Il valore farmacoeconomico della vaccinazione antipneumococcica

G. Gabutti

Dipartimento di Medicina Clinica e Sperimentale

Università degli Studi di Ferrara

Giornate di Pediatria Preventiva e Sociale

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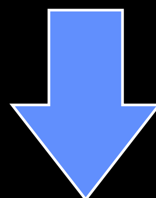
Che cosa è
la valutazione economica in Sanità ?

L’applicazione di principi economici e di tecniche di analisi per ottimizzare l’uso delle risorse disponibili in Sanità:



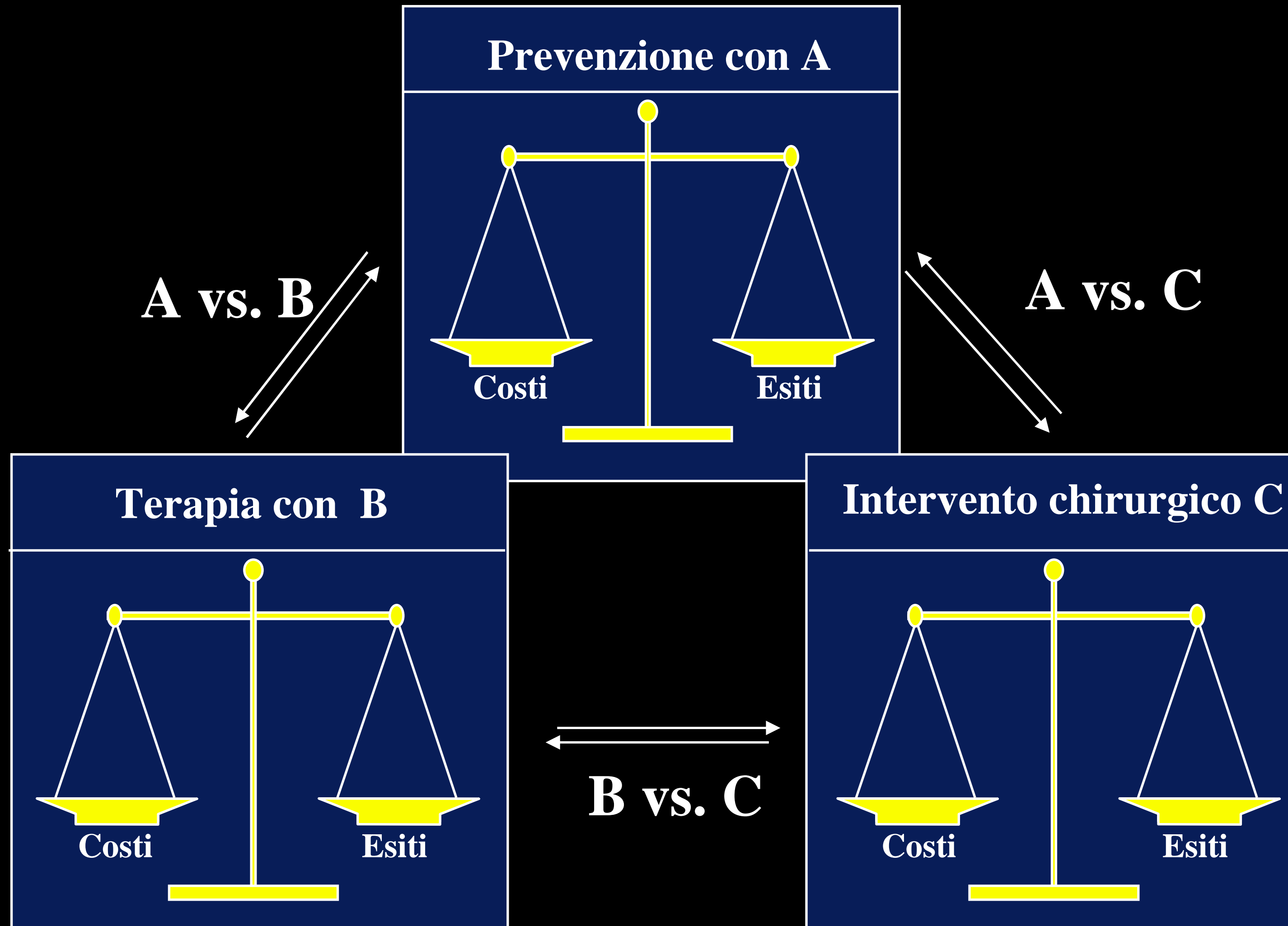
Obiettivo

massimizzare la redditività dell’investimento sanitario

Ruolo della valutazione economica

- incoraggia una decisione basata su costi/esiti piuttosto che sul taglio indiscriminato dei costi
- aiuta i decisori della Sanità a definire priorità di intervento
- aiuta i decisori della Sanità a scegliere le opportunità di prevenzione, diagnosi e cura più ‘cost-effective’ (cioè più redditizie in termini di risultato di salute in rapporto alle risorse impiegate)
- aiuta a definire politiche di prescrizione e di prevenzione ‘cost-effective’

Confronto tra costi e conseguenze di trattamenti alternativi



ITER E CRITERI PER IMPOSTARE LA VALUTAZIONE ECO NOMICA

- Definizione di oggetto ed obiettivi dell'analisi e alternative per il confronto dell'intervento in esame
- Scelta del tipo di analisi da utilizzare
- Conoscenza degli effetti (positivi e negativi) dell'intervento oggetto di studio (osservazione epidemiologica vs. *randomized controlled trial*)
- Definizione del punto di vista dell'analisi (paziente, SSN, fornitore di servizi, società in generale)
- Identificazione e classificazione di costi e benefici e loro misurazione (scelta di costi/benefici medi o marginali, costi fissi, costo-opportunità)
- Calcolo del tasso di sconto ed analisi della sensibilità
- Descrizione e discussione dei risultati

Costi diretti sanitari - 1

comprendono tutte le risorse di tipologia medica direttamente utilizzate (consumate) per gestire la malattia, tra questi troviamo:

le visite mediche (generiche, specialistiche)
la diagnostica (analisi e test)
le terapie (farmacologiche e non)
i ricoveri (acuto, day hospital, lungodegenza)

Costi diretti sanitari - 2

A seconda della situazione, cioè del problema che stiamo esaminando, queste risorse andranno valutate nei vari momenti in cui si articola il processo produttivo della salute:

- **prevenzione**
- **cura**
- **riabilitazione**

Costi diretti non sanitari

Comprendono tutti i costi sostenuti direttamente dai pazienti e dalle loro famiglie a seguito del trattamento cui il paziente è sottoposto, ma che non sono correlati con il settore sanitario, ad esempio:

- costi di trasporto fino al luogo di cura
- costo dell'alloggio della famiglia del malato durante la degenza del familiare (nel caso di interventi al di fuori della zona di residenza)
- costo dell'assistenza domiciliare,
- costo di alcune attrezzature e attività di riabilitazione

Costi indiretti

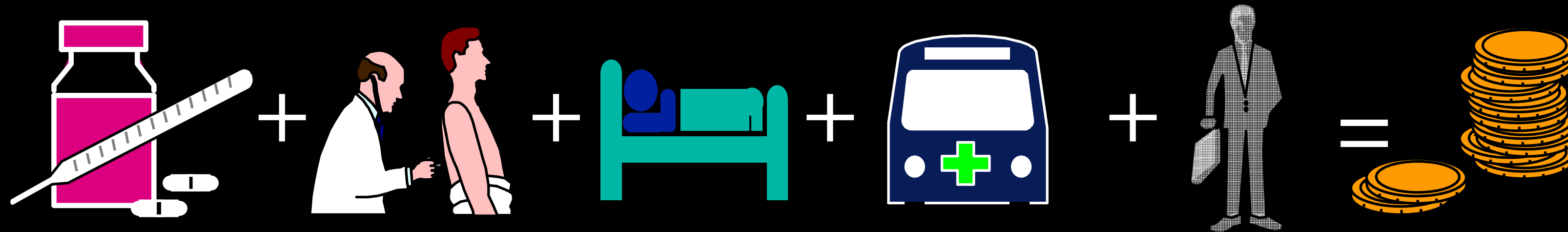
- Rientrano in questa categoria i mancati guadagni del paziente e/o dei suoi familiari, a causa dell'invalidità temporanea o permanente determinata dall'evento patologico.
- A seguito della specifica patologia, infatti, si possono determinare perdite di opportunità occupazionali, licenziamenti, riduzioni della capacità lavorativa, perdita di giornate lavorative (e dei relativi guadagni) non solo per i pazienti, ma anche per i familiari che se ne prendono carico

Costi - più in generale

- è di vitale importanza definire a priori qual è la prospettiva dell'analisi, cioè chi è interessato a conoscere i risultati della nostra analisi, per stabilire quali costi (e quali esiti) dovranno essere inseriti
  - ad esempio, nell'ottica di una ASL potrà non essere significativo inserire i costi indiretti, ma questo potrà essere invece di fondamentale importanza in un'ottica di costo sociale valutato a livello della collettività

Quanto costa la patologia?

COI = Cost of Illness



L'analisi del costo di malattia evidenzia tutte le risorse consumate per gestire una patologia (Costi Diretti, Costi Indiretti)

"UN'ONCIA DI PREVENZIONE EQUIVALE A UNA LIBBRA DI CURE"

(B.Franklin, "Poor Richard's Almanac")

Valutazione dei costi e benefici dei programmi di immunizzazione di massa: spesso fatta in passato in modo implicito (es. vaccino antipolio, antidifterico).

Oggi: necessità di una valutazione economica quantitativa che supporti le decisioni di politica sanitaria.

Quali dati reperire?

- quanti sono i pazienti
  - età
  - sesso
- che cosa consumano
  - che cosa utilizzano,
  - come si ripartiscono i consumi,
  - come variano i consumi rispetto alla gravità della malattia
- come valorizzare i consumi
  - quali valori applicare

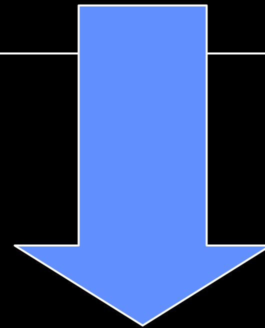
Quali consumi ci aspettiamo?

farmaci

ricoveri

visite

analisi



per la malattia

per le complicanze

VALUTAZIONE DEI COSTI DEI PROGRAMMI DI VACCINAZIONE

- Costo del vaccino e della sua somministrazione
- Costo del trattamento delle complicanze vaccinali
- Perdita di ore lavorative per accesso ai servizi di vaccinazione

BENEFICI ECONOMICI DEI PROGRAMMI DI VACCINAZIONE

- Riduzione della morbosità (ospedalizzazione, spese per farmaci, assistenza ai disabili, ecc.)
- Riduzione della mortalità
- Riduzione delle assenze lavorative (guadagno produttivo)
- Valore monetario dello stato di buona salute (difficile quantificazione)

COSTI E BENEFICI DIRETTI ED INDIRETTI

Costi Diretti	Benefici diretti
- Acquisto vaccino - Somministrazione vaccino - Trattamamento effetti avversi	- Risparmio spese mediche per malattia - Risparmio costi sequele - Risparmio prevenzione disabilità
Costi indiretti	**Benefici indiretti**
- Guadagno perso per accesso ai servizi - Guadagno perso per inabilità da effetti indesiderati	- Risparmio su visite mediche - Risparmio su mancato guadagno per disabilità o morte prematura

Tecniche di analisi economica in Sanità

La vera analisi farmacoeconomica mette a confronto costi ed esiti per più opzioni di trattamento !

FORME DI ANALISI ECONOMICA IN AMBITO SANITARIO

- **Analisi della minimizzazione dei costi**
- **Analisi costi-efficacia**
- **Analisi costi-utilità**
- **Analisi costi-benefici**

(R. Robinson, B.M.J. 1993)

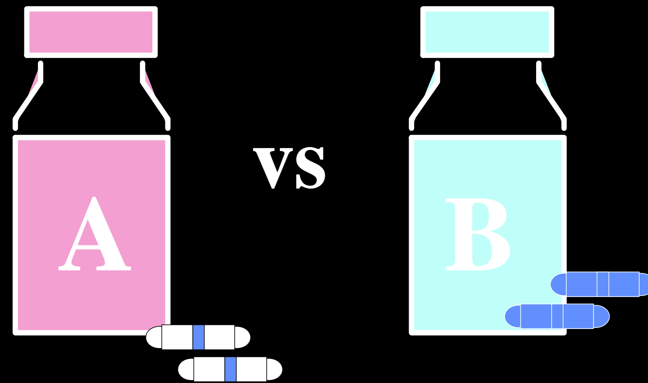
ANALISI DELLA MINIMIZZAZIONE DEI COSTI

- Utilizzata quando l'esito dei diversi interventi che si stanno considerando è lo stesso (la presunta equivalenza è attentamente vagliata da evidenze della letteratura)

- Concentra l'attenzione sul versante dei costi: quale dei programmi di intervento alternativi costa meno?

A parità di efficacia, quale costa meno?

CMA



Alternativa
a costo più basso

La Cost Minimization Analysis confronta i Costi di terapie alternative per le quali sia stata dimostrata pari Efficacia (è un sottotipo della CEA)

$$E_A = E_B$$

$$C_A \gtrless C_B$$

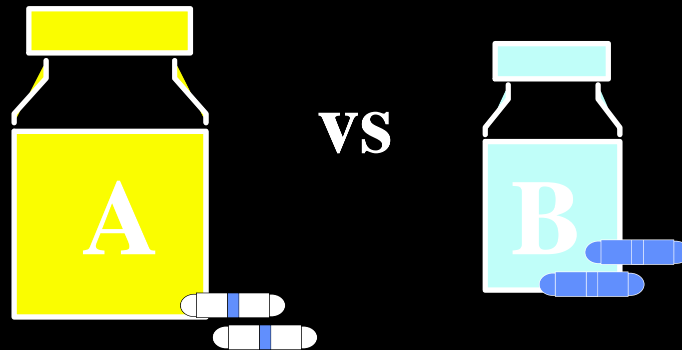
I risultati della CMA evidenziano l'alternativa a Minor Costo

ANALISI COSTI-EFFICACIA

- I vantaggi dell'azione intrapresa sono misurati in unità naturali comuni (o fisiche): casi di malattia evitati, anni di vita guadagnati, ecc.
- Diversi obiettivi sanitari, tutti inizialmente posti sullo stesso piano, vengono paragonati per valutare quale di essi sia raggiungibile con la minore spesa per unità di esito
- E' (insieme all'analisi costi-utilità) la forma di analisi economica più utilizzata in campo sanitario, in cui è difficile assegnare un valore monetario allo stato di salute / malattia

Quale trattamento dà la maggiore efficacia al minor costo?

CEA



Costo per unità di esito clinico

La Cost Effectiveness Analysis confronta Costi e Conseguenze di scelte sanitarie alternative che abbiano un obiettivo sanitario comune

$$\frac{C_A}{E_A} \gtrless \frac{C_B}{E_B}$$

$$\frac{€}{\%_{efficacia}}$$

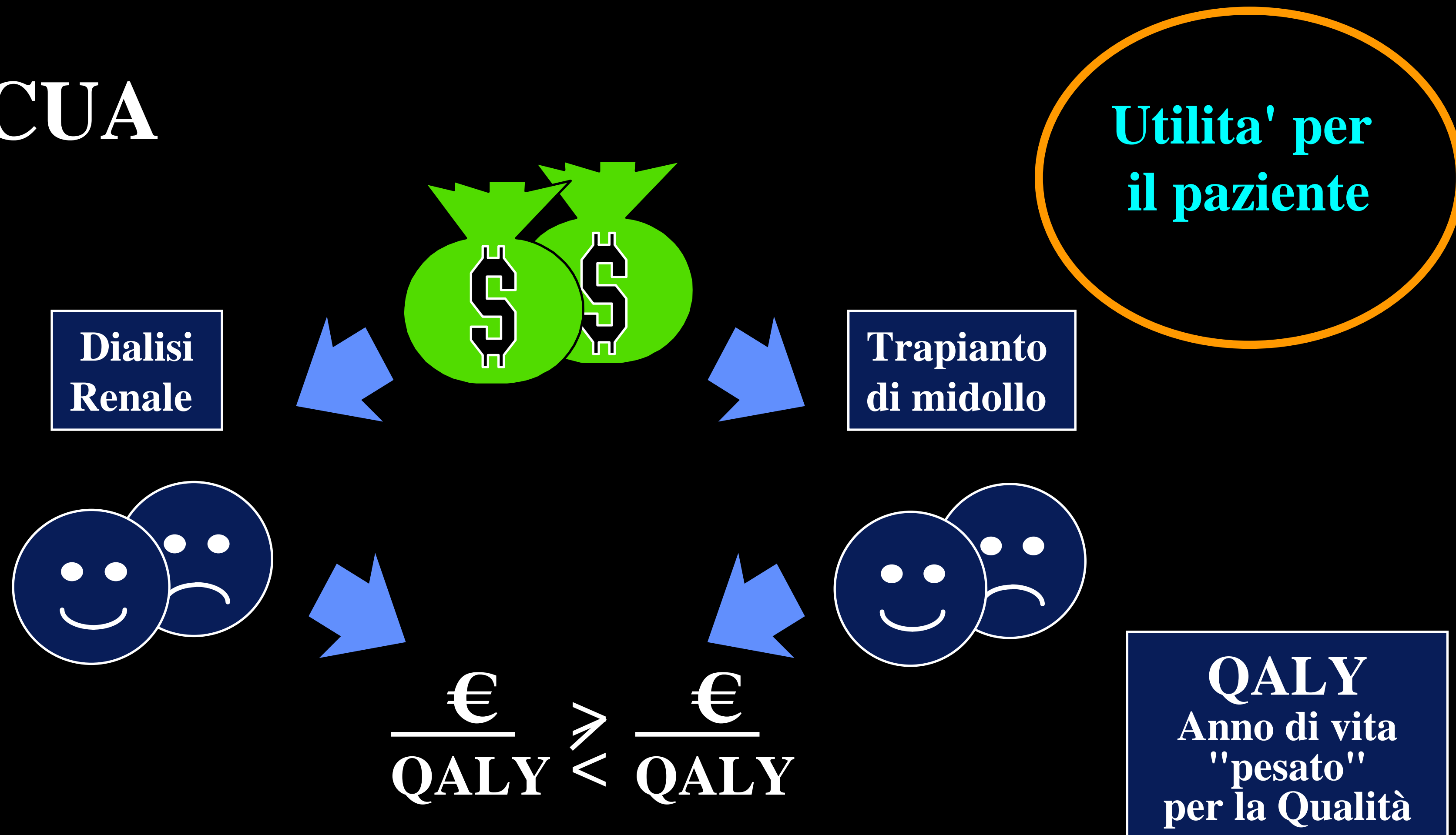
I risultati della CEA vengono espressi in termini di <u>Rapporto Costo/Efficacia</u>

ANALISI COSTO - UTILITÀ

- è un tipo di CEA in quanto considera contemporaneamente l'effetto clinico e l'utilità di questo effetto per il soggetto
- l'unità di esito più utilizzata in questo tipo di analisi è il QALY (pesa il numero di anni di vita guadagnati per un valore di utilità che viene attribuito con apposite tecniche)

Uso: confronta interventi che possono anche essere diversi in termini di tipologia di esito poiché ne misura l'utilità

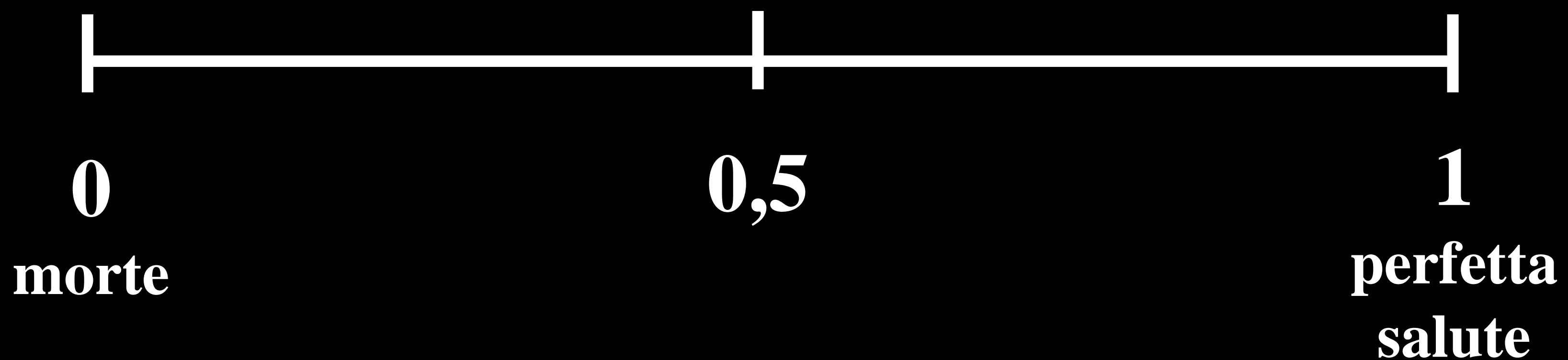
Quale intervento sanitario massimizza l'utilità per il paziente?



La Cost Utility Analysis confronta i Costi e le Conseguenze di interventi sanitari alternativi in termini di: € / Unità di Utilità (€/QALY)

Valutazione dell'utilità

l'utilità viene valutata con varie tecniche e di solito viene espressa come valore su una scala



Theme Articles

Priorities Among Effective Clinical Preventive Services

Results of a Systematic Review and Analysis

Michael V. Maciosek, PhD, Ashley B. Coffield, MPA, Nichol M. Edwards, MS, Thomas J. Flottemesch, PhD, Michael J. Goodman, PhD, Leif I. Solberg, MD

Conclusion: This study identifies the most valuable clinical preventive services that can be offered in medical practice and should help decision-makers select which services to emphasize.

(Am J Prev Med 2006;31(1):52–61) © 2006 American Journal of Preventive Medicine

Am J Prev Med 2006; 31: 52-61

Priorità degli interventi: costi o morbosità?

Table 1. Scoring ranges

Score	CPB range: QALYs saved, undiscounted	CE range: $/QALY saved, discounted
5	≥360,000	Cost saving
4	≥185,000 <360,000	>0 <14,000
3	≥40,000 <185,000	≥14,000 <35,000
2	≥15,000 <40,000	≥35,000 <165,000
1	<15,000	≥165,000 <450,000

CE, cost effectiveness; CPB, clinically preventable burden; QALY, quality-adjusted life year.

Am J Prev Med 2006; 31: 52-61

ANALISI COSTI-BENEFICI

- Utilizzata da lungo tempo in diverse aree di politica economica e sociale per sostenere le decisioni di intervento
- Valori monetari vengono assegnati anche ai benefici, oltre che ai costi
- Possibilità di valutare se un intervento sanitario costituisce in termini globali un risparmio per la società
- Svantaggi: difficoltà di monetizzare tutti gli esiti favorevoli dell'azione

- Due approcci:

  Capitale umano ('Human capital') = potenziale produttivo o di guadagno di ciascun soggetto

  Disponibilità a pagare ('Willingness to pay') = volontà di pagare per avere un servizio o accettato per correre un rischio

ANALISI COSTI-BENEFICI

Il risultato è espresso

- come confronto tra i 2 rapporti beneficio/costo
- oppure come confronto di costo netto o beneficio netto

Uso: misurazione del beneficio sociale di 2 programmi sanitari che producono esiti diversi (e dove quindi potrebbe non essere possibile usare la CEA)

Qual è il beneficio sociale dell'investimento sanitario?

CBA

BENEFICIO SOCIALE

Vaccinazione contro l'epatite

Campagna contro i rischi del fumo

C_B/B_B vs C_A/B_A

C_B-B_B vs C_A-B_A

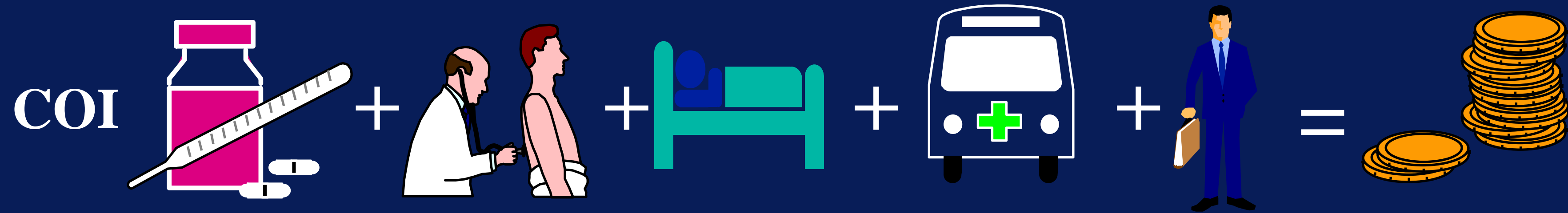
La Cost Benefit Analysis confronta i Costi ed le Conseguenze di interventi sanitari alternativi valorizzando in termini monetari il Beneficio Sociale che ne deriva.

Sintesi dei metodi della farmacoeconomia

metodo	esiti	risultati
Costo minimizzazione	uguali	il costo più basso
Costo-efficacia	unità di efficacia	confronta il costo per unità di esito
Costo-utilità	unità di utilità	confronta il costo per unità di utilità
Costo-beneficio	€	trasforma gli esiti in un valore monetario

Quanto costa la patologia?

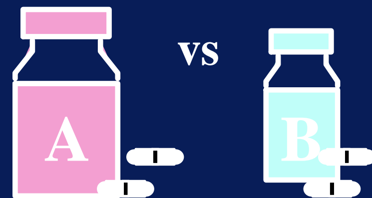
COI



quale trattamento dà la maggiore efficacia al minor costo?

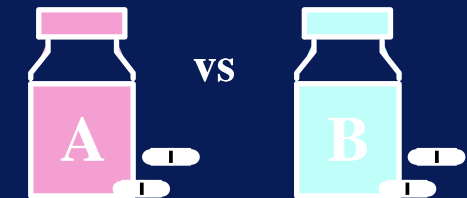
CEA

COSTO / EFFICACIA



CMA

MINOR COSTO



come investire le risorse della collettività?

CBA

BENEFICIO SOCIALE

CUA

UTILITA' PER IL PAZIENTE

Componenti

Costi	Effetti	Benefici	Utilità
Diretti Indiretti Intangibili	Salute in unità naturali	Diretti Indiretti Intangibili	Salute in QALYs

CALCOLO DEL TASSO DI SCONTO NELLA VALUTAZIONE COSTI-BENEFICI

- I costi futuri sono meno cari di quelli presenti (interesse composto ottenibile sul denaro non speso)
- I benefici sono di minor valore se differiti al futuro

ANALISI DELLA SENSIBILITA’

Valutazione dell’impatto sull’analisi economica della variazione di alcuni parametri chiave. (Guyatt, 1993)

Costruzione di scenari estremi (ottimistico e pessimistico) dal punto di vista economico.

DECISIONI DI POLITICA SANITARIA

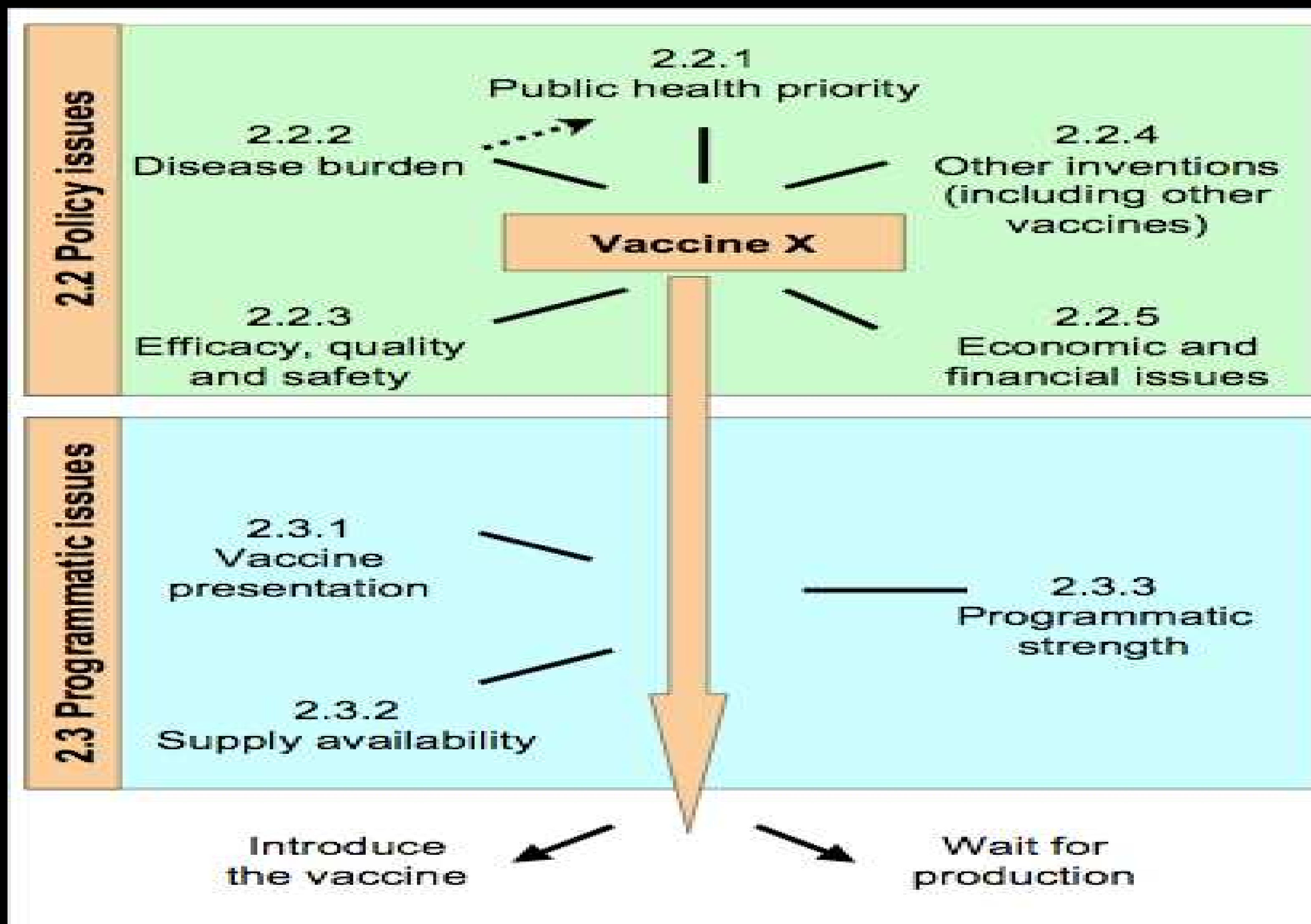
Analisi economica

Supporto al ragionamento sui problemi sanitari, non elemento definitivo di scelta

Priorità stabilite in base a:

- **opinioni della popolazione e dei professionisti**
- **pressioni dei politici**
- **risultati degli studi effettuati**

Deciding on the introduction of a vaccine: key-issues (WHO 2005)



Studi di Costo-Efficacia
Differenti conclusioni

- In Finlandia (Petit et Al 2005), Inghilterra e Galles (Melegaro et al 2004), Canada (De Wals 2003), Australia (Claes et Al 2003) ed Olanda (Bos et Al 2003), la vacccinazione universale non è risultata costo-efficace

- In Canada gli studi di Lebel et Al (2003) e di Moore et Al (2003) sono stati più favorevoli alla vaccinazione universale dei bambini con PCV7 che quello di De Wals et Al (2003)

- Questa strategia è risultata avere un accettabile rapporto costo-efficacia in Spagna (Asensi et Al 2004), Canada, Germania (Claes et Al 2003) e Svizzera (Ess et Al 2003)

Motivo delle differenze

- Le divergenze dei risultati forniti dai vari studi sembrano principalmente dipendere:
  - dalla differente stima dei costi di ciascun stadio di malattia,
  - dalla incertezza, sottolineata da molti dei ricercatori, sul "burden" locale della patologia pneumococcica.

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Vaccine 22 (2004) 4203–4214

Vaccine

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Cost-effectiveness analysis of pneumococcal conjugate vaccination in England and Wales

A. Melegaro[a,b,*], W.J. Edmunds[a,c]

[a] *Modelling and Economics Unit, Health Protection Agency, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK*

[b] *Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK*

[c] *Department of Economics, City University, London EC1V 0HB, UK*

Received 11 February 2004; accepted 4 May 2004

Abstract

Aim: To establish whether universal vaccination of infants with the pneumococcal conjugate vaccine is likely to be cost-effective from the perspective of the health care provider (NHS). *Method*: Two hypothetical cohorts – one vaccinated and one unvaccinated – were followed over their lifetime, and the expected net costs and benefits (measured in terms of life-years and quality adjusted life years (QALY) gained) were compared in the two cohorts. The impact of indirect effects of the vaccine, such as herd immunity and serotype replacement, were investigated and their relative importance was assessed by performing univariate sensitivity analysis and multivariate Monte Carlo simulations. *Results*: Under base-case assumptions (no herd immunity and no serotype replacement) the programme is not expected to be cost-effective from the NHS perspective at the current price of the vaccine (assumed £30 per dose, three-dose programme). A reduction of the cost of the vaccine to half of its current level could bring the cost per QALY gained within normally acceptable ranges. If the burden of disease is significantly underestimated by current surveillance systems, then the cost per QALY gained approaches acceptable levels at the current vaccine price. Herd immunity may substantially reduce the burden of pneumococcal disease, particularly of pneumonia among the elderly, leading to a significant improvement in the cost per life year and QALY gained. Serotype replacement would partly offset these benefits, although only with a complete substitution of vaccine types with non-vaccine types and a low level of herd immunity, would pneumococcal vaccination programme would not be cost-effective. *Conclusions*: Conclusions on the cost-effectiveness of pneumococcal conjugate vaccine are sensitive to assumptions regarding the current burden of pneumococcal disease and the future impact that vaccination will have in the unvaccinated and on the future serotype distribution. This study quantifies, for the first time, how these indirect effects may change the cost-effectiveness of pneumococcal vaccination.

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Vaccine 23 (2005) 4565–4576

Vaccine

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Cost-effectiveness of universal pneumococcal vaccination for infants in Italy

M. Marchetti [a,b,*], G.L. Colombo [b]

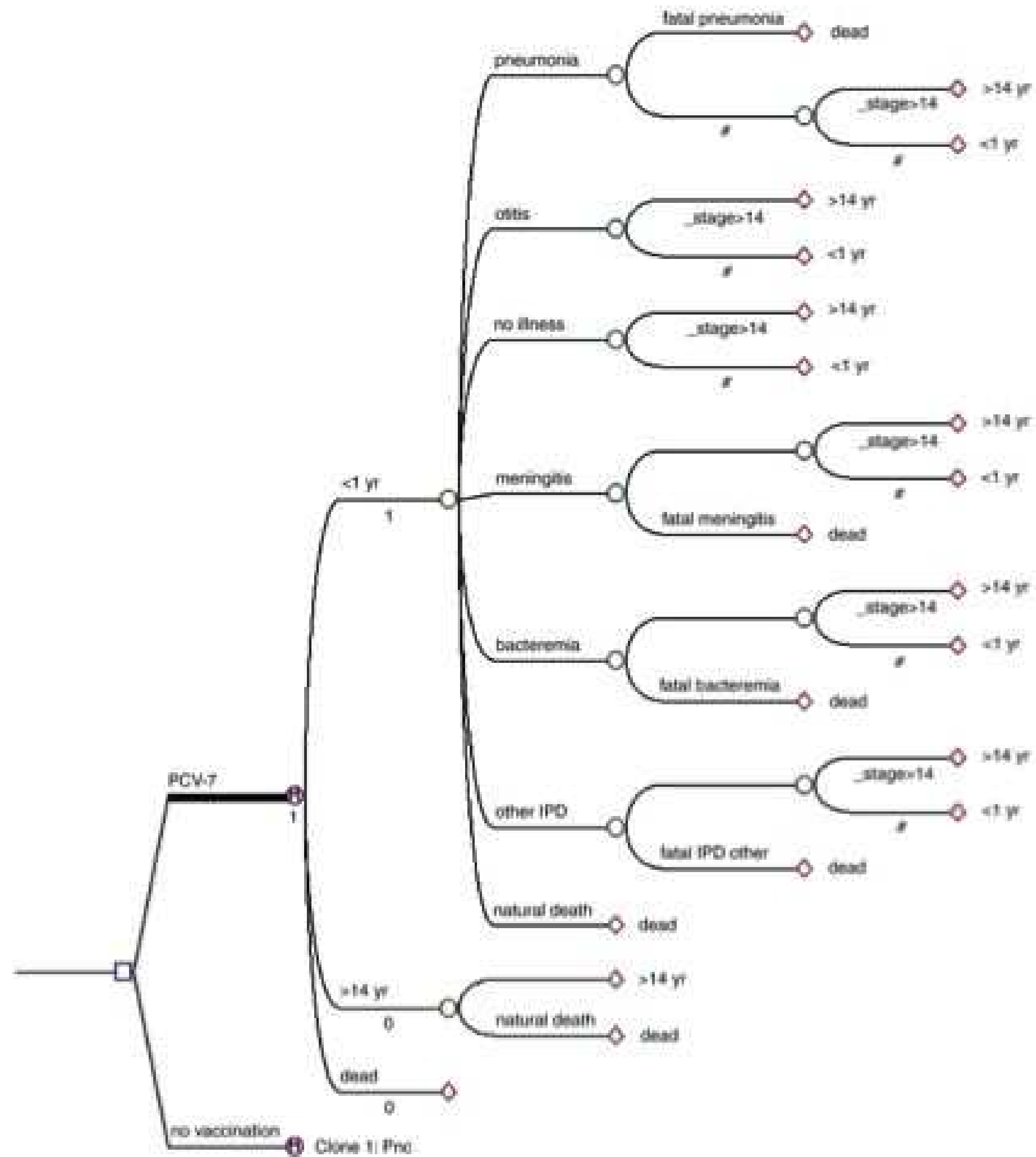

Fig. 1. Decision tree.

Table 1
Baseline input data for PCV-7

		Baseline value	Range	Source
Uptake	Three doses	100%	82–100%	[9,49]
Efficacy	IPD	89.1%	74–96%	[9,14]
Efficacy	Otitis media (overall episodes)	6.4%	3.9–8.7%	[9,10]
Efficacy	Pneumonia[a]	17.7%	5–29%	[54]
Side effects	Fever over 39 °C	1%/dose	0–2%	[51]
Direct cost	Vaccine (1 dose)	€39	€15–80	[76]
Direct cost	Administration of vaccine (1 dose)	€0	€0–10	Assumption [57]
Direct cost	Pediatrician visits for adverse effects (fever)	€20.56	€10–30	[59]
Indirect cost	Parents' productivity loss for vaccination (4 h work)	€0	€0–52	Assumptions [60]
Indirect cost	Parents' productivity loss for a visit due to PCV-7 adverse effects (3 h work)	€39	€0–39	[60]

[a] Clinical pneumonia with a positive chest X-ray film.

Table 2
Baseline input clinical parameters

	Baseline value	Range	Source
PNC meningitis			
Yearly incidence			[1,25,28]
Age <1	7.6/100000	2.3–8.0	
Age 1–4	2.1/100000	0.4–3.0	
Age 5–14	0.5/100000	0.1–1.0	
Case fatality rate			[1,35,31]
Age 0–1	14%	7–17%	
Age 2–4	7%	2–10%	
Age 5–10	1%	0–2%	
Cost (direct)	€20532 (€7536)	€16000–30000 (€5000–12000)	[58]
PNC bacteremia			
Yearly incidence			[43]
Age <1	12.7/100000	8–16	
Age 1–4	13.6/100000	8–16	
Age 5–14	3.3/100000	1–5	
Case fatality rate	0.9%	0–2%	[24]
Cost (direct)	€3816 (€2916)	€3000–5000 (€2000–4000)	[58]
Other PNC IPD			
Yearly incidence			[43]
Age <1	6.8/100000	3–8	
Age 1–4	5.2/100000	3–8	
Age 5–14	1.2/100000	0–2	
Case fatality rate (age 0–1)	0.9%	0–2%	[24]
Cost (direct)	€3816 (€2916)	€3000–5000 (€2000–4000)	[58]
Pneumonia			
Yearly incidence			[28]
Age <1	0.89%	0–2%	
Age 1–4	0.63%	0–2%	
Age 5–14	0.15%	0–1%	
Cost (direct)	€2280.88 (€1440.09)	€1400–3000 (€1000–2000)	[58]
Otitis			
Yearly incidence			[36,31]
Age 0–4	23%	20–60%	
Age 5–14	6%	2–10%	
Number of episodes per patient per year	1.24	1–1.8	[36,39,31]
Cost (direct)	€236.68 (€75.91)	€150–300 (€50–100)	[58]

Table 3
Baseline cost-effectiveness analysis (undiscounted) per patient and for the birth cohort of 538,138 infants (last column on the right)

	Without vaccine	With vaccine	Difference	Absolute[a]
Infections	2.223	2.083	0.140	75
All IPD	0.00165	0.000237	0.00143	769
Meningitis	0.000265	0.000034	0.000231	124
Bacteraemia	0.000978	0.000144	0.000834	449
Pneumonia	0.0517	0.0430	0.087	46818
Otitis media (episodes/pt)	2.17	2.04	0.13	69,958
Death due to IPD	0.0000392	0.0000051	0.0000341	18
Life expectancy	73.96530 (76.18426)	73.96776 (76.18679)	0.00246 (0.00253)	1323 (1361)
Direct medical costs	€221.1 (€252.1)	€315.1 (€343.3)	€94.0 (€91.1)	M€50.58
IPD	€5.6	€2.6	€3.0	M€1.61
Pneumonia	€67.6	€56.4	€11.2	M€6.03
Otitis media	€147.9	€139.1	€8.8	M€4.73
Overall cost	€577.8 (€660.2)	€642.8 (€718.8)	€64.9 (€58.7)	M€34.92

Incremental cost-effectiveness		Discounted	Undiscounted
Direct medical cost per event averted	€/event averted	671	651
Direct medical cost per IPD averted	€/event averted	1305555	1266111
Direct medical cost per death averted	€/death averted	2756891	2673313
Direct medical cost per life-year saved	€/LYS	38286	36046
Overall cost per event averted	€/event averted	463	419
Overall cost per IPD averted	€/event averted	901388	815277
Overall cost per death averted	€/death averted	1903225	1721114
Overall cost per life-year saved	€/LYS	26449	23205

[a] M = millions.

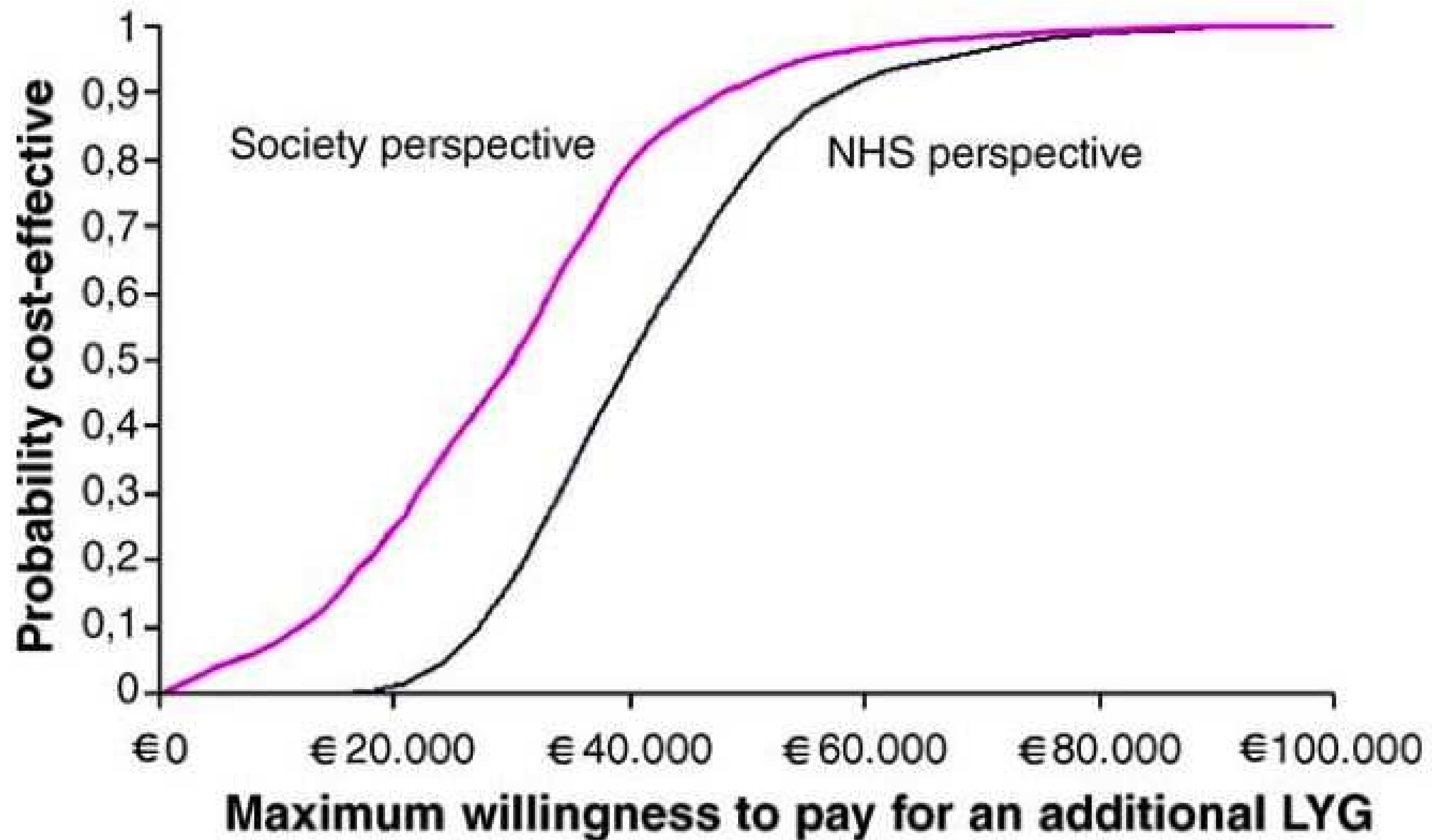

Fig. 2. Acceptability curve of PCV-7 universal infant vaccination versus no vaccination.

Cost-effectiveness of universal pneumococcal vaccination for infants in Italy

M. Marchetti[a,b,*], G.L. Colombo[b]

[a] Laboratory of Medical Epidemiology, IRCCS Policlinico San Matteo, viale Golgi 19, 27100 Pavia, Italy
[b] S.A.V.E., via Previati 74, 20149 Milan, Italy

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"…Considering yearly incidence of invasive pneumococcal disease reported for Veneto and Sardinia regions, PCV-7 vaccination would result highly cost-effective determining a cost of Euro 10,479 and Euro 16,890 per life year-save in the NHS and the societal perspective, respectively".

Vaccine, 2005

Available online at www.sciencedirect.com
SCIENCE DIRECT
Vaccine 24 (2006) 5690–5699
Vaccine
www.elsevier.com/locate/vaccine

Cost effectiveness of adding 7-valent pneumococcal conjugate (PCV-7) vaccine to the Norwegian childhood vaccination program

Torbjørn Wisløff[a,*], Tore G. Abrahamsen[b,c], Marianne A. Riise Bergsaker[d], Øistein Løvoll[d], Per Møller[e], Maren Kristine Pedersen[d], Ivar Sønbø Kristiansen[a,f,g]

Results: When indirect costs were disregarded, and four vaccine doses used, the incremental cost per life year gained was €153,000 when herd immunity was included, and €311,000 when it was not. When accounting for indirect costs as well, the cost per life year gained was €58,000 and €124,000, respectively. Assuming that three vaccine doses provide the same protection as four, the cost per life year gained with this regimen was €90,000 with herd immunity and €184,000 without (when indirect costs are disregarded). If indirect costs are also included, vaccination both saves costs and gains life years.

Interpretation/conclusion: In Norway, governmental guidelines indicate that only interventions with cost per life year of less than €54,000 should be implemented. This implies that four dose vaccination is not cost-effective even if decision makers includes both herd immunity and indirect costs in their decisions. If three doses offer the same protection as four doses, however, vaccination would be cost-saving when indirect costs are included, but not with only herd immunity.

Comment: In the autumn of 2005, the Norwegian Government decided to include PCV-7 in the vaccination program. This analysis was used by the Ministry of Health and Ministry of Finance during the decision process.

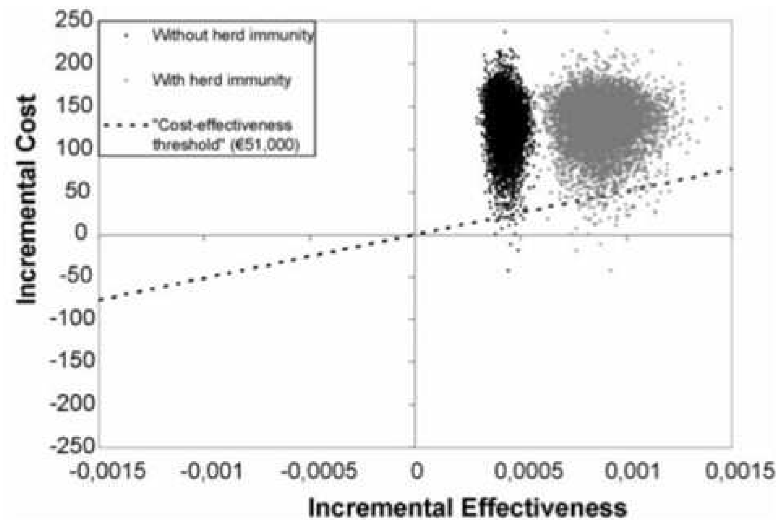

Fig. 4. Incremental cost versus incremental effect based on Monte Carlo simulation with 10,000 iterations. The dotted line indicates the Norwegian cost-effectiveness threshold (€51,000).

5. Conclusion

The cost-effectiveness of vaccination with pneumococcal vaccine of infants will in particular depend on the price of the vaccine, the efficacy of the vaccine, the efficacy of three versus four vaccine shots, the extent of herd immunity, the valuation of future health benefits and costs (i.e. the discount rate) and the valuation of indirect costs. For decision makers who adopt the World Bank cost-effectiveness rule (i.e. €42,000 per life year gained) and who believe in herd immunity from vaccination with pneumococcal vaccine, the results of this analysis indicate that vaccination is cost-effective in comparison with several health care programs that are generally accepted (e.g. antihypertensive treatment, use of statins, use of PCI (Percutaneous coronary intervention) for stable angina, etc.). For those who choose to disregard herd immunity, the results are less unambiguous in that cost-effectiveness ratios are below the threshold only if three doses of vaccine offer the same protection as four doses, and indirect costs are included.

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Available online at www.sciencedirect.com

Vaccine 25 (2007) 1355–1367

Vaccine

www.elsevier.com/locate/vaccine

Review

Convincing or confusing? Economic evaluations of childhood pneumococcal conjugate vaccination—a review (2002–2006)

Philippe Beutels[a,b,*], Nancy Thiry[a], Pierre Van Damme[a]

We review 15 economic analyses of pneumococcal conjugate vaccines, published between 2002 and 2006, in terms of methodology, assumptions, results and conclusions. We found a great diversity in assumptions (eg, vaccine efficacy parameters, incidence rates for both invasive and non-invasive disease) mainly due to local variation in data and opinions. Accordingly, the results varied greatly, from total net savings to over €100,000 per discounted QALY gained. The cost of the vaccination program (determined by price per dose and schedule (4 or 3 doses, or fewer)), and likely herd immunity impacts are highly influential though rarely explored in these published studies. If the net long-term impact (determined by a mixture of effects related to herd immunity, serotype replacement, antibiotic resistance and cross reactivity) remains beneficial and if a 3-dose schedule confers near-equivalent protection to a 4-dose schedule, the cost-effectiveness of PCV7 vaccination programs can be viewed as attractive in developed countries.

Results of published economic evaluations of conjugate pneumococcal vaccine (08/2002–03/2006)

Study	Country	Original currency (year)	Studies' results (2002 Euro): incremental cost-effectiveness ratios (ICER)		
			Vaccination scenarios	Payer's perspective[a]	Societal perspective[b]
Salo et al. [17]	Finland	Euro (2004)	Infants: 4 doses (schedule not stated)	€ 208,570 per disc LYG € 75,922 per undisc LYG € 44,563 per disc QALY gained	€ 133,563 per disc LYG € 23,725 per undisc LYG € 28,536 per disc QALY gained
McIntosh et al. [12]	UK	£ (2002)	Infants: 4 doses (2, 3, 4, 12–15 m)	€ 6,932 per disc LYG € 6,394 per undisc LYG	NA
Navas et al. [16]	Catalonia, Spain	Euro (2000)	Infants: 4 doses (2, 3, 4, 12–15 m)	€ 65,929 per disc LYG € 85,727 per disc DALY averted[c]	€ 15,908 per disc LYG € 47,307 per disc DALY averted BCR: 0.59
Marchetti and Colombo [15]	Italy	Euro (2002)[d]	Infants: 3 doses (2, 4, 6 m)	€ 38,286 per disc LYG	€ 26,449 per disc LYG
Butler et al. [7]	Australia	$AU (1997–1998)	Infants: 4 doses (2, 4, 6, 12 m)	€ 175,540 per disc LYG € 92,374 per disc DALY averted	NA
Asensi et al. [5]	Spain	Euro (1999)[d]	Infants: 4 doses (2, 3, 4, 12–15 m) Infants catch-up: all <60 months	€ 78,235 per disc LYG € 99,773 per disc LYG	Savings Savings
Melegaro and Edmunds [14]	England & Wales	£ (2002)	Infants: 3 doses (protected from 4 m)	€ 166,060 per disc LYG € 95,792 per undisc LYG € 87,913 per disc QALY gained € 57,087 per undisc QALY gained	NA
Mcintosh et al. [11]	England & Wales	£ (2002)	Infants: 4 doses (2, 3, 4, 12–15 m)	€ 46,214 per undisc LYG	€ 41,292 per undisc LYG
Ess et al. [18]	Switzerland	CHF (2001)[d]	Infants: 4 doses (2, 4, 6, 12–15 m) Infants catch-up 1: all <24 months Infants catch-up 2: all <60 months	€ 19,279 per undisc QALY gained € 16,483 per undisc QALY gained € 79,470 per undisc QALY gained	NA
Ruedin et al. [13]	Switzerland	Euro (2002)	Infants: 3 doses (2, 4, 6 m) PCV9-MenC Toddler: 1 year—1 dose of PCV9-MenC	€ 39,000 per disc QALY gained € 34,000 per undisc QALY gained € 15,000 per disc QALY gained € 13,000 per undisc QALY gained	NA
Claes and Graf von der Schulenburg [8]	Germany	Euro (2002)[d]	Infants: 4 doses (2, 3, 4, 12–15 m)	€ 68,201 per disc LYG	Savings[c]
Bos et al. [6]	The Netherlands	Euro (2001)	Infants: 4 doses (2, 3, 4, 12–15 m)	€ 80,006 per disc QALY gained	€ 71,703 per disc QALY gained € 83,226 per disc LYG
Lebel et al. [10]	Canada	$CAN (2000)	Infants: 4 doses (2, 4, 6, 12–15 m)	€ 125,469 per disc LYG	€ 63,938 per discounted LYG
De Wals et al. [9]	Canada	$CAN (2000)	Infants: 4 doses (2,4,6,12–15 m)	€ 152,584 per disc LYG € 142,033 per disc QALY gained	€ 101,452 per disc LYG € 94,148 per disc QALY gained
			Infant catch-up: 3 doses (7–12 m)	–	€ 194,788 per disc LYG € 193,165 per disc QALY gained
			Toddler catch-up: 2 doses (12–18 m)	–	€ 163,135 per disc LYG € 163,947 per disc QALY gained
			Child catch-up: 1 dose (24–48 m)	–	€ 167,943 per disc LYG € 163,947 per disc QALY gained
Moore et al. [19]	Canada (British Columbia)	$CAN (2000)	Infants: 4 doses <18 months	€ 34,528 to € 73,457 per undisc LYG	NA

The divergences in studies' conclusions are showing the difficulties with obtaining reliable burden of disease data, as well as the constantly changing insights about the effectiveness of this vaccine. However, the following is emerging in various countries: with a 3-dose schedule and taking observed herd immunity effects into account, childhood PCV7 vaccination is likely to be judged relatively cost-effective to the health care payer and potentially even cost-saving to society. Nonetheless, the long-term net effects on antimicrobial use and resistance, serotype replacement and cross reactivity need to be monitored, to verify that they remain beneficial to the overall cost-effectiveness of the program. It is encouraging that recent evidence from the US supports this [26,27,30,36,38–40].

Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis

Anushua Sinha, Orin Levine, Maria D Knoll, Farzana Muhib, Tracy A Lieu

Summary

Background Routine vaccination of infants against *Streptococcus pneumoniae* (pneumococcus) needs substantial investment by governments and charitable organisations. Policymakers need information about the projected health benefits, costs, and cost-effectiveness of vaccination when considering these investments. Our aim was to incorporate these data into an economic analysis of pneumococcal vaccination of infants in countries eligible for financial support from the Global Alliance for Vaccines & Immunization (GAVI).

Methods We constructed a decision analysis model to compare pneumococcal vaccination of infants aged 6, 10, and 14 weeks with no vaccination in the 72 countries that were eligible as of 2005. We used published and unpublished data to estimate child mortality, effectiveness of pneumococcal conjugate vaccine, and immunisation rates.

Findings Pneumococcal vaccination at the rate of diptheria–tetanus–pertussis vaccine coverage was projected to prevent 262 000 deaths per year (7%) in children aged 3–29 months in the 72 developing countries studied, thus averting 8·34 million disability-adjusted life years (DALYs) yearly. If every child could be reached, up to 407 000 deaths per year would be prevented. At a vaccine cost of International $5 per dose, vaccination would have a net cost of $838 million, a cost of $100 per DALY averted. Vaccination at this price was projected to be highly cost-effective in 68 of 72 countries when each country's per head gross domestic product per DALY averted was used as a benchmark.

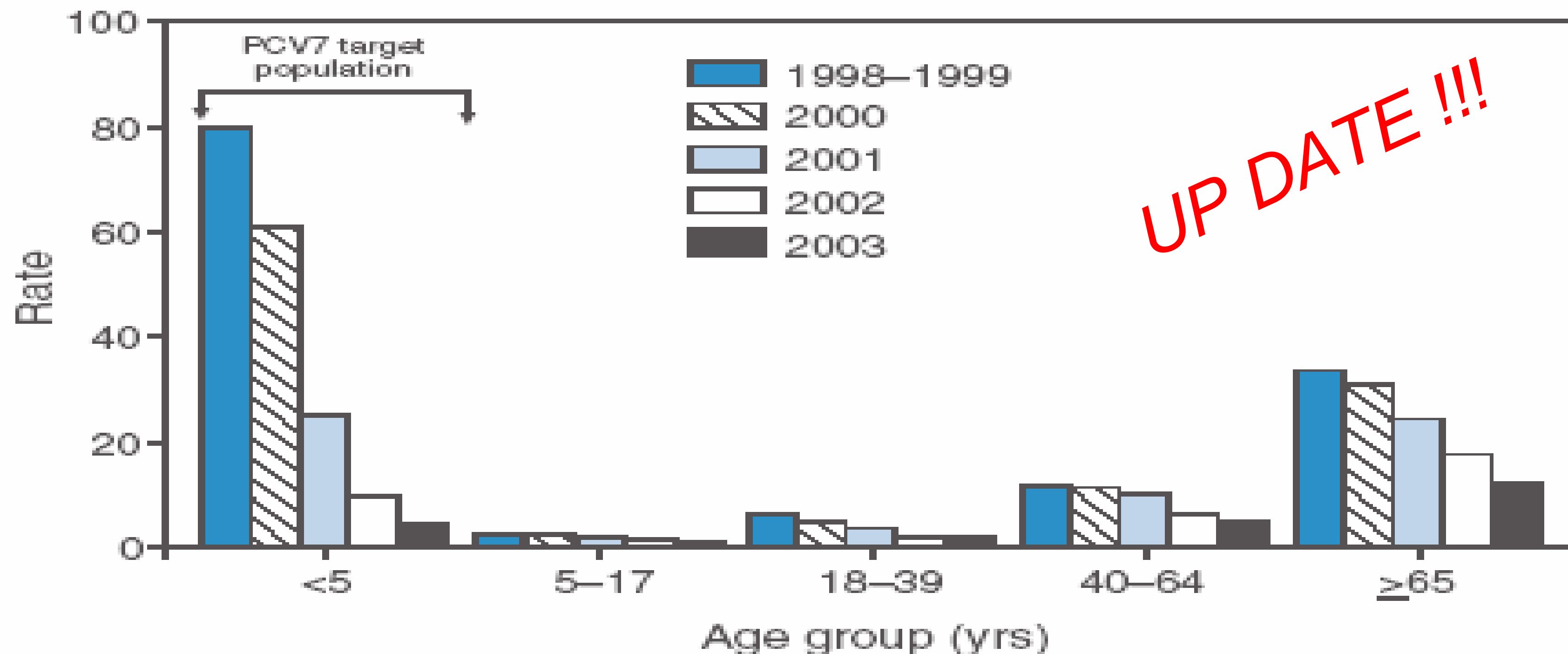
Interpretation At a vaccine cost of between $1 and $5 per dose, purchase and accelerated uptake of pneumococcal vaccine in the world's poorest countries is projected to substantially reduce childhood mortality and to be highly cost-effective.

Lancet 2007; 369: 389–96

Department of Preventive Medicine and Community Health, University of Medicine & Dentistry of New Jersey—New Jersey Medical School, Newark NJ 07101, USA (A Sinha MD); Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MA, USA (O Levine PhD, M D Knoll PhD, F Muhib MPH); and Center for Child Health Care Studies, Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School (T A Lieu MD); and Division of General Pediatrics, Children's Hospital, Boston, MA, USA (T A Lieu)

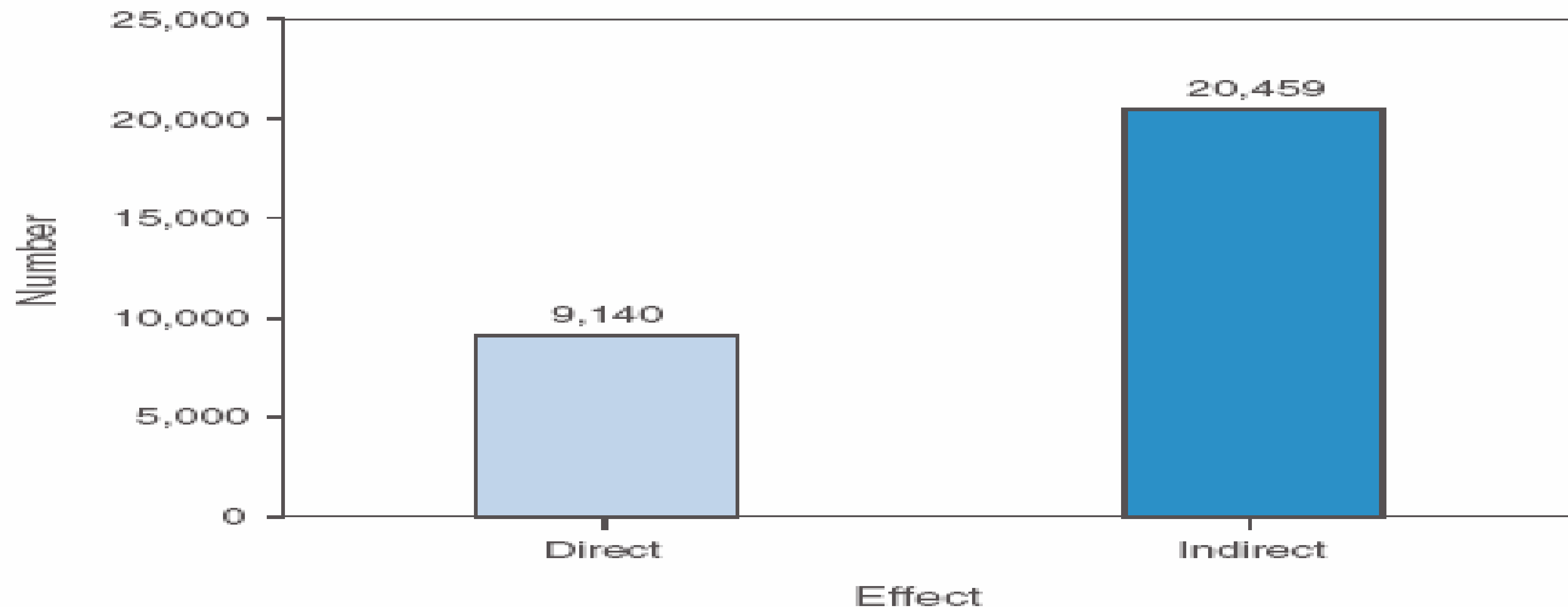
Correspondence to:

Direct and Indirect Effects of Routine Vaccination of Children with 7-Valent Pneumococcal Conjugate Vaccine on Incidence of Invasive Pneumococcal Disease United States, 1998--2003



MMWR, 2005/54(36);893-897

US - Universal immunization strategy with PCV : the herd effect on IPDs



MMWR, 2005/54(36);893-897

The positive effect of herd immunity in the economic analyses of the PCV universal immunization strategies

Melegaro A and Edmunds (UK), Vaccine 2004 (CUA)
Base-case cost-utility ratio from Euro 87.913 per disc. QALY gained
Including herd immunity effects: Euro 7.352 per disc. QALY gained
Including complete serotype replacement: Euro 39.132 per disc. QALY gained

McIntosh ED et al (UK), Vaccine 2005 (CEA)
Including herd immunity effects, 4 doses of PCV at Euro 6.394 per LY gained: hyghly cost-effective!

Ray GT et al (US), Ped Infect Dis J 2006 (CEA)
Analysis including herd immunity effects observed through a 5 years period, comparing it with another US analysis performed before PCV introduction not including the indirect effects of the vaccination program (Lieu TA, JAMA 2004):
7.500 US dollars per LY gained: hyghly cost-effective!

Cost-Effectiveness of Pneumococcal Conjugate Vaccine

Evidence From the First 5 Years of Use in the United States Incorporating Herd Effects

G. Thomas Ray, MBA, Cynthia G. Whitney, MD, MPH,† Bruce H. Fireman, MA,**
Vincent Ciuryla, PhD,‡ and Steven B. Black, MD§

TABLE 4. Estimated Pneumococcal Disease Episodes Prevented, Costs and Cost-Effectiveness in the First 5 Years after Introduction of the Pneumococcal Conjugate Vaccine (2000–2004), by Vaccination Status and Age, U.S. Population

Variable	Vaccinated Children	Nonvaccinated Children Under 5 Yr of Age	Nonvaccinated Children and Adults 5 to <65 Yr of Age	Nonvaccinated Adults 65 Yr of Age and Older	All Persons
Estimated number of children vaccinated	13,800,000				13,800,000
Estimated number of vaccinations	51,600,000				51,600,000
Disease episodes prevented (discounted)					
Otitis	2,600,[illegible]				[illegible],000,000
Pneumonia (inpatient and outpatient)	154,000				154,000
Invasive disease	38,000	15,600	33,100	22,600	109,300
Total deaths prevented (undiscounted)	421	163	1885	2690	5159
Total life-years saved (discounted)	11,200	4500	40,900	23,000	79,600
Costs (in $ millions)					
Vaccination costs	2940		—		2940
Direct medical costs (savings)	(902)		(343)		(1541)
Parent out-of-pocket and work loss costs (savings)	(780)		—		(800)
Net costs (savings)	1257	(101)	(343)	(214)	599
Cost per episode of invasive pneumococcal disease prevented	33,000				5500
Cost per life-year saved	112,000				7500

Ped Inf Dis J, June 2006

Cost-Effectiveness of Pneumococcal Conjugate Vaccine

Evidence From the First 5 Years of Use in the United States Incorporating Herd Effects

G. Thomas Ray, MBA, Cynthia G. Whitney, MD, MPH,† Bruce H. Fireman, MA,* Vincent Ciuryla, PhD,‡ and Steven B. Black, MD§*

Cost-effectiveness estimates have become a key component of decisions on whether to adopt public health measures. Although useful, such estimates are often of necessity made using assumptions and expert opinion when data are lacking. Our results show that the cost-effectiveness of PCV in actual use has likely been much more favorable than predicted by estimates developed before the vaccine was licensed and may even be cost-saving if the indirect effect extends to reducing pneumonia in the nonvaccinated population.

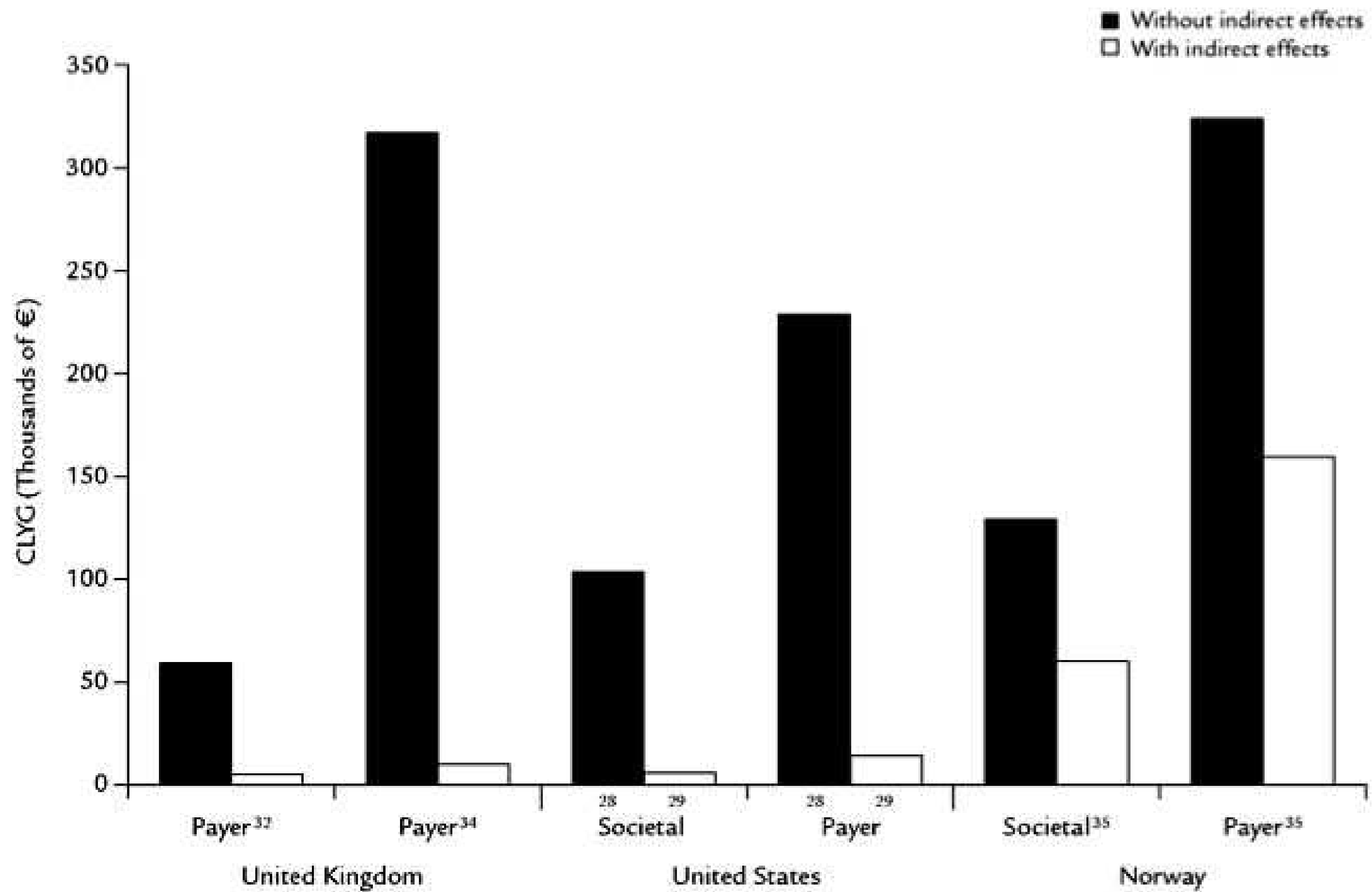
There is evidence that the PCV has caused an increase in pneumococcal disease caused by nonvaccine serotypes through "serotype replacement."[11] Because our assumptions regarding rates of disease in the nonvaccinated were based on observed rates of IPD regardless of serotype, our results implicitly incorporate any serotype replacement that might be taking place. However, if serotype replacement increases over time, it is possible that the efficacy of the vaccine—both for the vaccinated and nonvaccinated populations—could decline in the future.

Ped Inf Dis J, June 2006

Clinical Therapeutics/Volume 30, Number 2, 2008

The Impact of Indirect (Herd) Protection on the Cost-Effectiveness of Pneumococcal Conjugate Vaccine

Daniel J. Isaacman, MD[1]; David R. Strutton, PhD[2]; Edward A. Kalpas, MD[3]; Nathalie Horowicz-Mehler, MS[3]; Lee S. Stern, MS[3]; Roman Casciano, MS[3]; and Vincent Ciuryla, PhD[2]


Without indirect effects
With indirect effects
CLYG (Thousands of €)
350
300
250
200
150
100
50
0
28
29
28
29
Payer 32
Payer 34
Societal
Payer
Societal 35
Payer 35
United Kingdom
United States
Norway

CONCLUSIONS

The findings of this review support and extend the findings of our previous review of the literature on IPD incidence, the indirect effect, and PCV7 published between 1998 and 2005. The results of the present analysis indicate that despite the wide variability in results, the models that included indirect effects consistently reported more favorable cost-effectiveness ratios. This is highlighted by the sensitivity analyses, in which the indirect effect was a consistent driver of the cost-effectiveness ratio. These data strongly suggest that earlier studies that did not include the indirect effect may have underestimated the cost-effectiveness of PCV7. In most cases, cost-effectiveness ratios for PCV7 were well within monetary thresholds for favorability. Addition of the indirect effect to cost-effectiveness models appears to be an important factor supporting the routine vaccination of young children.

Further comments

- **Considering all age groups together, <u>the estimated number of IPD cases caused by strains with reduced susceptibility to penicillin or multiple antibiotics fell by 50%</u> after PCV introduction in the U.S.**

- **<u>Reduction of trasmission of V-type strains among vaccinees and their household members explains the decrease in rates of resistant disease among adults</u> (5 of 7 serotypes in PCV are responsible for most penicillin-resistant infections).**

- **<u>Replacement</u> phenomenon <u>was observed but the magnitude of this effect was relatively small.</u>**

- **Most of resistant infections from non-vaccinal serotypes were caused by 19A. Genetic typing showed evidence of <u>capsular switching</u>.**

- **Policymakers have to consider this reduction in resistant infections as an added benefit to routine vaccine use**

N Engl Med J, April 2006

Efficacia del vaccino PCV vs principali *outcome* indagati negli studi della letteratura

(Consensus Conference: metanalisi Angelillo I et Al.)

IPDs:

70-85% (forme sostenute da tutti i sierotipi - solo da sierotipi vaccinali)

CAP:

6-29% (forme dg. clinica - forme dg. radilogica)

AOMs:

36-57% (dg. colturale, forme sostenute da tutti i sierotipi - solo da sierotipi vaccinali)

Volume 11 • Number 5 • 2008
VALUE IN HEALTH

Economic Evaluation of a Universal Childhood Pneumococcal Conjugate Vaccination Strategy in Ireland

Lesley Tilson, BSc (Pharm), PhD,[1] Cara Usher, BSc, PhD,[1] Karina Butler, MB, FRCPI,[2] John Fitzsimons, MB, MRCPI,[2] Fiona O'Hare, MB,[3] Suzanne Cotter, MB, FRCPI, FFPHMI,[4] Darina O'Flanagan, MB, FRCPI, FFPHMI,[4] Howard Johnson, MB, FRCPI, FFPHMI,[5] Michael Barry, MD, PhD, FRCPI[1]

Table 2 Assumptions used in the base-case and herd immunity models, including direct medical costs

Model assumptions	Base-case model	Herd immunity model
Vaccination strategies	Three-dosage schedule (i.e., two doses separated by a 2-month period and third dose at 13 months of age).	
Vaccine efficacy	IPD 93.9% (CI 79.9–98.5%) [11] All-cause pneumonia (positive film) 17.7% (CI 4.8–28.9%) [12] All-cause AOM 7% (CI −5–17%) [13] Serotypes producing invasive disease in Ireland accounted for [14].	Reduction in cases of IPD [6] and hospital pneumonia [7]
Vaccine onset	50% vaccine efficacy 2–6 months 100% vaccine efficacy 6 months–5 years	
Duration of protection	5 years	Vaccination of one infant cohort reduces incidence of neumococcal infection in adults for 1 year [6].
Vaccine uptake	85% [15]	
Vaccine costs	Ex-wholesale price €63.18 plus administration fee €15/dose Total cost per infant per course €234.54	
Direct medical costs	Adapted to Irish setting from UK expert panel [16]	
Pneumococcal infection	Pneumococcal meningitis €7352 Pneumococcal septicemia €5467 All-cause pneumonia €2283 All-cause AOM €148	Meningitis €7330[6] Septicemia €6810[8] Hospital-treated pneumonia €4618[8]
Long-term sequelae of meningitis costs/infection (discounted over 10 years)	Adapted to Irish setting from UK resource utilization Hearing loss €35,925 Developmental delay €61,875 Focal neurological deficits €58,802 Chronic seizures €12,458	
Discounting	Costs and benefits discounted annually at 3.5%	

Objective: To evaluate the cost-effectiveness of implementing a universal infant 7-valent pneumococcal conjugate vaccine (PCV7) vaccination program in the Irish health-care setting from the health-care payers' perspective.

Methods: A model was constructed in MS Excel to follow a cohort of vaccinated and unvaccinated individuals from birth over a 5-year period. The reduction in events that would be associated with PCV7 vaccination and the mortality and cost resulting from these events were analyzed. In a separate sub-model, the effect of herd immunity was investigated.

Results: Implementing a PCV7 vaccine program in Ireland in a birth cohort of 61,000 infants would be expected to prevent 7703 cases of pneumococcal-related infections over 5 years, resulting in costs avoided of €2.05 million increasing to €4.6 million if the effect of herd immunity was included. The baseline incremental cost-effectiveness ratio was €249,591/life years gained (LYG), which reduced to €5997/LYG when the effect of herd immunity was included.

Conclusions: A universal infant pneumococcal conjugate vaccination could be considered highly cost-effective in the Irish health-care setting from a health-care payers' perspective, if viewed in terms of the herd immunity effect. The results of this study have positive ramifications for countries in the early stages of health technology assessment.

Keywords: childhood, cost-effectiveness, herd immunity, pneumococcal conjugate vaccination.

Position Paper WHO (Weekly Epidemiol Rec n.12, 2007)
Il vaccino pneumococcico coniugato per l'immunizzazione infantile

World Health Organization

L'OMS sottolinea che il PCV-7 è attualmente l'unico vaccino pneumococcico coniugato disponibile in commercio e autorizzato in oltre 70 paesi.

PCV-7 garantisce ai bambini da 2 mesi fino a 5 anni di età una elevata protezione verso le malattie pneumococciche invasive, quali meningite, sepsi, batteriemie, e, sia pure ad un livello più contenuto, non invasive quali polmonite e otite media causate dai sierotipi contenuti nel vaccino.

Diversi trial in Paesi in via di sviluppo hanno dimostrato l'efficacia di un ciclo vaccinale a 3 dosi nel primo anno di vita, senza la dose booster successiva. Questa schedula vaccinale è, peraltro, gia adottata da molti Paesi sviluppati. Nuovi studi potranno meglio indagare l'indicazione a somministrare una successiva dose di vaccino nel secondo anno di vita o ad adottare schedule alternative.

PCV-7 può essere facilmente integrato nei programmi di vaccinazione di routine. Lo si può somministrare contemporaneamente, anche se in un sito diverso, ad altri vaccini inseriti nei programmi di immunizzazione infantile.

Conclusioni

- Le valutazioni economiche del vaccino anti-pneumococcico coniugato effettuate nel passato hanno dato risultati eterogenei
- Il costo del vaccino ha un impatto determinante nelle valutazioni economiche esaminate
- Considerando il fenomeno dell'herd immunity si ottengono sempre migliori risultati relativi ai rapporti costo/efficacia e costo/utilità
- Il fenomeno del replacement dei sierotipi andrà attentamente considerato nelle valutazioni economiche in quanto si stima influenzi in maniera determinante i rapporti costo/efficacia e costo/utilità
- Un programma di vaccinazione universale con 3 dosi è il migliore dal punto di vista economico, ma anche dal punto di vista dei vaccinatori e dei familiari dei vaccinandi.