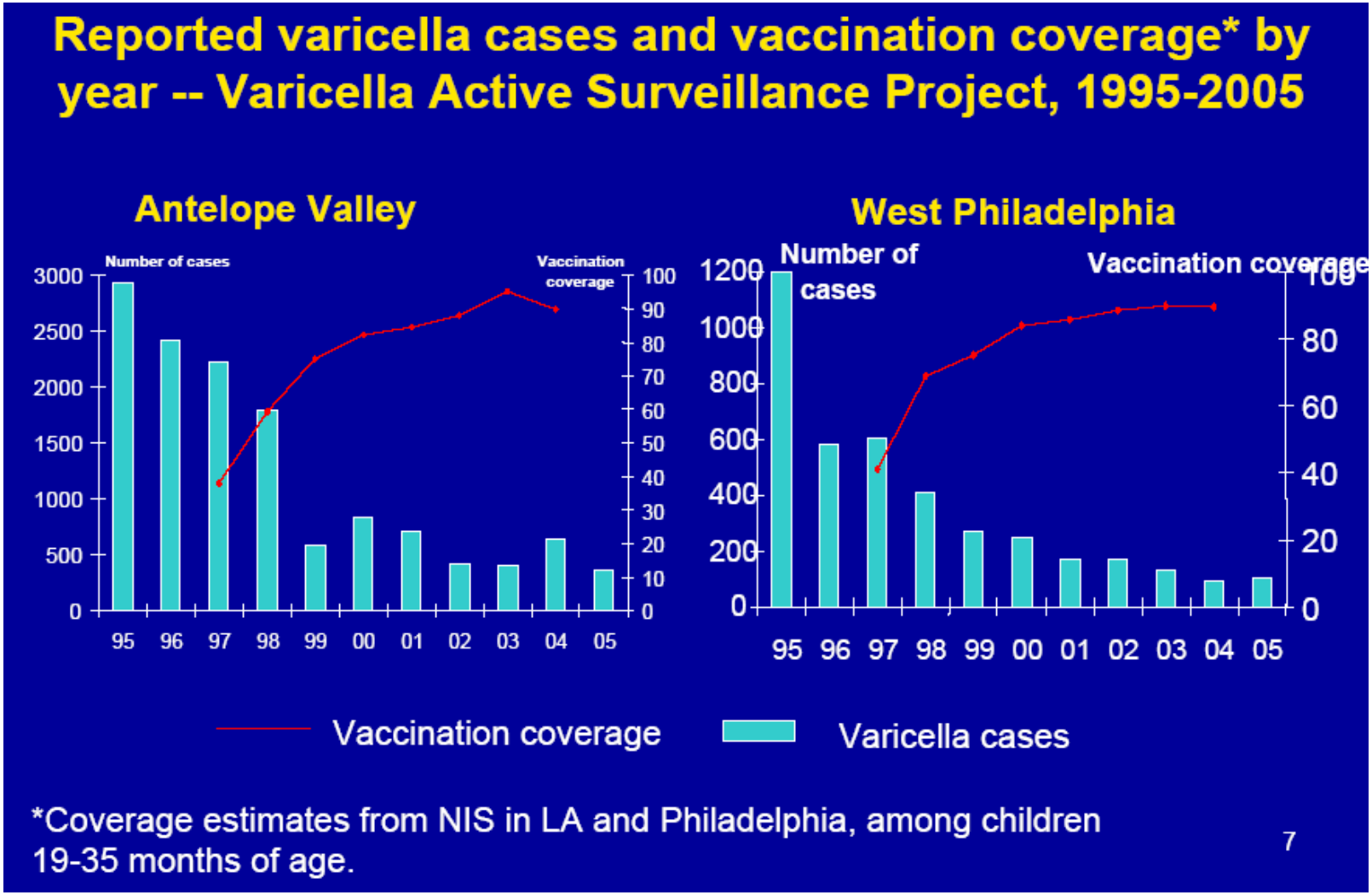
Monovalent varicella vaccines

- 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



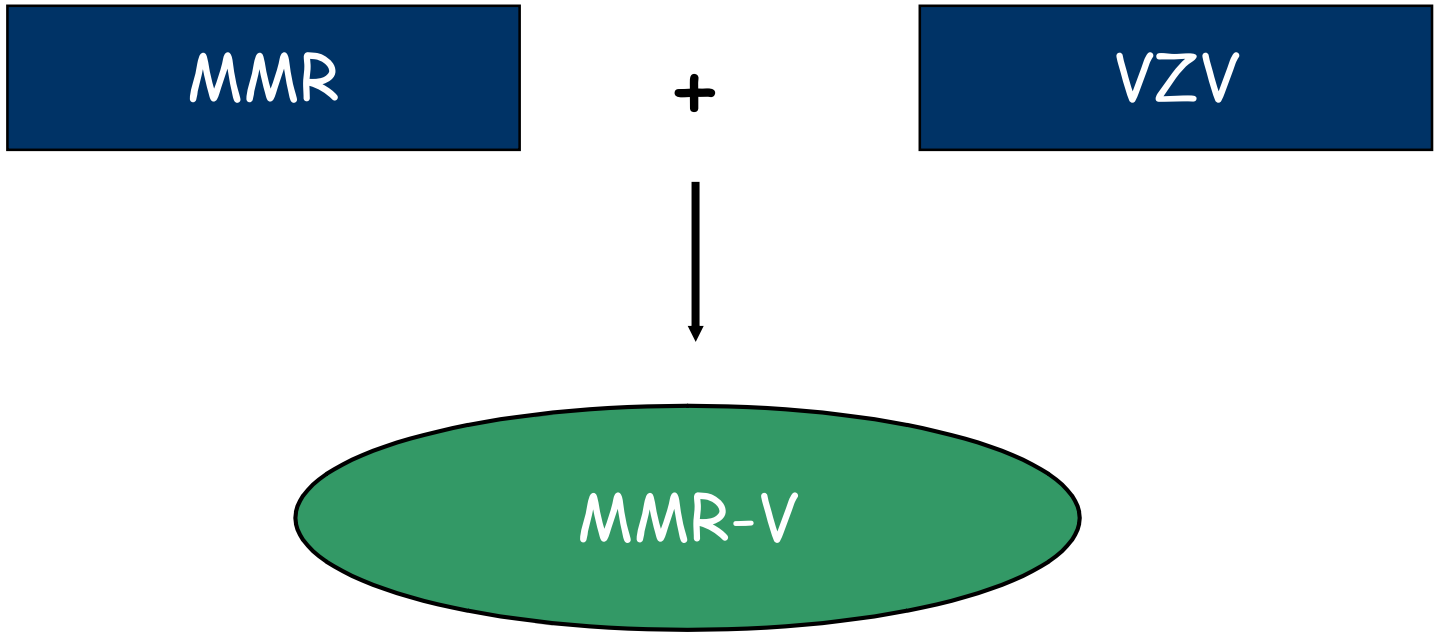
Monovalent varicella vaccines

- 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%
  - Recommandation 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



Priorix-Tetra™ **(GSK)**

ProQuad™ **(Sanofi-Merck)**

ProQuad™ (Sanofi)

VIRUS STRAIN Median Cell Cuture Infective Dose		Control vaccines	
	ProQuad™ ($CCID_{50}$)	**M-M-R-II™** ($CCID_{50}$)	**Varivax™** (pfu)
Measles Enders-Edmonton	**> $10^{3.5}$**	**> $10^{3.5}$**	
Mumps Jeryl Lynn	**> $10^{4.4}$**	**> $10^{4.4}$**	
Rubella Wistar RA 27/3	**> $10^{4.0}$**	**> $10^{4.0}$**	
Varicella Oka	**> $10^{4.8}$**		**> $10^{3.5}$**

Priorix-Tetra™ (GSK)

Virus strain Median Cell Cuture Infective Dose		Control vaccines	
	Priorix-Tetra™ ($CCID_{50}$)	***Priorix™*** ($CCID_{50}$)	**Varilrix™** (pfu)
Measles Schwarz	> $10^{3.0}$	> $10^{3.0}$	-
Mumps RIT 4385 Jeryl Lynn	**> $10^{4.4}$**	**> $10^{3.7}$**	-
Rubella Wistar RA 27/3	> $10^{3.0}$	**> $10^{3.0}$**	-
Varicella Oka	**> $10^{3.3}$**	-	**$10^{3.3}$**

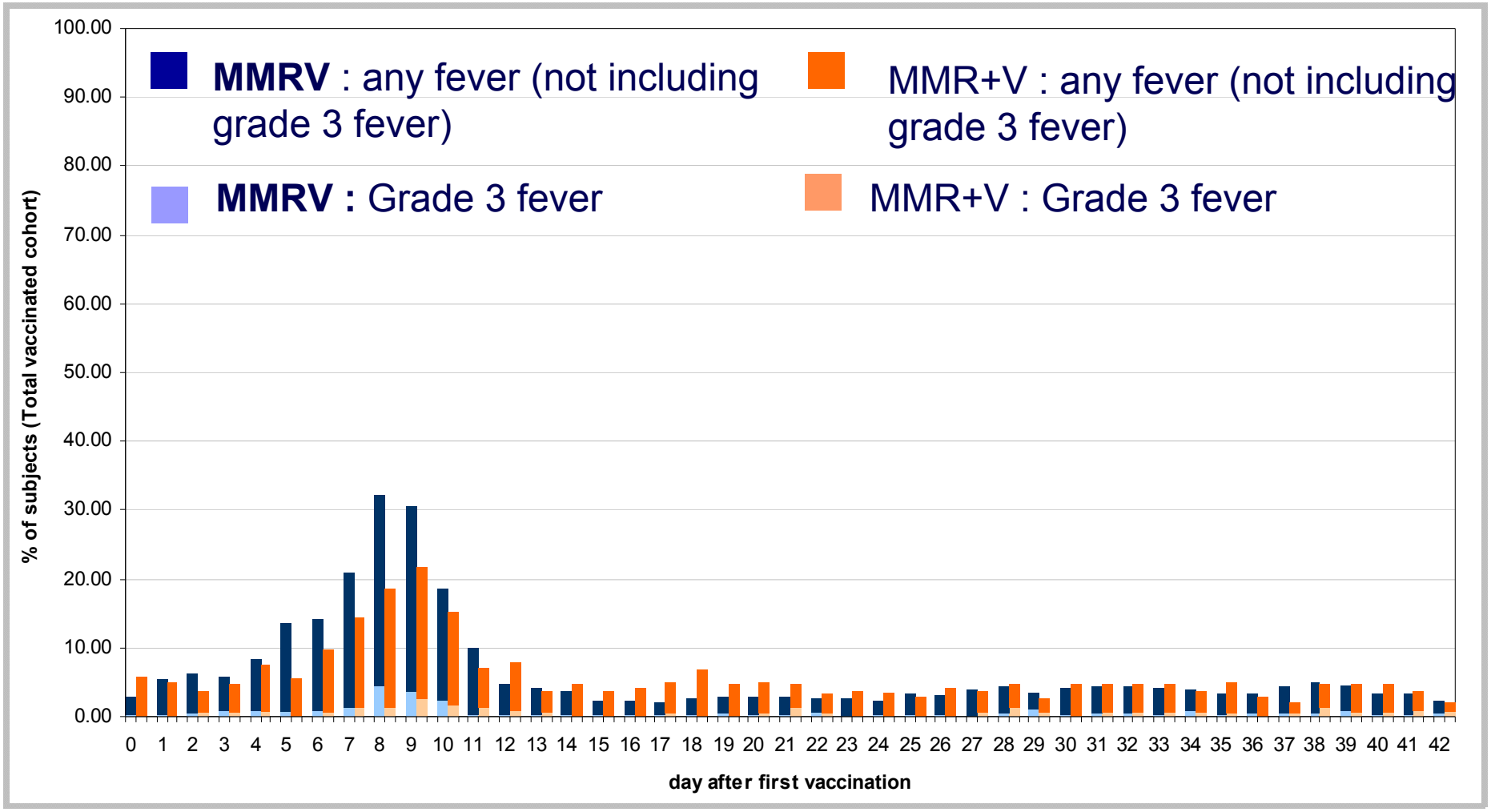
Combined MMR-V vaccine

- 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)

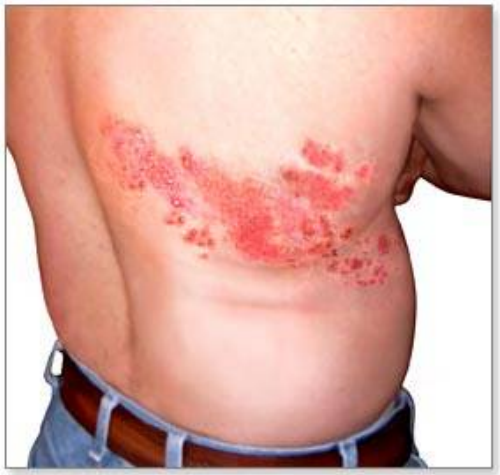
  → Possible impact on adhesion ?

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

Combined MMR-V vaccine

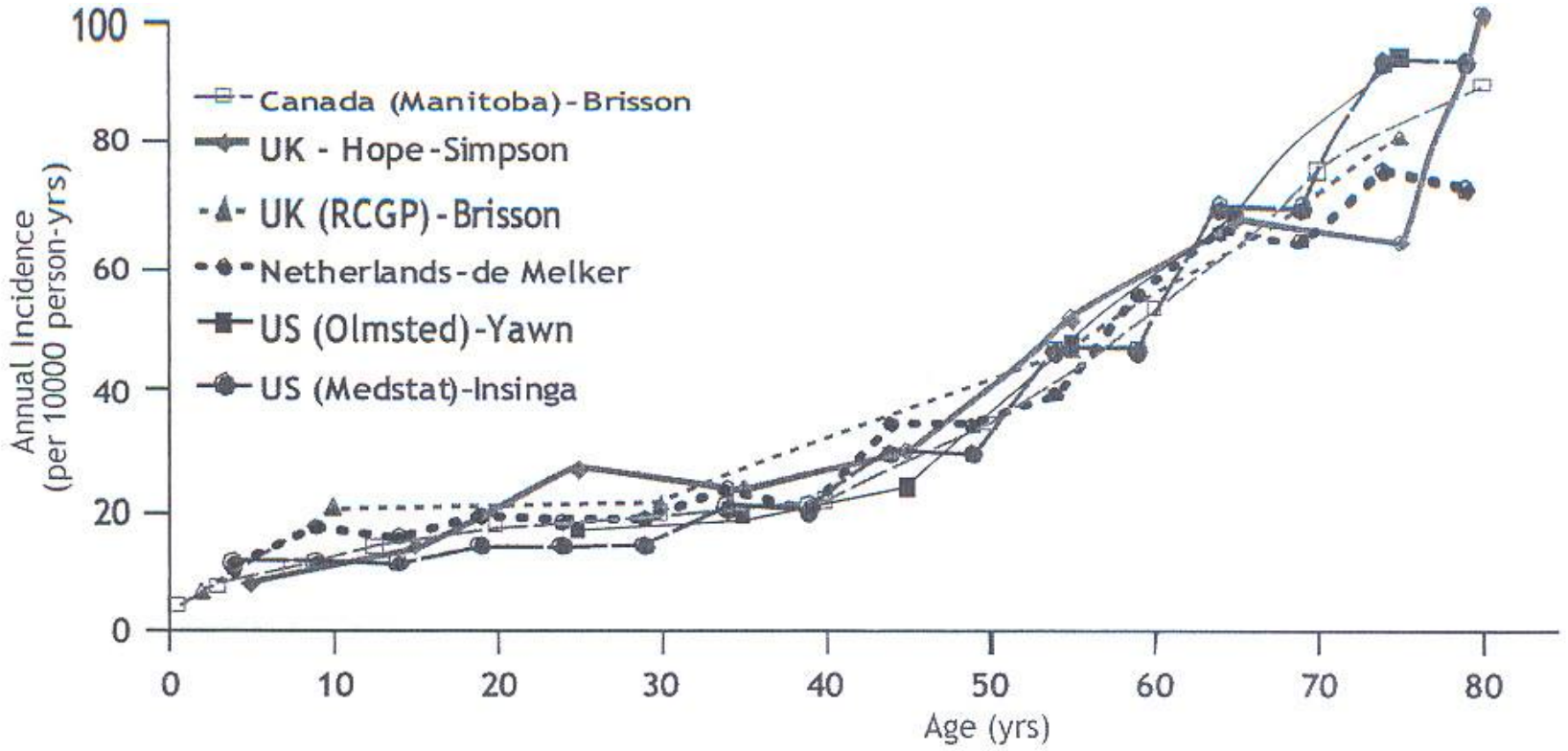
- License of ProQuad™ and Priorix-Tetra™ granted by EMEA
- Priorix-Tetra™ available in Belgium
- Recommendations of the CSS/HGR under review

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

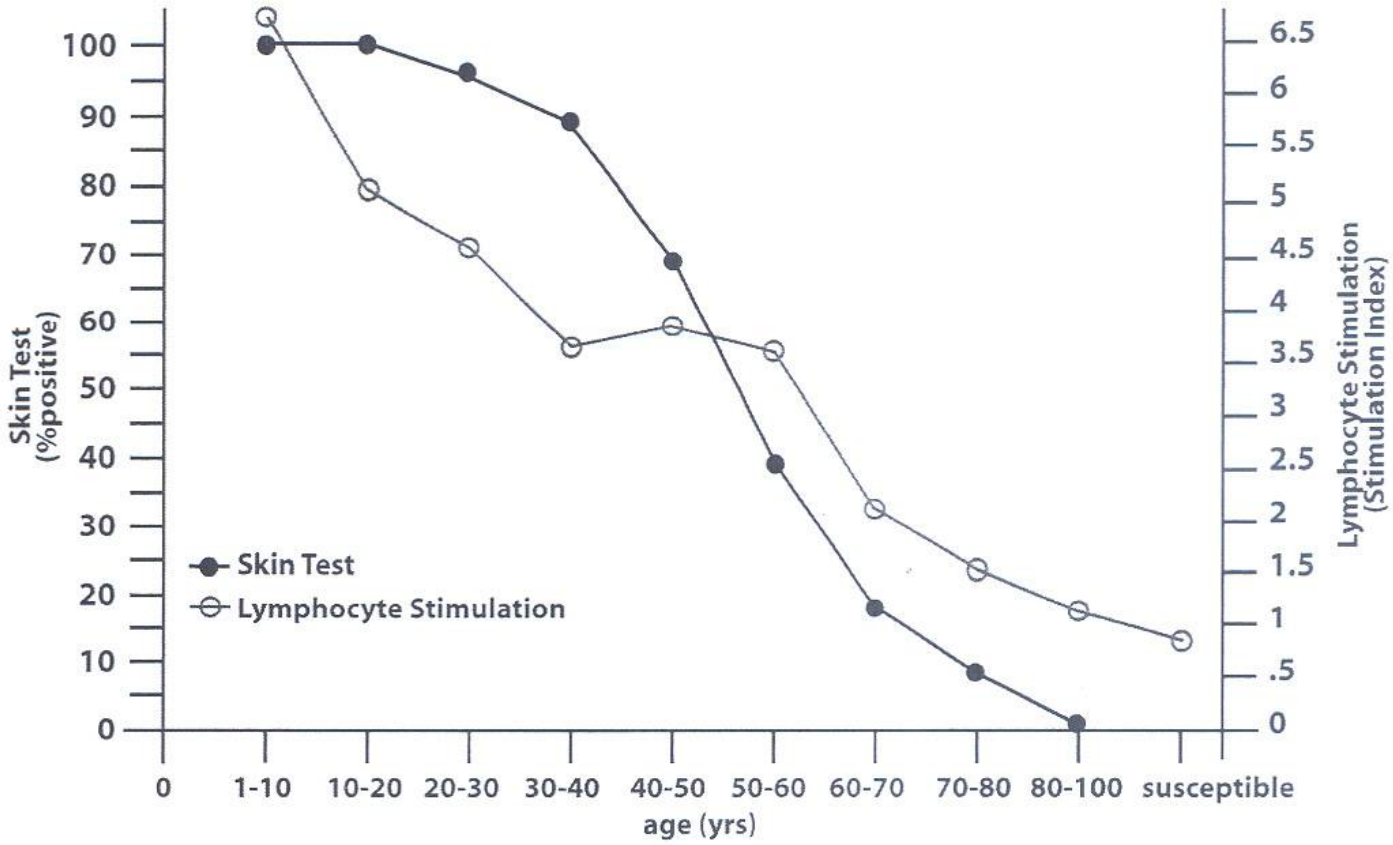
Incidence of zoster according to age



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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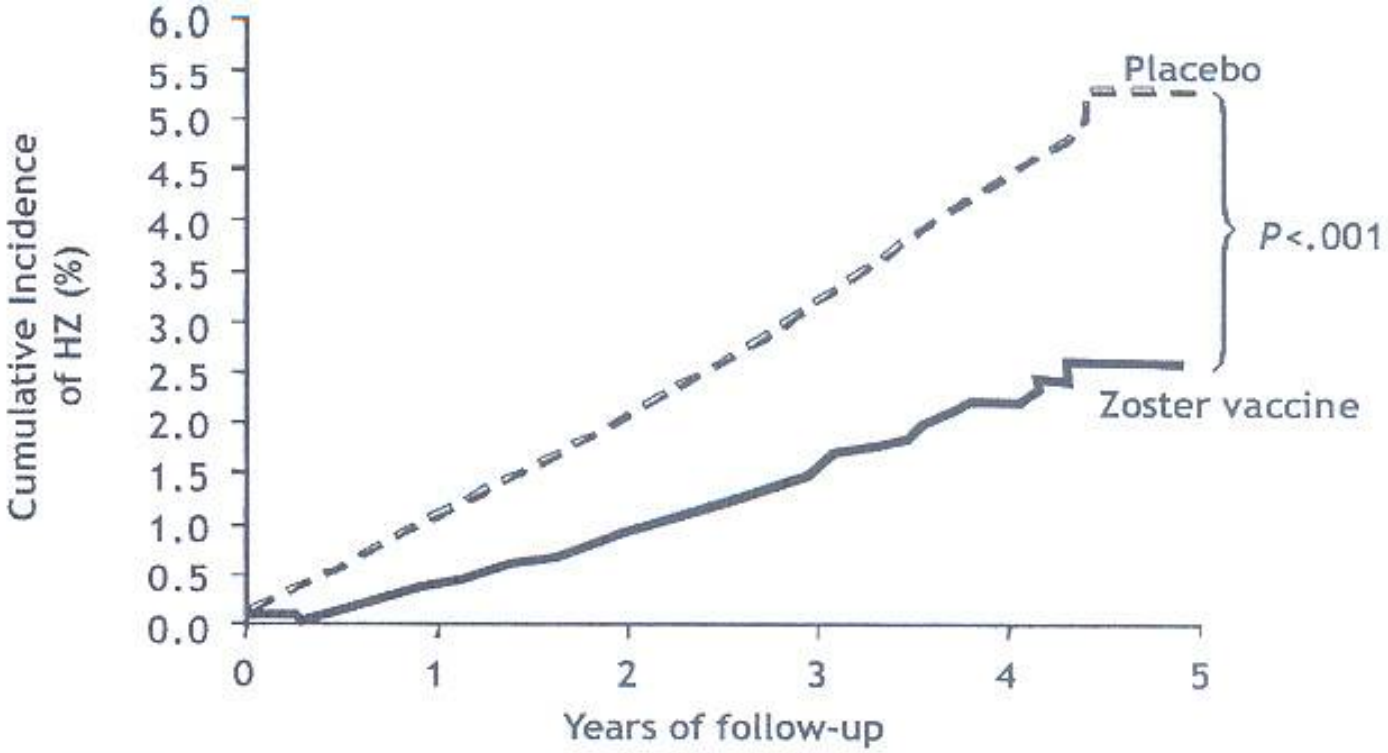
  - Boosting cell mediated immunity with a vaccine might protect against zoster
- Live attenuated Oka/Merk VZV vaccine
- Minimum potency: 19.400 PFU (4.29 $\log_{10}$)
- Evaluated in a double blind placebo controlled trial involving 38.546 adults older than 60 years

Oxman et al NEJM 2005

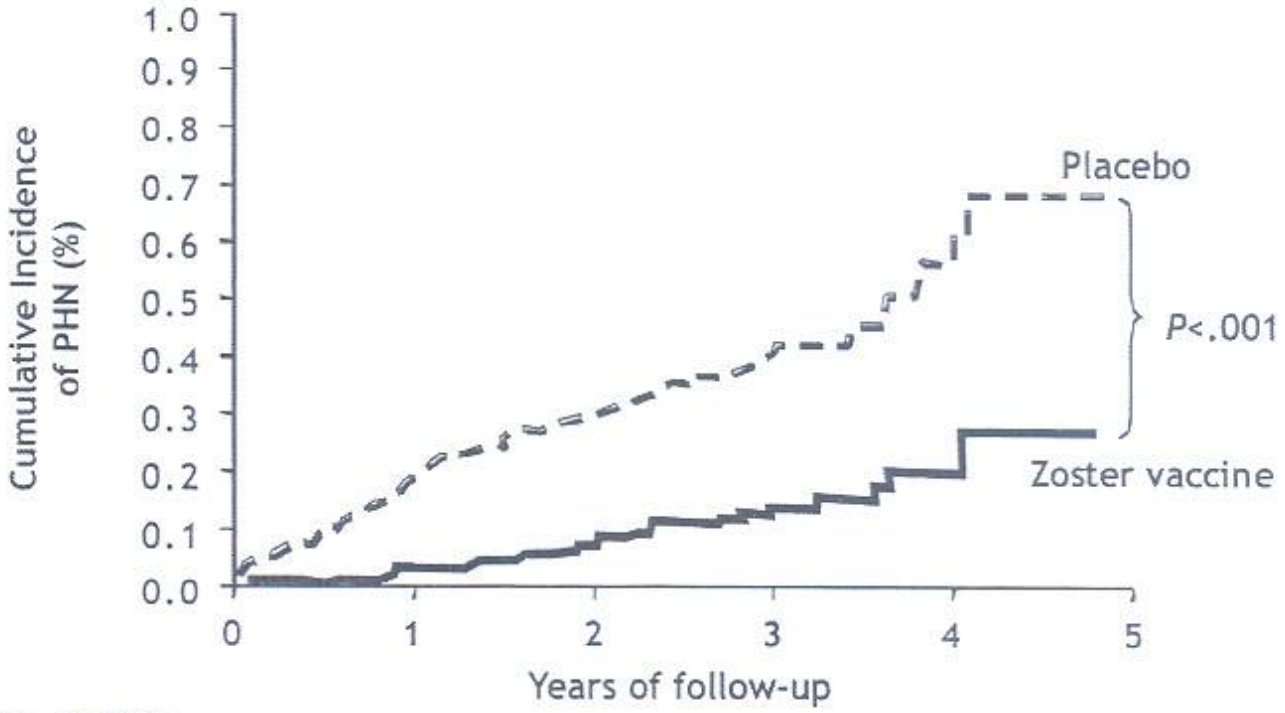
Effect of zoster vaccine on the cumulative incidence of zoster



No. at Risk					
Placebo	19247	18915	18422	9806	1856
Vaccine	19254	18994	18626	9942	1906

Oxman et al NEJM 2005

Effect of zoster vaccine on the cumulative incidence of post herpetic neuralgia



No. at Risk					
Placebo	19247	18915	18422	9806	1856
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Efficacy of zoster vaccine by age stratum

Measure	Age (yr)		
	Overall	60–69	≥70
VE_{BOI} (%)	61.1 (51–69)	65.5 (52–69)	55.4 (40–70)
VE_{PHN} (%)	66.5 (48–79)	65.7 (20–87)	66.8 (43–81)
VE_{HZ} (%)	51.3 (44–58)	63.9 (55–71)	37.6 (25–49)

Oxman et al NEJM 2005

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 $\log_{10}$)
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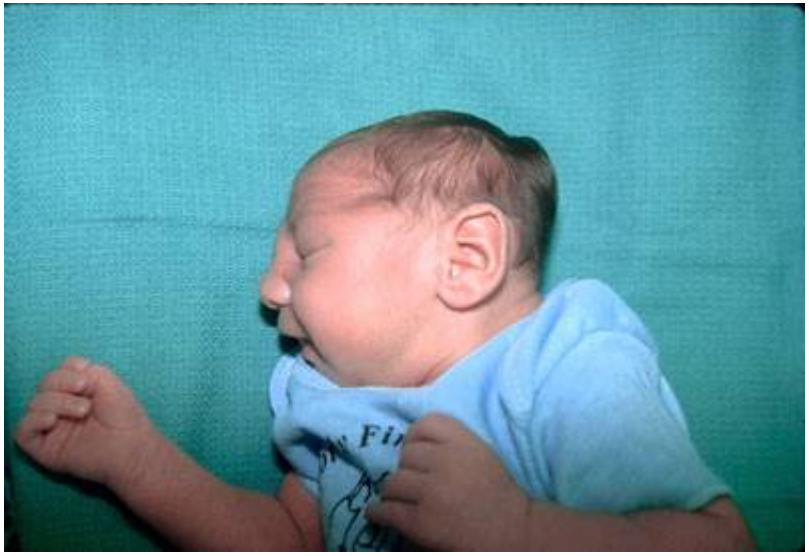
Oxman et al NEJM 2005

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

Cytomegalovirus vaccines

Human Cytomegalovirus

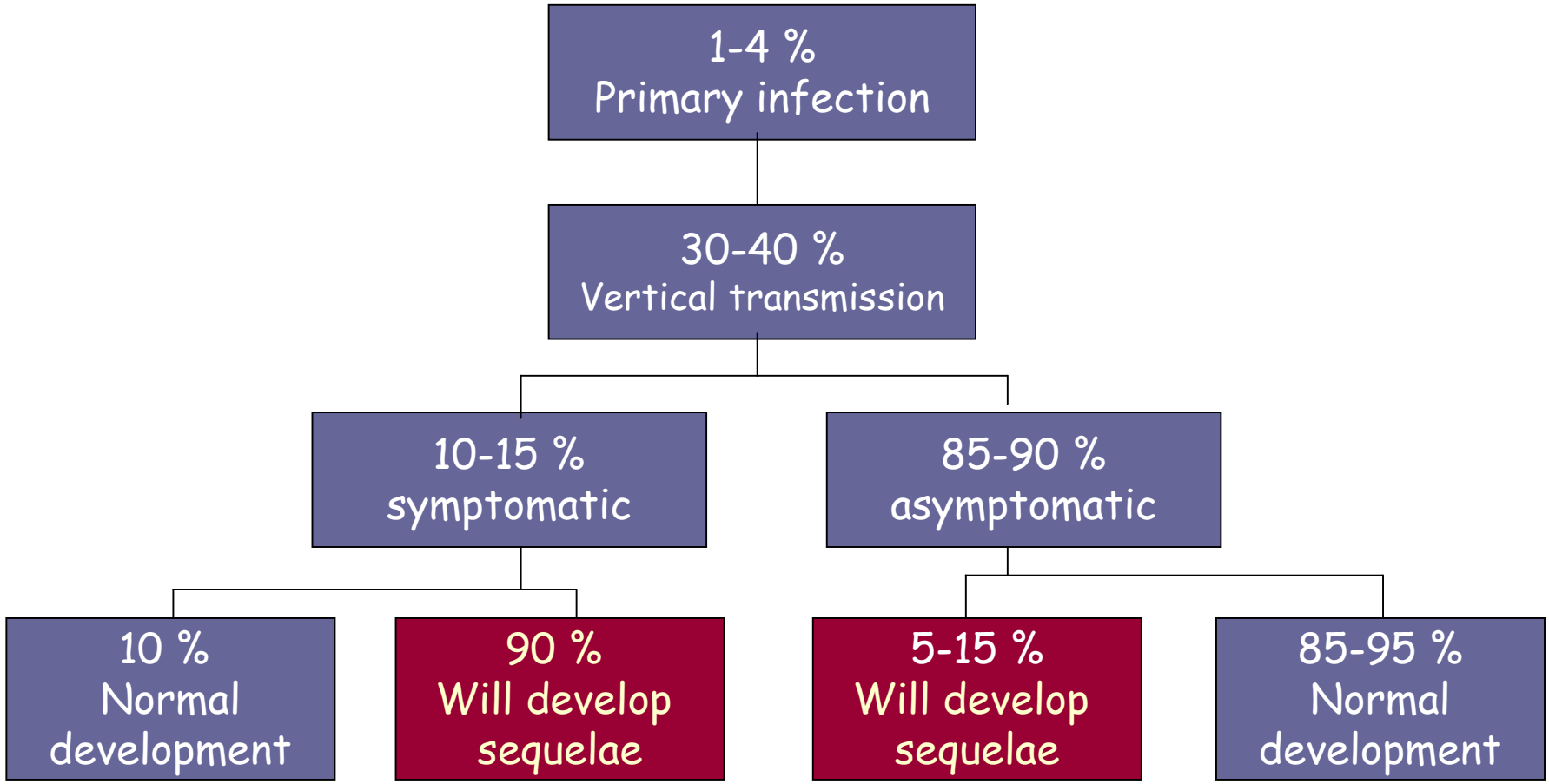


- Transmission :
  - Horizontal by close contact with body fluids, transfusion/transplantation
  - Vertical
- Latency established in myelomonocytes , endothelial cells..
- Clinical manifestations
  - mononucleosis syndrome
  - congenital disease
  - severe infections in immunodepressed subjects

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



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 à 2%)
- Most infected newborn asymptomatic at birth
- 10 à 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 verical 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/volonteers
- 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

The NEW ENGLAND JOURNAL of MEDICINE

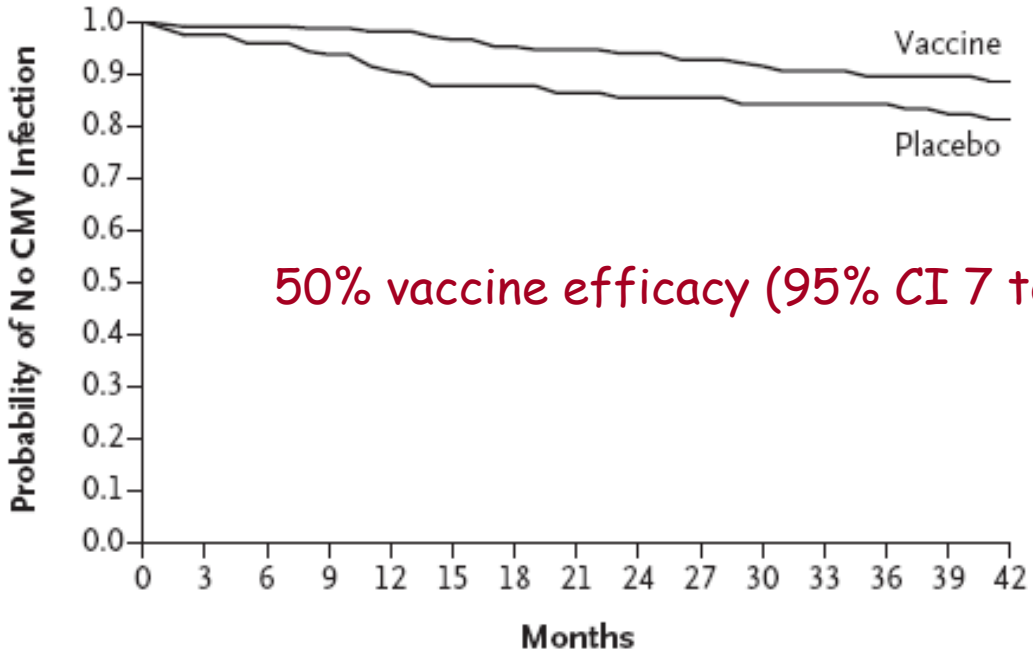
ORIGINAL ARTICLE

Vaccine Prevention of Maternal Cytomegalovirus Infection

Robert F. Pass, M.D., Changpin Zhang, M.D., Ashley Evans, M.D., Tina Simpson, M.D., William Andrews, M.D., Meei-Li Huang, Ph.D., Lawrence Corey, M.D., Janie Hill, R.N., Elizabeth Davis, R.N., M.P.H., Cynthia Flanigan, B.S., and Gretchen Cloud, M.S.

Pass et al NEJM 2009

- 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



50% vaccine efficacy (95% CI 7 to 73)

No. at Risk															
Vaccine	225	213	211	204	195	178	160	154	145	136	127	116	112	98	88
Placebo	216	193	185	178	169	153	141	128	121	114	108	104	97	87	75

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.

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Pass et al NEJM 2009

- 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

The New England Journal of Medicine

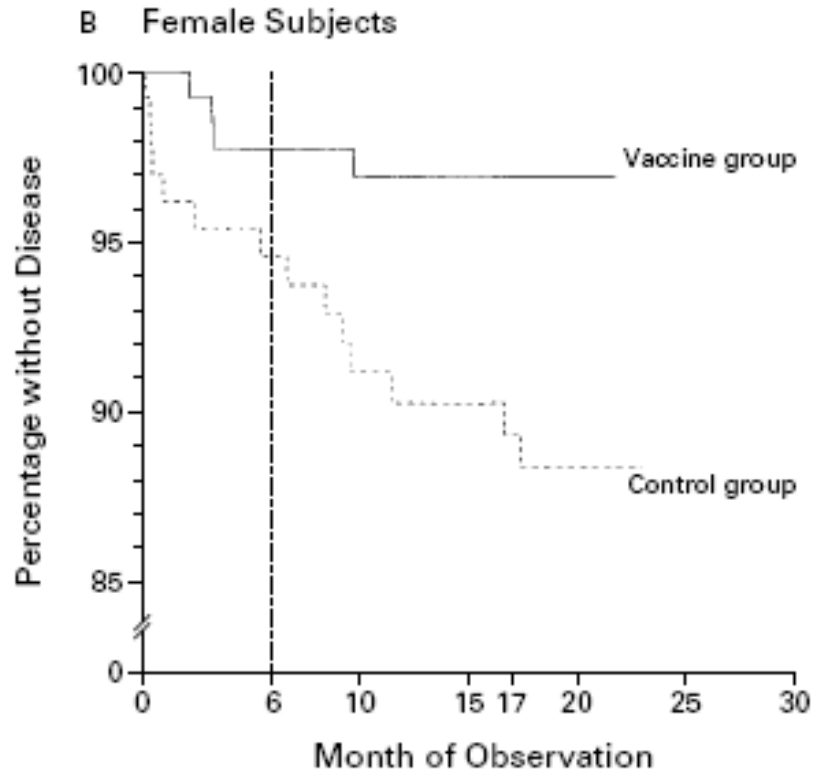
GLYCOPROTEIN-D–ADJUVANT VACCINE TO PREVENT GENITAL HERPES

LAWRENCE R. STANBERRY, M.D., PH.D., SPOTSWOOD L. SPRUANCE, M.D., ANTHONY L. CUNNINGHAM, M.D., DAVID I. BERNSTEIN, M.D., ADRIAN MINDEL, M.D., STEPHEN SACKS, M.D., STEPHEN TYRING, M.D., PH.D., FRED. Y. AOKI, M.D., MONCEF SLAOUI, PH.D., MARTINE DENIS, PH.D., PIERRE VANDEPAPELIERE, M.D., AND GARY DUBIN, M.D., FOR THE GLAXOSMITHKLINE HERPES VACCINE EFFICACY STUDY GROUP*

NEJM 2002

- 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

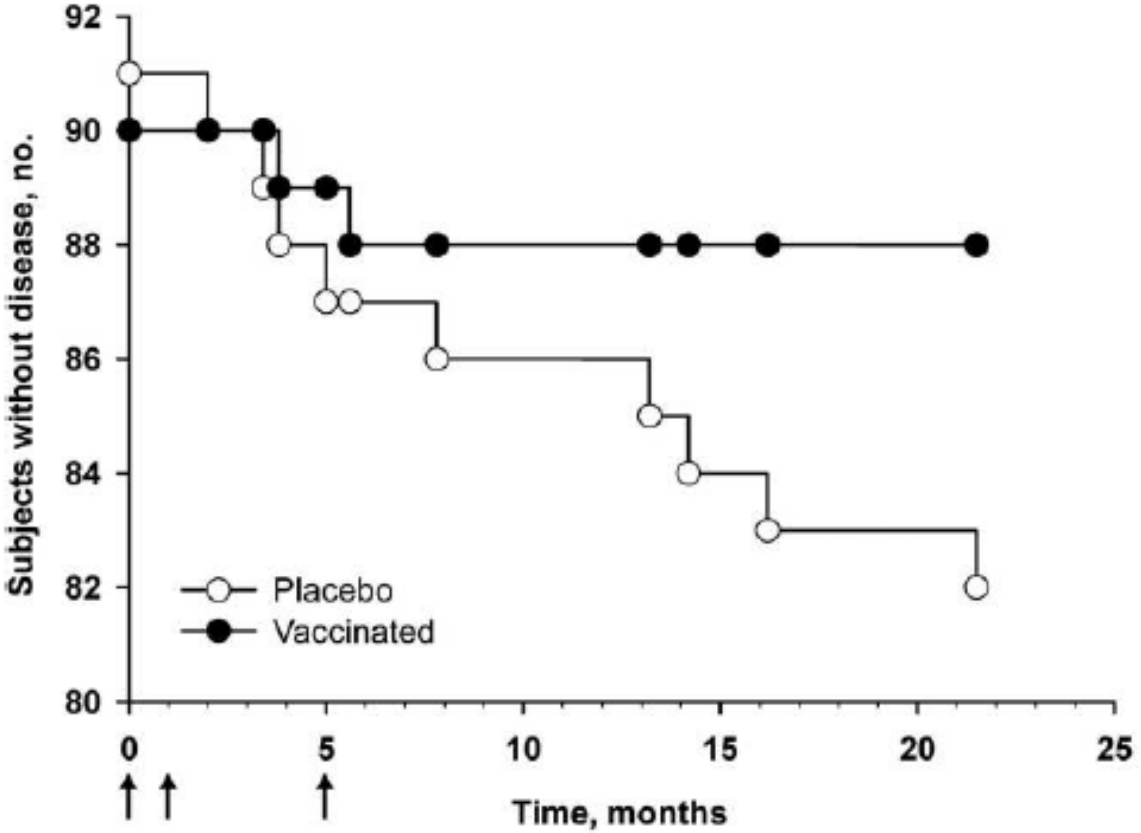
Etienne M. Sokal,[1] Karel Hoppenbrouwers,[3] Corinne Vandermeulen,[3] Michel Moutschen,[4] Philippe Léonard,[4] Andre Moreels,[2] Michèle Haumont,[5] Alex Bollen,[5] Françoise Smets,[1] and Martine Denis[6]

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

JID2007

- 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