Health Economics.... A New Toxicity?

"The drug itself has no side effects - but the number of health economists needed to prove its value may cause dizziness and nausea"
SPECIFICITIES OF HEALTH ECONOMICS IN THE AREA OF VACCINES EVALUATION

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OVERVIEW

- **Decision-making context**
  - Introduction into the current Dutch landscape
  - Role of cost-effectiveness
  - Thresholds

- **Guidelines**
  - Discounting
  - Modeling
  - Perspective

- **Examples**
  - HPV
  - Influenza
  - ...
4th HURDLE IN THE DUTCH NATIONAL IMMUNIZATION PROGRAM
Economic evaluation of meningococcal serogroup C conjugate vaccination programmes in The Netherlands and its impact on decision-making

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4th HURDLE

- **Hepatitis B**
  - 2000 ⇒ not cost-effective
  - 2008 ⇒ cost-effective

- **Meningococcal Vaccination 2001**
  - 3 shots not cost-effective

- **HPV, no full catch-up due to unfavourable cost-effectiveness**

- **Conjugate pneumococcal vaccination**
  - 2001 ⇒ not cost-effective
  - 2005 ⇒ cost-effective
  - 2010 ⇒ not cost-effective
ISSUES

- **General**
  - How to interpret the cost-effectiveness ratio?
  - Types of costs to include: broader societal, production losses, indirect medical ...

- **Specific for vaccines**
  - Lack of hard endpoints in trials
  - Discounting
  - Type of model to use

Funding of drugs: do vaccines warrant a different approach?

Philippe Beutels, Paul A Scuffham, C Raina Macintyre

Vaccines have features that require special consideration when assessing their cost-effectiveness. These features are related to herd immunity, quality-of-life losses in young children, parental care and work loss, time preference, uncertainty, eradication, macroeconomics, and tiered pricing. Advisory committees on public funding for vaccines, or for pharmaceuticals in general, should be knowledgeable about these special features. We discuss key issues and difficulties in decision making for vaccines against rotavirus, human papillomavirus, varicella-zoster virus, influenza virus, and *Streptococcus pneumoniae*. We argue that guidelines for economic evaluation should be reconsidered generally to recommend (1) modelling options for the assessment of interventions against infectious diseases; (2) a wider perspective to account for impacts on third parties, if relevant; (3) a wider scope of costs than health-care system costs alone, if appropriate; and (4) alternative discounting techniques to explore social time preference over long periods.

Introduction

In many high-income countries, public funding of preventive vaccines is assessed based on the same criteria as the funding of curative pharmaceutical drugs. Such a criterion is often considered to be a threshold value for the cost-effectiveness ratio of a vaccine at a specified level of confidence. However, this approach may not adequately account for the unique features of vaccines. To address these issues, we discuss the following points:

1. **Herd Immunity**
   - Vaccines can provide indirect benefits to those not vaccinated through herd immunity. This effect is not easily captured in traditional cost-benefit analysis.

2. **Quality-of-Life Losses**
   - Young children often experience significant health-related quality of life losses due to vaccine-preventable diseases. These losses should be taken into account in economic evaluations.

3. **Parental Care and Work Loss**
   - Parental care and work loss are common consequences of vaccine-preventable diseases. These costs are often not adequately considered in traditional economic evaluations.

4. **Time Preference**
   - The time horizon for economic evaluations should be expanded to account for long-term benefits and costs associated with vaccine programs.

5. **Uncertainty**
   - Uncertainty in vaccine efficacy and cost estimates can significantly affect the results of economic evaluations. Methods for handling uncertainty should be employed.

6. **Eradication**
   - Some vaccines, such as those for polio and smallpox, can lead to population-level eradication of diseases. Economic evaluations should consider the potential for long-term benefits through eradication.

7. **Macroeconomics**
   - The economic impact of vaccine-preventable diseases can extend beyond the direct costs of treatment and hospitalization. Macroeconomic impacts, such as reduced productivity and increased healthcare spending, should be included.

8. **Tiered Pricing**
   - Tiered pricing strategies can be used to make vaccines more accessible in low-income settings. Economic evaluations should consider the potential cost savings and impact of tiered pricing.

Discounting

Discounting is a critical aspect of economic evaluations. It is used to account for the time value of money and to compare costs and benefits over different time horizons. Discounting rates are often determined by societal preferences and can vary widely. In the context of vaccines, discounting can be particularly challenging due to the long-term benefits associated with eradication and herd immunity.

Modeling Options

Modeling options for the assessment of interventions against infectious diseases are important. Different models can be used to estimate the costs and benefits of vaccines, including population-level models, individual-level models, and cost-effectiveness models. Each model has its strengths and limitations, and choice of model should be guided by the specific research question and available data.

In conclusion, vaccine cost-effectiveness evaluations require a comprehensive approach that accounts for unique features of vaccines. Addressing these issues can lead to more accurate and relevant economic evaluations, informing public health decision-making.
Since 2005 cost-effectiveness plays a role in reimbursement for new innovative drugs

- For example, diabetes, psychotropic and haematological/oncological drugs
- Oseltamivir, but also HPV
- Dutch Foundation for Health Care Insurance (CVZ)
- NICE (SMC, KCE)

No threshold

- € 20,000 per QALY
- € 80,000 per QALY
- Assessment based on qualitative criteria
- 11 guidelines for good pharmacoeconomic research
- Really no threshold...??
Fig 3 | The effect on cost effectiveness ratios of varying the level of net indirect effect of vaccination for individuals aged 5 years or older. The horizontal dashed line shows the threshold at €50 000 per QALY. PCV-7/10/13, seven/10/13 valent pneumococcal conjugated vaccine (3+1 dose schedule); QALY, quality adjusted life year
'Grens noodzakelijk voor kosten gezondheidszorg'

REPORTAGE
GRENS AAN ZORGKOSTEN

- Hoogleraar: 50.000 euro per gewonnen levensjaar is redelijk
- Debat over geld verdienen aan gezondheid gaat snel over grenzen

Door Arend van Wijngaarden

Groningen De kosten van de gezondheidszorg in Nederland lopen gigantisch uit de hand en daarom moet er maar eens een grens getrokken worden, betoogde professor Maarten Postma, hoogleraar farmacie en economie aan de Rijksuniversiteit Groningen gisteren tijdens een debat. "Ik stel voor 50.000 euro per gewonnen levensjaar. Dat is een redelijke grens."
Tabel I. Proportie aanvaardbare incrementale kosten-effectiviteits simulaties, gegeven de bereidheid €50000 te betalen voor een extra 'gezond levensjaar' (Quality Adjusted Life Year, QALY) (gebaseerd op 1000 simulaties). Resultaten voor vaccinatie met Rotarix® en RotaTeq® vanuit het perspectief van de betaler voor de gezondheidszorg. Scenarios waarbij geen, één of twee verzorgers per kind in rekening gebracht werden, en waarbij de last van kinderen (en hun verzorger(s)) die ziek zijn door rotavirusinfectie, maar voor wie geen medische hulp gezocht wordt, al dan niet in rekening gebracht werd.

<table>
<thead>
<tr>
<th></th>
<th>ROTARIX® 'geen medische hulp' niet in rekening gebracht</th>
<th>ROTARIX® 'geen medische hulp' in rekening gebracht</th>
<th>ROTATEQ® 'geen medische hulp' niet in rekening gebracht</th>
<th>ROTATEQ® 'geen medische hulp' in rekening gebracht</th>
</tr>
</thead>
<tbody>
<tr>
<td>geen verzorger</td>
<td>2%</td>
<td>8%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>1 verzorger</td>
<td>6%</td>
<td>46%</td>
<td>1%</td>
<td>13%</td>
</tr>
<tr>
<td>2 verzorgers</td>
<td>26%</td>
<td>81%</td>
<td>6%</td>
<td>46%</td>
</tr>
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</table>
ISSUES

- How to interpret the cost-effectiveness ratio?
- Lack of hard endpoints in trials
- Discounting
- Type of model to use
- Perspective

Quantification of the Potential Impact of Cost-effectiveness Thresholds on Dutch Drug Expenditures Using Retrospective Analysis

Cornelis Boersma, PhD, Adriaan Broere, Maarten J. Postma, PhD Prof

Unit of PharmacoEpidemiology & Pharmacoeconomics (PE²), Department of Pharmacy, University of Groningen, Groningen, The Netherlands
SPECIFIC FOR VACCINES

- How to interpret the cost-effectiveness ratio?
- Lack of hard endpoints in trials
- Discounting
- Type of model to use
- Societal perspective
MODELLING

- To extrapolate from intermediate endpoints to "hard endpoints"
  - Blood pressure
  - Immunogenic parameters

- Time horizon
  - From short-term trial to lifetime in the economic models following a cohort, for example, in a Markov model
  - Although long-term effects are “discounted away”
SPECIFIC FOR VACCINES

- How to interpret the cost-effectiveness ratio?
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DISCOUNTING

- Rationale for discounting is *time preference*
- €100 \((t=0)\) is preferred over €100 \((t=1)\)
- €100 \((t=0)\) = €100\((1+r)\) \((t=1)\)
- Netherlands: \(r=4\%\)
- The exact rate is derived from real rate-of-return on investment
- Discount rate comes over and above the deflator
- Discounting relates to real *economic growth* (90%) and uncertainty (10%)
- Also applied to life years (and QALYs) related to *growth in life expectancy*
Discounting

- Developed for money, but also applied to health
  - $1 \text{ life year (t=1)} = 1/1.04 \text{ life year (t=0)}$
  - $1 \text{ life year (t=2)} = 1/1.04^2 \text{ life year (t=0)}$
  - ...
  - $1 \text{ life year (t=80)} = 1/1.04^{80} \text{ life year (t=0)}$

- $80 \Leftrightarrow 20$
Education and debate

Summary points

New National Institute for Health and Clinical Excellence guidelines change the discount rates for costs and effects from 6% and 1.5% respectively to 3.5% for both.

This change gives a lower weight to future health effects and may worsen the cost effectiveness ratio, especially for preventive interventions.

Differential discounting is more appropriate when non-monetary outcomes like QALYs are used.

NICE should return to a 1.5% discount rate for effects.

Need for differential discounting of costs and health effects in cost effectiveness analyses

Werner B F Brouwer, Louis W Niessen, Maarten J Postuma, Frans F H Rutten

The decision of the National Institute for Health and Clinical Excellence to abandon differential discounting of future health is a step backwards and could change funding decisions.
SPECIFIC FOR VACCINES

- How to interpret the cost-effectiveness ratio?
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DISCOUNTING

- **NL**
  - Costs: 4%
  - Health: 1.5%

- Most countries do equal discounting

- Differential discounting
  - NL
  - Belgium
  - Estonia
  - Swiss

- Constant or decreasing?
Intervention

Infectious disease

Transmission of pathogen* between humans

Intervention has influence on susceptibility to infection or transmission of infection

Interventions in groups which contribute significantly to the transmission of the infection

Decision maker is interested in all outcomes for the entire population (e.g., full societal perspective)

Dynamic model

Non-infectious disease

No transmission of pathogen* between humans (e.g. tetanus, rabies)

Intervention has no influence on susceptibility to infection and transmission of infection (e.g. therapeutic interventions)

Selective interventions in small groups which do not contribute significantly to the transmission of the infection (hepatitis A vaccination in travellers from low to high endemicity countries)

Decision maker is solely interested in the direct outcomes in the target group that receives the intervention (e.g., a limited payer’s perspective)

Static model
Intervention

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Static model
Intervention

Infectious disease
- Transmission of pathogen* between humans
  - Intervention has influence on susceptibility to infection or transmission of infection
    - Interventions in groups which contribute significantly to the transmission of the infection
      - Decision maker is interested in all outcomes for the entire population (e.g., full societal perspective)
        - Dynamic model
      - Decision maker is solely interested in the direct outcomes in the target group that receives the intervention (e.g., a limited payer’s perspective)
    - Selective interventions in small groups which do not contribute significantly to the transmission of the infection (hepatitis A vaccination in travellers from low to high endemicity countries)

Non-infectious disease
- No transmission of pathogen* between humans (e.g. tetanus, rabies)
  - Intervention has no influence on susceptibility to infection and transmission of infection (e.g. therapeutic interventions)

Dynamic model
Static model
Figure 3: Flow chart to help determine when dynamic or static models are appropriate

- Vaccination in humans
  - Infectious disease (at equilibrium)
    - Human to human transmission non-existent or exceptional (e.g. rabies, tetanus, Q fever, Japanese encephalitis)
      - Static model (2)
      - There are no negative externalities from vaccination, or these are very likely to be smaller than positive externalities
        - Dynamic model (5)
      - Static model shows unfavourable or borderline favourable** result for vaccination
        - Dynamic model (9)
  - Non-infectious disease (e.g. leukaemia, breast cancer)
    - Human to human transmission common (including via a vector e.g. malaria)
      - Vaccine reduces susceptibility to infection and/or infective transmission potential (e.g. measles, varicella zoster, hepatitis B)
        - Static model (4)
        - Static model shows favourable** results for vaccination
          - Static model acceptable (10)
      - The eligible target groups are not or do not include an epidemiologically influential subgroup (e.g. the elderly for influenza or pneumococcus, travellers from low to high endemic areas for HAV)
        - Static model (3)
        - There are negative externalities from vaccination, which potentially exceed positive externalities
          - Static model (5)
          - Static model including observations on externalities from a comparable setting acceptable (6)
            - Dynamic model (7)
Static Model

- Constant force of infection / chronic disease
- No herd immunity

- Modellers
  - Keep it as simple as possible
  - However, grasp all essentials

- Used
  - Cocooning in pertussis
  - Initially in pneumococcal
Results: In the base-case analysis, cocooning and maternal immunization were found to be effective in reducing the incidence of pertussis among infants (123 and 174 infant cases were expected to be prevented, respectively). Furthermore, cocooning and maternal immunization were estimated to be cost-effective from a payer’s perspective (€4600 [US $6400]/QALY and €3500 [$4900]/QALY, respectively) and even cost-saving from a societal perspective (savings of up to €7200 [$10,100] and €5000 [$7000], respectively). Sensitivity
DYNAMIC MODELLING

- Describing/simulating the spread of disease in populations
- Herd immunity

- Other effects
  - Negative effects
  - Age shift
  - Serotype replacement

- Age shift
  - VZV
  - Pertussis
DYNAMIC MODEL

Susceptible $\rightarrow$ Infected $\rightarrow$ Susceptible (SIS)

\[ \frac{dS}{dt} = -\beta \cdot k \cdot S(t) \frac{I(t)}{N} + \nu I(t) \]
\[ \frac{dI}{dt} = \beta \cdot k \cdot S(t) \frac{I(t)}{N} - \nu I(t) \]

- $S(t)$ = number susceptible
- $I(t)$ = number infected
- $\beta$ = transmission parameter
- $\nu$ = recovery rate
- $k$ = number of partners
- $N$ = total population
\[ \frac{dS}{dt} = -\beta \cdot k \cdot S(t) \frac{I(t)}{N} + \nu I(t) \]

\[ \frac{dI}{dt} = \beta \cdot k \cdot S(t) \frac{I(t)}{N} - \nu I(t) \]
Nieuwe uitdagingen voor de farmaco-economie

Introductie HPV-vaccin

Met de recente introductie van Gardasil en de verwachte registratie van Cervarix tegen humaan papillomavirus, rijst de vraag naar de kosteneffectiviteit van vaccinatie tegen baarmoederhalskanker, en naar de beste vaccinatiestrategie.

Tekst | Maarten Postma, Hans Nijman, Toos Daemen, Ate van der Zee, Jan Wilschut

UBC
United BioSource Corporation
Evidence Matters

university of groningen
HPV-VACCINE

- HPV-vaccination in NL
  - 12 year-old girls
  - Bivalent vaccine was selected after tendering
  - Catch-up up-to-and-including 16 years
  - On top of successful screening program

- Unexpected low coverage of HPV vaccination at 50%

- Model calibration on
  - HPV-incidence for a sentinel study
  - National cancer registries
Cervical cancer incidence vs. Age (years)
T Westra, Submitted
<table>
<thead>
<tr>
<th>Threshold ($/QALY)</th>
<th>Cost-effective</th>
<th>% of Simulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$20,000</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>$50,000</td>
<td>64%</td>
<td>70%</td>
</tr>
<tr>
<td>$100,000</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>
GUIDELINES

- How to interpret the cost-effectiveness ratio?
- Lack of hard endpoints in trials
- Discounting
- Type of model to use
- Societal perspective
SOCIETAL PERSPECTIVE

- As opposed to TPP (NICE)
- All benefits and losses, irrespective of who gains and loses
- Morbidity (sickness leave) and mortality (life years lost)
- Friction costs vs. human capital
- Double counting
SUMMARIZING

- Role of health economics
  - NIP
  - RP

- Discounting
  - Do
  - Differential or not?
  - Decreasing or constant?

- Dynamic models and beyond
  - As simple as possible
  - As complex as required, often the case
  - However, major investment

- Perspective
  - Differs per country, inclusive specific method used