Enjeux et défis de l'évaluation médico-économique des vaccins

La Vaccination en France
Matinée thématique du CES
Paris, 29 juin 2017

Bénéfices de la vaccination : l'importance des effets indirects

- L'évaluation des stratégies vaccinales nécessité de prendre en compte les effets indirects (externalités) :
  - Immunité grégaire (+)
  - Déplacement en âge des cas (+/-)
  - Remplacement séro/génotypique (-)
- Une question étroitement liée au choix de la modélisation
  - Modèles dynamiques
  - Modèles statiques

Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis

Mary E Ramsay, Nick J Andrews, Caroline L Trotter, Edward B Kaczmarski, Elizabeth Miller

Attack rate of confirmed meningococcal serogroup C infection in unvaccinated children before and after the launch of the vaccination campaign

	July 1998-June 1999				July 2001-June 2002					
Cohort	Date of birth	Cases	Population	Attack rate per 100 000 (95% CI)	Date of birth	Cases	Estimated coverage (%)	Estimated population	Attack rate per 100 000 (95% CI)	% reduction (95% CI)*
Adolescent	1 Sep 1978 to 31 Aug 1981	96	1 818 034	5.28 (4.2 to 6.3)	1 Sep 1981 to 31 Aug 1984	11	66	614 110	1.79 (0.7 to 2.8)	66 (37 to 82)
School years 7-10	1 Sep 1981 to 31 Aug 1985	141	2 546 938	5.54 (4.6 to 6.4)	1 Sep 1984 to 31 Aug 1988	4	86	359 118	1.11 (0.02 to 2.2)	80 (46 to 93)
School years 1-6	1 Sep 1985 to 31 Aug 1991	76	3 911 606	1.94 (1.5 to 2.4)	1 Sep 1988 to 31 Aug 1994	5	87	498 068	1.00 (0.1 to 1.9)	48 (–28 to 79)
Preschool	1 Sep 1991 to 31 Dec 1994	81	2 055 120	3.94 (3.1 to 4.8)	1 Sep 1994 to 31 Dec 1997	6	76	501 449	1.20 (0.2 to 2.2)	70 (30 to 87)
Toddlers	1 Jan 1995 to 31 Dec 1995	41	601 045	6.82 (4.7 to 8.9)	1 Jan 1998 to 31 Dec 1998	2	84	97 369	2.05 (–0.7 to 4.9)	70 (–24 to 93)
Infants	1 Jan 1996 to 28 Jul 1996	24	320 562	7.49 (1.5 to 10.5)	1 Jan 1999 to 28 Jul 1999	1	80	64 112	1.56 (–1.5 to 4.6)	79 (–54 to 97)
Overall		459	11 235 305	4.08 (3.7 to 4.5)		29		2 134 226	1.36 (0.86 to 1.85)	67 (52 to 77)

*95% confidence intervals were estimated by using the Taylor series method for relative risks.

range of 48% to 80% across the age groups (table). A smaller fall occurred in adults not eligible for vaccination (aged ≥25 years), for whom the incidence declined by 35% (20% to 49%) from 0.53 (193/36 315 726) to 0.34 (123/36 315 726) per 100 000.

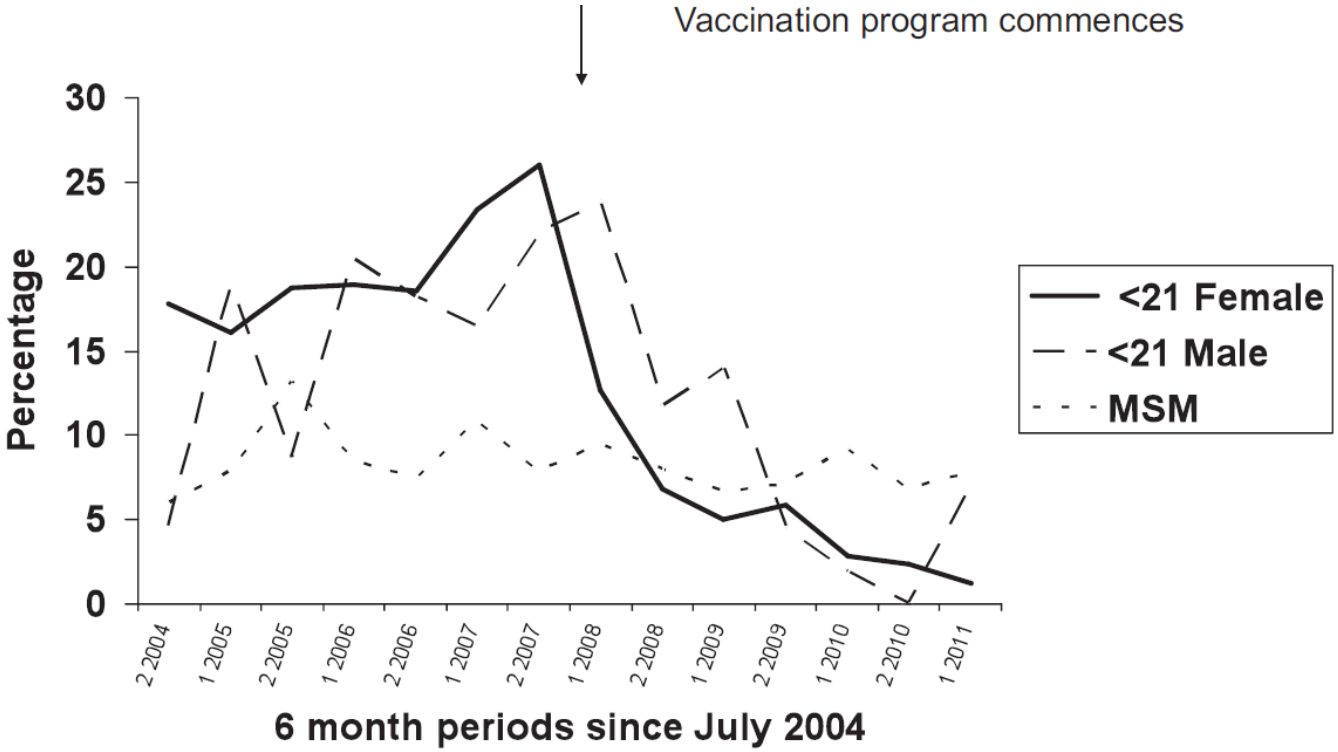
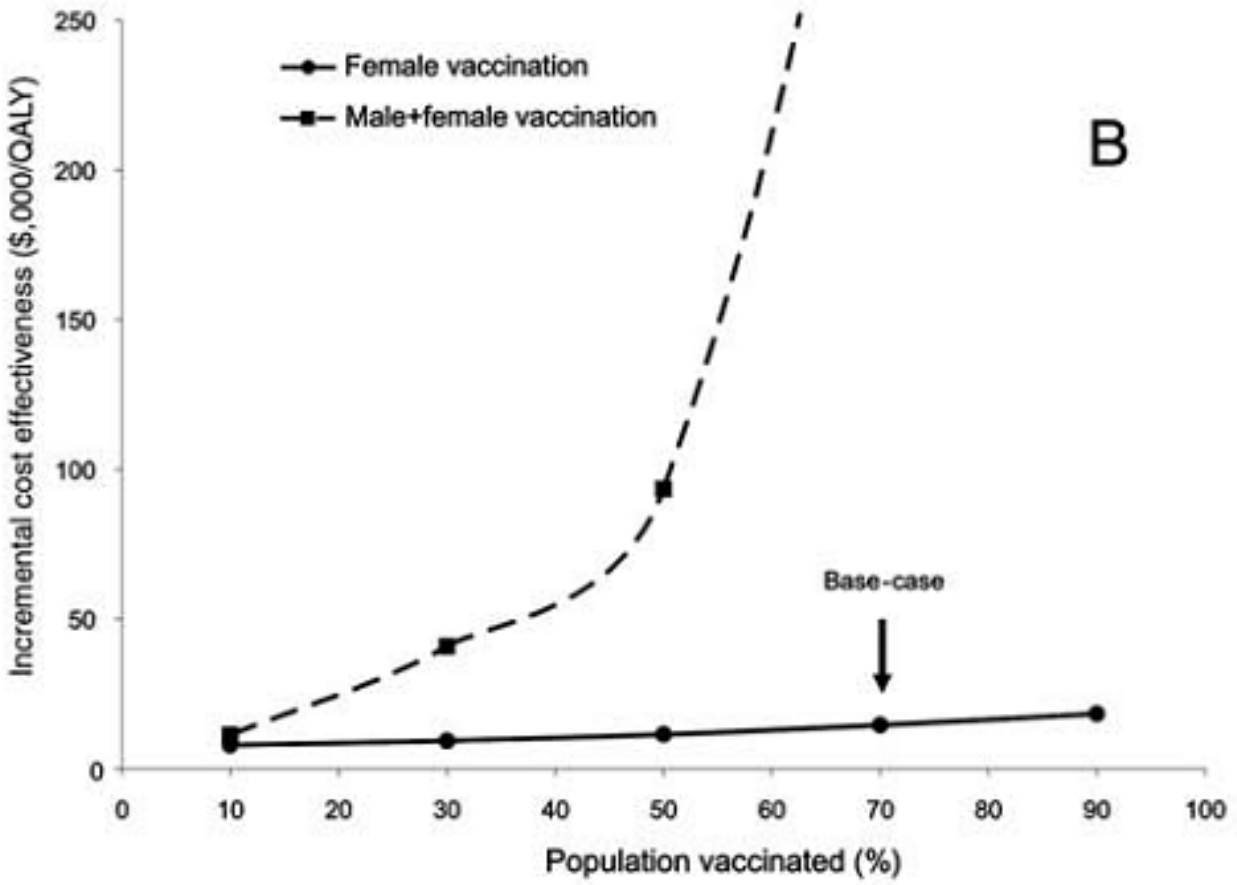


Figure 1 Proportion of patients aged <21 years, diagnosed as having genital warts by risk group compared with MSM of all ages: MSM, men who have sex with men, men <21 years excluded MSM, and non-residents excluded.

Read et al. (Sex Transm Infect, 2011)



Taira et al. (Emerg Infect Dis.2004)

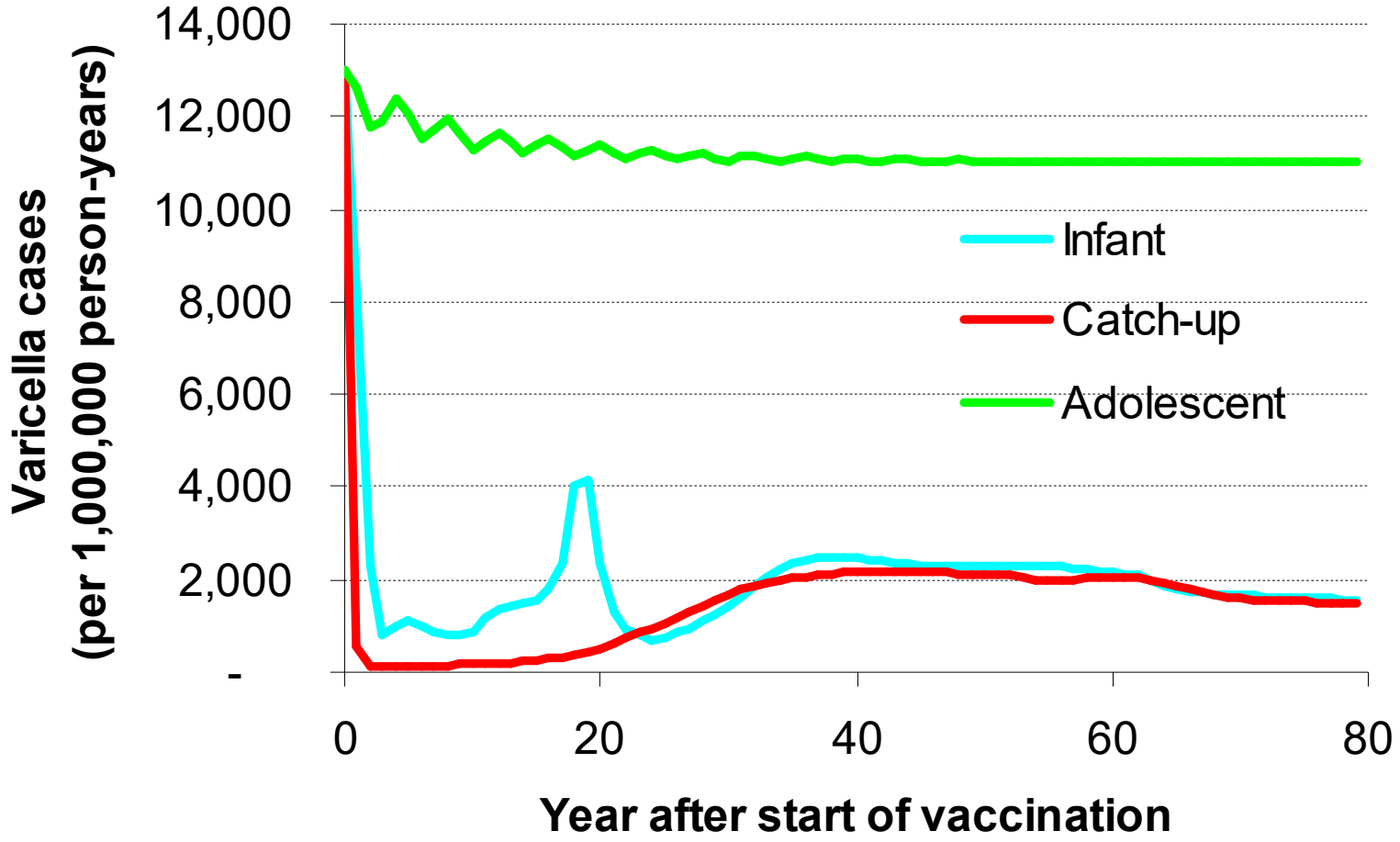
L'estimation de la couverture vaccinale:
La question de l'implémentation

- L'estimation de la couverture vaccinale est un enjeu majeur de l'évaluation au moment de l'introduction de la vaccination ainsi qu'au moment de la ré-évaluation
- Le RDCR dépend de la couverture vaccinale de manière non monotone : il est décroissant puis croissant
- Couverture vaccinale : coût marginal croissant
  - « Vaccine hesitancy »
  - « Free riding »
- Intégration des coûts de la stratégie d'implémentation dans l'évaluation médico-économique
- Qui est responsable de la stratégie d'implémentation (Pouvoirs publics, industriel) ?

Bénéfices de la vaccination : la question de l'équité

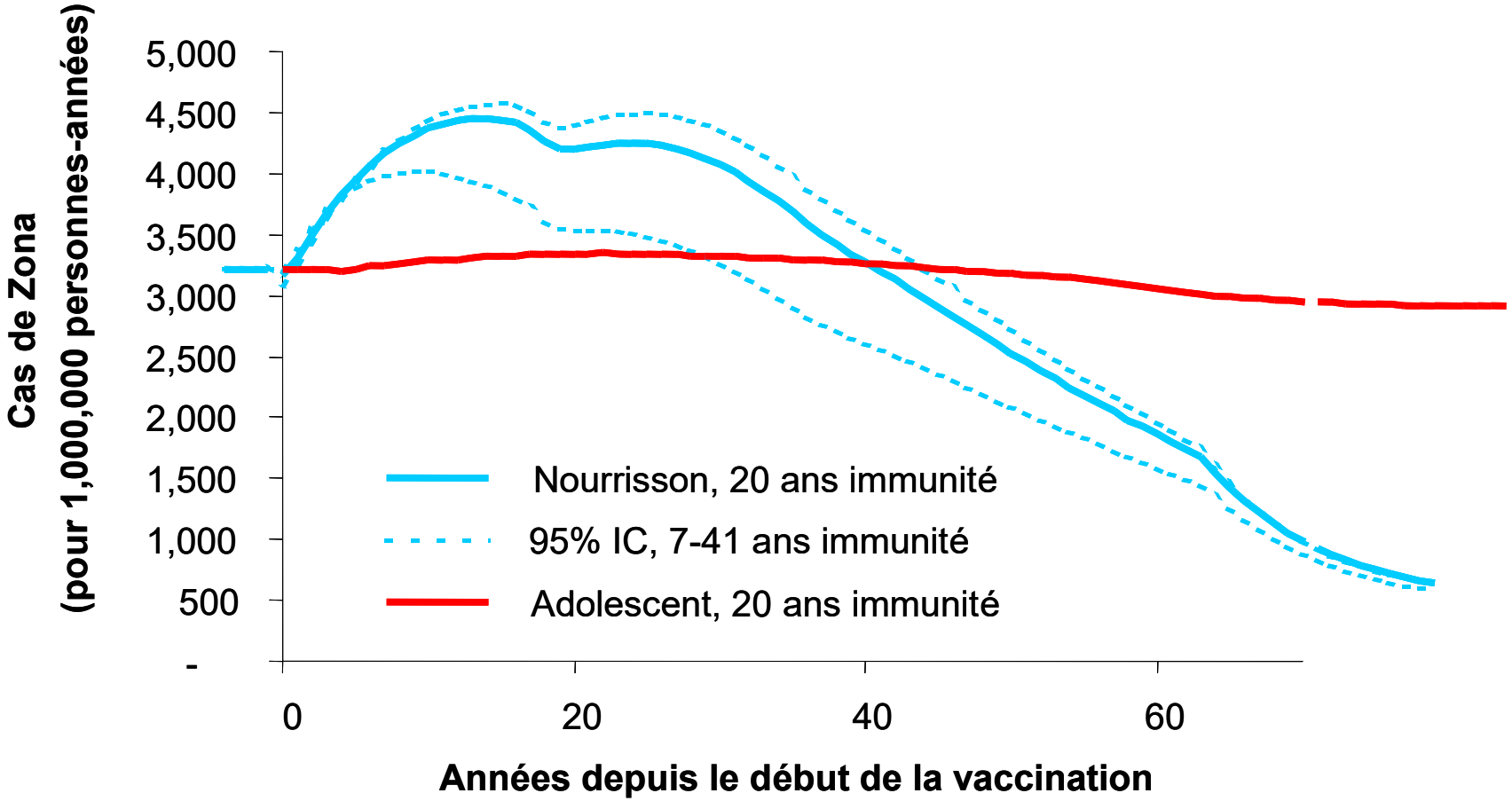
- Prise en compte de l'équité
  - Au-delà du débat général / allocation des ressources
  - Au-delà du débat sur les inégalités sociales de santé (ex. la constatation de couvertures vaccinales différentes selon le statut socio-économique des personnes)
  - Effets indirects → transferts de morbi-mortalité entre sous-groupes de population
    - Immunité grégaire (∇ exposition au risque)
    - Varicelle : déplacement en âge des cas (au départ, une infection souvent bénigne qui touche 100% des enfants, à l'arrivée une infection potentiellement sévère pour les seules personnes non vaccinées)
    - Varicelle : sous l'hypothèse du « boost exogène », la vaccination de routine des nourrissons conduit à une augmentation de l'incidence du zona chez les sujets âgés
    - HPV : extension de la vaccination aux HSH

Impact sur l'incidence
scénario de base, CV = 90%



Brisson *et al*. J Med Virol 2003

Impact sur l'incidence du zona

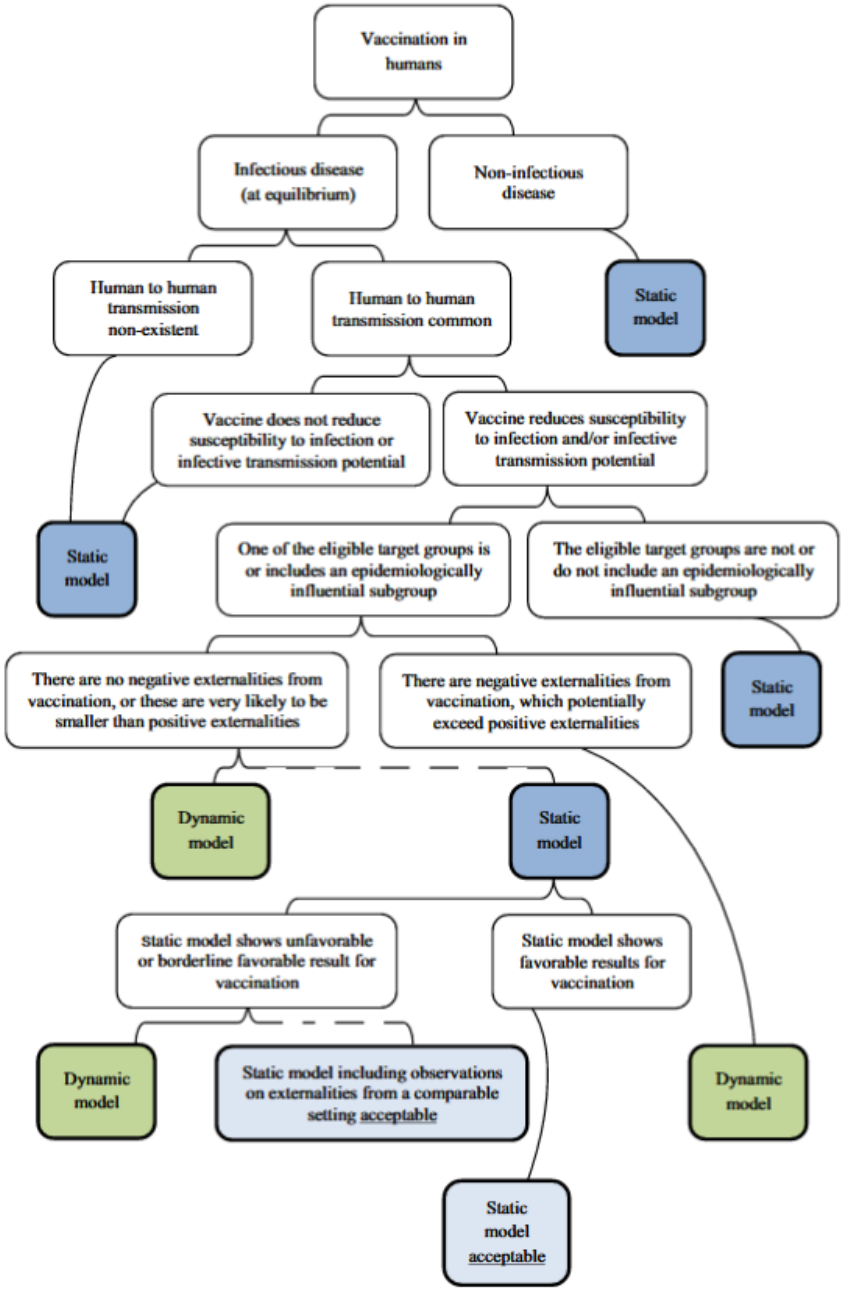


Brisson *et al*. J Med Virol 2003

Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community

Bernhard Ultsch[1] · Oliver Damm[2] · Philippe Beutels[3] · Joke Bilcke[3] · Bernd Brüggenjürgen[4] · Andreas Gerber-Grote[5] · Wolfgang Greiner[2] · Germaine Hanquet[6] · Raymond Hutubessy[7] · Mark Jit[8,9] · Mirjam Knol[10] · Rüdiger von Kries[11] · Alexander Kuhlmann[12] · Daniel Levy-Bruhl[13] · Matthias Perleth[14] · Maarten Postma[15] · Heini Salo[16] · Uwe Siebert[17,18] · Jürgen Wasem[19] · Ole Wichmann[1]

PharmacoEconomics (2016) 34:227–244

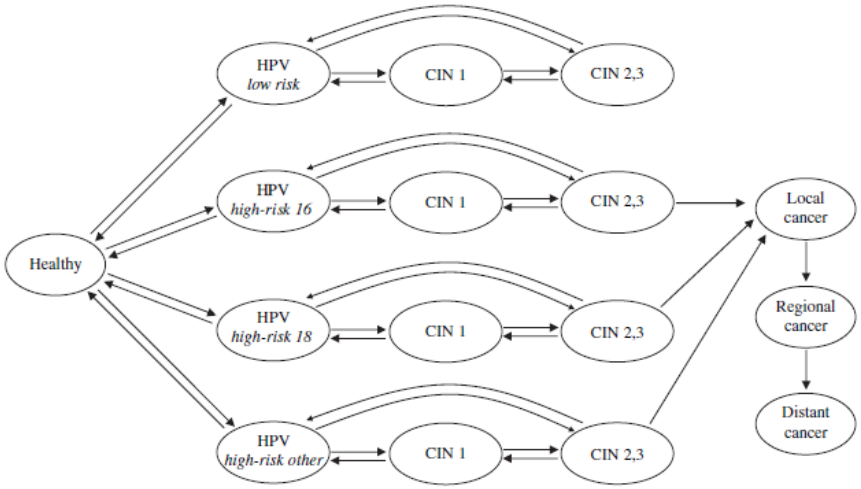


Bénéfices de la vaccination :
Une modélisation complexe

- Référence = modèles dynamiques
- Mais :
  - Des modèles complexes et sensibles
  - De nombreux paramètres inconnus ou mal connus → très fort degré d'incertitude
- Des difficultés pour :
  - La calibration des modèles (multi-paramètres → corrélation)
  - La réalisation des analyses de sensibilité probabiliste

Multiparameter Calibration of a Natural History Model of Cervical Cancer

Jane J. Kim[1], Karen M. Kuntz[1], Natasha K. Stout[1], Salaheddin Mahmud[2], Luisa L. Villa[3], Eduardo L. Franco[2], and Sue J. Goldie[1]



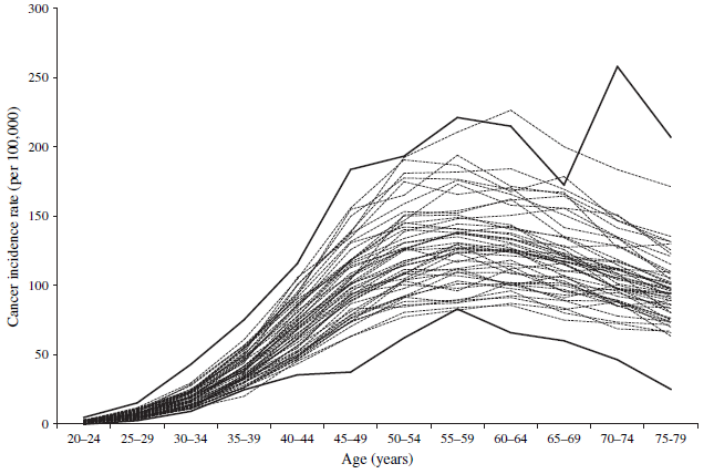


FIGURE 5. Age-specific incidence of cervical cancer per 100,000 women in Brazil. Dotted lines, model output for 50 sampled good-fitting sets. Solid lines, 95% confidence intervals of age-specific incidence data from the International Agency for Research on Cancer (15, 16).

Bénéfices de la vaccination :
Elargir le scope ?

- Un cadre d'évaluation plus large, prenant en compte des impacts macroéconomiques
  - Comment faire ?
  - Spécificité de la vaccination ?
  - Un biais systématique en défaveur de la vaccination (/ d'autres interventions, d'autres champs) ?

The broader economic impact of vaccination: reviewing and appraising the strength of evidence

Mark Jit[1,2], Raymond Hutubessy[3*], May Ee Png[4], Neisha Sundaram[4], Jananie Audimulam[4], Safiyah Salim[4] and Joanne Yoong[4]

Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible?

Mark Jit[1,2] · Raymond Hutubessy[3]

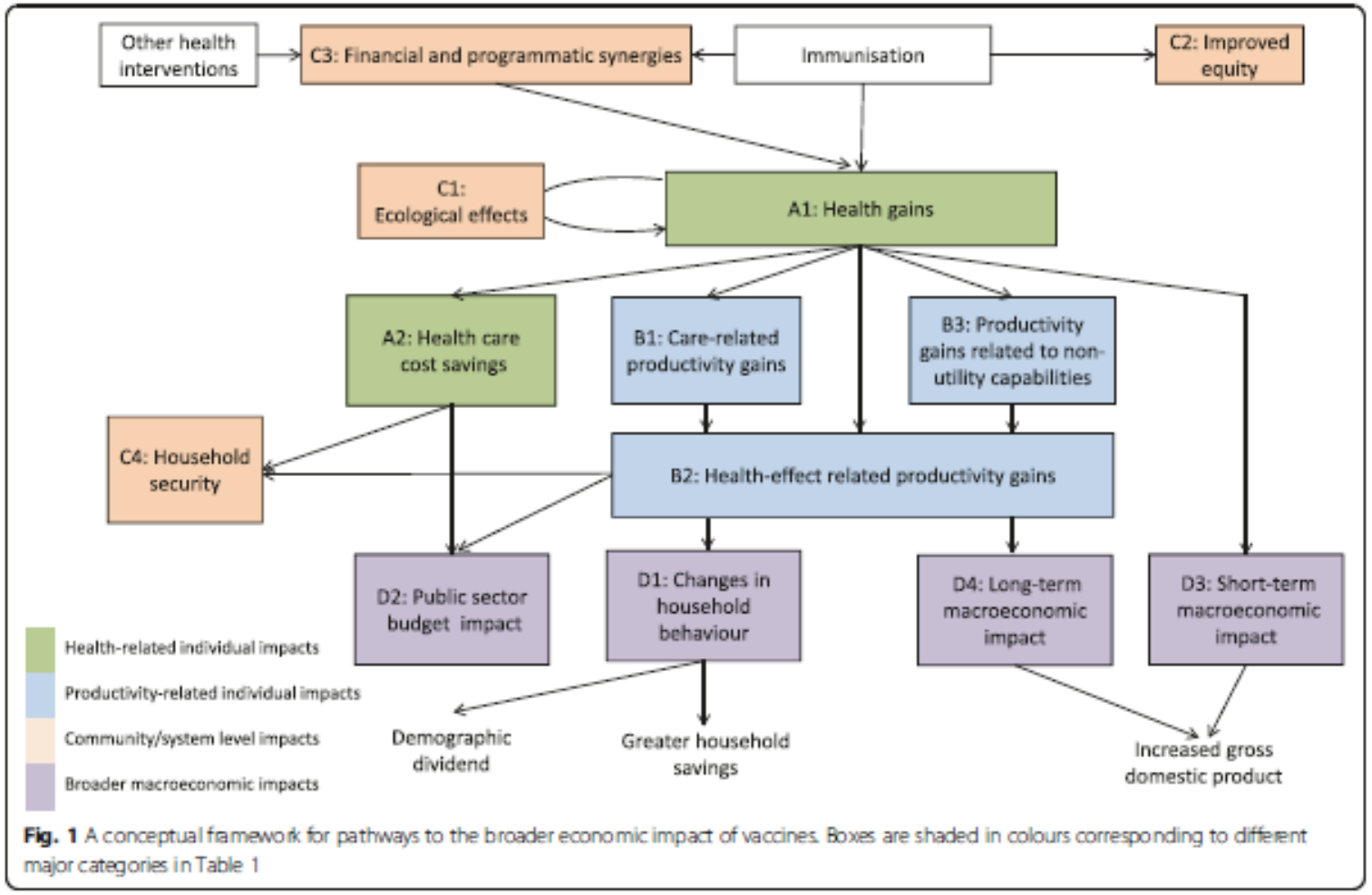


Fig. 1 A conceptual framework for pathways to the broader economic impact of vaccines. Boxes are shaded in colours corresponding to different major categories in Table 1

Bénéfices de la vaccination :
la prise en compte du temps

- Les questions posées :
  - Choix du taux
    - 4% [Lebegue] → 2,5% ± prime de risque [Quinet]
  - Actualisation différenciée des coûts et des résultats
  - Choix du modèle d'actualisation
- Des questions qui ne sont pas spécifiques à la vaccination
- Une question de degré plus que de nature

Le choix du taux d'actualisation

Table 2: Guidelines on Discounting in Selected Countries

Country	Discount rate		
	Costs	Health Outcomes	Sensitivity analysis
Australia (PBAC) [10]	5%	5%	0%
UK (NICE)** [11]	3.5%	3.5%	1.5%
France[9]	4% < 30 years, 2% ≥ 30 years	4% < 30 years, 2% ≥ 30 years	0% to 6%
Netherlands (CVZ)[8]	4%	1.5%	0%
Germany (IQWiG) [12]	3%	3%	0, 5, 7 and 10%
Finland[13]	3%	3%	0%
Portugal[14]	5%	5%	0% for health outcomes
Canada (CADTH)[15]	5%	5%	0% and 3%
New Zealand (PHARMAC) [16]	3.5%	3.5%	0, 5 and 10%

Abbreviations: CADTH denotes Canadian Agency for Drugs and Technologies in Health, CVZ College Voor Zorgverzekeringen, IQWiG Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen, NICE National Institute for Health and Care Excellence, PBAC Pharmaceutical Benefits Advisory Committee, PHARMAC Pharmaceutical Management Agency.

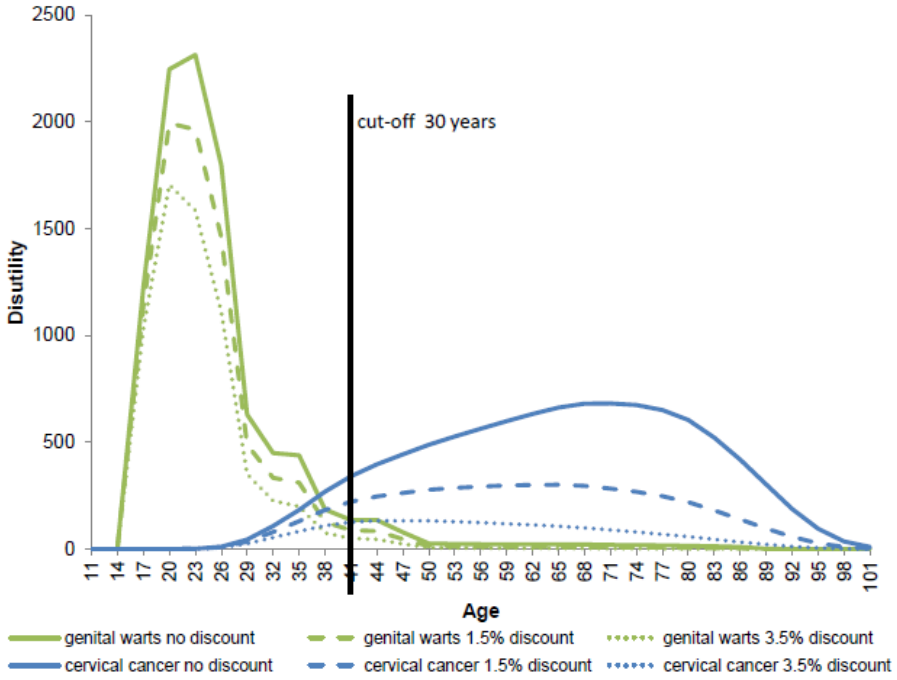
Short Communication

Does it matter? Discounting and its role in the cost-effectiveness of preventative interventions. The case of HPV vaccination☆

H. Starkie Camejo [a,*], X. Li [b], G. Van Kriekinge [b]

Impact of time				
% of total undiscounted QALYs gained	After 30 years		After lifetime	
	At 1.5%	At 3.5%	At 1.5%	At 3.5%
GW-related	76%	59%	80%	62%
CC-related	5%	3%	60%	24%

Supplementary Figure 1: The impact of discounting on cost and lifetime utility difference vaccinated with qHPV vs. no vaccination



Footnote:

Solid lines: undiscounted total QALYs over time for the entire cohort in the model

Broken lines: total QALYs over time with a 1.5% discount rate

Dotted lines: total QALYs over time with a 3.5% discount rate

HEALTH ECONOMICS
Health Econ. **20**: 2–15 (2011)
Published online 12 May 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.1612

DISCOUNTING AND DECISION MAKING IN THE ECONOMIC EVALUATION OF HEALTH-CARE TECHNOLOGIES

KARL CLAXTON[a,b,*], MIKE PAULDEN[a], HUGH GRAVELLE[a,c], WERNER BROUWER[d] and ANTHONY J. CULYER[b,e]

MAXIMISING THE PRESENT VALUE OF HEALTH

MAXIMISING THE PRESENT CONSUMPTION VALUE OF HEALTH

Exogenous budget constraint

No budget constraint

$$v_1 \Delta h_1 + \frac{v_2 \Delta h_2}{(1+r_c)} > \Delta c_1 + \frac{\Delta c_2}{(1+r_c)}.$$

$$d_h \approx r_c - g_v$$

$$d_c = r_c$$

L’actualisation (1)

- Choix d’un taux d’actualisation constant (modèle exponentiel) :

$$a(t)=\frac{1}{(1+r)^t}$$

- Choix d’un taux d’actualisation décroissant au cours du temps (modèle hyperbolique ou proportionnel) :

$$a(t)=\frac{1}{(1+r)^{\alpha(t)}} \quad \alpha(t), \text{ une fonction concave de t}$$

L’actualisation (2)

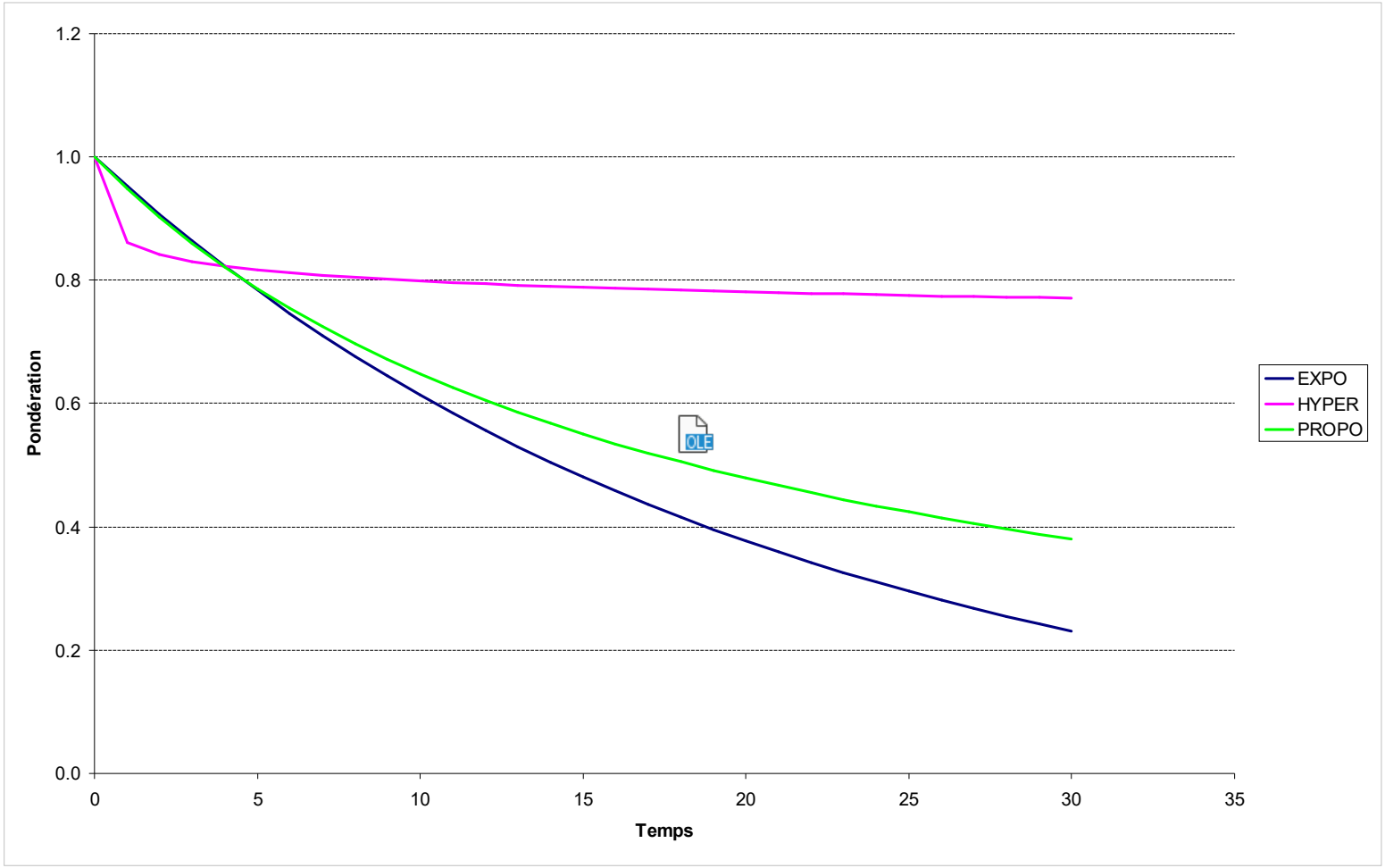
- Modèle hyperbolique [Cairns et Van der Pol (2000) :

$$a(t) = \frac{1}{(1+gt)^{h/g}}$$

- Modèle proportionnel [Harvey (1994)] :

$$a(t) = \frac{b}{b+t}$$

L’actualisation (3)



Source : Beutels (2002)

On Discounting of Health Gains from Human Papillomavirus Vaccination: Effects of Different Approaches

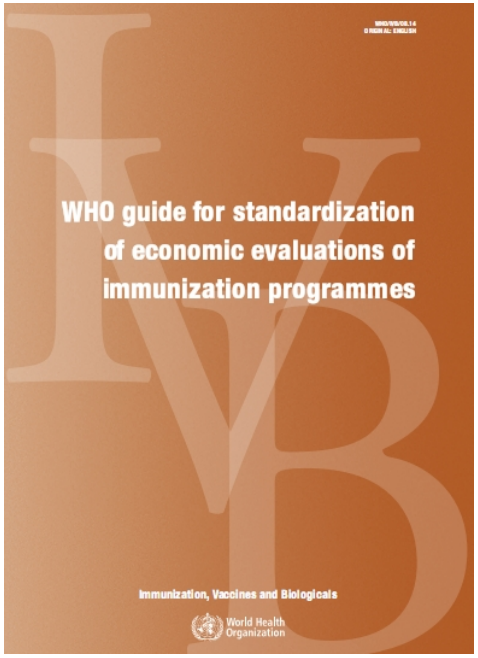
Tjalke A. Westra, MSc[1,], Mehraj Parouty, MSc[2], Werner B. Brouwer, PhD[3], Philippe H. Beutels, PhD[4], Raina M. Rogoza, MSc[5], Mark H. Rozenbaum, MSc[2], Toos Daemen, PhD[1], Jan C. Wilschut, PhD[1], Cornelis Boersma, PhD[2], Maarten J. Postma, PhD[2,6]*

Table 3 – Discounted health outcomes of HPV vaccination using the different discounting approaches.

Discounting approach	QALYs gained	ICER (€/QALY)
Undiscounted	3462	7,600
Constant 1.5%	1423	18,400
Constant 3%	715	37,000
Constant 4%	438	59,100
Proportional	164	165,400
Hyperbolic	160	164,500
Stepwise*	718	36,800
Shifted 4%	2117	13,200
Shifted 1.5%	2811	9,400

HPV = human papillomavirus; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

* As proposed by the UK treasury.



Recommandations OMS (2008)

7.3 Recommendations

- Discount costs and effects initially using the rate in the country in question (for studies to inform local decision-makers) and then using a 3% discount rate (consistent with WHO-CHOICE and DCP2);
- Conduct sensitivity analysis using discount rates of 0%, near-zero, 5% and 10% to reflect the (probably) higher real risk-free cost of capital in developing countries;
- A non-constant (declining or 'slow') discounting procedure may be applied where the effects begin only long after the intervention, e.g. vaccination against HBV or HPV, or last for an exceptionally long time, e.g. polio eradication.

Bénéfices de la vaccination : la prise en compte du temps

- "Prevention is better than cure"?
  - Des travaux montrent que les individus privilégient les interventions de prévention par rapport aux interventions à visée curative [Luyten et al (2015), NICE Citizens Council (2011), Mortimer et Segal (2008), Ubel et al (1998), Johannesson et Johansson (1997)] $\pm$ sévérité et hétérogénéité des préférences
  - Prise en compte :
    - Choix du taux d'actualisation
    - Valorisation différentielle des QALY
    - Choix du seuil (?)

Bénéfices de la vaccination :

la mesure de la qualité de vie en pédiatrie

Tableau 1 : Présentation des instruments génériques fondés sur les préférences et adaptés à une population pédiatrique.

<table>
<tr><th>Instrument</th><th>Questionnaire</th><th>Âge</th><th>Valorisation des préférences</th></tr>
<tr><td>HUI2

HUI3</td><td colspan="2"><table>
<tr><th>Age of Subject</th><th colspan="2">Self-Administration (15Q)</th><th colspan="2">Interviewer Administration (40Q)</th></tr>
<tr><th></th><th>Self-Assessment</th><th>Proxy Assessment</th><th>Self-Assessment</th><th>Proxy Assessment</th></tr>
<tr><td>< 5 years</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>5–8 years</td><td>NR</td><td>Yes[1]</td><td>NR</td><td>Yes[1]</td></tr>
<tr><td>9–12 years</td><td>NR</td><td>Yes[2]</td><td>Yes[1]</td><td>Yes[2]</td></tr>
<tr><td>> 12 years</td><td>Yes[1]</td><td>Yes[2]</td><td>Yes[1]</td><td>Yes[2]</td></tr>
</table></td><td>HUI2 (CAN) : SG auprès de parents

HUI2 (UK) : valorisation population générale

HUI3 (France) : valorisation population générale</td></tr>
<tr><td>HSCS-PS</td><td>Adapté de HUI2 et HUI3</td><td>2,5 - 5</td><td>Pas d'algorithme publié</td></tr>
<tr><td>CHU9D
(Stevens)</td><td>Auto-questionnaire
Proxy</td><td>7-17</td><td>Valorisation UK : SG auprès d'une population générale adulte

Valorisation australienne : méthode de choix discret auprès de 11-17 ans.</td></tr>
<tr><td>EQ-5D-Y
(van Reene, 2014)</td><td colspan="2"><table>
<tr><td>0-7 ans</td><td>Pour les enfants de 4 à 7 ans une version proxy peut être utilisée.</td></tr>
<tr><td>8-11 ans</td><td>EQ-5D-Y en auto-administration</td></tr>
<tr><td>12-15 ans</td><td>Le questionnaire EQ-5D-Y est recommandé, mais en fonction des besoins de l'étude, la version standard peut également être utilisée.</td></tr>
</table></td><td>Pas de matrice de valorisation disponible
Eurogol ne recommande pas d'utiliser la matrice adulte.</td></tr>
<tr><td>EQ-5D</td><td></td><td>A partir de 16 ans</td><td>Valorisation française : TTO auprès d'une population générale adulte</td></tr>
</table>

Sources and Characteristics of Utility Weights for Economic Evaluation of Pediatric Vaccines: A Systematic Review

Michael Herdman, MSc[1,*], Amanda Cole, PhD[1], Christopher K. Hoyle, PhD[1], Victoria Coles, PhD[2], Stuart Carroll, MSc, MBA[2], Nancy Devlin, PhD[1]

Table 3 – Key overall findings.

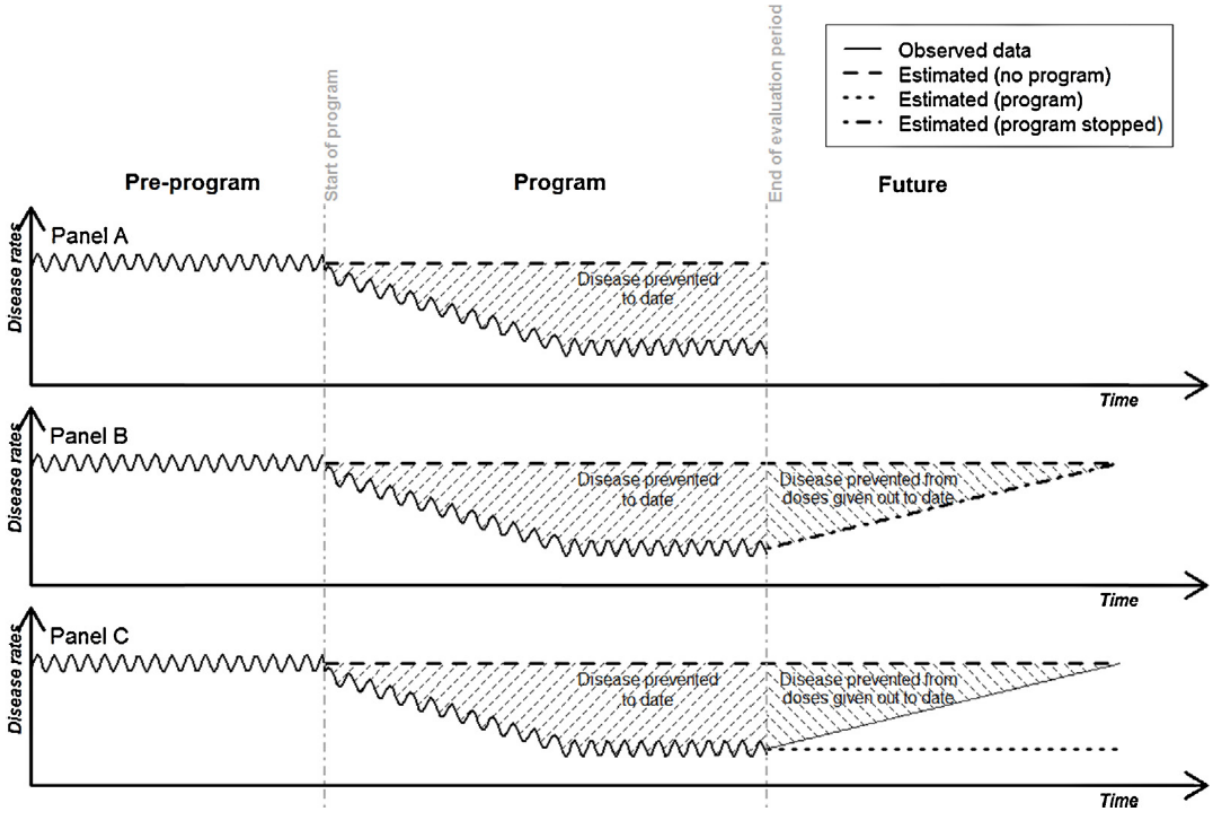
1. Lack of any utility values or modeling studies for some of the infectious diseases studied
2. Where utility values exist, these have been generated using widely differing methodologies, often leading to large differences in values for similar states
3. Limited research into whether utilities associated with health states vary by age group; the research that has been performed tends to suggest that values do differ, but this is often not taken into account in modeling studies
4. Use of value sets from other countries to "translate" health profile data into utilities
5. Use of adult preference-based measures in the target populations, e.g., the EQ-5D and the HUI, relying on strong assumptions about the relevance of both the descriptive systems and the value sets for children and adolescents
6. Collection of data took a considerable time after the illness episode, leading to possibility of recall bias
7. Reliance on potentially outdated value sets and measurement methods
8. Poor standards of reporting and occasionally a lack of transparency about the methods and assumptions used
9. Use of untested assumptions in some modeling studies and no exploration of impact of assumptions in sensitivity analysis
10. Occasional errors in using utility weights from source studies

La question de l'articulation primo-évaluation / réévaluation

- Primo-vaccination :
  - Données incomplètes
  - Très fort degré d'incertitude
  - → quantification de l'incertitude et identification des paramètres-clefs (PSA, VOI)
- Réévaluation
  - Validation

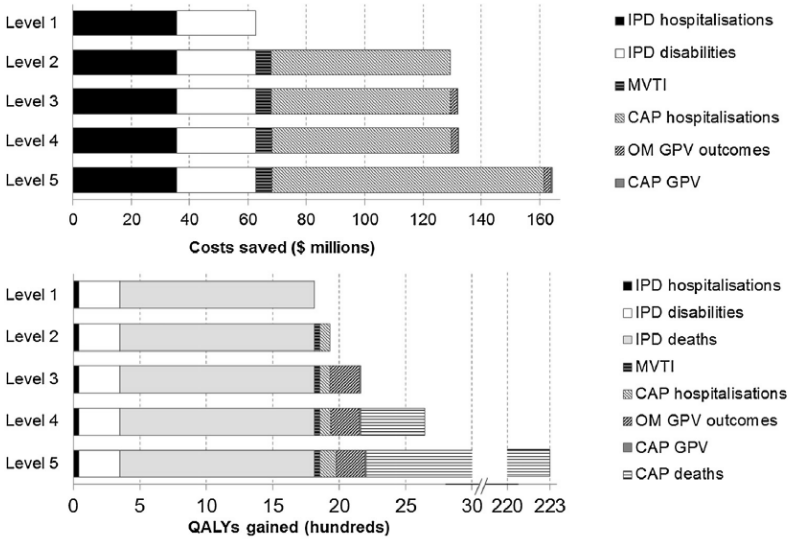
Economic evaluations of implemented vaccination programmes: key methodological challenges in retrospective analyses

A.T. Newall [a,*], J.F. Reyes [a], J.G. Wood [a], P. McIntyre [b], R. Menzies [b], P. Beutels [a,c]



Retrospective economic evaluation of childhood 7-valent pneumococcal conjugate vaccination in Australia: Uncertain herd impact on pneumonia critical

A.T. Newall[a,*], J.F. Reyes[a], P. McIntyre[b], R. Menzies[b], P. Beutels[a,c], J.G. Wood[a]



Potential PCV7 program total cost (including cost savings), quality-adjusted life years (QALYs) gained and ICER by level.

Scenario	Total cost – median (95% CI)[a]	Total QALY – median (95% CI)[a]	ICER $/QALY – median (95% CI)[a]
Level 1	$302,316,705 ($278,313,861–$320,684,818)	1816 (1456–2173)	$166,172 ($132,385–$213,370)
Level 2	$235,331,211 ($214,250,090–$256,946,443)	1934 (1562–2340)	$121,492 ($95,796–$156,403)
Level 3	$232,455,863 ($211,343,000–$254,097,138)	2166 (1791–2574)	$107,314 ($86,090–$134,933)
Level 4	$232,144,229 ($198,303,354–$258,098,975)	2605 (1500–4142)	$88,562 ($56,909–$151,946)
Level 5	$200,145,944 ($160,547,811–$236,569,488)	22,295 (16,370–29,484)	$8980 ($6964–$12,111)

Conclusion

- Des différences de nature (externalités) et de degré (complexité, temporalité)
- Opportunité de définir des guidelines et/ou d'adopter des règles de décision spécifiques à la vaccination ?
  - Choix du modèle (+)
  - Mesures d'utilité (+)
  - Réévaluation (+)
  - Calibration, analyse de sensibilité (-/+)
  - Taux d'actualisation (-)

Merci de votre attention

Benoît DERVAUX

benoit.dervaux@chru-lille.fr

benoit.dervaux@univ-lille2.fr