Varicella in Belgium
Results of a 1-year National survey and discussion on vaccination

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Varicella: a frequent but not always benign disease

- Varicelle zoster virus (VZV) : α-herpesvirus

- VZV primary infection (varicella, chickenpox)
  - Vesicular eruption with often fever and malaise (7 to 10d)
  - Latent phase (persisting sensory nerves ganglia)

- Reactivation: Shingles (herpes zoster)
  (painful vesicular rash, unilateral spread along a dermatome)

- Varicella: high attack rate 61-100%
  - Endemic worldwide
  - 50% children 2y old and 98% adult population seropositive
  - Incidence +/- 113000 cases/year in Belgium

Heininger, Seward Lancet 2006
Varicella: not always benign disease...

- Severe varicella in healthy subjects
- Disseminated in immuno-compromised
- Neonatal varicella
- Secondary complications
- More severe in ado/ adults
- Congenital varicella

*Image reproduced with kind permission from Dr. Barbara Watson*
Varicella: significant burden of disease

- **Uncomplicated cases**
  (hundreds of lesions, severe constitutional symptoms, school absenteeism, medications, GP consultations…)

- **Complicated cases** (1 to 6%)
  (hospitalization, morbidity, mortality, sequelae..)

- **Parents and family**
  (absenteeism or work loss, secondary cases …)

**Prevention: vaccination**
- Live attenuated vaccine (*Oka strain*)
- Routine implementation in some countries (USA, Uruguay, Canada, Germany, Australia etc)
- High effectiveness (2 doses) and herd immunity
ECDC preliminary guidance 2014
Heterogeneous varicella vaccine recommendations in EU: only 5 countries with varicella UMV (+2 countries at regional level).
In Belgium?

- Incidence of GP consultations: 28.8-35.7 cases/10^4 people.year (Flanders)
- Maximum incidence between 1 to 4 years (91% < 10y old)
- Herpes zoster: 38.3 to 46.4/10^4 people.year

Vaccine coverage for children 18 to 24 months old
3.9% (1 dose) and 2.5% (2 doses) in Wallonia
1.5% (1 dose) and 0.2% (2 doses) in Brussels

E. Robert, B Swennen
Enquête de couverture vaccinale des enfants de 18 à 24 mois en Fédération Wallonie-Bruxelles/ à Bruxelles Capitale; Rapports 2012
Objectives
- **Primary**
  To assess the **burden of disease** of varicella in children in Belgium (rate of hospitalization, morbidity, mortality and sequelae) and compare with European data
- **Secondary**
  To provide **new additional data to support or not** the routine implementation of the live-attenuated **vaccine** in Belgium

Methods
- All Belgian paediatrics wards were invited to participate
- Prospective and retrospective collection of ALL paediatric varicella related hospitalized cases*
- 0 to 15 years of age
- One year study period (November 2011 till October 2012)
- Medical data recorded through the PediSurv network
- Approval of the Ethic Committee of HUDERF

This study was supported by a **scientific grant** from GSK Belgium

*defined as any hospitalization for which varicella was considered to the main reason for or that occurred within the 21 days after the first skin lesions
Results

- 101 Participating Hospitals

→ 97.7% of total paediatrics beds in Belgium

- 552 children enrolled

Seasonal peak (spring)

<table>
<thead>
<tr>
<th>N Belgian children 2011-2012</th>
<th>Incidence hospitalization for varicella*</th>
<th>Incidence hospitalization for complicated varicella cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14y</td>
<td>1873326</td>
<td>29.5/10⁵</td>
</tr>
<tr>
<td>0-4 y</td>
<td>647171</td>
<td>79/10⁵</td>
</tr>
<tr>
<td>5-14 y</td>
<td>1226155</td>
<td>3.3/10⁵</td>
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<td></td>
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<td>19/10⁵</td>
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<td></td>
<td></td>
<td>51/10⁵</td>
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<td></td>
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<td>2.45/10⁵</td>
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</tbody>
</table>
Results

- **Cohort’s description**
  - Sex ratio M/F: 1.3
  - Median age 2.1y (IQR 1-3.5y, range 0 to 15.7y)
  - 92.5% cohort: 0-4 y old; 25% <1y of age

- 4 children vaccinated with one dose varicella vaccine (1w to 6months before)
- Underlying chronic condition 16%
  (4% respiratory disease, 3% asthma, 3% prematurity history, 2% neurological disease, 2% immuno-compromised)

- Median delay first lesions/hospitalization: 3d (IQR 2-5d)
- Median duration of hospitalization: 3d (IQR 2-5d)

- **Severity of lesions on admission**
  - high (>500) 14%
  - middle (50-500) 39%

- **Main Reasons for hospitalization**
  - Suspicion of bacterial superinfection involved in 48% of admission
  - Superficial cutaneous infection 28%
  - Cellulitis 15%
  - Pneumonia 9%
  - Neurological complications 10%
  - Poor general status 20%
  - Anorexia/ dehydration/stomatitis 11%
  - Others (severe lesions of varicelle, underlying condition, concurrent bronchiolitis, other bacterial infections, young age, eye/liver involvement, social….)
Complications: 65% of cases

Bacterial complications: 43% of children (2/3 of complicated cases)
Mainly *S. aureus* and GAS; 3 MRSA

Haematological disorders on admission
- 13% of children with thrombocytopenia (<150,000/mm³)
- 5% of children with lymphopenia (<1000/mm³)
- 4% of children with leucopenia (<5000/mm³)
- 4% of children with neutropenia (<1500/mm³)

No Reye syndrome
Treatments

- **Acyclovir 26% (141/546)**
  - Median duration: 5d (IQR 3 to 5d)
  - 72% IV, 13% PO, 11% both
  - No use of valacyclovir

- **Antibiotics 58%**
  - Median duration: 7d (IQR 5-10, range 1 to 42d)
  - Amoxy-clav (31%), penicillin/oxacillin (22%), clindamycin (7%)
  - Parenteral administration: 287 (52%)

- **Surgery 3%** (Abscess or pleural drainage, joint puncture, wound unbridling)

- **ICU 4% (20 patients)**
  - Median duration: 5d (2 to 14d)
  - Reasons: neurological involvement (5), sepsis (4), poor general status (pain/dehydration) (4), intensive observation (3), SCID (1), ileus (1)
  - Four children: mechanical ventilation support; 14 transfer to a tertiary centre

- **Outcome**
  - Important scares: 9%
  - Sequelae 1%
    - ataxia, epilepsy, arthritis, phlebitis
  - Death 0.5%
    - 1 girl 17m old,
    - Toxic Shock Syndrome (probably GAS)

<table>
<thead>
<tr>
<th>Mortality rate</th>
<th>among belgian children 0-4ans</th>
<th>1,5/10^6</th>
<th>(1/647171)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>among belgian paediatric population</td>
<td>0,5/10^6</td>
<td>(1/1873326)</td>
</tr>
<tr>
<td></td>
<td>among global belgian population</td>
<td>0,1/10^6</td>
<td>(1/10,438,353)</td>
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</table>

<table>
<thead>
<tr>
<th>Fatality rate</th>
<th>among varicella hospitalized cases</th>
<th>0,50%</th>
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<tbody>
<tr>
<td></td>
<td>among complicated varicella hospitalized cases</td>
<td>0,60%</td>
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</table>
As compared to other European studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of survey</th>
<th>Incidence (/ 10⁵ people-year)</th>
<th>Hospitalization rate (/ 10⁴ varicella cases)</th>
<th>N of cases</th>
<th>Median age (years)</th>
<th>Hospit. duration (median in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron JC et al</td>
<td>UK and Ireland</td>
<td>2002-2003</td>
<td>0,82</td>
<td>na</td>
<td>188</td>
<td>3</td>
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<tr>
<td>Arch Dis Child 2007</td>
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<tr>
<td>(severe hospitalized cases)</td>
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<tr>
<td>Ziebold C et al</td>
<td>Germany</td>
<td>1997</td>
<td>0,85</td>
<td>5</td>
<td>119</td>
<td>na</td>
</tr>
<tr>
<td>Pediatrics 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>na</td>
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<tr>
<td>(severe hospitalized cases)</td>
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<td></td>
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<tr>
<td>Eur J Ped 2005</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>(all hospitalized cases)</td>
<td></td>
<td></td>
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<tr>
<td>Dubos F et al</td>
<td>North of France</td>
<td>2003</td>
<td>25</td>
<td>na</td>
<td>162</td>
<td>1,75</td>
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<tr>
<td>Epidemiol Infect 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4,2</td>
</tr>
<tr>
<td>(all hospitalized cases)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>National Belgian survey</td>
<td>Belgium</td>
<td>2011-2012</td>
<td>29,5*</td>
<td>na</td>
<td>553</td>
<td>2,1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>3</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Complications (mostly in healthy children!!)</td>
<td>N deaths</td>
<td>Fatality rate (/ 1 hospitalized cases)</td>
<td>Sequellae</td>
<td>Mortality rate (/ 10⁵ people-year)</td>
<td></td>
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<tr>
<td>----------------------------</td>
<td>------------------------------------------------</td>
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</tr>
<tr>
<td>Cameron JC et al</td>
<td>UK and Ireland</td>
<td>bacterial superinfection 46%</td>
<td>5</td>
<td>2,6</td>
<td>37% (ataxia)</td>
<td>0,04</td>
</tr>
<tr>
<td>Arch Dis Child 2007</td>
<td></td>
<td>CNS involvement 27%</td>
<td></td>
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<td></td>
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<tr>
<td>Ziebold C et al</td>
<td>Germany</td>
<td>bacterial superinfection 61%</td>
<td>3</td>
<td>na</td>
<td>6,7%</td>
<td>na</td>
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<tr>
<td>Pediatrics 2001</td>
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<td>CNS involvement 35%</td>
<td></td>
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<tr>
<td>Bonhoeffer J et al</td>
<td>Switzerland</td>
<td>bacterial superinfection 36%</td>
<td>3</td>
<td>0,5</td>
<td>4%</td>
<td>na</td>
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<td>bacterial superinfection 29%</td>
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<td>1,8</td>
<td>na</td>
<td>0,5</td>
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<td>Epidemiol Infect 2006</td>
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<td>CNS involvement 26%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Belgian survey</td>
<td>Belgium</td>
<td>bacterial superinfection 43%</td>
<td>1</td>
<td>0,20</td>
<td>1%</td>
<td>0,5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS involvement 8%</td>
<td></td>
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</tbody>
</table>

*among the paediatric population
Incidence GP consultations for varicella: 28.8-35.7 cases/10^4 people.year (Flanders)

Maximum incidence between 1 to 4y old: **495 cases/10^4 people.year** (btw 414.1 to 509.9 cases/10^4)

91% < 10y old

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### Belgian National Study for Varicella 2011-2012

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<td>1226155</td>
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- Extrapolated Incidence of **hospitalisation among varicella cases** (population 0 to 4 y)
  → 1.56/100 cases

- Extrapolated Incidence of **hospitalisation for complications among varicella cases** (population 0 to 4y)
  → 1.03/100 cases
Universal Mass Vaccination (UMV) for varicella?
Effectiveness data

- **USA: UMV from 1997**
  - Global incidence reduced from 89.8% (1995 to 2004) (coverage 92% in 2005, 1 dose schedule)
  - Mortality ↓ 88% (0.41/10^6 to 0.05/10^6)
    Reduction in all age groups
    (<20 ans : -97%; <50 ans : -96%; >50 ans : -67%)
  - Significant reduction of varicella-related
    - hospitalizations (↓ 88%),
    - out-patients clinic visits (↓ 59%)
    - annual medical costs (↓ 74%)


- **Germany: UMV from 2004**
  - ↓ 90% of notified varicella cases (78% coverage)
  - ↓ 81% of complicated cases
  - Reduction in all age groups (herd immunity)
  - Highest impact in preschool children

  *Spackova et al, PIDJ 2010; Siedler et a, Euro Surveill 15*
Varicella URV in Uruguay
Ambulatory visits

URV, universal routine vaccination

Varicella vaccine: why 2 doses?

- Effectiveness of 1-dose schedule: 80%
  - Primary failure or waning immunity or both?
  - Risk of breakthrough infection in 1/5 children
  - Epidemics in day-care centres/schools
  - Increased risk of late severe varicella

- Effectiveness of 2-doses schedule: 98.3% (USA)
  - Significant reduction of breakthrough infections
  - Odds of developing varicella 95% lower if 2 doses versus 1
  - ↓↓ virus transmission and risk of late herpes zoster

→ 2 dose-schedule recommended (USA 2007, Germany 2009)

Dose 2 at 4-6 years or 15-23 months (at least 6w after dose 1)
Reasons for increase in at risk subjects with a 1-dose schedule:

- Waning immunity
- Primary vaccine failure
- Immuno-suppressed individuals
- Sub-optimal vaccine coverage
- Reduced natural exposure in childhood

Accumulating pool of susceptible individuals

Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine versus one dose of monovalent varicella vaccine: a multicentre, observer-blind, randomised, controlled trial

5803 children 12-22 months
10 European countries
3 years prospective follow up
2 doses 6w apart
2 doses MMRV vs MMR +V vs 2 doses MMR

Major efficacy of the 2-dose schedule
+ Risk of breakthrough infections 7 times less likely (vs 1 dose)
+ Decreased viral shedding among cases
→ ↓ VZV circulation and risk of HZ

Fever grade 3 (peak at day 9)
12.9% MMRV vs 7.3% MMR+V and 6.3% MMR

Supports a short 2-dose schedule in the 2nd year of life
(to avoid spread of varicella in daycare centres/schools and resurgence of measles!)

<table>
<thead>
<tr>
<th>MMRV</th>
<th>n/N</th>
<th>Total time to event (years)</th>
<th>Attack rate (97.5% CI) per 100 personyears</th>
<th>Vaccine efficacy (97.5% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>37/2279</td>
<td>6690</td>
<td>0.6 (0.4-0.8)</td>
<td>94.9 (92.4-96.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate</td>
<td>2/2279</td>
<td>6740</td>
<td>0.0 (0.0-0.1)</td>
<td>99.5 (97.5-99.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMR+V</td>
<td>All</td>
<td>243/2263</td>
<td>6455</td>
<td>3.8 (3.3-4.3)</td>
<td>65.4 (57.2-72.1)</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>37/2263</td>
<td>6698</td>
<td>0.6 (0.4-0.8)</td>
<td>90.7 (85.9-93.9)</td>
<td>..</td>
</tr>
<tr>
<td>MMR</td>
<td>All</td>
<td>201/743</td>
<td>1934</td>
<td>10.4 (9.1-11.9)</td>
<td>..</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>117/743</td>
<td>2647</td>
<td>5.7 (4.8-6.9)</td>
<td>..</td>
<td></td>
</tr>
</tbody>
</table>

Risk of vaccination?

- **Age shift?**
  Significant impact in all age groups
  ↓↓ hospitalization and complications (absolute numbers)

- **Duration of vaccine-induced immunity?**
  Need for further doses?

- **Increased risk of herpes zoster?**

  - Hypothesis “importance of an exogen boosting”?  
    *Thomas et al. Lancet* 2002
  - Never confirmed
  - Recent US surveillance:
    Slight increase in herpes zoster incidence but not attributable to the varicella vaccination program (started before UMV!)

*Hambleton S et al, J Infect Dis 2008  
Leung J et al, Clin Infect Dis 2011*
US experience: data after 10 years of varicella UMV implementation

ACIP

“Numerous studies and surveillance data have failed to demonstrate systematic increases in the incidence of herpes zoster infection in the USA since the implementation of UMV against varicella in 1995”

- USA: increase in no of HZ infection does not appear to be linked to vaccination:
  - Already present before vaccination
  - Increase strongest from ‘93-’96 = pré-vaccine era
  - High coverage States = Low coverage States
  - Incidence in children from States with high coverage confirms protective effect of vaccination

2Donahue et al. 1995; 3Marin et al. 2007; 4Hambleton et al. 2008
Does Monastic Life Predispose to the Risk of Saint Anthony’s Fire (Herpes Zoster)?

Background. The consequences of the epidemiology of varicella for zoster epidemiology are still debated. We therefore compared the frequency of herpes zoster in an adult population with virtually no varicella zoster virus (VZV) exposure with that in the general population (GP).

Methods. We performed a national, multicenter, observational, exposed versus nonexposed, comparative study. The nonexposed population consisted of members of contemplative monastic orders (CMO) of the Roman Catholic Church living in 40 isolated monasteries in France. The exposed population consisted of a sample of the GP representative of the French population in terms of age group, sex, socio-occupational categories, and regions.

Results. The primary analysis population comprised 920 members of CMO (41.5% nuns; mean age, 64.2 years) and 1533 members of the GP (51.9% women; mean age, 64.6 years). The reported frequency of zoster was 16.2% among CMO and 15.1% in the GP ($P = .27$, adjusted for sex and age). The reported mean age of onset of zoster was 54.8 and 48.6 years, respectively ($P = .36$).

Conclusions. This study failed to demonstrate an increased risk or earlier onset of zoster in members of CMO not exposed to VZV, compared with that in the GP. Although adults highly exposed to VZV could have a reduced risk of zoster, compared with the GP, our results suggest that the opposite is not true: adults not exposed to VZV are not at increased risk of zoster when compared with the GP, challenging the relevance of the assumptions and forecasts of current epidemiological models.

Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review

Benson Ogunjimi$^{1,2}$, Pierre Van Damme$^3$, Philippe Beutels$^{1,4}$

1 Centre for Health Economics Research and Modeling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, 2 Interuniversity Institute for Biostatistics and Statistical Bioinformatics, Hasselt University, Hasselt, Belgium, 3 Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium, 4 School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia

Abstract
Varicella-zoster virus (VZV) causes chickenpox and may subsequently reactivate to cause herpes zoster later in life. The exogenous boosting hypothesis states that re-exposure to circulating VZV can inhibit VZV reactivation and consequently also herpes zoster in VZV-immune individuals. Using this hypothesis, mathematical models predicted widespread chickenpox vaccination to increase herpes zoster incidence over more than 30 years. Some countries have postponed universal chickenpox vaccination, at least partially based on this prediction. After a systematic search and selection procedure, we analyzed different types of exogenous boosting studies. We graded 13 observational studies on herpes zoster incidence after widespread chickenpox vaccination, 4 longitudinal studies on VZV immunity after re-exposure, 9 epidemiological risk factor studies, 7 mathematical modeling studies as well as 7 other studies. We conclude that exogenous boosting exists, although not for all persons, nor in all situations. Its magnitude is yet to be determined adequately in any study field.
Current European recommendations for varicella vaccine

- **SIEVE 2008** (Society of Independent European Vaccination experts)
  
  “the SIEVE recommends such a policy as soon as financially and practically possible”  
  

- **BMC Medicine 2009, Review article** (experts opinion)

  “The clinical burden of varicella in Europe demonstrates a medical need for prevention strategies against the disease”……”Targeted vaccination in susceptible adolescents or high-risk groups is a strategy that does not have the potential to interrupt viral transmission and is far less effective in achieving high coverage rates when compared with childhood programmes”

- **ECDC (preliminary guidance, April 2014)**

  “Growing evidence that varicella vaccines are highly immunogenic, efficacious and safe in preventing varicella disease. Evidence from countries that have implemented UMV of infants demonstrates a significant and sustained decrease in the burden of varicella with no increases in HZ to date.”

  “Health economic models suggest that introduction of the vaccine may be cost-effective if there is no associated increase in HZ incidence, and may even be cost-saving.”

  In countries providing UMV: cost-efficiency of the vaccine was confirmed

  “If the HZ boosting hypothesis is assumed, then models predict a net increase in morbidity and healthcare costs for up to 50 years in some countries, after which net morbidity and healthcare costs will decrease.”

  “High heterogeneity in EU in varicella incidence and recommendations…Better post-vaccination surveillance and epidemiological research is needed to fill the knowledge gaps..”

- **Current status in Belgium**

  - Varicella vaccination kept for risk groups (CSS N°8145)
  - KCE (report 151A, 2010) “However, if the boosting hypothesis is not true <…>, different options for universal 2-dose vaccination against chickenpox in Belgium would be cost-effective at a vaccine price of €43/dose or lower.
  - Working group on varicella vaccine in the National Ministry Council for vaccination to assess cost/benefit balance
Conclusions

● **Varicella: common infection but high burden of disease**
  ▪ Individual discomfort
  ▪ Frequent and potentially severe complications
  ▪ Societal burden for patients, parents and caregivers

● **Effective protection by vaccination**
  ▪ 2-dose schedule
  ▪ Long-term protection and herd immunity
  ▪ Importance of a high population coverage rate

● **Belgian National data**
  ▪ In the line with other European countries (pre-vaccine era)
  ▪ Significant burden, especially among previously healthy young children

→ support the use of varicella vaccine (pending cost-economic evaluation)

● In countries where no UMV: **importance of active national prospective surveys** to assess the benefits achievable by new vaccination policies
Acknowledgements

101 participating hospitals all over our country!!

ISP and Pedisurv network

Mrs Véronique Leon
UMV (1 dose) varicella in USA: Despite high coverage, decrease in incidence of varicella is plateauing