HTA12

Modeling Approaches for Vaccine Indirect Effects in Economic Evaluations: A Scoping Review of Published Reviews and Methodological Guidance

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Background

- While vaccines provide direct protection by reducing the risk of infection among vaccinated persons, they can also generate indirect effects (e.g. herd effects, serotype replacement, and age shift) that affect disease transmission and incidence at the population level[1]
- Assessment of both direct and indirect effects has been identified as being essential for comprehensively understanding the outcomes and costs associated with vaccination strategies
- Herd effects are one of several potential indirect effects that can result in protection being conferred upon unvaccinated individuals as persons around them become vaccinated. Over time, an increasing number of economic evaluations have considered herd effects as part of their modelling from 20% in 1998 to 53% in 2015[2]
- Serotype replacement and age shift, which often lead to negative impacts, are less frequently modeled
- The methods used to incorporate indirect effects in economic evaluations vary widely and are not standardized. Current guidance recognizes the importance of indirect effects, but there is uncertainty on how well they are modeled in practice

Objectives

- To investigate whether and how indirect effects such as herd effects, serotype replacement, and age shift have been considered within the existing body of literature on economic evaluations of vaccines
- To review recommendations and guidance from advisory bodies and assess the extent to which current economic evaluations of vaccines align with recommended approaches for the inclusion of indirect effects

Methods

- A scoping review was conducted to identify the following types of records:
  - Literature reviews examining whether and/or how indirect effects were modeled in vaccine economic evaluations
  - Methodological guidelines from advisory bodies or working groups outlining best practices or considerations for incorporating indirect effects
  - Perspective or commentary articles providing contextual or methodological discussion on approaches to incorporating indirect effects
- This review included a search of both MEDLINE and Embase (from inception to May 7, 2025) as well as a supplementary search
  - The supplementary search was conducted to identify methodological guidance from national immunization technical advisory groups (NITAGs) and/or health technology assessment (HTA) agencies from seven countries (Australia, Canada, France, Germany, the Netherlands, the United Kingdom, the United States of America)
- For literature reviews, data extracted include:
  - Model structure (static, dynamic or hybrid)
  - Data sources of indirect effect inputs
  - Key modelling assumptions related to indirect effects
- For methodological guidance, data extracted include:
  - Recommended modelling approaches
  - Structural assumptions
  - Input requirements related to indirect effects
- Perspective or commentary articles were included for contextual discussion and were not subject to formal data extraction
- Extracted data were synthesized descriptively to summarize patterns in current practice and to compare observed approaches with existing methodological recommendations. No assessment of study quality or methodological appropriateness was undertaken

Results

Overview of identified studies

- A total of 903 records were identified in the database search, of which after removal of duplicates 741 unique records were screened
  - 22 literature reviews were identified (**Table 1**)
  - Four guidelines from advisory bodies were included
  - Four perspective articles were included for contextual discussion
- The supplementary search identified guidance from seven NITAGs or HTA agencies related to the countries of interest

Table 1. Summary of included literature reviews

First author, publication year	Vaccine area(s) covered	Years covered by review	Number of studies including[1]				Proportion of studies incorporating indirect effects that employed dynamic models, n (%)
			Any indirect effect, n (%)	Herd effects, n (%)	Serotype replacement, n (%)	Age shift, n (%)	
Ma, 2022[3]	PCV, rotavirus, HPV, influenza, other	2000 – 2018	44/243 (18%)	44 (18%)	–	–	11 (25%)
Nymark, 2017[2]	PCV, HPV, rotavirus, influenza, varicella, HepB, HepA, meningococcal, Hib, pertussis	1976 – 2015	172/625 (28%)	172 (28%)	–	4 (1%)	59 (34%)
Issacman, 2008[4]	PCV7	2000 – 2006	4/16 (25%)	4 (25%)	1 (6%)	–	4 (100%)
Millier, 2012[5]	Pertussis	From inception – 2010	7/12 (58%)	7 (58%)	–	–	2 (29%)
Aballea, 2013[6]	Rotavirus	2001 – 2011	2/28 (7%)	2 (7%)	–	–	1 (50%)
Dirmesropian, 2015[7]	PCV13	From inception – 2024	6/10 (60%)	6 (60%)	4 (40%)	–	1 (10%)
Wang, 2022[8]	PCV7, PCV10, PCV13	2006 – 2019	6/9 (67%)	5 (56%)	3 (33%)	–	1 (11%)
Wu, 2015[9]	PCV10, PCV11, PCV13	2006 – 2014	20/28 (71%)	19 (68%)	18 (64%)	–	2 (10%)
Treskova, 2019[10]	PCV10, PCV13	2006 - 2018	13/13 (100%)	13 (100%)	7 (54%)	–	0 (0%)
Saokaew, 2016[11]	PCV7, PCV10, PCV13	2007 – 2013	16/22 (72%)	10 (45%)	13 (59%)	–	0 (0%)
Van de Vooren, 2014[12]	PCV7, PCV10, PCV13, PPSV23	2007 – 2013	9/10 (90%)	9 (90%)	9 (90%)	–	1 (10%)
Farkouh, 2012[13]	PCV7, PCV9, PCV10, PCV13	2006 - 2011	14/16 (88%)	14 (88%)	6 (33%)	–	0 (0%)
de Peuter, 2010[14]	HPV	2000 - 2009	7/8 (88%)	7 (88%)	–	–	5 (71%)
Rozenbaum, 2012[15]	Pertussis	NR	4/4 (100%)	3 (75%)	–	2 (50%)	4 (100%)
Løchen, 2020[16]	PCV7, PCV10, PCV13	From inception to 2020	19/21 (90%)	19 (90%)	16 (76%)	–	0 (0%)
Nwogu, 2021[17]	MenB	NR	6/13 (46%)	6 (43%)	–	–	5 (83%)
Teoh, 2018[18]	OCV	From inception to 2015	9/14 (64%)	9 (64%)	–	–	2 (14%)
Nymark, 2021[19]	PCV, Rotavirus, OCV, Hib, HPV, typhoid, dengue, polio, measles, DPT, Tb	2009 - 2019	44/177 (24%)	44/177 (24%)	–	–	13 (29%)
Ray, 2008[20]	PCV7	2000 - 2006	4/16 (25%)	4 (25%)	1 (6%)	–	NR
Ortega-Sanchez, 2008[21]	HPV, meningococcal, pertussis	From inception to 2005	4/25 (16%)	4 (16%)	–	–	1 (25%)
Cho, 2025[22]	PCV15, PCV20 and PPSV23	From inception to 2024	13/26 (50%)	12 (46%)	2 (8%)	–	0 (0%)
Deogaonkar, 2012[23]	Cholera, PCV, HepA	1990 - 2011	8/26 (31%)	8 (31%)	1 (4%)	–	1 (13%)

DPT, diphtheria, tetanus, and pertussis; HepA, hepatitis A; HepB, hepatitis B, Hib, Hemophilus influenza type b; HPV, human papilloma virus; MenB, meningococcal group B; OCV, oral cholera vaccine; PCV, Pneumococcal conjugate vaccine; Tb, tuberculosis.

Notes:

1. n indicates the number of publications reviewed by authors. Unless otherwise specified the percentage calculated is among all studies included in the review.

Literature reviews of vaccine economic evaluations

- PCV followed by HPV were the most frequently studied vaccines in the literature reviews, followed by pertussis and rotavirus vaccines
- All 22 reviews reported that herd effects were discussed in the economic evaluations included, 12 reviews identified economic evaluations that incorporated serotype replacement, and 2 identified economic evaluations incorporating age shift
  - Herd effects were typically incorporated via simplified adjustments by adding a fixed percentage improvement to vaccine effectiveness or fixed reductions in disease incidence in unvaccinated persons
  - Serotype replacement was included in some economic evaluations, primary in PCV studies, and was most commonly included via fixed approaches through reduction in herd effect estimates or increasing the incidence for non-target serotypes
  - Age shift was rarely considered and only discussed in the context of dynamic models
- 21 reviews specified whether static, dynamic, or hybrid models were used, with static models being most used
  - Reporting of data sources used to inform indirect effects was inconsistent, with some reviews reporting sources and others not. When sources were specified, estimates were commonly derived from national surveillance data, historically observed epidemiological data, or prior models

Literature reviews of vaccine economic evaluations

- Reviews agreed that indirect effects have an important impact on the benefits and costs of a vaccination program, however despite an increasing proportion of studies including indirect effects in recent years their inclusion has been inconsistent[2]
- Exclusion of indirect effects may underestimate potential benefits (e.g., from herd effects) or overlook potential negative consequences (e.g., from age shift or serotype replacement) of vaccination programs
  - Several reviews reported that excluding herd effects may underestimate cost-effectiveness of vaccination, or that omitting indirect effects such as age shift could overestimate vaccine effectiveness[5,11,13,16]
  - Exclusion of indirect effects increases uncertainty around the cost-effectiveness of vaccination strategies[15,16,22]

Guidance from NITAGs, HTA agencies, and advisory bodies

- Among the guidance identified, all except the ACIP explicitly mention that indirect effects should be considered
  - France's HTA agency, HAS, did not specifically mention an indirect effect but does require all individuals indirectly affected to be included
- For the guidance documents that discuss indirect effects, all emphasize the importance of accounting for them, though the level of detail on methods for inclusion vary between guidance documents
  - Herd effects are recommended for consideration by all guidance documents discussing indirect effects, with three NITAGs (NACI, STIKO, JCVI) explicitly recommending consideration of both positive and negative indirect effects
- Dynamic models are recommended by most guidance documents for consideration when infectious diseases are modeled
  - The WHO guide for standardization of economic evaluations of immunization programmes as well as the ISPOR Task Force Report on economic analysis of vaccinations provide high-level guidance on selecting between static and dynamic model structures
  - Guidance documents indicate that static models may be appropriate in a limited number of circumstances (e.g. when herd effects are expected to be negligible or when vaccination is targeted at non-transmissible diseases)
- NACI and ISPOR Task Force Report recommend the use of long-term observational or surveillance data to inform the estimates of indirect effects

Table 2. Indirect effects explicitly mentioned for consideration by advisory bodies

Country/region – Agency (year of guidance)	Herd effects	Age shift	Serotype replacement	Disease elimination or eradication
Canada – NACI (2023)	✓	✓	✓	✓
Germany – STIKO (2024)	✓	✓		✓
United Kingdom – JCVI (2016)	✓	✓		✓
Global – ISPOR Task Force Report (2018)[24]	✓	✓	✓	
Belgium – Annemans et al. (2021)[25]	✓	✓	✓	✓
Europe – Ultsch et al (2015)[26]	✓		✓	✓
Global – *WHO guide for standardization of economic evaluations of immunization programmes (2019)*[27]	✓		✓	
Australia – PBAC (2016)	✓			
Netherlands – Gezondheidsraad (2023)	✓			
France – HAS (2020)				
United States – ACIP (2019)				

Notes: Advisory bodies recommend considering broader indirect effects, including exposure modification and reduced antibiotic use/resistance (Annemans et al., 2021; Belgium); ecological and other effects such as host genetic selection, behavioral change, waning maternal immunity, and vaccination as a platform for other interventions (Ultsch et al., 2015; Europe); and cross-protection, mutation, and antimicrobial resistance (WHO).

Summary of findings

- While the inclusion of indirect effects into economic evaluations has increased over time, their inclusion has been inconsistent and approaches vary widely, with documentation of assumptions and data sources is often limited
  - The importance of considering indirect effects is clearly stated by advisory bodies; however, the methodological guidance and standards for their inclusion is limited
- Static modelling approaches are used more often than dynamic approaches, despite guidance from most advisory bodies recommending the use of dynamic models
  - The use of static models may not adequately capture the full impacts of vaccination strategies
- Herd effects were the most commonly included indirect effect, whereas serotype replacement and age shift were identified far less frequently. Inclusion of just positive indirect effects without considering negative indirect effects may lead to an overestimation of a vaccine's positive impact
- In the current body of literature, indirect effects were typically represented through simplifying assumptions in static models, such as fixed reductions in disease incidence or adjustments to model inputs
  - These assumptions are not always well documented; limiting transparency and interpretability
  - Fixed reductions in disease incidence or crude adjustments to model inputs do not align with guidance from advisory bodies

Limitations

- As a scoping review, the focus of this study was on identifying the range of methods applied to incorporate indirect effects rather than evaluating the quality of individual models
- This review relied on information collected in previous literature reviews, which may not fully capture modeling decisions or justifications provided in individual economic evaluations

Conclusions

- This scoping review highlights that indirect effects are widely recognized as important components of vaccine economic evaluations, yet their inclusion in published models remains inconsistent
- While methodological guidance from advisory bodies recommends the consideration of indirect effects and suggests the use of dynamic modeling approaches as the preferred approach, there is a lack of detailed operational instructions
  - Given the potential continued reliance on static models, additional guidance on how best to mitigate the limitations of their usage or best adapt the static model to generate more reliable estimates of efficacy could be developed
- These findings underscore the need for clearer reporting and greater methodological consistency in incorporating indirect effects, including more detailed guidance on acceptable modeling approaches, data requirements, and documentation of methodological choices to support more consistent and policy-relevant economic evidence

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