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Economic evaluation of pediatric influenza immunization program compared with other pediatric immunization programs: A systematic review

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ABSTRACT

This study compared the economic value of pediatric immunisation programmes for influenza to those for rotavirus (RV), meningococcal disease (MD), pneumococcal disease (PD), human papillomavirus (HPV), hepatitis B (Hep B), and varicella reported in recent (2000 onwards) cost-effectiveness (CE) studies identified in a systematic review of PubMed, health technology, and vaccination databases. The systematic review yielded 51 economic evaluation studies of pediatric immunisation — 10 (20%) for influenza and 41 (80%) for the other selected diseases. The quality of the eligible articles was assessed using Drummond's checklist. Although inherent challenges and limitations exist when comparing economic evaluations of immunisation programmes, an overall comparison of the included studies demonstrated cost-effectiveness/cost saving for influenza from a European-Union-Five (EU5) and United States (US) perspective; point estimates for cost/quality-adjusted life-years (QALY) from dominance (cost-saving with more effect) to ≤45,444 were reported. The economic value of influenza programmes was comparable to the other vaccines of interest, with cost/QALY in general considerably lower than RV, Hep B, MD and PD. Independent of the perspective and type of analysis, the economic impact of a pediatric influenza immunisation program was influenced by vaccine efficacy, immunisation coverage, costs, and most significantly by herd immunity. This review suggests that pediatric influenza immunisation may offer a cost effective strategy when compared with HPV and varicella and possibly more value compared with other childhood vaccines (RV, Hep B, MD and PD).

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Introduction

Influenza infections pose a significant health concern and have been responsible for substantial mortality and morbidity worldwide.[1] In many countries, influenza immunisation strategies exist, targeting those at risk of significant complications or death from influenza infections; such groups are the primary target of immunisation programmes across all European countries.[2] However, the burden in the pediatric population is under-represented (even with increased awareness) in many childhood immunisation programmes, despite the fact that children are believed to be the major transmitters.[3] For example, in young children aged less than 2 years, hospitalisation rates for influenza-related events are similar to those observed for other vulnerable groups considered to be at a higher risk of influenza-related complications, including the elderly population.[4]

Numerous studies have modeled the health, clinical, and economic implications of influenza prevention strategies including pediatric immunisation coverage.[5–8] The broad consensus of these studies is that childhood immunisation is cost-effective or cost-saving and should be prioritised.[7] Infants and young children are at a higher risk of influenza-related hospitalisations and complications. Decreasing influenza virus transmission among children attending day care centers and schools has been shown to reduce the burden of influenza, providing both direct and indirect protection in the wider community.[6,9]

The aim of this study was to compare the economic value of pediatric influenza immunisation programmes with other commonly implemented immunisation programmes, based on articles retrieved from the systematic review conducted here. To allow comparison with recent pediatric immunisation programmes in similar contexts, vaccines for rotavirus (RV), meningococcal disease (MD), pneumococcal disease (PD), human papillomavirus (HPV), hepatitis B (Hep B) and varicella have been considered in this study.

Results

Overview of the included studies

The literature search identified in total 9,043 articles, 8,335 in PubMed and 688 in other databases (Fig. 1). Following the removal of duplicates ($n = 268$), and evaluation of the titles ($n = 8436$) and abstracts (n = 212), 87 studies were considered eligible for full-text screening. Of these, 9 full texts were unavailable and 27 were excluded because they included

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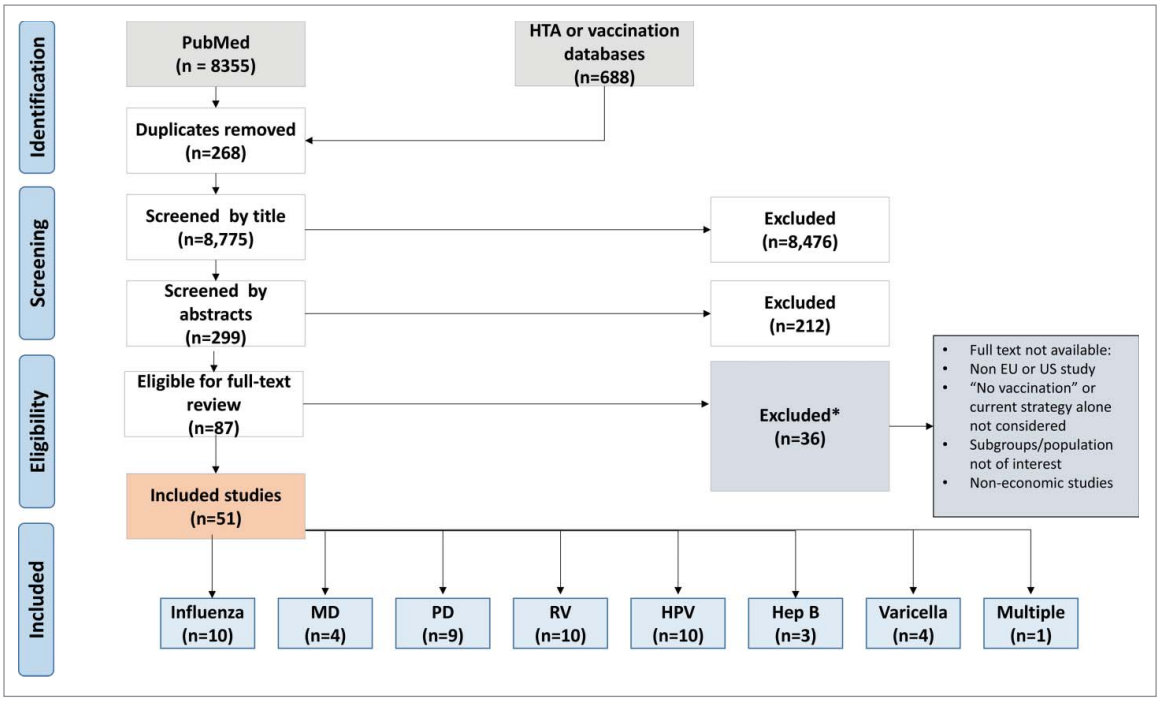

Figure 1. PRISMA flowchart of the literature search, selection process and study inclusion. *EU* European Union, *Hep B* Hepatitis B, *HPV* Human papillomavirus, *HTA* Health technology assessment, *MD* Meningococcal disease, *PD* Pneumococcal disease, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *RV* Rotavirus, *US* United States.

non-pediatric or alternative populations not of interest, reviews for models, framework and systematic reviews, or intervention comparisons excluding immunisation strategies of 'no immunisation' (alone) and studies conducted outside the US- or EU5-setting. In total, 51 full economic evaluations were included in the review. Of the 51 studies included, 16 (31%) were conducted in the US, 10 (20%) in the UK, and 7 (14%) in Italy; the remaining 18 studies (35%) were conducted in Germany, Spain or France or in more than a single country (including the UK). With the exception of one study on multiple diseases,[10] all included studies reported on single diseases. Influenza,[6,9,11–17] HPV[18–27] and RV[28–37] were covered in 10 studies each, constituting 59% of all included studies. Hep B[38-40] was covered in the lowest number of included studies (6%).

Overview of the economic evaluations

The studies included in the review largely described economic models of hypothetical patient cohorts, where literature values are used to populate model parameters – a few studies[11,13,14] applied clinical trial data to the model framework. The majority (43/51, 84%) of the studies provided outcomes for QALY (Fig. 2a–2c), LYG (life years gained) or LYS (life years saved) and consisted of cost-effectiveness analysis (CEA) (42/43, 98%) and cost-utility analysis (CUA) (1/43, 2%) studies. Many studies (23/32, 72%) reported QALY outcomes below the willingness to pay threshold (WTP) within each country setting. Lower cost per QALY outcomes were influenced by herd immunity (5/32, 16%) and high risk group stratification (4/32, 13%). The remaining studies (8/51, 16%) reported overall savings (CEA: 2/8, 25% and cost-benefit analysis [CBA]: 3/8, 38%) and the number of cases averted (CEA: 3/8, 38%); studies on influenza vaccines reported the number of events averted for hospitalisations, influenza-related-events or mortality. While many perspectives were considered, most studies took a societal (26/51, 51%) or healthcare perspective (24/51, 48%); some considered third party payer or insurer perspectives (common in Germany) and others considered more than one perspective. The economic analyses largely included both direct and indirect costs — some also mentioned the direct medical and non-medical costs and have been reported, where relevant, in the data-extraction tables (Table 1 and Table 2).

From the included studies, 10 (20%) investigated pediatric influenza immunisation programmes[6,9,11–17] (Table 2) and the remaining 41 (80%) studies investigated programmes for RV,[28–37] MD,[41–44] PD,[45–53] HPV,[18–27] Hep B,[38–40] varicella[54–57] and multiple indications[10] (Table 2). The primary alternatives considered were immunisation and no-immunisation, which refers to either baseline standard of care or the absence of routine immunisation policies within the pediatric-population; 2 studies considered an additional alternative treatment for influenza[6] or a catch-up campaign for varicella.[57]

The included studies followed cohorts of various ages for various time horizons using a range of cost-effectiveness measures. Studies on influenza immunisation considered pediatric populations primarily aged less than 5 years in 4 studies[11–13,16] and a wider pediatric age range in 5 studies,[6,9,13,15,17] following these between 1 year and lifetime horizons. The primary effectiveness measures were cost per QALY, LYS and cases averted.

Studies on RV immunisation strategies[28–37] primarily followed birth cohorts for up to 5 years across[29,30,35–37] various perspectives including statutory health insurance (SHI)[35,37] and regional health service (RHS).[31] Cost per QALY and cases averted were the most common effectiveness measures

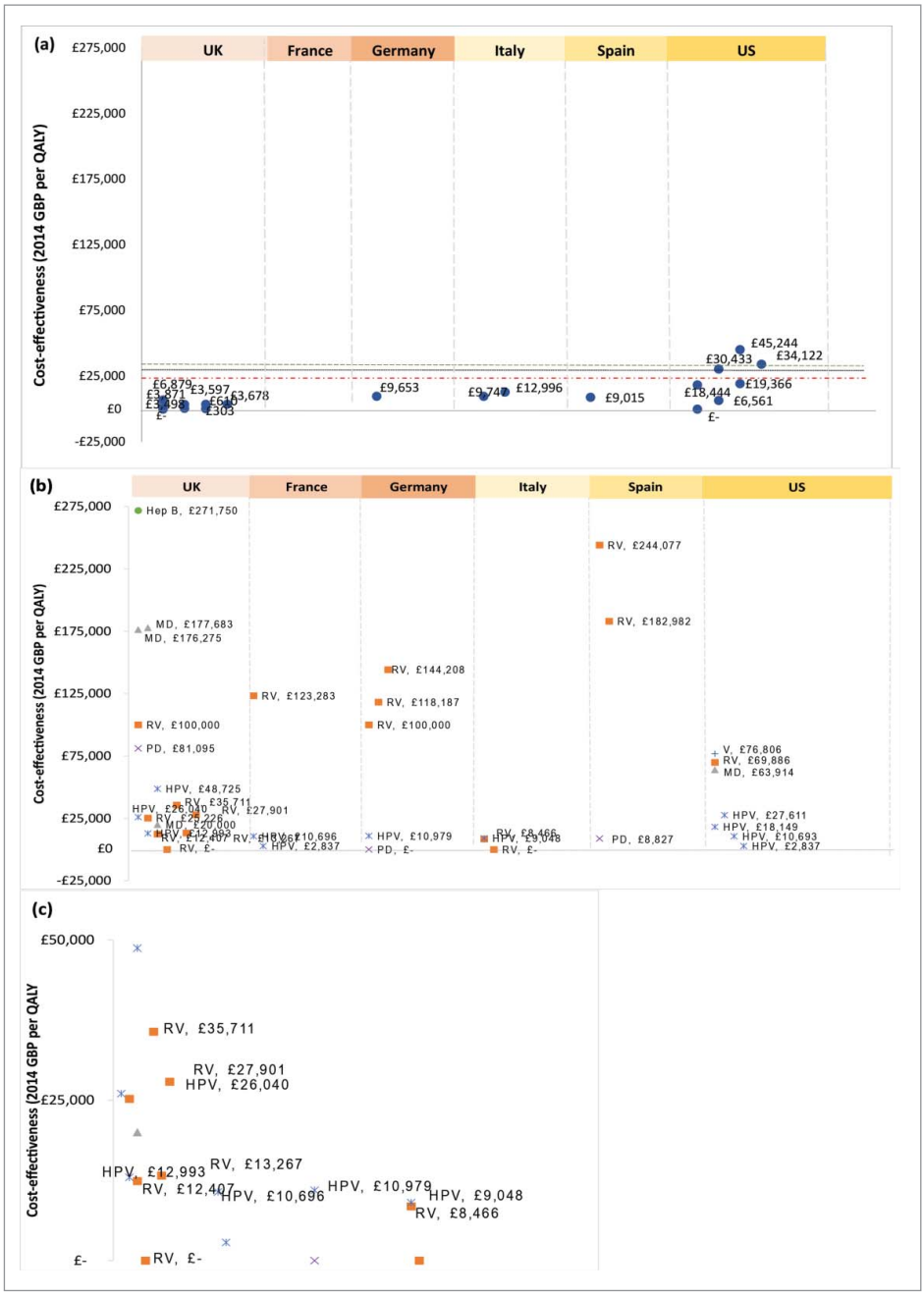

Figure 2. Cost-effectiveness by country per quality adjusted life year (QALY) of vaccinating the pediatric population against (a) influenza or (b) all other selected indications (rotavirus, pneumococcal disease, meningococcal disease, hepatitis B, human papillomavirus and varicella). A detailed view of cost/QALY between ≤0–50,000 in (b) can be found in (c). Willingness to pay (WTP) thresholds are represented by black (UK, ≤30,000), red (remaining EU5 countries) and green (US) dashed horizontal lines. GBP Great British Pound, ICER Incremental cost-effectiveness ratio, EU5 European Union 5, Hep B Hepatitis B, HPV Human papillomavirus, MD Meningococcal disease, PD Pneumococcal disease, QALY Quality adjusted life year, RV Rotavirus, UK United Kingdom, US United States, V Varicella [a]Cost savings are denoted by ≤- [b]ICER thresholds are represented by dashed horizontal lines for the UK (black —-), US (green - - -) and EU5 (red – – –).

provided. Studies on MD[41–44] and PD[45–53] vaccination programmes followed birth cohorts (with the exceptions of Ortega-Sanchez et al. [2008][42] [cohort of 11–17 year olds] and Trotter et al. [2002][41] [0–17 years] for MD and Ray et al. [2006][47] [cohort of < 5 year olds and > 5 year olds], Lieu et al. [2000][48] [cohort of infants and young children], Ray et al. [2009][50] and Diez-Domingo et al. [2011][53] [cohort of <1 year olds], for PD) between 5 years and lifetime horizons. The primary effectiveness measures included cost per QALY, cases averted, and LYS.

Studies on HPV vaccines followed mainly cohorts of children aged 12 years and above over a lifetime horizon.[18–20,22–25,27] Common effectiveness measures were cost per QALY and LYG.

Studies on Hep B and varicella vaccines followed cohorts of infants and adolescent age groups for up to 30 years and lifetime durations.[38-40,54-56] From the small number of studies, cost per QALY, cases averted, LYG, and benefit–cost ratio (BCR) were used to determine the cost-effectiveness outcomes.

Table 1. Overview of economic evaluations of annual pediatric influenza immunisation when compared with no immunisation/existing strategies in the UK, France, Germany, Italy, Spain and the US.

Study	Type of analysis	Alternatives*	Country	Perspective	Cohort	Coverage	Time horizon	Effectiveness measure	Cost measures	Sensitivity analysis	Outcomes[65-67]
Luce et al. 2001[11]	CEA	(1) Immunisation No immunisation	US	Societal	15–71 m	80% (1 dose) 20% (2 doses)	2 y	Cases averted	Direct and indirect	One-way & PSA Model sensitive to the cost of vaccine, proportion of children needing 2 doses per year and group setting	Cost/averted case: cost saving (if vaccine cost was <£21)
Muennig et al. 2001[15]	CEA	Immunisation Treatment No immunisation	US	Societal	15–64 y	95%	1 y	QALY	Direct and indirect (1997, $US)	One-way & PSA Model sensitive to ILI incidence, transportation costs, caregiver costs and cost of vaccine	Cost/QALY: cost saving with immunisation vs. treatment/ support care
Marchetti et al. 2007[12]	CEA	(1) Immunisation No immunisation	IT	Healthcare and societal	(1) 6–60 m 6–24 m	30%	5 y	Cases averted and QALY	Direct and indirect (2005, €)	One-way & PSA Model sensitive to protection rate of vaccines for households	Cost/QALY: Healthcare £9,747 (6–60 months) £12,996 (6–24 months) Societal Net savings – £62 million
Hibbert et al. 2007[13]	CEA	(1) Immunisation No immunisation	US	Societal	12–23 m	47%	2 y	Saving	Direct and indirect (2007, $US)	One-way Model sensitive to attack rate, duration of work absenteeism and duration of child or adult sickness	Cost saving: £4–116/child vaccinated
Navas et al. 2007[14]	CEA	(1) Immunisation No immunisation	ES	Provider and societal	3–14 y	—	6 m	LYS, QALY loss & BCR	Direct and indirect (2006, €)	One-way Model sensitive to vaccine price and cost of work absenteeism	Cost/QALY loss (provider): £9,015 Cost/LYS (provider):£11 NPV (societal): £7,179 BCR (societal): 1.80
Baguelin et al. 2010[6]	CEA	(1) Immunisation No immunisation	EW	NHS	(1) <1 y 1–4 y 5–14 y 25–44 y 45–64 y 65 y and over	70% (high risk) 40% (low risk)	Lifetime	QALY	Direct (2008, £)	One-way & PSA Model sensitive to overall size of epidemic without vaccination, QALY loss, hospitalisation rates, costs and case-fatality ratios	Cost/QALY £3,871 (0–4 years) £3,498 (5–14 years) £3,597 (0–14 years) £3,678 (0–14 and 65+) Extending to school children is the most cost effective.
Prosser et al. 2011[16]	CEA	(1) Immunisation No immunisation	US	Societal	0.5 – 64 y	—	1 y	QALY	Direct and indirect (2009, $US)	One-way Model was sensitive to number of doses, vaccine price and time of vaccine delivery	Cost/QALY: Cost saving (high risk subgroups) £6,561–45,244 (low risk subgroups risk)
Prosser et al. 2011[17]	CEA	(1) Immunisation(s) No immunisation	US	Societal	<5 y	—	5 y	QALY	Direct and indirect (2006, $US)	One-way & PSA Model sensitive to probability of hospitalisation	Cost/QALY: £18,444–30,433 (LAIV) £19,366–34,122 (IIV)
Lugner et al. 2012[18]	CEA	(1) Immunisation(s) No immunisation	DE, NL and UK	Payer and societal	(1) 5–19 y (high risk) 65 y and over	90%	Duration of pan-demic flu 2009	QALY	Direct and indirect (2008, €)	One-way Model sensitive to vaccine price, coverage and pre-existing immunity.	Cost/QALY 5–19 years £6,879 (UK) £9,653 (Germany)
Pitman et al. 2013[9]	CEA	(1) Immunisation No immunisation	EW	NHS	(1) 0–1 y 2–4 y 5–10 y 11–18 y 19–49 y 50–64 y 65 y and older	50%	Lifetime	QALY	Direct (2008, £)	One-way & PSA Model sensitive to coverage	Cost/QALY LAIV Cost saving (2–4 years) £610 (2–10 years) £303 (2–18 years) TIV Dominated* (TIV)

BCR Benefit–cost ratio, *CEA* Cost–effectiveness analysis, *DE* Germany, *ES* Spain, *EW* England and Wales, *FR* France, *IIV* Inactivated influenza vaccination, *ILI* Influenza-Like Illness, *IT* Italy, *LAIV* Live attenuated influenza vaccination. *LYG* Life year gained, *LYS* Life years saved, *m* months, *NHS* National Health Service, *NL* The Netherlands, *NPV* Net present value, *PSA* Probabilistic sensitivity analysis, *QALY* Quality adjusted life years, *TIV* Trivalent influenza vaccination, *UK* United Kingdom, *US* United States, *y* years.

Exchange rate 1 EUR = £0.79 and 1 USD = £0.63; all costs have been converted to 2014 GBP (where possible) [66].

* No immunisation refers to either baseline standard of care or the absence of routine immunisation policies within the pediatric-population.

**Dominated: More costly and less effective than comparator.

Table 2. Overview of economic evaluations of pediatric immunisation for rotavirus (RV), meningococcal disease (MD), pneumococcal disease (PD), human papillomavirus (HPV), hepatitis B (Hep B), varicella (V) and multiple indications (Mult.) in the UK, France, Germany, Italy, Spain and the US.

Disease	Study	Type of analysis	Alternatives*	Country	Perspective	Cohort	Coverage	Time horizon	Effectiveness measure	Cost measures	Sensitivity analysis	Outcomes [65-67]
RV	Melliez et al. 2008[29]	CEA	(1) Immunisation (2) No immunisation	FR	Societal	Birth cohort	75%	3 y	Cases averted, LYS & QALY	Direct cost (2005, €)	One-wayModel sensitive to coverage, disease incidence, probability of death, diarrhea complications and discount rates	Cost/QALY: £123,283Cost/ LYS: £266,219
RV	Jit et al. 2009[30]	CEA	(1) Immunisation (2) No immunisation	Europe (BE, EW, FI, FR and NL)	Healthcare	0- 5 y	BE: 97.5–98%EW: 95–95.18%FI: 97%FR:75%NL: 97%	5 y	QALY	Direct and indirect (2005–2006, €)	One-wayModel is sensitive to number of carers and herd immunity	Cost/QALY: >£100,000 (E&W and France)
RV	Giammanco et al. 2009[31]	CEA	(1) Immunisation(2) No immunisation	IT	NHS Societal	0–5 y	90%	5 y	Cases averted and net savings	Direct and indirect (2004–2005, €)	One-wayModel sensitive to coverage	Net savings: >−£9m (NHS) >£24 (societal)
RV	Panatto et al. 2009[32]	CEA	(1) Immunisation(2) No immunisation	IT	RHSSocietal	0–5 y	90%	1 y	QALY	Direct and indirect(2009, €)	–	Cost/QALY: £ 8,466 (RHS)Cost-saving (societal)
RV	Martin et al. 2009[33]	CEA	(1) Immunisation(2) No immunisation	UK	NHS	Birth cohort (< 5 y)	88%	Lifetime	Cases averted & QALY	Direct cost (2006–07, £)	One-way & PSAModel sensitive to hospitalisation costs, number of GP visit and duration of absenteeism	Cost/QALY: £25,226 (NHS)£ 12,407 (societal)
RV	Shim et al. 2009[34]	CEA	(1) Immunisation(2) No immunisation	US	NHSSocietal	< 5 y	75%	20 y	Cases averted & QALY	Direct and indirect (2007, US$)	One-wayModel sensitive to coverage and vaccine efficacy	Cost/QALY: £69,886Cost/averted case: £51.91
RV	Atkins et al. 2012[35]	CEA	(1) Immunisation(2) No immunisation	EW	NHS	< 5 y	95%	50 y	QALY	Direct costs (2010–11, £)	One-way & PSAModel sensitive to the vaccine price, immunity waning and vaccine administration cost	Cost/QALY: Static model (without herd immunity)Cost saving - £21,077 (£45/ course)£9,313 – 35,711 (£60/ course)Dynamic model (with herd immunity)Cost-saving - £13,267 (£45/course)£6,841 – 27,901 (£60/ course)
RV	Knoll et al. 2013[36]	CEA	(1) Immunisation(2) No immunisation	DE	SHI	Birth cohort	100%	5 y	Cases averted and savings	Direct and indirect (2011, €)	One-way & PSAModel sensitive to the frequency of seeking medical advice, RV disease and hospital visits	Net saving: >£9 million
RV	Imaz et al. 2013[37]	CUA	(1) Immunisation(2) No immunisation	ES	Societal Healthcare	Birth cohort	100%	5 y	QALY	Direct and indirect (2011, €)	One-wayModel sensitive to the vaccine price, vaccine efficacy and utility values	Cost/QALY:£244, 077 (healthcare)£ 182,982 (societal)

RV	Aidelsburger et al. 2014[38]	CEA	(1) Immunisation(s) (2) No immunisation	DE	SHI	< 5 y	80%	5 y	QALY	Direct and indirect costs (2010, £)	One- and 2-wayModel sensitive to herd immunity, utility values, the vaccine price and administration costs	Cost/QALY: £118,187–144,208
MD	Trotter et al. 2002[42]	CEA	(1) Immunisation (2) NoImmunisation	EW	NHS	0–17 y	<1 y: 89%1–4 y:82%5–13 y: 97%14–15 y: 83%16–17 y: 65%	Lifetime	Cases averted & LYS	Direct costs (2000, £)	One-way & PSAModel sensitive to disease incidence	Cost/LYS: £8,467
MD	Ortega–Sanchez et al. 2008[43]	CEA	(1) Immunisation + catch upNo immunisation	US	Payer and societal	11–17 y	70%	10 y	Cases averted, LYS & QALY	Direct and indirect (2005, US$)	One-way & PSAModel sensitive to herd immunity, vaccine price and vaccination campaign	Cost/QALY: £63,914 (societal)Cost/LYS:£92,240 (payer), £106,766 (societal)
MD	Christensen et al. 2013[44]	CEA	(1) Immunisation (2) No immunisation	UK	NHSPSS	Birth cohort	91%	Lifetime	Cases averted & QALY	Direct (2008, £)	One-way & PSAModel sensitive to disease incidence, vaccine efficacy, immunity and case-fatality	Cost/QALY: £176,275 (early infant vaccination); £177,683 (late infant vaccination)
MD	Christensen et al. 2014[45]	CEA	(1) Immunisation (2) No immunisation	UK	NHSPSS	Birth cohort	88%	Lifetime	Cases averted & QALY	Direct and indirect (2011, £)	One-wayModel sensitive to herd immunity and disease incidence	Cost/QALY: <£20,000
PD	Claes et al. 2003[46]	CEA	(1) Immunisation(2) No immunisation	DE	Healthcare payer, public authority and societal	< 2 y	100%	10 y	Cases averted & LYS	Direct and indirect costs (1999–2000,€)	One-wayModel sensitive to coverage, productivity loss, vaccine price and discount rates	Cost/LYS:£62,147 (healthcare)
PD	Melegaro et al. 2004[47]	CEA	(1) Immunisation(2) No immunisation	EW	NHS	Birth cohort	–	Lifetime	Burden reduction, LYG & QALY	Direct costs (2002, £)	One-way & PSAModel sensitive to disease incidence, vaccine price and herd immunity	Cost/QALY: £81,095 Cost/LYG: £153,182
PD	Ray et al. 2006[48]	CEA	(1) Immunisation(2) No immunisation	US	Societal-Healthcare	0–23 m	70%	5 y	Cases averted & LYS	Direct and indirect (2004, US$)	One-wayModel sensitive to herd immunity, perspective and pneumonia events	Cost/LYS:£83,955 (without herd effects)£5,622 (with herd immunity)
PD	Lieu et al. 2000[49]	CEA	(1) Immunisation(2) No immunisation	US	Societal	Infants and young children	100%	5 y	Cases averted & LYS	Direct and indirect costs (1997, US$)	One-wayModel sensitive to disease incidence, vaccine efficacy and administration costs	Cost/LYS:£64,440 (societal)
PD	Lloyd et al. 2008[50]	CEA	(1) Immunisation(2) No immunisation	DE	Healthcare payer	Birth cohort	83%	Lifetime	Cases averted & LYG	Direct costs (2004, €)	One-wayModel sensitive to herd immunity, vaccine efficacy and pneumonia events	Cost/LYG:£67,696 (entire cohort without herd immunity)£25,711 (high risk)
PD	Ray et al. 2009[51]	CEA	(1) Immunisation(2) No immunisation	US	Healthcare	(1) < 5 y(2) 5 y and over	76% (children born 2000–2002)85% (children born 2003–2006)	5 y	Cases averted & LYS	Direct costs (2006, US$)	One-wayModel sensitive to disease incidence, herd immunity and hospital visits	Cost/LYS:£141,633 (without herd immunity)£7,328 (with herd immunity)
PD	Giorgi- Rossi et al. 2009[52]	CEA	(1) Immunisation(2) No immunisation	IT	Public healthcare	Birth cohort	12 m: 80%24 m: 82%	10 y	Cases averted, LYG & DALY	Direct costs (2005, €)	One-way & PSA Model sensitive to disease incidence, mortality, vaccine price and vaccine efficacy	Cost/LYG: £108, 668 Cost/DALY: £50,193 Cost/averted case: £830 £172,324/ IPD£669,022/ meningitis£3,791, 124/ death

(*Continued on next page*)

Table 2. (*Continued*)

Disease	Study	Type of analysis	Alternatives*	Country	Perspective	Cohort	Coverage	Time horizon	Effectiveness measure	Cost measures	Sensitivity analysis	Outcomes [65-67]
PD	Claes et al. 2009[53]	CEA	(1) Immunisation(2) No immunisation	DE	SHI	Birth cohort	70%	Lifetime	Cases averted, LYS & QALY	Direct costs (2005–2007, €)	One-wayModel sensitive to vaccine price, coverage and schemes	Cost/QALY: cost-savingCost/LYG: cost-saving
PD	Díez- Domingo et al. 2011[54]	CEA	(1) Immunisation(2) No immunisation	ES	Payer	< 1 y	95%	Lifetime	LYG & QALY	Direct (2009, €)	One-wayModel sensitive to herd immunity, disease incidence, hospital events, vaccine price and coverage	Cost/QALY: £8,827 Cost/LYG: £10,851
HPV	Sanders et al. 2003[19]	CEA	(1) Immunisation(2) No immunisation	US	Payer	12 y	70%	Lifetime	Case averted & QALY	Direct costs (2001, US$)	One-way & PSAModel sensitive to vaccine efficacy, vaccine price and disease incidence	Cost/QALY: £18,149
HPV	Jit et al. 2008[20]	CEA	(1) Immunisation + catch up(2) No immunisation	UK	NHS	12 y	80%	Lifetime	QALY	Direct (2006–07, £)	One-way & PSAModel sensitive to vaccine efficacy, immunity, vaccine price & QALY loss	Cost/QALY: £26,040
HPV	Insinga et al. 2008[21]	CBA	(1) Immunisation(2) No immunisation	US	Health economic	16–23 y	–	2.5 y	Healthcare costs	Direct (2006, US$)	One-way Model sensitive to disease incidence, resource use and costs	Reduction of £28 per patient
HPV	Goldhaber-Fiebert et al. 2008[22]	CEA	(1) Immunisation(2) No immunisation	US	Societal	9–12 y	100%	Lifetime	QALY	Direct and indirect cost (2004, US$)	One-way, 2-way & PSA Model sensitive to screening tests	Cost/QALY: £27,611
HPV**	Chesson et al. 2008[23]	CEA	(1) Immunisation + screening(2) No immunisation	US	Societal	12 y	70%	Lifetime	QALY	Direct medical costs (2005, US$)	One-way Model sensitive to herd immunity, discount rates and time horizon	Cost/QALY: £10,693 (without herd immunity) £ 2,837 (with herd immunity)
HPV	Bergeron et al. 2008[24]	CEA	(1) Immunisation(2) No immunisation	FR	Direct and third party	14 y	80%	Lifetime	QALY & LYG	Direct (2004, €)	One-way Model sensitive to discount rates	Cost/QALY: £10,696 (direct)£2,837 (third party) Cost/LYG£14,447 (direct)£18,839 (third party)
HPV	Mennini et al. 2009[25]	CEA	(1) Immunisation(2) No immunisation	IT	NHS	12 y	80%	Lifetime	QALY	Direct costs (2004–2005,€)	One-way & PSA Model sensitive to vaccine efficacy, coverage % discount rates	Cost/QALY: £9,048
HPV	Hillemanns, et al. 2009[26]	CEA	(1) Immunisation +Screening(2) No immunisation	DE	Healthcare	12 y	80%	Lifetime	QALY & LYG	Direct costs (2006, €)	One-way Model sensitive to vaccine protection, booster vaccination and discount rates	Cost/QALY: £10,979 Cost/LYG: £16,353

HPV	Diaz et al. 2010[27]	CEA	(1) Immunisation(2) No immunisation	ES	Societal	11–14 y	90%	Lifetime	LYS	Direct and indirect (2006, €)	One-way Model sensitive to vaccine price, coverage and immunity	Cost/LYS: £19,686
HPV	Jit et al. 2011[28]	CEA	(1) Immunisation(s) (2) No immunisation	UK	NHS	12–75 y	80%	Lifetime	QALY	Direct costs (2008–09, £)	One-way & PSA Model sensitive to discount rates	Cost/QALY: £12.993–48,725 (depending on vaccination and specific cancer prevention)
Hep B	Szucs et al. 2000[39]	CEA	(1) Immunisation(2) No immunisation	DE	Third party	(1) 1–15 y (2) 11–15 y	100%	30 y	Cases averted and savings	Direct costs (1997, DM)	–	Cost/averted: £100,365 Net saving: £55,758
Hep B	Siddiqui et al. 2011[40]	CEA	(1) Immunisation(2) No immunisation	UK	NHS	Infants and adolescents	90%	Lifetime	QALY	Direct (2006, £)	One-way & PSA Model sensitive to vaccine protection and discount rates	Cost/QALY: £271,750
Hep B	Boccalini et al. 2013[41]	CBA	(1) Immunisation(2) No immunisation	IT	NHS and societal	New-borns and 12 y	95%	20 y	BCR & ROI	Direct and indirect costs (2010, €)	One-way Model sensitive to coverage and number of symptomatic patients	BCR: 2.46
V	Thiry et al. 2004[55]	CEA	(1) Immunisation(s) + no screening/ blood tests(2) No immunisation	IT	Societal and payer	11 y	70%	Lifetime	LYG	Direct or indirect costs (2002 , €)	One-way Model sensitive to the vaccine price	Cost/LYG: £8,928
V	Lenne et al. 2006[56]	CEA	(1) Immunisation(2) Immunisation + catch up No immunisation	ES	Healthcare & Societal	1–2 y	12m: 90% 24 m: 97%	Lifetime	Cases averted & LYG	Direct and indirect(2004, €)	One-way & PSA Model sensitive to coverage, vaccine efficacy and discount rates	Cost/LYG: £3,393 (healthcare), £5,909 (societal + catch-up)
V	Coudeville et al. 2008[57]	CEA	(1) Immunisation(2) Immunisation + catch up No immunisation	FRDE	Societal Third party	1–2 y	90% 70%45%	Lifetime	Cases averted & LYG	Direct and indirect costs (2002, €)	One-way & PSA Model sensitive to the vaccine price and cost of varicella episodes	Cost/LYG: France & Germany– cost saving (both)
V	Zhou et al. 2008[58]	CEA	(1) Immunisation(2) No immunisation	US	Societal	Infants	95%	Lifetime	BCR, QALY	Direct and indirect(2006, US$)	One-way Model sensitive to discount rates	Cost/QALY: £76,806 BCR:2.73
Mult	Zhou et al. 2014[10]	CBA	(1) Immunisation (2) No immunisation	US	Payer and societal	Birth cohort	53%	Lifetime	Cases averted & BCR	Direct and indirect (2009, US$)	One-way Model sensitive to administration cost	BCR: >1 PCV<1 for RV

BCR Benefit–cost ratio, *BE* Belgium, *CBA* Cost–benefit analysis, *CEA* Cost-effectiveness analysis, *CER* Cost-effectiveness ratio, *CUA* Cost-utility analysis, *DALY* Daily adjusted life years, *DE* Germany, *DM* Deutsche Mark, *EW* England & Wales, *ES* Spain, *FR* France, *Hep B* Hepatitis B, *HPV* Human papillomavirus, *IT* Italy, *IPD* Invasive pneumococcal disease, *LYG* Life year gained, *LYS* Life years saved, *m* months, *MD* Meningococcal disease, *Mult*. Multiple, *NHS* National Health Service, *NHSPSS* National Health Service Personal Social Services, *NL* The Netherlands, *PCV* Pneumococcal conjugate vaccination, *PD* Pneumococcal disease, *RHS* Regional Health Service, *ROI* Return on investment, *RV* Rotavirus, *SHI* Statutory Health Insurance, *PSA* Probabilistic sensitivity analysis, *QALY* Quality adjusted life years, *UK* United Kingdom, *US* United States, *V* Varicella, *y* years.

Exchange rate 1 EUR = £0.79 and 1 USD = £0.63; all costs have been converted to 2014 GBP (where possible)[66].

* No immunisation refers to either baseline standard of care or the absence of routine immunisation policies within the pediatric-population.

**The study adopts a societal perspective and includes all direct medical costs and benefits regardless of who incurred the costs or received the benefits.

Table 3. Quality appraisal of included studies (based on Drummond's checklist[68]).

		Yes	No	Unclear	Inappropriate
1	The research question is stated	51 (100%)	0 (0%)	0 (0%)	0 (0%)
2	The economic importance of the research is stated	29 (56%)	17 (33%)	5 (10%)	0 (0%)
3	The viewpoint(s) of the analysis are clearly stated and justified	49 (96%)	2 (4%)	0 (0%)	0 (0%)
4	The rationale for choosing the alternative programmes or interventions compared is stated	15 (29%)	35 (69%)	1 (2%)	0 (0%)
5	The alternatives being compared are clearly described	45 (88%)	5 (10%)	1 (2%)	0 (0%)
6	The form of economic evaluation used is stated	46 (90%)	5 (10%)	0 (0%)	0 (0%)
7	The choice of form of economic evaluation is justified in relation to the questions addressed	10 (20%)	35 (69%)	5 (10%)	1 (2%)
8	The source(s) of effectiveness estimates used are stated	40 (78%)	5 (10%)	5 (10%)	1 (2%)
9	Details of the design and results of effectiveness study are given (if based on a single study)	25 (49%)	9 (18%)	5 (10%)	12 (24%)
10	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	0 (0%)	0 (0%)	0 (0%)	51 (100%)
11	The primary outcome measure(s) for the economic evaluation are clearly stated	45 (88%)	4 (8%)	2 (4%)	0 (0%)
12	Methods to value health states and other benefits are stated	39 (76%)	7 (14%)	5 (10%)	0 (0%)
13	Details of the subjects from whom valuations were obtained are given	25 (49%)	20 (39%)	6 (12%)	0 (0%)
14	Productivity changes (if included) are reported separately	9 (18%)	0 (0%)	2 (4%)	40 (78%)
15	The relevance of productivity changes to the study question is discussed	9 (18%)	5 (10%)	2 (4%)	35 (67%)
16	Quantities of resources are reported separately from their unit costs	26 (51%)	22 (43%)	3 (6%)	0 (0%)
17	Methods for estimation of quantities and unit costs are described	44 (86%)	0 (0%)	7 (14%)	0 (0%)
18	Currency and price data are recorded	45 (88%)	4 (8%)	2 (4%)	0 (0%)
19	Details of currency of price adjustment for inflation or currency conversion are given	38 (75%)	8 (16%)	5 (10%)	0 (0%)
20	Details of any model used are given	43 (84%)	6 (12%)	2 (4%)	0 (0%)
21	The choice of model used and the key parameters on which it is based are justified	10 (20%)	34 (67%)	7 (14%)	0 (0%)
22	Time horizon of costs and benefits is stated	38 (75%)	6 (12%)	7 (14%)	0 (0%)
23	The discount rate(s) is stated	43 (84%)	5 (10%)	3 (6%)	0 (0%)
24	The choice of rate(s) is justified	26 (51%)	22 (43%)	3 (6%)	0 (0%)
25	An explanation is given if costs or benefits are not discounted	2 (4%)	2 (4%)	0 (0%)	47 (92%)
26	Details of statistical tests and confidence intervals are given for stochastic data	15 (29%)	30 (59%)	6 (12%)	0 (0%)
27	The approach to sensitivity analysis is given	41 (80%)	5 (10%)	5 (10%)	0 (0%)
28	The choice of variables for sensitivity analysis is justified	30 (59%)	15 (29%)	6 (12%)	0 (0%)
29	The ranges over which the variables are varied are stated	30 (59%)	10 (20%)	11 (22%)	0 (0%)
30	Relevant alternatives are compared	51 (100%)	0 (0%)	0 (0%)	0 (0%)
31	Incremental analysis is reported	38 (75%)	10 (20%)	3 (6%)	0 (0%)
32	Major outcomes are presented in a disaggregated as well as aggregated form	36 (71%)	15 (29%)	0 (0%)	0 (0%)
33	The answer to the study question is given	51 (100%)	0 (0%)	0 (0%)	0 (0%)
34	Conclusions follow from the data reported	51 (100%)	0 (0%)	0 (0%)	0 (0%)
35	Conclusions are accompanied by the appropriate caveats	38 (75%)	8 (16%)	5 (10%)	0 (0%)

The relative percentages may not equate to 100% due to rounding errors

The study on multiple indications considered vaccination for PD and RV in birth cohorts followed over a lifetime horizon with effectiveness measures of BCR and cases averted was used to determine the health benefit.[10]

Assessment of the included studies with Drummond's checklist (Table 3)[58] showed that in all studies, the research question was stated (item 1), relevant alternatives were compared (item 30), the study question was given (item 33) and conclusions followed from the data reported (item 34). All but 6 studies reported the primary outcomes (item 11); the majority of studies stated the alternatives described (item 5), the form of economic evaluation used (item 6), methods for estimation of quantities and unit costs (item 17) and currency and price data (item 18). The productivity changes (item 14) were not relevant to 40 studies, as the focus was the pediatric population. Some studies did consider the impact of vaccine programmes on parents and work loss days from caring for children — this was common in the RV studies which considered children under the age of 5 years.[32,33] Several studies including Hibbert et al. (2009),[13] Jit et al.(2010)[29] and Giammanco et al. (2009),[30] did not mention some of the main features of interest including the inflation rates, effectiveness measure and type of sensitivity analysis used.

Comparison of economic evaluations in the included studies

Pediatric influenza

Compared with no immunisation, the implementation of influenza immunisation in the pediatric-population offers an overall cost-effective strategy in each of the EU-5 or US countries of up to ≤19,366, with the exception of Prosser et al. (2011)[15] who reported cost per QALY up to ≤45,244 in the US, and in some cases provides a cost-saving potential when compared to treatment with supportive care or vaccination in those aged 6 months – 64 years (Muennig et al. [2001][14] and Prosser et al. [2011][16]). Pitman et al. (2013)[9] and Lugner et al. (2012)[17] measured the indirect protection of the rest of the population via herd immunity by considering both pediatric and older population groups. Extending the immunisation either to a select or full pediatric population will benefit individuals within the targeted age group and also provide wider protection in other non-targeted age groups who may come into contact with the pediatric population.[12,14,16]

Other diseases relative to influenza

The included studies on pediatric immunisation programmes for the other selected diseases reported a wide range of cost-

effectiveness, with cost per QALY mostly higher compared to that of influenza (Fig. 2a–2c). For RV, the cost per QALY was in general substantially higher (Table 2) than those presented for influenza. The values ranged from cost-saving from an Italian[31] to ≤244, 077/QALY from a Spanish healthcare perspective.[36] Similar to RV, studies of PD and MD immunisation yielded a wide range of cost-effectiveness, from cost saving to ≤177,683/QALY,[43] with differences in outcomes notably influenced by the inclusion or exclusion of measurements of herd immunity. Studies of HPV immunisation yielded a similar range of cost-effectiveness to influenza of between ≤2,837[23] and ≤48,725/QALY,[27] with differences in outcomes influenced by vaccine type, perspective, and cancer-specific prevention. Varicella immunisation[57] yielded a cost per QALY of ≤76,806 and a BCR of 2.73 for varicella prevention, demonstrating a high number of cases averted in the pediatric population. Hep B prevention is associated with a ≤271,750/QALY and a similar BCR of 2.43 (new-borns and 12-year-olds);[39] however, the limited number of studies in the pediatric population included in this review may not be truly reflective of the extent to which vaccines may prevent disease burden, particularly for varicella and Hep B vaccines, as the small number of studies provide inaccurate estimates of impact.

Due to the paucity of data and variability across the indications, comparisons of other outcome measures, such as LYG and cases averted (hospitalisations or mortality events) are not conclusive enough to be presented here but are summarised in Table 1 and Table 2.

Discussion

Overview

In 2005 the World Health Organization (WHO) published guidelines on policy issues to help decision makers consider the broader implications of adding a vaccine to a national immunisation program. In addition to economic and financial questions, other aspects such as the public health priority of particular vaccines, the disease burden, public health surveillance and comparisons with other interventions should be taken into consideration.[59] Subsequently, in 2008, the WHO published specific advice for standardising economic evaluations of vaccination programmes for current and emerging diseases (including pandemic influenza) to meet decision-makers' needs for relevant, reliable and consistent economic information in this area.[60] This is because compared to most drugs assessed by health economic analyses, vaccines have characteristics that require special considerations when evaluating their cost effectiveness. These characteristics are related to herd immunity, quality-of-life losses in young children, parental care and associated work loss, time preference, uncertainty, eradication, macroeconomics and tiered pricing.[61] Specific to infant influenza, complicating factors that contribute to uncertainty are seasonal variations in incidence, severity of disease and vaccine efficacy.[62] Against this background, this review compared the economic value of pediatric influenza immunisation and a selection of existing pediatric immunisation programmes within similar contexts. For influenza, all studies demonstrated that pediatric immunisation offers a valuable health intervention demonstrating, in most cases, a cost-effective or cost-saving potential across societal, payer, National Health Service (NHS), and provider perspectives with incremental cost- effective ratios (ICER) below the respective thresholds in the US and EU5 (cost per QALY up to ≤19,366 reported) — consistent with the literature within this area.[2,5–8]

The derived ICER for pediatric influenza immunisation suggests that it fits well within the overall cost range of recent pediatric immunisation programmes already in place, particularly to HPV and varicella and across the other indications (MD, PD, RV, Hep B) considered here. The cost-effectiveness ratios derived from the included studies on the other diseases of interest (MD, PD, HPV, Hep B, varicella, and RV) demonstrated an overall cost per QALY range between cost-saving up to ≤271,750[39] across all indications. For HPV, the modeled vaccines targeted those aged 12 years or older over a lifetime horizon, in most cases; similarly for varicella the average age ranges from those aged 1–2 and 11 years old, also modeled over a lifetime-horizon (in most cases) although cost-effectiveness outcomes varied considerably. The difference in age groups considered in these studies may provide further challenges when comparing cost-effectiveness across studies. Chesson et al. (2008)[22] modeled the impact of an HPV immunisation program, given in addition to current cervical screening, in the US and concluded that it was a cost-effective strategy, with an ICER of ≤10,693 when herd immunity was ignored and an ICER of ≤2,837 when herd immunity was included. Jit et al. (2011)[27] used a model to compare bivalent and quadrivalent HPV immunisations versus no immunisation in the UK and concluded that both vaccines were cost effective when protection against anal, penile, and oropharyngeal cancers was assumed. For the licensed endpoints including the incidence of cervical cancers bivalent HPV immunisation exceeds the UK's ≤30,000 WTP threshold. It is ≤48,725 per QALY. Coudeville et al.(2005)[56] found that routine childhood varicella immunisation represents a cost saving health intervention in both France and Germany. Similarly, Lenne et al.(2006)[55] concluded that routine varicella immunisation in Spain is cost saving from the societal perspective and highly cost-effective from the healthcare perspective.

Besides demonstrating cost effectiveness compared to other vaccinations, the included studies on pediatric influenza vaccinations also demonstrate the importance and impact on the cost-effectiveness outcomes with herd immunity. Analyses modeling the direct effects of pediatric vaccines (immunising children aged less than 5 years old)[11,13,16] or both pediatric and adult vaccines[6,9,17] on the wider population demonstrated a lower cost-effectiveness ratio associated with herd immunity.

While the quality of the analyses across the included studies was fairly robust the differences between age groups and characteristics of each disease may limit the comparability of cost-effectiveness within and across indications. Indeed the reported cost-effectiveness values fall within a wide range, which may be explained by factors such as vaccine efficiency but also by choice of study design, including (1) difference in time horizon, (2) inclusion of herd immunity, (3) coverage, (4) pediatric population age groups, for example variations in the patient cohort (e.g. <5 years and 5–19 years), and (5) perspectives, which are presented as part of the scenario/sensitivity analyses.

Furthermore, the lack of a single outcome measure to quantify the impact of pediatric immunisation may lead to inconsistencies when comparing overall results and benefits (Table 1). The outcome measures chosen by the included studies consist of (1) cases averted, (2) overall net saving or BCR (value >1 implies incremental benefits exceed incremental costs), (3) cost per QALY, (4) cost per LYG, and (5) cost per LYS. The non-inclusion of certain costs may also result in different estimates of cost-effectiveness; particularly with pediatric diseases the impact on parents/guardians is not considered in many studies included in this review. This may understate the overall cost-effectiveness outcome, potentially underestimating the true impact of these diseases and the associated benefit of routine childhood immunisation.

Limitations

The approach used to conduct this review has several limitations. The search was conducted on selected databases. Conference proceedings and other sources, such as bibliographies from included studies, were excluded in the preparation of this review. Studies selected were based on availability of full texts and those exclusive to, or inclusive of the pediatric population. The selection process excluded subgroups, such as children with asthma, where the impact of immunisation programmes could highlight an even greater economic benefit, particularly so in the case of influenza. Studies were only selected for inclusion if they were conducted after 2000, were limited to EU5 and US settings and involved comparisons between immunisation and no immunisation(s). Existing systematic reviews for each indication or combined indications were also excluded from the review. Such reviews could have potentially provided a wider scope of studies conducted in this area and highlighted those studies not identified from the literature search *per se*. Many existing reviews in these indications have not been limited to geographical locations although the results presented here can be compared/found in existing reviews.[2,42,55,63,64] One of the key issues in this review was the economic measure used to determine the cost-effectiveness of immunisation across the studies and indications. Although most studies provided an economic value (before final negotiated price by the national governments) predominantly expressed as an ICER (cost/QALY), where QALY is a well-accepted generic measure of mortality and morbidity across different indications, the lack of other standardised measures compromises comparability across studies. If studies had been limited to those providing ICER values only, the number of studies included in the review would have been limited further. The approach carried out here was consistent with existing systematic reviews where all effectiveness measures were considered.[63,64] Comparability across the studies was further compromised by differences in age groups, time horizons, and perspectives.

Implications for new research

Future considerations, particularly for influenza immunisation studies, should try to capture the full population to allow comparisons within and across different age groups and incorporate the impact of herd immunity to illustrate the wider protection to society.

When comparing economic measures in the same or across different indications, the context of each cost-per-QALYs should be recognized to allow a reasonable comparison of one indication vs. another, for example influenza and HPV. Results should be interpreted with caution and some authorities will require supporting/further evidence of the benefits of routine immunisations beyond the comparison of cost-per-QALYs.[64] Keeping in mind that economic evaluations offer useful tools to inform decisions and price discussions of implementing pediatric immunisation programmes, future studies should also report, or at least acknowledge, the available funding and policy implications for routine immunisation programmes, to help assess the discrepancies in each country setting and the cost-effectiveness outcomes considered.

Conclusion

The findings of this review suggest that pediatric influenza immunisation could provide a valuable health intervention with cost-effective potential from both healthcare and societal perspectives when compared with no immunisation or existing policies. Influenza immunisation programmes were located within the lower range of overall ICER values across immunisation programmes of the selected indications; although various age groups were considered within the same and across indications (e.g., <5 and 5–19 years). For influenza, extending immunisation to the full pediatric population (major transmitters) was generally the most cost-effective strategy.[9,65] Although, it could be argued that the most efficient way to implement pediatric influenza immunisation programmes would be from programmes that offer cost-saving potential; possibly achieved with increased vaccination coverage to allow optimal herd immunity. Many factors remain unclear or confounding, such as the level of vaccination coverage needed and differences in existing country policies and in this respect further research is required.

Methods

This review is reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations,[66] and compares economic evaluations of the vaccines of interest according to their licensed indications and contraindications as defined in each study.

Searches

A comprehensive literature review of published evidence on economic evaluations (cost-effectiveness analysis [CEA], cost–benefit analysis [CBA] or cost-utility analysis [CUA]) across the 7 disease areas was conducted using an electronic medical-journal database (PubMed), health technology databases (NIHR CRD [National Institute for Health Research Centers for reviews and dissemination], HAS [French National Authority for Health], IqWiG [Institute for Quality and Efficiency in Healthcare], Medicare, and vaccination databases (JCVI [Joint Committee on Vaccination and Immunisation], STIKO

[Standing Committee on Vaccination], CTV [Technical Vaccination Committee]).

The search strategy grouped keywords into categories for disease, economic outcomes, model type, and programmes. Search terms for the disease category were "influenza a virus; influenza b virus," "pneumococcus; pneumococcal," "meningitis," "varicella zoster virus; chicken pox," "hepatitis B," "human papillomavirus vaccines" and "rotavirus;" for the economic outcomes category "cost-effectiveness," "cost utility," "cost benefit" and "economic evaluation;" for the model type category "economic models," "decision tree," "economic decision models," "Markov," "transmission model" and "SEIR;" and for the programmes category "immunisation," "vaccine" and "vaccination." Combined searches in PubMed were performed for "disease AND (economic outcomes OR model types) AND programmes." Searches conducted in the other databases combined "disease AND economic outcomes."

Inclusions

Studies were included in the review if they considered human subjects, were published in English language between 1st January 2000 to 16th December 2014 and had abstracts available. Studies were included according to the target group, comparisons, type of economic evaluation, and country perspectives. The target group is defined as the pediatric population (either the overall pediatric population aged less than 18 years, smaller age ranges such as 5–9 year olds, or pediatric groups consisting of both pediatric as well as adult population —an example being 5–9 and 18–65 year olds) without specific conditions, such as asthma, or other co-existing illnesses. Comparisons with no-intervention or current vaccination policy were included. Complete economic evaluation of CEA, CBA and CUA assessing both the benefits and costs of influenza, RV, MD, HPV, Hep B, PD and varicella, either independently or across multiple diseases, were included. Studies reporting on the UK, France, Germany, Italy and Spain (collectively known as the European Union Five, or EU5), and the US were included.

Full-text articles were retrieved and assessed to determine the final inclusion of studies. Articles were excluded: (1) if they reported systematic reviews on the economic evaluation across the 7 diseases either independently or combined; (2) if full-text articles were unavailable; (3) if studies were conducted outside the EU5 and US; and (4) if studies were exclusively based on the non-pediatric population. Additionally, studies that reported the impact of the disease in terms of epidemiology or clinical trial data were also excluded.

All included papers assess the impact of vaccination on standard vaccination schedules, which for pediatric influenza immunization is an annual event. While mismatches between vaccine strains and circulating strains may occur and have an impact on vaccine effectiveness, mismatch averages out over the duration of the modeling time horizon for the health economic outcomes of adding pediatric immunisation programmes into current practice. In addition, the effectiveness results are usually not statistically significant due to the low numbers for individual vaccine and age groups in influenza.

Data extraction

Eligible articles were independently screened by 2 researchers (NB and BS) on the basis of titles and abstracts retrieved by the search from the electronic databases (Fig. 1), alternative extraction methods of screening reference list from relevant studies or hand searching key journals and conference proceedings were not adopted in this review. In the case of disagreement a third reviewer was consulted (SR) for discussions on population(s), setting, immunisation programmes and type of studies included. Data on economic evaluations was extracted at the full text stage by 2 researchers (NB and BS) and entered into an extraction table comparing cost-effectiveness outcomes according to the type of analysis, immunisation strategies, country, perspective, vaccination coverage, time horizon, effectiveness measure, cost measure, sensitivity analysis and outcome measures. All monetary outcomes were converted based on currency conversions taken from the XE website and inflated accordingly to 2014 GBP using the European Central Bank (ECB) and Medical Expenditure Panel Survey (MEPS) databases.[67–69]

Willingness to pay thresholds

WTP were used to assess and compare cost-effectiveness of pediatric immunisation programmes within each country setting and across the vaccines considered. The WTP for the UK was ≤30,000.[70] The assumed WTP for all other European countries,[26] including Italy, is €30,000 = ≤23,780 (€1 = $0.79), and for the US is $50,000[21] = ≤31,780 ($1 = ≤0.63) based on currency conversions taken from the XE website (20 December 2014) and inflated to 2014 GBP.[67–69]

Quality assessment

The quality of each included study was assessed independently by 2 researchers (NB and BS) using Drummond's checklist.[58] Discrepancies were resolved by discussion and consensus with a third investigator if needed (EG) for clarity on choice of economic evaluation, parameter description and subjects considered in the studies. Table 3 presents the overall results for each item on Drummond's list categorised by study design (items 1–7), data collection and analysis (items 8–21), and interpretation of results (items 22–35). Responses to the items in the list were completely satisfied (yes), not satisfied (no), unclear or not-applicable (inappropriate).

Disclosure of potential conflicts of interest

This work was funded by AstraZeneca (AZ) who currently has a licensed Live Attenuated influenza vaccine (Fluenz® Tetra or Flumist Quadrivalent). AS, JH and SR are current employees of AZ. EG and NB are employed by Wickenstones Ltd (at the time of the study BS was employed by Wickenstones Ltd) and were financed by AZ to complete this study. AZ have also funded EG to develop an economic model for pediatric influenza vaccination strategies.

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