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# Effect of Vaccinations on Human Health

(Pharmacoeconomical evaluation of vaccines)

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# Endpoints (targets) of vaccinations

Prevention of

Death

Permanent disability

Severe disease

Illness

Promotion of wellness



# The greatest impact on human health – elimination of a disease

However, continued vaccination programme  
will require continuing investment

The best result

- eradication of disease  
and
- stopping of vaccinations



The most important achievement of preventive medicine of all times:

Eradication of smallpox

Achieved in 1975 in Asia and in 1977 in Africa

Vaccinations discontinued worldwide in 1978



# The next eradication target: poliomyelitis

Not many deaths, but  
350.000 paralytic  
cases a year in 1988,  
before launch of  
eradication programme

First target year 2000



POLIO

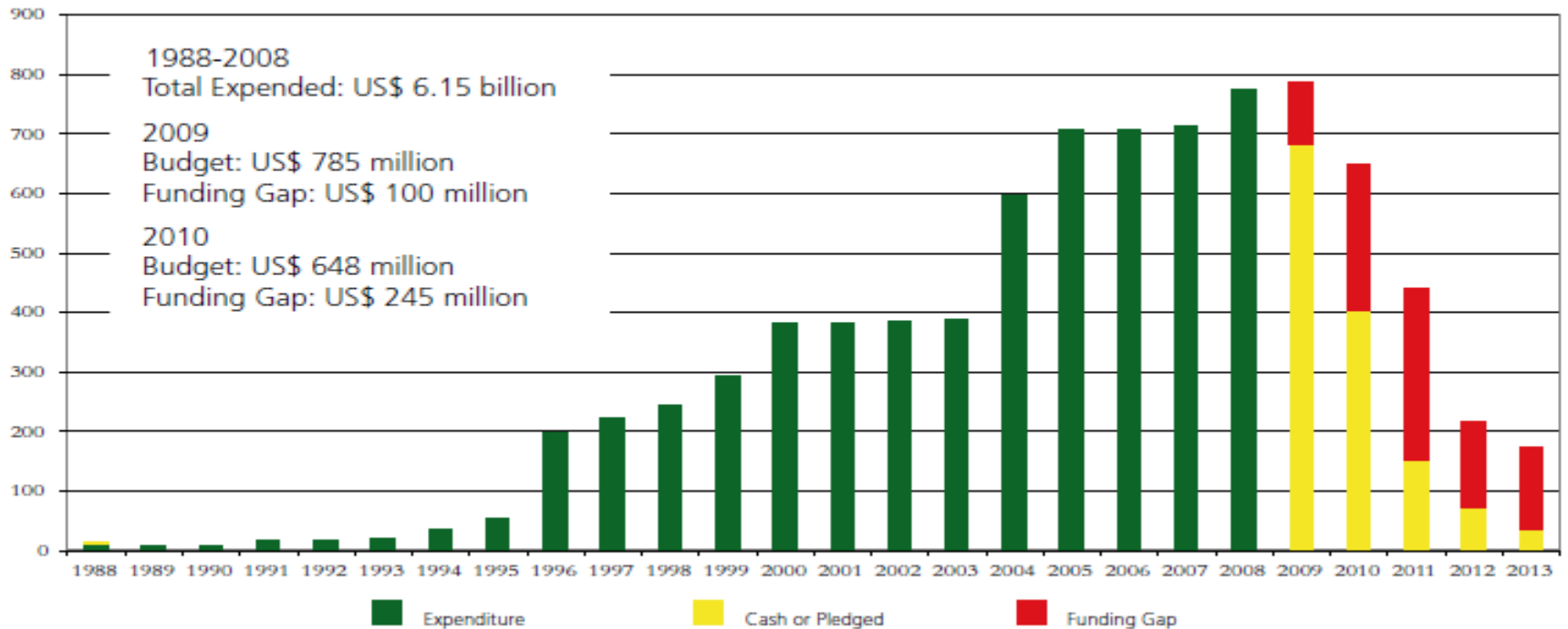
The beginning of the end

# Failure to achieve global eradication of poliomyelitis by 2009: Biology or cost?

Figure 1: Areas of indigenous transmission and 'wild poliovirus importation belt'



Figure 2: Annual Expenditure, 1988-2008  
 Financial Resource Requirements, Contributions, Funding Gap, 2009-2013



# Costs and benefits of polio eradication: a long-run global perspective

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Vaccine 2003;21:702–05

Total cost of polio eradication programme if vaccination is discontinued after 2010

**\$ 67 billion**

Medical care cost savings in 1970–2050

**\$ 128 billion**

In addition, the programme will prevent 855.000 deaths, 4 million paralysis and 40 million disability

# Eradication of measles

Already successful in the Americas

→ proof of principle

Overall reduction in deaths from 1.5 million to 250.000 annually in the world

Eradication not achieved because of

- poor coverage in Europe
- available funds used for poliomyelitis campaign



# MMR disease in Europe

## Measles

Recent outbreaks in Europe

Germany, France, Italy, Switzerland

The Netherlands, Ireland etc.



## Mumps

Major outbreak in UK

## Rubella

Outbreaks in Greece, Eastern Europe

# Mumps vaccine

Few permanent sequelae from mumps



Major argument for mumps vaccination of young men in Finland in the 1960's was orchitis

- 20–30 % of men susceptible
- most got mumps in the army
- rate of orchitis 10–20 %
- 1/3 bilateral



Not "cost-effective" as a stand alone (inactivated) vaccine  
Mumps can be eliminated as part of MMR vaccine

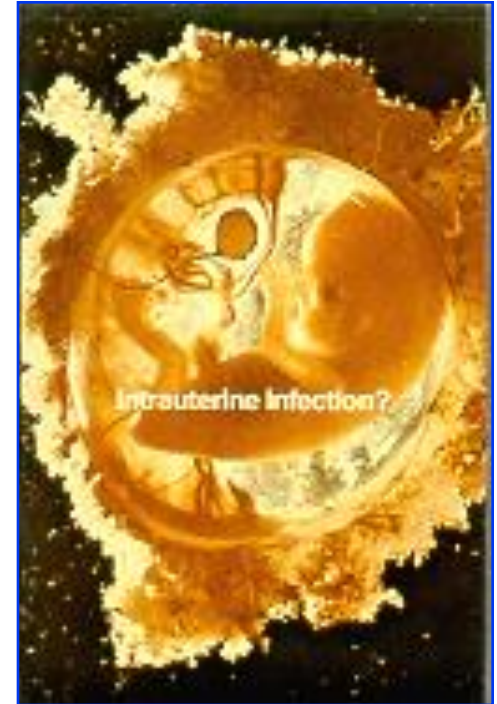
# Rubella vaccine

Not controversial because

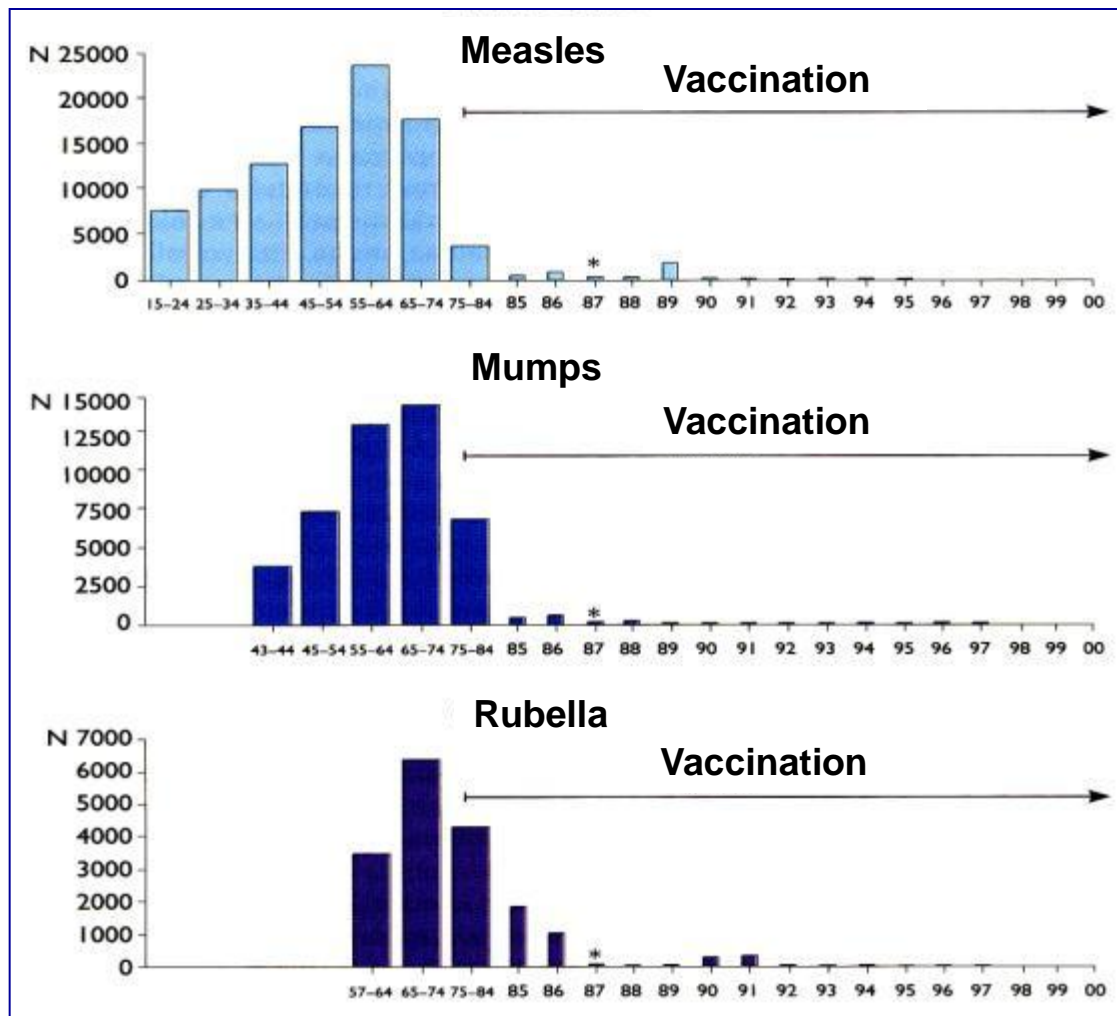
- causes permanent damage (deafness, blindness, cardiac problems, mental retardation)
- caused 20.000 birth defects in the US in 1964

Vaccine can be combined in  
MMR

Global elimination possible in  
conjunction with measles



# Elimination of indigenous measles, mumps and rubella from Finland after MMR-vaccination (2 dose programme at 15 months and 6 years of age)



# Control of MMR diseases



MMR diseases can be eliminated in Europe (Example Finland) by two-dose vaccination programme but vaccinations cannot be discontinued until global eradication

Shifting to early two-dose programme, example Germany, at 11–14 months and 15–23 months will help to reach elimination

Turkey has eliminated measles!



# Varicella

Can varicella be eliminated like MMR diseases?

Can the elimination be through combined MMRV vaccination?



# Varicella from medical perspective

## Severe varicella

adults vs. children  
pregnant women  
sibling contact  
atopic disease

## Immunocompromised

leukemia  
organ transplant  
corticosteroid therapy



# Complications of varicella

severe hemorrhagic varicella

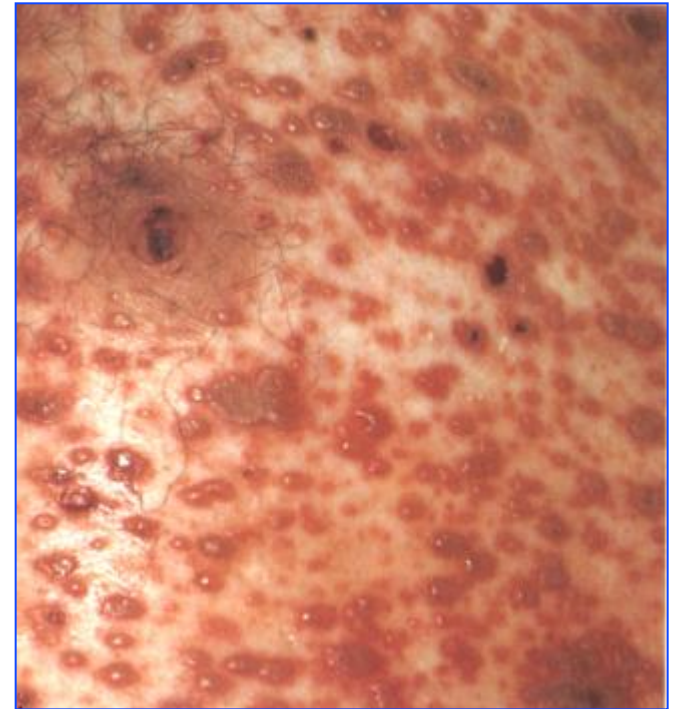
pneumonia

encephalitis

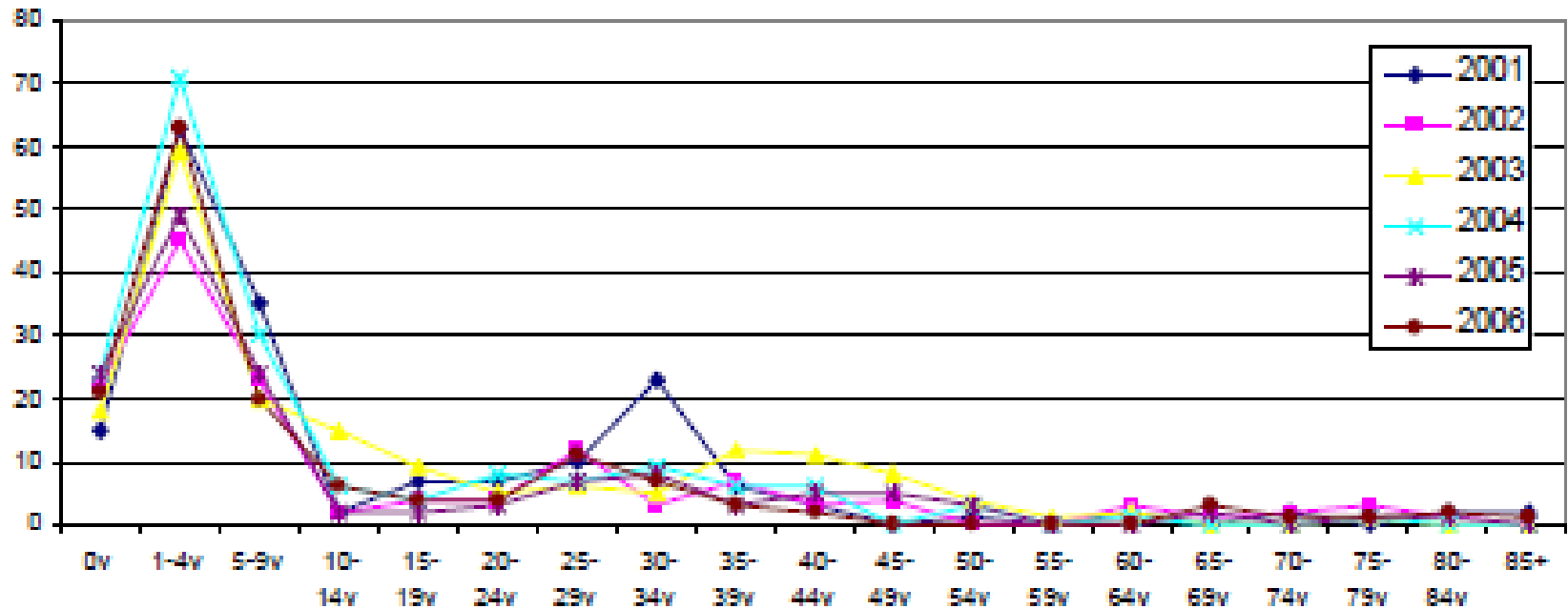
cerebellar ataxia

necrotizing fasciitis

(group A streptococcus)

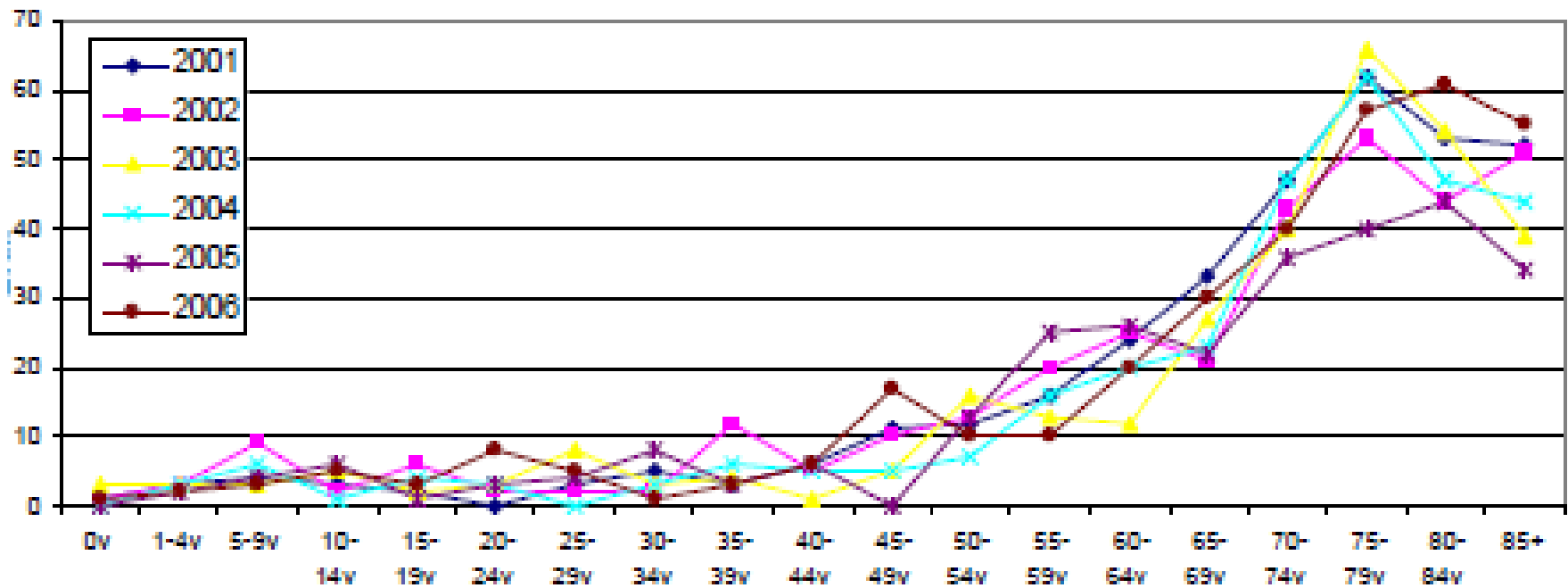


# Hospitalizations for varicella, Finland 2001–2006



(Only) 0.25 % of age group hospitalized  
3 deaths / 100.000 children

# Hospitalizations for zoster, Finland 2001–2006



Burden of disease from zoster 3 x greater than from varicella

# Elimination strategy for varicella (Varicella cannot be eradicated because of latency and zoster)



Dose

Age

Single varicella

12 months

MMR

15 months

MMRV combination

6 years

Catch-up vaccination

1–12 years

Zoster vaccination

60 years

# Elimination of wild type VZV with a 2-dose programme and catch-up

- Protection against severe varicella of vaccinated subjects
- Indirect protection of unvaccinated high risk children
- Elimination of (most of) zoster in the long run
- Temporary increase of zoster??

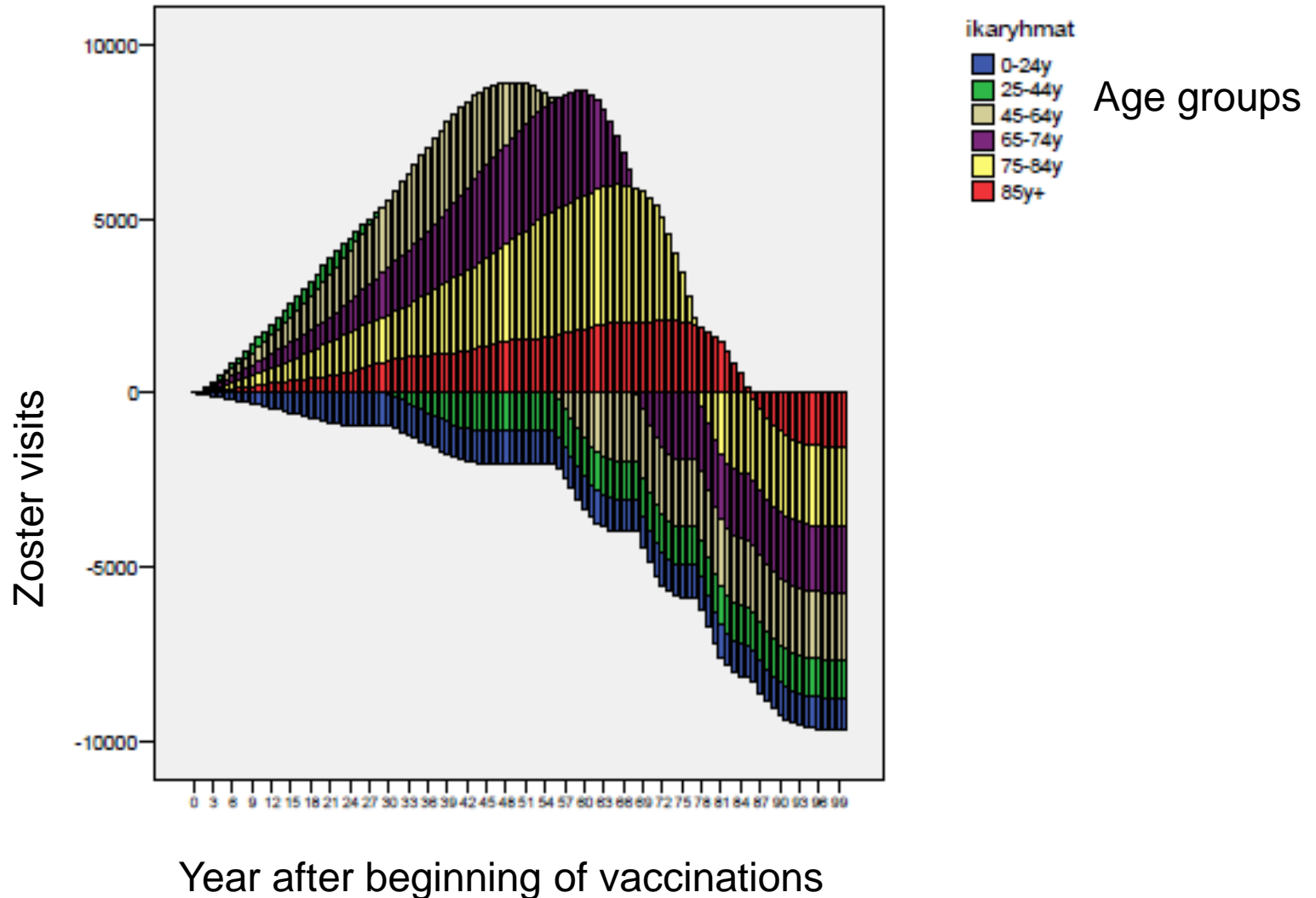
# Temporary increase of zoster

Will it happen?

How big is the increase?

Shift to an earlier age?

Medical significance?



# Varicella

Quality adjusted life years (QALY)

Additional QALYs gained with 2-dose  
varicella vaccine programme + catch-up  
30.000 Euros

but

increase in zoster (in worst case scenario)  
will increase additional QALYs to  
82.000 Euros

# Threshold for cost-effectiveness in economic evaluations for preventive measures (vaccinations) in Europe

Per QALY gained

20.000 €

The Netherlands

23.000 to 35.000 €

UK

1 Zwart-van Rijken et al., Pharmacoeconomics 2000;18:149–60

2 Devlin et al., Health Econ. 2004;13:437–52

# Background and comparison

”UK-standard” 35.000 Euros  
per additional QALYs gained

→ varicella vaccination programme leading  
to elimination of varicella is cost-effective  
but (critics say)  
is offset by increase of zoster (although  
not proven)

# Rotavirus disease

watery diarrhea

vomiting

fever

→ dehydration, death



Deaths from rotavirus gastroenteritis

440.000 to 600.000 worldwide

Globally, prevention of rotavirus associated deaths is the target of rotavirus vaccination

# Universal rotavirus vaccination programme in Mexico, since 2006 (M. Patel, VED 2009)



- Birth cohort 2 million
- Vaccine coverage  $\geq 74$  % (end of 2007)
- All cause diarrheal deaths

Pre-vaccine 2003–2006

Average 1792 deaths a year

Post-vaccine 2008

1107 deaths

**First indication of actual prevention of deaths**

# Burden of rotavirus disease in Europe

200 deaths / year in EU

100.000 hospitalizations

30.000 nosocomial infections

Severe RV disease

- distress of infant
- anxiety of family

Rotavirus vaccination will have a major impact on childhood morbidity, but not mortality



# Rotavirus Vaccines in Europe

Rotarix™ (GSK); 2 doses



RotaTeq™ (SP MSD); 3 doses



ESPID / ESPGHAN

Routine administration of rotavirus vaccine to all healthy infants is recommended

# Universal rotavirus vaccination in Europe

## Belgium 2007 (Rotarix™)

- coverage 85 %



## Austria 2008 (RotaTeq™ → Rotarix™)

- coverage 80–90 %



## Finland 2009 (RotaTeq)

- coverage 40 % (expected to increase rapidly to  $\geq 90$  %)



## State of Saxony

- coverage 37 %



# Rotavirus vaccination in Europe in 2009

## Moderate coverage

Greece	45 %	Hungary	12 %
Spain	36 %	Lithuania	10 %
Slovenia	37 %	Germany	10 %
Poland	20 %	Slovakia	9 %

## Low coverage $\leq 5$ %

France	Estonia
Czech Republic	Latvia
Romania	Italy



# Finland



## Estimation of true burden of disease attributable to rotavirus

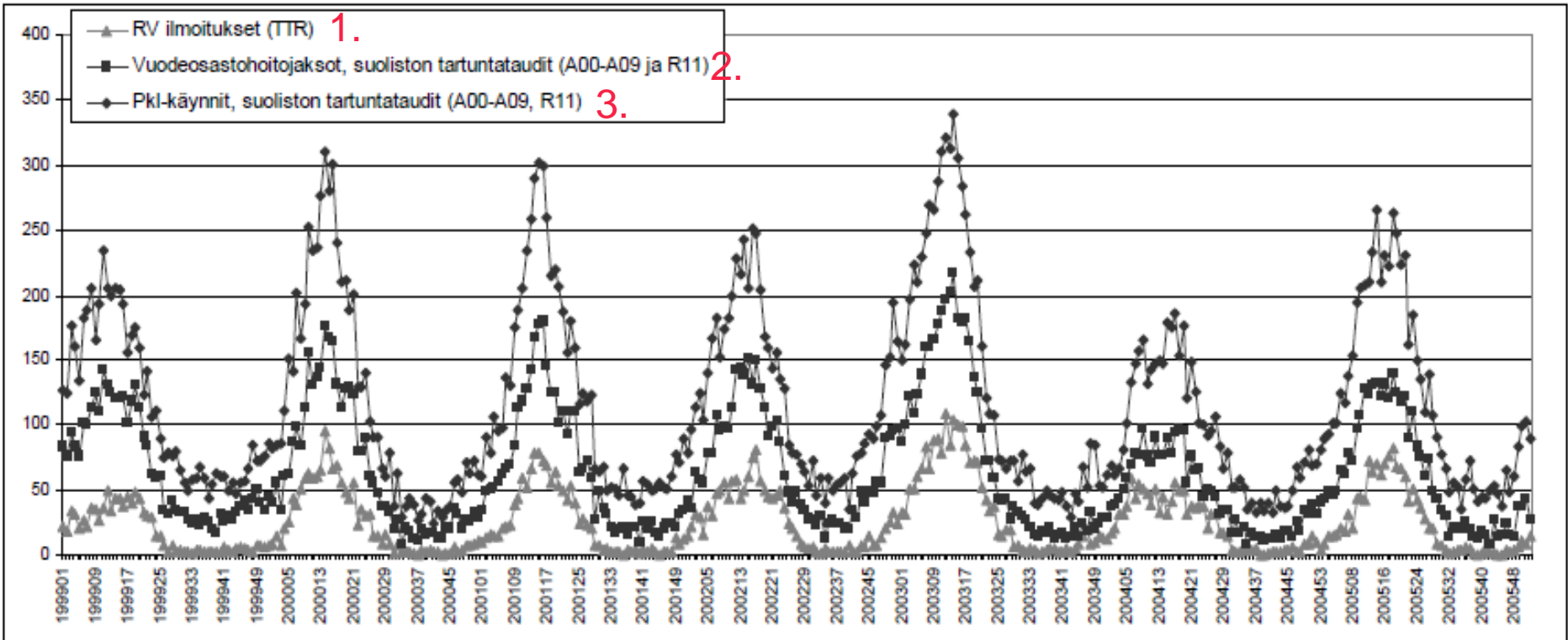
### Hospital discharge data

Confirmed rotavirus GE	100 %
All acute GE	71 %

### Outpatient clinic visits

All acute GE	50 %
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1. Confirmed RV diagnosis
2. Hospital discharges, unspecified infections
3. Outpatient clinic visits, unspecified acute diarrhea



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Cost-effectiveness of rotavirus vaccination programme in Finland, estimated on the basis of vaccine price 29.50 € to 39.50 € per dose

Additional QALYs gained

25.000–45.000 Euros

Actually, the vaccine was obtained at a much lower price, and the programme became much more cost-effective



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# Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



## The cost-effectiveness of rotavirus vaccination: Comparative analyses for five European countries and transferability in Europe

Mark Jit<sup>a,b,\*</sup>, Joke Bilcke<sup>c</sup>, Marie-Josée J. Mangen<sup>d,e</sup>, Heini Salo<sup>f</sup>, Hugues Melliez<sup>g</sup>,  
W. John Edmunds<sup>b,h</sup>, Yazdanpanah Yazdan<sup>g</sup>, Philippe Beutels<sup>c</sup>

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<sup>c</sup> Centre for Health Economics Research and Modelling of Infectious Diseases (CHERMID), Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Belgium

<sup>d</sup> Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment, Netherlands

<sup>e</sup> Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Netherlands

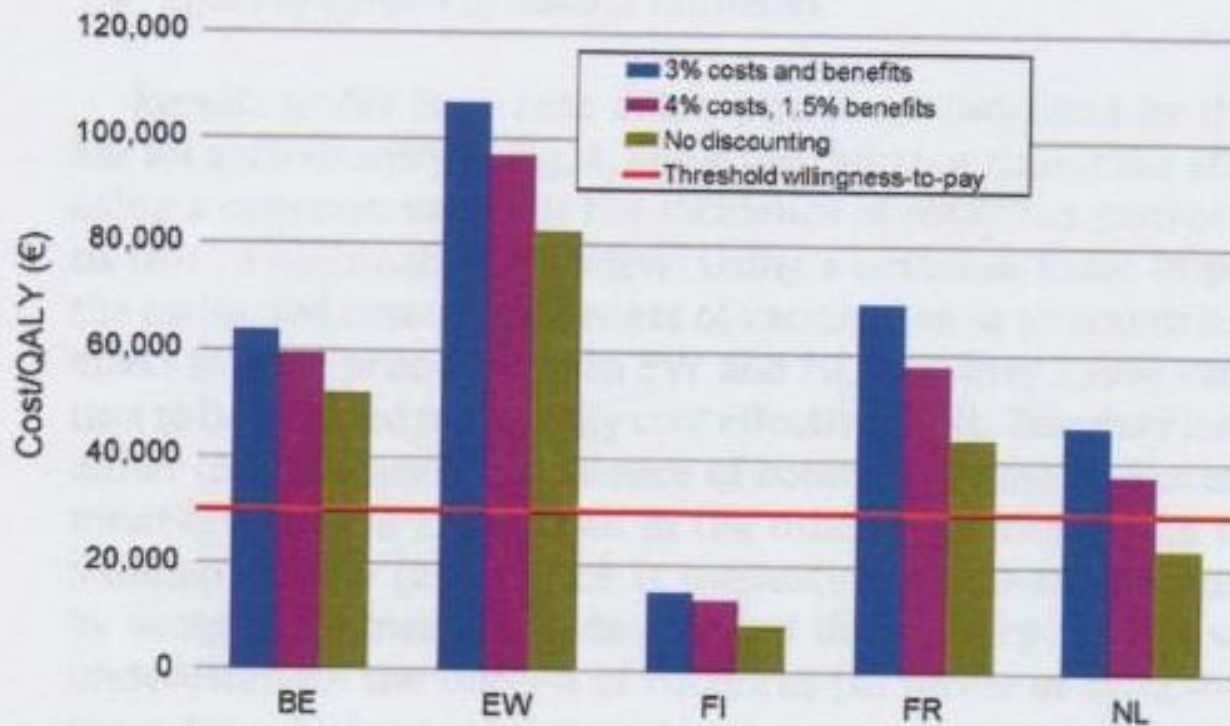
<sup>f</sup> National Institute for Health and Welfare (THL), Finland

<sup>g</sup> Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing, France

<sup>h</sup> London School of Hygiene and Tropical Medicine, United Kingdom

Jit M et al., Vaccine 2009, in press

The cost per QALY saved of vaccination under base case assumptions (as given in Table 1) is indicated by the leftmost bar for each country in Fig. 1, while the other bars show the effect of alterna-



**Fig. 1.** Cost per QALY saved of Rotarix® vaccination under different discounting regimes with a health care provider perspective.

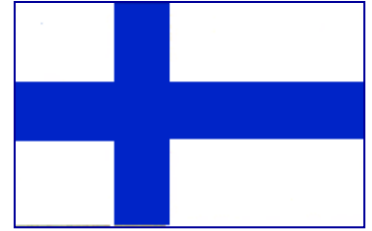
# Influenza vaccination of healthy children

## Objectives

- Protection of vaccinated children against
  - influenza
  - otitis media
  - pneumonia
- Control of transmission in population, indirect protection of persons of risk (Indirect benefits not included in the cost-effectiveness analysis)



# Finland



Recommendation in 2006 of universal influenza vaccination for all children aged 6 to 35 months

2 doses

Free vaccine available at well-baby clinics  
(Community health care centers)

Programme start in 2007



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

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Vaccine 24 (2006) 4934–4941

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[www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

## Cost-effectiveness of influenza vaccination of healthy children

Heini Salo<sup>a</sup>, Terhi Kilpi<sup>a</sup>, Harri Sintonen<sup>b</sup>, Miika Linna<sup>c</sup>,  
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Received 19 October 2005; received in revised form 10 March 2006; accepted 20 March 2006

Available online 7 April 2006

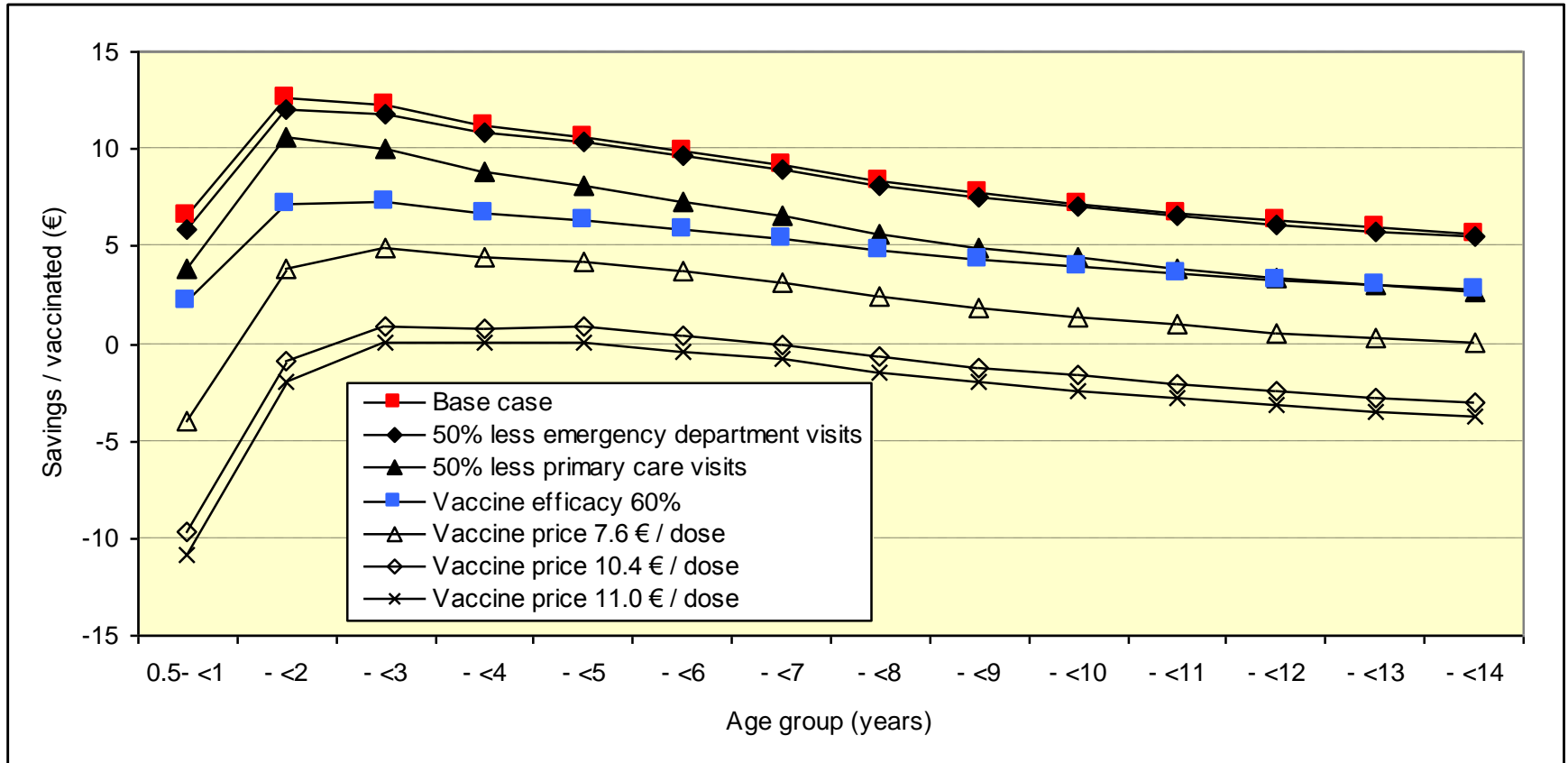
# Included in the cost-effectiveness analysis for influenza in children aged 6 to 35 months

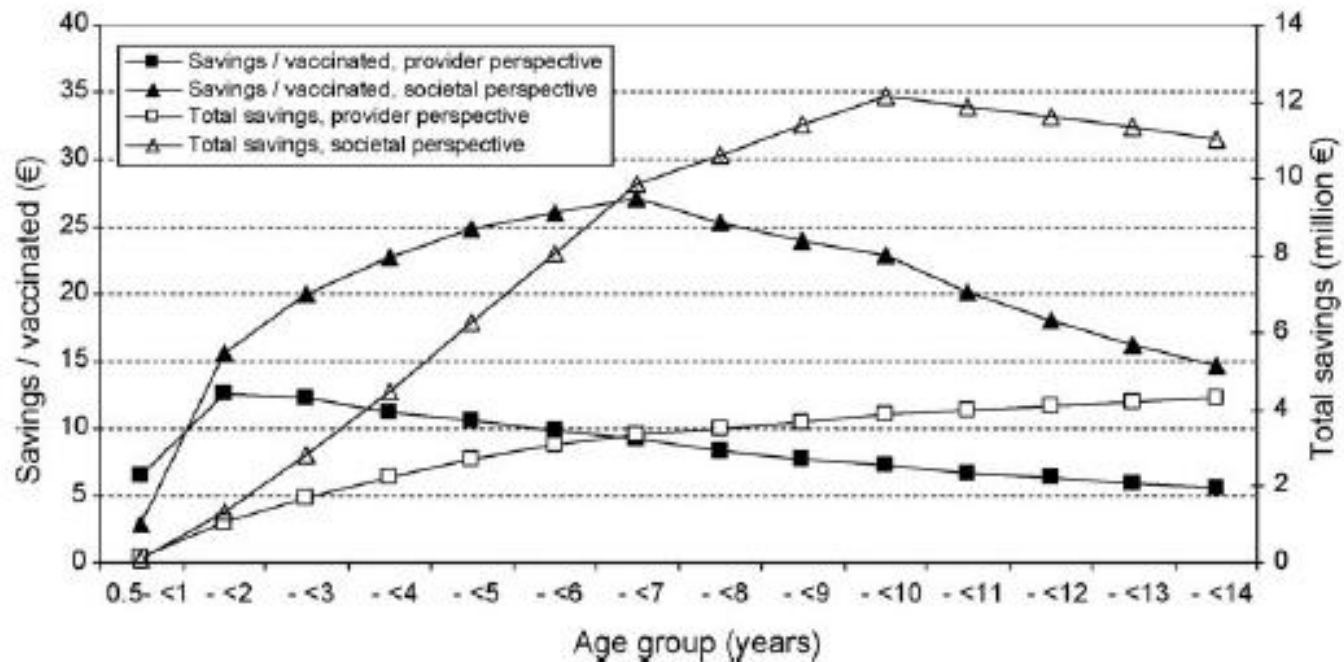
All influenza	18 %
Hospitalization	0.1 %
Outpatient clinic	0.4 %
Sinusitis	0.1 %
Pneumonia	0.5 %
Otitis media	7.2 %

Results driven by prevention of otitis media

# Annual savings per vaccinated child: sensitivity analyses

(Health care provider perspective)





Annual savings per vaccinated child and total annual savings from the health care provider and the societal perspective in cumulative cohorts of children in the vaccination program.

# Pneumococcal conjugate vaccine

Direct prevention (in children) of

Invasive pneumococcal disease (IPD)

- meningitis
- sepsis

Pneumonia

Otitis media

Indirect prevention (in adults) of

- IPD
- Pneumonia



# Pneumococcal conjugate vaccine



Of all costs

- 70 % associated with pneumonia
- Critical factor in cost-effectiveness analysis

In children < 5 years of age

- 90 % of costs associated with otitis media

# Pneumococcal conjugate vaccine (7 pcv)

Costs for additional QALYs gained by a vaccination programme



Direct effects in < 5 years 76.000 Euros

Indirect effects on IPD in all age groups 18.000 Euros



Indirect effects in IPD and pneumonia in all ages 5.500 Euros

# 13-valent pneumococcal conjugate vaccine

PC 7 serotypes +

1, 3, 5, 6A, 7F and 19 A

Increased coverage for IDP  
and

replacement serotype 19 A

Not much broader coverage for AOM

## PHiD-CV vaccine profile

Pneumococcal non-typeable Haemophilus influenzae-Protein D conjugate vaccine

**1 4 5 7F 6B 9V 18C 19F 23 F**

**Protein D**

**18C-TT 19F-DT**

PCV7 + highly invasive serotypes 1, 5 and 7F

Potentially offers protection against NTHi by value of Protein D carrier protein, based on clinical experience