Health economic evaluation of vaccine: the example of varicella-zoster virus

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Advances in infectious diseases modelling
Annecy, Les Pensières, December 10-12, 2007
Resource allocation in health care

- The Fourth hurdle to market:
  - Safety
  - Efficacy
  - Quality
  - Efficiency

- Economic evaluation = the «value for money» of new interventions
Types of economic evaluation

- How health consequences are valued?
  - Cost-effectiveness analysis: natural units
  - Cost-utility analysis: QALYs
  - Cost-benefit analysis: in monetary terms

- Ordered evaluations: CBA > CUA > CEA
Are vaccines different? (1)

- Vaccination has direct and indirect effects. Such externalities may be positive or negative (herd immunity).
- Epidemiological impacts of vaccination usually occur in the long term (sensitivity of the results to discounting rules).

IMPORTANCE OF MODELING

- Many vaccines prevent short-lived illness in very young children (QoL measurement, valuation of indirect costs).
- Some infections are eradicable.
Are vaccines different? (2)

- Key elements:
  - Herd immunity, externalities
  - Discounting, choice of end-points and time windows: prevention vs cure
  - Risk of underestimation of the value of vaccines
Discounting

- Should the health consequences be discounted?
- Do time preferences depend on decision time horizon? Should we use exponential or (quasi)-hyperbolic discounting models?
- What is the real objective of preventive programs? Should we consider risk reduction or long-term consequences on morbi/mortality as endpoints of vaccination programs?
- Are time preferences identical for all commodities? Should costs and health consequences be discounted at the same rate?
About varicella

- 90% of varicella cases occur in childhood, i.e. by the age of 15. Varicella is commonly regarded as a mild disease. Serious consequences are rare.
- The incidence of severe complications increases with age.
- Reactivation of dormant VZV results in herpes zoster (shingles).
- Immune response to VZV can be boosted via two mechanisms:
  - Sub-clinical reactivation of the virus ("endogeneous boosting")
  - Exposure to infectious individuals ("exogeneous boosting")
Vaccination strategies (1)

- **Mass childhood vaccination ± catch-up**
  - May lead to an increase in adult cases
    - Vaccination occurs in the youngest ages
    - As the risk of infection decreases, the average age at which exposure to varicella occurs increases
    - Waning vaccine-induced immunity may lead to a pool of susceptible older individuals
  - Significant number of breakthrough cases may occur
  - The loss of exogenous boosting may lead to an increase on the incidence of zoster
Age specific incidence of zoster for adults with and without children in their household

See also case-control study by Thomas (2002)
Vaccination strategies (2)

- **Targeted vaccinations:** susceptible adolescents and adults, health care workers, immunocompromised individuals

- **More recently, combined vaccinations**
  - Varicella vaccination (in childhood) and zoster vaccination (at older age)
What do we learn from US?

- Routine childhood varicella vaccination program has been introduced in US since 1995 (single injection)
- The recommendations for vaccination were strengthened in 1999 (varicella vaccination required before entry of a child into day care or school)
- In June 2006, the vaccination schedule has changed (2 doses)
Monthly Varicella Cases and Vaccine Coverage
Antelope Valley, CA, 1995 – 2003

Cases
Vaccine coverage

# Reduction in varicella incidence

<table>
<thead>
<tr>
<th>Age</th>
<th>Antelope Valley</th>
<th>Travis County</th>
<th>West Philadelphia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>73</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>1-4</td>
<td>88</td>
<td>91</td>
<td>87</td>
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<tr>
<td>5-9</td>
<td>71</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>10-14</td>
<td>51</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>15-19</td>
<td>60</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>20+</td>
<td>77</td>
<td>74</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>86</td>
<td>86</td>
</tr>
</tbody>
</table>

Seward JAMA 2002
Annual Hospitalization rates per 100,000 population
Varicella Active Surveillance Project, 1995-2002

Hospitalization Rate/100,000


0 0.5 1 1.5 2 2.5 3 3.5 4
Number of Varicella Deaths, 1990-2001

Average 107 deaths/year

Year


Number of deaths

120 100 124 115 99 81 26 6

Jumaan- CDC 2005
Adjusted annual rates of breakthrough varicella for children vaccinated between 12 mo-12 yrs: Antelope Valley, 1995-2004
Distribution of varicella cases by age: Antelope valley, CA, 1995 and 2004

1995: Peak incidence 3-6 years

2004: Peak incidence 9-11 years
Figure 2

Incidence: 2.77/1000 in 1999, 5.25/1000 in 2003 (+90%)
Epidemiological model (1)

Realistic Age Structured Dynamic Model

- Not vaccinated
  - Susceptibles
    - $M(a,t)$
    - $S(a,t)$
    - $E(a,t)$
    - $I(a,t)$
    - $V(a,t)$
    - $Sv(a,t)$
    - $Ev(a,t)$
    - $Rv(a,t)$
    - $Iv(a,t)$
    - $Vv(a,t)$
  - Latent infected
    - $E(a,t)$
    - $Ev(a,t)$
    - $Iv(a,t)$
  - Infectious
    - $I(a,t)$
  - Immune
    - $R(a,t)$

Not vaccinated
- Protected by maternal antibodies
  - $M(a,t)$
- Susceptibles
  - $S(a,t)$
- Latent infected
  - $E(a,t)$
- Infectious
  - $I(a,t)$
- Immune
  - $R(a,t)$

Vaccinated
- Protected by the vaccine
  - $V(a,t)$
- Partly Susceptibles
  - $Sv(a,t)$
- Latent infected
  - $Ev(a,t)$
- Infectious
  - $Iv(a,t)$
- Immune
  - $Rv(a,t)$

Symbols:
- $\delta$, $\lambda$, $\sigma$, $\nu$, $b$, $f$, $g$, $\tau$, $k$, $\lambda$
Epidemiological model (2)

\[ \lambda(a,t) \alpha \sigma \delta \]

\[ \rho(a) z \lambda(a,t) \]

\[ \kappa \lambda(a,t) \]
# Published economic evaluations

<table>
<thead>
<tr>
<th>Since 2000</th>
<th>Country</th>
<th>Herpes zoster</th>
<th>Waining</th>
<th>Herd immunity</th>
<th>model</th>
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</thead>
<tbody>
<tr>
<td>Scuffham et al. (2000)</td>
<td>Australia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Static</td>
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<tr>
<td><strong>Brisson et al (2002)</strong></td>
<td>Canada</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dynamic</td>
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<tr>
<td>Getsios et al (2002)</td>
<td>Canada</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Static</td>
</tr>
<tr>
<td>Banz et al. (2003)</td>
<td>Germany</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Dynamic</td>
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<tr>
<td>Hsu et al. (2003)</td>
<td>Taiwan</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Static</td>
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<tr>
<td>Coudeville et al. (2004)</td>
<td>Italy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Dynamic</td>
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<tr>
<td>Coudeville et al. (2005)</td>
<td>France &amp; Germany</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Lenne et al. (2006)</td>
<td>Spain</td>
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<tr>
<td>Hammerschmidt et al (2007)</td>
<td>Germany</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Dynamic</td>
</tr>
</tbody>
</table>
Models predictions (1)

- Incidence of varicella would rapidly decline following the implemention of vaccination
- After this “honeymoon period”, a rise in incidence would occur
- The post-vaccination equilibrium is always lower than the pre-vaccination level
- The age at infection is predicted to increase but the large reduction in incidence in children is likely to outweight any increase in incidence of chickenpox in adults
Impact on incidence:
Base case scenario, VC = 90%

Varicella cases
(per 1,000,000 person-years)

Year after start of vaccination

Infant
Catch-up
Adolescent

Impact on average age at infection:
Infant vaccination, VC = 90%

Impact on hospitalizations: Base case scenario, VC = 90%

Varicella inpatient days (per 1,000,000 person-years)

Year after start of vaccination

- Infant
- Catch-up
- Adolescent

Impact on herpes zoster incidence

- Infant, immunity 20 years
- 95% IC, immunity 7-41 years
- Adolescent, immunity 20 years

Varicella vaccination is less cost-effective from the health care payers perspective than from the societal perspective (time / leisure costs)

Routine vaccination of preteens is the preferred strategy under the health care payers perspective

Increases in zoster after routine vaccination of infants would render immunization highly cost-ineffective
<table>
<thead>
<tr>
<th>Persp</th>
<th>Infant</th>
<th>Catch-up</th>
<th>Preteen</th>
<th>Infant (BV)</th>
<th>Infant (zoster)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>0.61</td>
<td>0.60</td>
<td>0.73</td>
<td>0.59</td>
<td>0.16</td>
</tr>
<tr>
<td>Society</td>
<td>5.24</td>
<td>4.90</td>
<td>4.44</td>
<td>5.09</td>
<td></td>
</tr>
<tr>
<td>ICER ($/LYG)</td>
<td>44503</td>
<td>50866</td>
<td><strong>18508</strong></td>
<td>46896</td>
<td>118188</td>
</tr>
</tbody>
</table>

Models predictions (4)

## Models predictions (5)

<table>
<thead>
<tr>
<th>Infant vaccination (B/C ratio)</th>
<th>Country</th>
<th>Societal</th>
<th>Health care payers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scuffham et al. (2000)</td>
<td>Australia</td>
<td>2.79</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Brisson &amp; Edmunds (2002)</strong>*</td>
<td>Canada</td>
<td>5.24</td>
<td>0.61</td>
</tr>
<tr>
<td>Getsios et al. (2002)</td>
<td>Canada</td>
<td>1.69</td>
<td>0.62</td>
</tr>
<tr>
<td>Hsu et al. (2003)</td>
<td>Taiwan</td>
<td>2.06</td>
<td>0.34</td>
</tr>
<tr>
<td>Banz et al. (2003)</td>
<td>Germany</td>
<td>4.12</td>
<td>1.75</td>
</tr>
<tr>
<td>Coudeville at al. (2004)</td>
<td>Italy</td>
<td>3.50</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Without taking account zoster
Sensitivity analysis

- **Epidemiological factors:**
  - Vaccine efficacy
  - Vaccination coverage

- **Economic factors**
  - Vaccine price
  - Value of time/leisure lost (indirect costs)
  - Discount rate for health consequences and time horizon

- Predictive value of anamnestic screening (for targeted vaccinations)
Indirect costs (1)

- Should indirect costs be included in cost-effectiveness analysis?
- If yes, how to measure productivity lost?
  - Human-capital method:
    - Reference to welfare economics (wage rate = opportunity cost of time)
    - Easy to implement
    - Potential productivity costs
  - Friction-costs method:
    - More realistic estimates of productivity costs
    - More data need to be collected
  - The two methods lead to similar results when the period of absenteeism is short (as in chickenpox case)
Indirect costs (2)

- Indirect costs = driver for varicella vaccine demand?
- Few WTP studies in the field
  - Revealed preferences versus real demand (eg Australia)
  - Impacts on vaccination coverage (if CV is not high enough => increase in average age at infection)
Comparison of studies

- Transferability versus generalisability

- Differences between studies:
  - Hypothesis on key parameters (vaccine efficacy / waining / vaccination coverage)
  - Epidemiological factors
  - Organization of health care systems (impact on costs)
Treatment costs per varicella case according to age (€ 2002)

### FRANCE

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Additional Examinations</th>
<th>Hospitalisations</th>
<th>Pharmaceutical Prescriptions</th>
<th>Medical Consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17 years</td>
<td>4.2</td>
<td>13</td>
<td>0.2</td>
<td>30.1</td>
</tr>
<tr>
<td>&gt;= 18 years</td>
<td>1.9</td>
<td>0.0</td>
<td>0.0</td>
<td>40.8</td>
</tr>
</tbody>
</table>

### GERMANY

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Additional Examinations</th>
<th>Hospitalisations</th>
<th>Pharmaceutical Prescriptions</th>
<th>Medical Consultations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 years</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>20.35</td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>33.8</td>
</tr>
</tbody>
</table>

### Varicella Treatment Costs

- **FRANCE**:
  - Range: € 43.4-52.5
  - % Supported by HS: 63%

- **GERMANY**:
  - Range: € 49.3-65.7
  - % Supported by HS: 100%
Indirect costs per varicella case according to age (€ 2002)

<table>
<thead>
<tr>
<th>Indirect costs</th>
<th>FRANCE</th>
<th>GERMANY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-17 years</td>
<td>€ 97,0</td>
<td>€ 795,0</td>
</tr>
<tr>
<td>&gt;= 18 years</td>
<td>€ 933,4</td>
<td></td>
</tr>
<tr>
<td>1-12 years</td>
<td>€ 105,0</td>
<td></td>
</tr>
<tr>
<td>&gt; 12 years</td>
<td></td>
<td>€ 795,0</td>
</tr>
</tbody>
</table>

Range

- FRANCE: 83.8-110.7
- GERMANY: 84-126

% Supported by HS

- FRANCE: 1.5%
- GERMANY: 70%

Coudeville et al. (2004)
Average annual costs related to varicella (millions of 2002 €) according to coverage rate

**Germany – Payer’s perspective:**

- No vaccination
  - Sick leaves costs: 50.7
  - Treatment costs: 42.2
  - Vaccination costs: 0

- High coverage rate (90%)
  - Sick leaves costs: 5.4
  - Treatment costs: 35.3
  - Vaccination costs: 0

- Medium coverage (70%)
  - Sick leaves costs: 27
  - Treatment costs: 13.4
  - Vaccination costs: 12.1

- Low coverage (45%)
  - Sick leaves costs: 16.8
  - Treatment costs: 24.4
  - Vaccination costs: 2

**France – Payer’s perspective:**

- No vaccination
  - Sick leaves costs: 25
  - Treatment costs: 0
  - Vaccination costs: 0

- High coverage rate (90%)
  - Sick leaves costs: 23.8
  - Treatment costs: 1.4
  - Vaccination costs: 2.7

- Medium coverage (70%)
  - Sick leaves costs: 18
  - Treatment costs: 8.2
  - Vaccination costs: 2

- Low coverage (45%)
  - Sick leaves costs: 11
  - Treatment costs: 15.4
  - Vaccination costs: 1
Average annual costs related to varicella (millions of 2002 €) according to coverage rate

**Germany – Societal perspective:**

- **No vaccination:**
  - Sick leaves: 100.9
  - Treatment: 42.2
  - Vaccination: 0

- **High coverage rate (90%):**
  - Sick leaves: 42.2
  - Treatment: 35.3
  - Vaccination: 4.7

- **Medium coverage (70%):**
  - Sick leaves: 16.8
  - Treatment: 27
  - Vaccination: 12.1

- **Low coverage (45%):**
  - Sick leaves: 24.4
  - Treatment: 16.8
  - Vaccination: 70.4

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**France – Societal perspective:**

- **No vaccination:**
  - Sick leaves: 109.8
  - Treatment: 39.1
  - Vaccination: 0

- **High coverage rate (90%):**
  - Sick leaves: 12.6
  - Treatment: 36.7
  - Vaccination: 19.3

- **Medium coverage (70%):**
  - Sick leaves: 27.8
  - Treatment: 16.9
  - Vaccination: 56.7

- **Low coverage (45%):**
  - Sick leaves: 24.1
  - Treatment: 16.9
  - Vaccination: 84.6
Epidemiological model

Varicella: 1 Year old
Zoster: 60 years old

Combined strategies (2)
Mixing patterns
Zoster vaccination

Preliminary results