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REVIEW

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Economic evaluation of adolescents and adults' pertussis vaccination: A systematic review of current strategies

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ABSTRACT

The reemergence of pertussis in the last two decades led to the introduction of adolescents and adults immunization strategies of tetanus–diphtheria–acellular pertussis vaccines (Tdap) in several countries. The health authorities must consider economic aspects when deciding to recommend and fund new programs. Here we present a systematic review of worldwide full economic evaluations of pertussis vaccination targeting adolescents or adults published from 2000. Studies were identified by searching MEDLINE, Excerpta Medica, CRD, and Lilacs databases. Twenty-seven economic evaluations of different strategies with Tdap were identified. Booster vaccination for adolescents and adults were the most frequent, followed by cocooning and pregnant women vaccination. Strategies performance varied considerably among different studies. Assumptions regarding underreporting correction, herd protection and vaccine coverage were crucial to cost-effectiveness results. Understanding the model and the parameters used is essential to understand the results, and identify the major issues important to public health decisions.

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Introduction

Pertussis is a highly contagious respiratory disease mainly caused by *Bordetella pertussis*.[1,2] It causes uncontrollable violent coughing for long periods, most commonly affects infants and young children, and can be fatal, especially in infants up to 6 months of age.[1,2] Childhood immunization with whole-cell pertussis (wP) containing vaccines led to important reduction in pertussis incidence in countries that achieved high vaccine coverage.[2,3]

However, a global reemergence of pertussis has been observed in the last 20 years, in spite of sustained high vaccine coverage.[1-3] Hypotheses to explain this reemergence are post-vaccination waning immunity; reduced effectiveness of acellular vaccines; implementation of molecular methods for diagnosis; improvement of surveillance systems; enhanced disease awareness; and genetic changes in the pathogen.[2] The reemergence of epidemics, severe infections in very young not yet vaccinated infants, and pertussis in older children, adolescents and adults, resulted in renewed attention of the public health authorities to further improve pertussis control and optimize protection through vaccination.[2]

Tetanus–diphtheria–acellular pertussis vaccines (Tdap) for adolescents and adults were licensed in 2005 and additional immunization strategies were proposed: 1) booster doses for adolescents and adults; 2) cocooning strategy; 3) pregnant women and post-partum maternal vaccination; and 4) vaccination of healthcare workers.[2]

Pertussis among infants frequently presents as severe cases, with higher hospitalization and case-fatality rates.[4-6] Cocooning and pregnant women vaccination aim to avoid pertussis among infants aged less than one year, particularly infants younger than two months, who have not received any vaccine dose. Cocooning strategy is vaccinating neonates' contacts, potentially reducing household transmission and preventing infant infection. Pregnant women vaccination results in direct newborn protection through transplacental antibody transfer from mother to infant.[7-9]

Even though the health benefits of some of these pertussis vaccination strategies have been demonstrated,[7,8,10,11] national health authorities must also consider economic aspects when deciding to recommend and fund new programs. Economic evaluation of vaccination programs may support decision-making, and is considered an essential tool in a context of rising budget constraints.[12]

Health economic evaluation depends on good quality data of the disease epidemiology, not easily available in this case. Pertussis burden is underestimated by the surveillance systems, due to limited demand/access to healthcare, cases' underrecognition or misdiagnosis, and underreporting.[5]

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Supplemental data for this article can be accessed here.

Higher rates of underreporting have been observed in older children, adolescents and adults.[13]

Despite the methodological difficulties, the efficiency of pertussis vaccination strategies has been evaluated in several studies worldwide. The objectives of this article are to provide a critical literature review of economic evaluations of adolescents and adults' pertussis vaccination, to investigate the studies results' disparity and the reasons for such differences, and to identify most cost-effective vaccination strategies. This review attempts to provide guidance and suggestions for improvement, contributing to future economic evaluations.

Results

Search results

The initial searches identified 1,318 articles. After duplicates removal and the titles and abstracts reading, 33 studies were considered potentially relevant and retrieved in full text. After reading the full text, 27 studies met the eligibility criteria and were included in this review (Figure 1).

Methodological studies characteristics

Table 1 describes the methodological characteristics of economic evaluations of pertussis immunization programs for adolescents and adults. Most studies considered developed countries: 12 in the United States of America, four in the Netherlands, three in Canada, two in England, and one each in Australia, Germany, Italy, Japan, and Spain. Only one referred to a developing country (Brazil).

The studies evaluated 7 different strategies involving Tdap vaccine: 1) adolescents vaccination; 2) adults vaccination; 3) healthcare workers vaccination and its impact on hospital outbreak control; 4) cocooning; 5) pregnant women vaccination; 6) postpartum maternal vaccination; and 7) adults with chronic obstructive pulmonary disease.

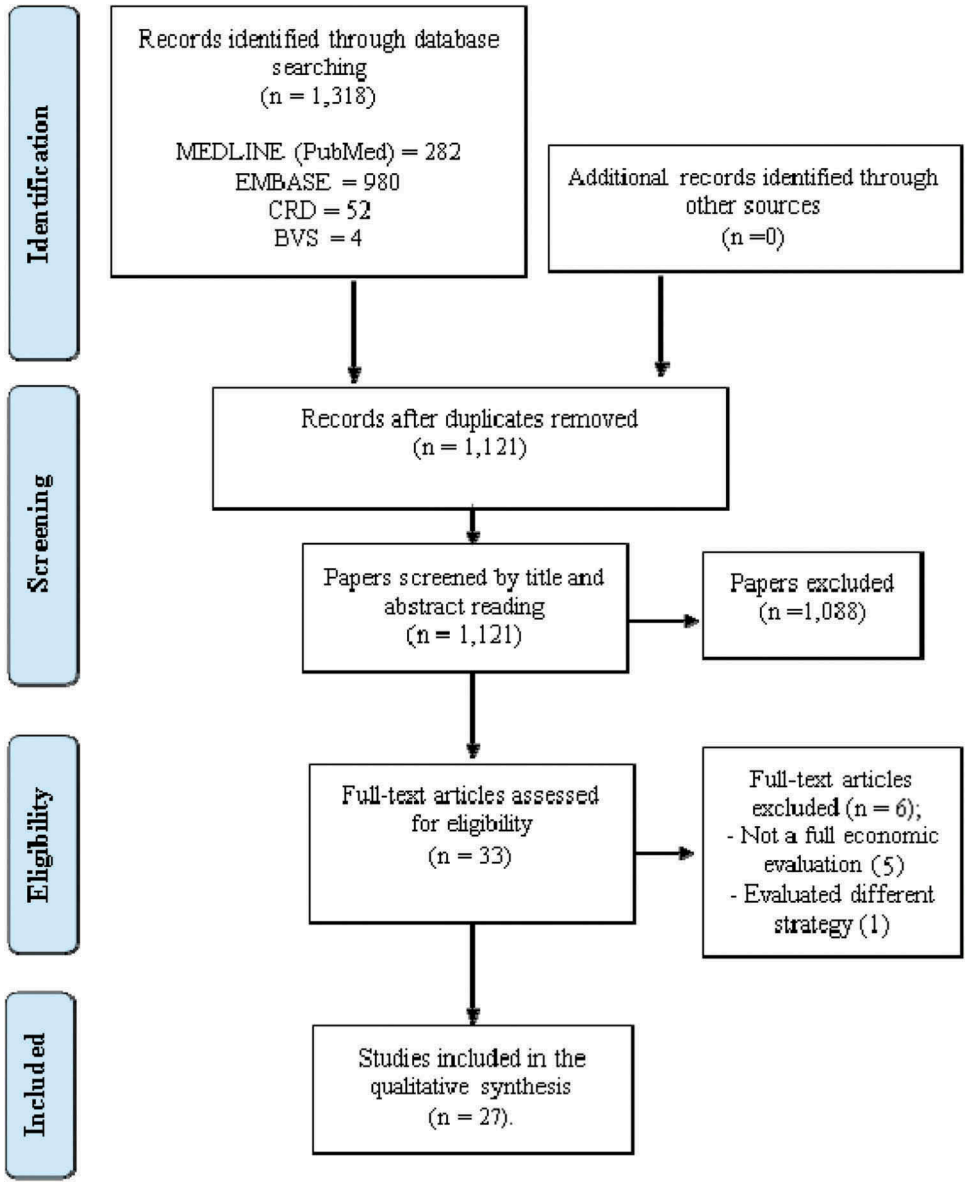

Figure 1. Flowchart of selection of studies included in the review.

Table 1. Methodological characteristics of the economic evaluations of pertussis vaccination for adolescents and adults.

Study/ Country	Year	Targeted population	Vaccination strategies compared	Type of study	Perspective	Model	Time horizon	Monetary unit / year	Health outcomes	Discount rate
Edmunds *et al.*/ England and Wales[14]	2002	Pre-school Adolescents	(0) no vaccination; (1) vaccination at 4 years of age; (2) Adolescents vaccination	CEA	Healthcare provider and societal	Dynamic	Lifetime	UK£, 1999/2000	LYG	C and B – 3%
Scuffham e McIntyre/ Australia[15]	2004	Both parents after birth (cocooning) and neonates	(0) childhood vaccination; (1) at-birth immunization; (2) 1-month vaccination; (3) Cocooning	CEA	Healthcare system	Markov	6 months	AUS$, 2000	DALY	B – 3%
Purdy *et al.*/ USA[16]	2004	Adolescents, adults (different ages) and healthcare workers	(0) no vaccination; (1) Adolescents vaccination; (2) Adults aged >20 years; (3) Adults aged >50 years; (4) Adults aged ≥18 years with chronic obstructive pulmonary disease; (5) Adults aged ≥15 years caretakers of infants <1 year of age; (6) Healthcare workers vaccination; (7) 10-year boosters	CBA	Societal	NR	10 years	US$, 2002	Cases prevented	C and B – 3%
Iskedjian *et al.*/ Canada (Ontario)[17]	2004	Adolescents (12 years of age)	(0) No vaccination; (1) Adolescents vaccination	CEA	Ministry of Health and societal	Dynamic	10 years	CAD$, 2003	Cases prevented	C – 3%
Caro *et al.*/ USA[18]	2005	Adolescents (11–18 years)	(0) no vaccination; (1) Adolescents vaccination	CEA	Healthcare payer and societal	Cohort Simulation	Lifetime	US$, 2002	LYG	B – 3%
Iskedjian *et al.*/ Canada (Quebec)[19]	2005	Adolescents (14 years of age)	(0) no vaccination; (1) Adolescents vaccination	CEA	Ministry of Health and societal	Dynamic	10 years	CAD$, 2003	Cases prevented	C – 3%
Lee *et al.*/ USA[20]	2005	Adolescents (11 years of age); adults (20 years of age); mothers immediately after birth and all other close contacts before the birth (cocooning)	(0) no vaccination; (1) Adolescent vaccination; (2) one-time adult vaccination; (3) adult vaccination with 10-year boosters; (4) Adolescent + adult + 10-year boosters; (5) Cocooning	CEA	Healthcare payer and societal	Markov	Lifetime	US$, 2004	Cases prevented and QALY	C and B – 3%
Calugar et al./ USA[21]	2006	Healthcare workers	(0) No vaccination; (1) Healthcare workers vaccination	CBA	Hospital perspective	Dynamic	10 years	US$, 2004	Exposures to pertussis cases prevented	C and B – 3%
Lee *et al.*/ USA[22]	2007	Adults	(0) No vaccination; (1) Adult vaccination; (2) 10-year boosters	CEA	Societal	Markov	Lifetime	US$, 2005	Cases prevented and QALY	C and B – 3%
Lee *et al.*/ Germany[23]	2008	Adults	(0) No vaccination; (1) One-time adult vaccination at 20–64 years of age; (2) 10-year boosters	CEA	Healthcare payer and societal	Markov	Lifetime	€, 2006	Cases prevented and QALY	C and B – 3%
Coudeville *et al.*/ USA/ 2009[24]	2009	Adolescents, adults and both parents after birth (cocooning)	(0) No vaccination; (1) Adolescents vaccination; (2) Adolescents vaccination + cocooning; (3) Adolescents + adult + cocooning; (4) Adolescents + adults + 10-year boosters	CEA	Societal	Dynamic	100 years	US$, 2006	LYG	C and B – 3%
Westra *et al.*/ Netherlands[25]	2010	Father before and mother after the delivery (cocooning), pregnant women and neonates	(0) No vaccination; (1) Vaccination at birth; (2) Cocooning; (3) Pregnant women; (4) combining (2)+(3)	CEA	Healthcare payer and societal	Decision-tree	8 years	€ and US$, 2008 (1 € = 1.4 US $)	QALY	C – 4%, B – 1.5%
de Vries *et al.*/ Netherlands[26]	2010	Adolescents (12 years of age)	(0) No vaccination (1) Adolescents vaccination	CEA	Societal	Dynamic	25 years	€, 2008	QALY	C – 4%, B – 1.5%
Greer and Fisman/ Canada[27]	2011	Healthcare workers	(0) No vaccination; (1) Healthcare workers vaccination	CEA	Societal	Markov	10 years	US$, 2008	QALY	B – 3%
Rozenbaum *et al.*/ Netherlands[28]	2012	Adolescents and adults	(0) No vaccination; (1) A single dose for adolescents or adults; (2) single dose for both adolescents and adults vaccination; (3) booster doses with 10-year intervals	CEA	Societal	Dynamic	25 years	€, 2011	QALY	C – 1.5%, B – 4%

(*Continued*)

Table 1. (Continued).

Study/ Country	Year	Targeted population	Vaccination strategies compared	Type of study	Perspective	Model	Time horizon	Monetary unit / year	Health outcomes	Discount rate
Itatani *et al.*/ Japan[29]	2013	Adolescents, adults and both parents after birth (cocooning)	(0) No vaccination; (1) Adolescents vaccination; (2) Adolescents + 10-year booster; (3) Adolescents + cocooning	CEA	Societal	Markov	40 years	Yen	QALY	C and B – 3%
Meregaglia *et al.*/ Italy[30]	2013	Both parents and other close contacts during pregnancy or immediately after delivery (cocooning)	(0) No vaccination; (1) Cocooning	CEA CBA	National Health Service	NR	1 year	€, 2011	Cases prevented	Not considered
Ding *et al.*/ USA[31]	2013	Mothers after birth	(0) No vaccination; (1) Postpartum maternal vaccination	CBA	Healthcare system and societal	Decision tree	10 years	US$, 2012	Cases and deaths prevented	C – 3%
Terranella *et al.*/ USA[32]	2013	Mothers immediately after birth, all other close contacts vaccinated before the birth (cocooning) and pregnant women	(0) No vaccination; (1) Pregnant women; (2) Postpartum maternal vaccination; (3) Cocooning	CEA	Societal	Markov	1 year	US$, 2011	Cases averted, QALY and LYG	C and B – 3%
Lugnér *et al.*/ Netherlands[33]	2013	Both parents after birth (cocooning), pregnant women and neonates	(0) No vaccination; (1) neonate immunization at birth; (2) cocooning; (3) Pregnant women.	CEA	Societal	NR	10 years	€, 2009	QALY	C – 4%, B – 1.5%
McGarry *et al.*/ USA[34]	2013	Adults aged ≥65 years	(0) No vaccination; (1) Adults vaccination	CEA	Healthcare payer and societal	Decision tree	35 years	US$, 2010	Cases prevented and QALY	C and B – 3%
McGarry *et al.*/ USA[35]	2014	Adults aged ≥65 years	(0) No vaccination; (1) Adults vaccination	CEA	Healthcare payer and societal	Dynamic	Lifetime	US$, 2010	QALY	B – 3%
Fernández-Canoa *et al.*/ Spain[36]	2015	Both parents after birth (cocooning) and pregnant women	(0) No vaccination; (1) Cocooning; (2) Pregnant women	CBA	Healthcare system	Decision tree	1 year	€, 2012	Hospitalizations and cases prevented	Not considered
Kamiya et al./ USA[37]	2016	Adolescents and adults	(0) No revaccination; (1) Adolescent revaccination; (2) Adult revaccination	CEA	Society	Decision tree	20 years	US$, 2010	Cases prevented and QALY	C and B – 3%
Atkins et al./ USA[38]	2016	Adults, both parents (cocooning) and pregnant women	(0) No vaccination; (1) Adult vaccination; (2) Mother antepartum and (3) postpartum vaccination; (4)Both parents antepartum and (5) postpartum	CEA	Healthcare provider	Dynamic	20 years	US$, 2013	QALY	C and B – 3%
Sartori et al./ Brazil[39]	2016	Pregnant women	(0) No vaccination; (2) Pregnant women	CEA	Healthcare system and societal	Decision tree	1 year	US$, 2011	Cases and deaths prevented and LYG	Not considered
Hoek et al./ England[40]	2016	Pregnant women	(1) No vaccination; (2) Pregnant women	CEA	Healthcare payer	Dynamic	5, 10, 30 and 200 years	UK£ (reference year not reported)	QALY	C -1.5%, B - 3.5%

C: Costs; B: Benefits; CEA: cost-effectiveness analyses; CBA: cost-benefit analyses; CUA: cost-utility analyses; LYG: life year gained; QALY: quality-adjusted life year; LYG: Life of years gained; NR: Not Reported

Adolescents and adults immunization were the most frequent strategies evaluated: 11/27 each. The adults vaccination strategies were: one-time vaccination at 20 to 64 years of age (8/11), decennial boosters (6/11), and vaccination at 65 years of age or older (2/11). Six studies evaluating adolescents' immunization were published from 2002 to 2005.

The economic evaluations of Tdap considered different strategies as cocooning: vaccinating both parents immediately after birth; or assuming that fathers would be vaccinated during the pregnancy and mothers would be vaccinated immediately after delivery; or vaccinating mothers and another adult caregiver after birth; or vaccinating mothers immediately after birth and all other close contacts before the birth; or vaccinating both parents and other close contacts during pregnancy or immediately after delivery.

The first study evaluating pregnant women immunization was published in 2010. This strategy and cocooning were the most frequent strategies evaluated since then (7 studies each), followed by adult immunization (6), adolescents (4), postpartum maternal vaccination (3), and health professionals (1).

Ten studies used dynamic models, which were more frequently used to evaluate adolescents vaccination (6), followed by adults vaccination (4), cocooning (2), pregnant women (2), and health professionals vaccination (1). Thirteen studies used static models: seven used Markov, and six used decision tree. Most of them evaluated cocooning, and/or adults vaccination (6 each), followed by pregnant women vaccination (4), adolescents (3), postpartum maternal vaccination (2), and health professionals (1). Three papers did not report the model used and one used cohort simulation.

Vaccines and vaccination programs assumptions

Vaccines and vaccination programs data are presented in Table 2.

Ten studies that evaluated adolescents or adults vaccination considered vaccine coverage >50%, six of them considered >80%. Coverage varied from 20 to 96%, for cocooning, and from 57 to 96%, for pregnant women vaccination.

Ten studies clearly stated they incorporated herd protection in the model. Among them, six evaluated adolescent immunization, seven adult immunization, three cocooning, one pregnant immunization, one postpartum maternal immunization. Seven studies that evaluated adolescents and/or adults strategies did not consider herd protection.

Three studies used Markov model to evaluate adolescent and adult vaccination and considered herd protection applying a reduction factor on pertussis incidence in unvaccinated infants and adults or in the base case analysis. Caro et al. used a cohort simulation to evaluate adolescent vaccination and considered indirect impact on other age groups and on unvaccinated adolescents. Four studies that used dynamic models did not clearly state they incorporated herd protection in the model.

McGarry et al. used a dynamic model age-structured with compartments repeated for each month of age below 1 year and 1-year age groups from 1 to 99 years old. This model made possible evaluate a Tdap vaccination of adults aged 65 years in addition to DTaP vaccination from age 2 months to 4–6 years, and one dose of Tdap once to individuals 11–64 years of age in place of the decennial Td booster.

Studies that evaluated pregnant women immunization made different assumptions regarding efficacy of maternal antibodies in infant protection and duration of protection of maternal antibodies (Table 2). One study considered that 60% of maternal antibodies would pass through placenta. Duration of maternal antibodies protection was assumed as two months, three months, four months and six months. Just one study considered interference of maternal antibodies in the infant response to active pertussis vaccination, assuming a negative impact (10% reduction) in the infant responses to the second and third vaccine doses.

Fourteen studies included adverse events following immunization in the model (Table 2). Just three studies considered vaccine wastage rate in the model, assumed as 15%, 10% and 5%.

Epidemiological estimates

Table 3 shows pertussis incidence estimates used in the studies. Pertussis incidences among adolescent or adults were considered in 20 of 27 studies, and 18 of them used some strategy to correct pertussis underreporting.

Ten studies used official incidence data multiplied by a correction factor, which varied from 2.5 to 660; four studies considered a range of incidences for adults or adolescents; and four studies derived pertussis incidence from local studies data. The approaches for estimating pertussis incidences among adolescents and adults and the correction factor were based on serological surveys (8 studies), clinical trials (6), authors' assumption (2), capture-recapture studies (1), enhanced surveillance (1), and compilation of data from previous dTpa economic studies (1). One study applied the infants' disease incidence to women of childbearing age. Lee et al. (2005) estimated the burden of disease among adolescents and adults in the USA based on 2003 Massachusetts State incidence data. Massachusetts was the only state in the USA that had a single-serum enzyme-linked immunosorbent assay for IgG anti-pertussis toxin available as a diagnostic test, which allows enhanced disease detection among adolescents and adults. Two studies corrected disease data for infants to take underreporting into account, using an underreporting factor of 2 and 1.15.

Pertussis incidence rates varied from 22 to 435 per 100,000, for infants, from 10 to 511 per 100,000, for adolescents, and from 5.33 to 2,606 per 100,000, for adults.

Supplementary Table 1 shows outpatient cases, hospitalizations, complications and case-fatality rates estimates. Even after correcting underreporting, most studies considered that all pertussis cases among adolescents and adults use health care services, resulting in cost. Among adolescents and adults, mild outpatient cases varied from 1% to 79.3%, while severe cases ranged from <1% to 66%. Caro et al. and McGarry et al. assumed that 70% of unreported cases would be significantly milder than typical cases. Coudeville et al. considered 2% of infected adults would be asymptomatic and calibrated the model for their potential infectiousness. Three studies

Table 2. Characteristics of vaccines and vaccination programs used in the economic evaluations of pertussis vaccination for adolescents and adults.

Study	Vaccine coverage	Vaccine efficacy /effectiveness	Adverse events following immunization	Duration of protection / Waning Immunity	Herd protection
Edmunds *et al.*[14]	84%	95%	NC	5 years	Yes
Scuffham e McIntyre[15]	95% (adults)	Adults 75%; At birth 67%; 1-month 75%	NC	NC	No
Purdy *et al.*[16]	40% (adolescents and adults)	88%	1%	10 years	No
Iskedjian *et al.*[17]	95%	85%	NC	NC	No
Caro *et al.*[18]	80%	85%	2%	10 years	Yes
Iskedjian *et al.*[19]	85%	85%	NC	NC	Not
Lee *et al.*[20]	Coverage by age: 10 years 76%; 20 years 36%; 30 years 34%; 40 years 29%; 50 years 21%; 60 years 14%; 70 years 5%; postpartum 66%	100%	Local reaction 2%; Systemic reaction 1%; Anaphylaxis 0.0001%	15 years	Yes
Calugar et al.[21]	66%	71.4%	Anaphylaxis 0.0001%	10 years	No
Lee *et al.*[22]	20–49 years of age: 66%; 50–64 years of age: 57%	87%	Local reactions: 2%; Systemic reactions: 1%; Anaphylaxis: 0,0001%	15 years	Yes
Lee *et al.*[23]	Coverage by age: 20 years 82%; 30 years 58%; 40 years 40%; 50 years 75%; 60 years 62%	87%	Local reactions 2%. Systemic reactions 1%. Anaphylaxis 0,0001%	15 years	Yes
Coudeville *et al.*[24]	Adolescents 75%; adults 40%; cocooning 65%	92%	Additional medical consultations for AEFI (2%) in vaccination cost	12 years	Yes
Westra *et al.*[25]	96%	89%	NC	4 months (persistence of maternal antibodies in infants)	No
de Vries *et al.*[26]	96%	89%	NC	Two scenarios: 8 and 15 years	Yes
Greer and Fisman[27]	25 to 95%	100%	Anaphylaxis 0.00001%	NC	No
Rozenbaum *et al.*[28]	70%	89%	NC	10 years	Yes
Itatani *et al.*[29]	11–12 years of age 70%; >12 years 20%	85%	Severe (anaphylaxis) 0.0001%; moderate 2%	10 years	No
Meregaglia *et al.*[30]	NR	89%	NC	NC	No
Ding *et al.*[31]	25 to 60%	80%	Local reaction 2%; Systemic reaction 1%; Anaphylaxis 0.0001%	10 years	No
Terranella *et al.*[32]	72%	Adults vaccination: 85%; Efficacy of maternal vaccination on newborn protection 60%	NC	2 months (persistence of maternal antibodies in infants)	No
Lugnér *et al.*[33]	75%	89%	NC	5 years	No
McGarry *et al.*[34]	10%	89%	Included in the vaccine cost	8 years	No
McGarry *et al.*[35]	10% (at 65 years of age)	89%	Included in the vaccine cost	8 years	Yes
Fernández-Canoa *et al.*[36]	50%, 80% and 100%	Adults vaccination: 85% Efficacy of maternal vaccination on newborn protection 60%	NC	2 months (persistence of maternal antibodies in infants)	No
Kamiya et al.[37]	Coverage by age: 11 years 78%; 16 years 50%; 21 years 64%	74%	Medically-attended allergic reactions 0.003%; Anaphylaxis 0.00006%	15% decrease of vaccine effectiveness each year post-vaccination	No
Atkins *et al.*[38]	75%	Adults vaccination: 100%; Maternal vaccination on newborn protection 89%	US$0.93 added to vaccination cost	2.7 years	Yes
Sartori *et al.*[39]	57%	78%	NC	6 months (duration of maternal antibody protection); 4 months in SA	No
Hoek et al.[40]	60%	Infants 91%; Mother 89%	NC	3 months (persistence of maternal antibodies); 5 years among adults	No

NC – Not Considered; NR – not reported: SA – Sensitivity analyses; AEFI - adverse event following vaccination

Table 3. Pertussis incidence and underreporting correction factor used in economic evaluations of pertussis vaccination for adolescents and adults.

Study	Incidence rates by age groups	Source of incidence data	Strategies to account for underreporting	Source of correction factor
Edmunds *et al.*[14]	Consultation rates: <3 months: 38.58/100,000; 3 months to 4 years: 107.88/100,000; 5 to 14 years: 49.27/100,000; 15 to 44 years: 5.33/100,000; >45 years: 2.21/100,000	Royal College of General Practioners Weekly Returns Service (RCGP); Hospital Episode Statistics (HES); Office of National Statistics (ONS)	Used correction factor of 2.5	Authors' assumption
Scuffham e McIntyre[15]	5.171 notified cases / 100,000 infants per week	Health Outcomes Information Statistical Toolkit of the New South Wales Department Australian Childhood Immunization register	Not considered	Not considered
Purdy *et al.*[16]	Adolescents and adults: 450/100,000 person-years; distribution by age: 10–19 years: 41%; 20–29 years: 7%; 30–39 years: 17%; 40–49 years: 28%	Centers for Disease Control and Prevention; Acellular Pertussis Vaccine Trial (APERT) (clinical trial).	Children aged 0–9 years: correction factor of 2	Authors' assumption
Iskedjian *et al.*[17]	Adolescents aged 12–17 years: 511/100,000; Adults aged 18–21 years: 65/100,000	Health Canada	Adolescents: correction factor of 9	Enhanced surveillance with serosurvey
Caro *et al.*[18]	0.2–57/100,000 (age-specific rates used)	Centers for Disease Control and Prevention	Used correction factor of 7.6	Local study using capture-recapture methods to analyze morbidity data from independent surveillance systems
Iskedjian *et al.*[19]	Adolescents (14–17 years) 511/100,000; Adults (18–24 years) 65/100,000	Health Canada	Used correction factor of 9	Enhanced surveillance with serosurvey
Lee *et al.*[20]	Infants 58.5/100,000; Adolescents 155/100,000; Adults 11/100,000	Massachusetts Department of Public Health (pertussis surveillance data)	Not considered	Not considered
Calugar *et al.*[21]	Proportion of infections in healthcare workers: 6.75%	Two local studies	Not considered	Not considered
Lee *et al.*[22]	Incidence in adults ranged from 10 to 500/100,000; Infants 58.5/100,000	Infants: 2 local studies; Adults: Massachusetts Department of Public Health (official data)	Range of incidences	Tdap efficacy study; 3 studies of pertussis prevalence among persons with cough
Lee *et al.*[23]	Adults 165/100,000; Adolescents 95/100,000; Infants 22/100,000.	Adults: Local study (17160764); Adolescents and infants: governmental epidemiological data	Adults' Incidence varied from 50 to 500 / 100,000 in sensitivity analysis	Studies in Europe and USA
Coudeville *et al.*[24]	Adult cases requiring medical care 90/ 100,000	Acellular Pertussis Vaccine Trial (APERT) and Centers for Disease Control and Prevention (CDC)	Children data were adjusted using age-specific underreporting estimates (data not shown)	Capture-recapture study
Westra *et al.*[25]	Incidence in infants <1 year of age: 129/100,000. Distribution of cases among infants <1 year: 0 months: 7.0%; 1 month: 21.4%; 2 months: 18.1%; 3 months: 11.2%; 4 months: 5.3%; 5 months: 2.7%; 6 months: 7.8%; 7 months: 4.2%; 8 months: 8.0%; 9 months: 5.5%; 10 months: 5.0%; 11 months: 3.8%. Incidence in adults 25–34 years of age: 17.9/100,000	Centre for Infectious Disease Control of the Dutch National; Institute for Public Health and the Environment	Adults: correction factor of 200 Children: no correction	Serological survey and dynamic transmission model study
de Vries *et al.*[26]	Age specific (data not shown)	RIVM report – *Rijksinstituut voor Volksgezondheid en Milieu*	Age specific correction factor of (up to 660)	Serological survey
Greer and Fisman[27]	Average number of exposures/case: 8.73 Symptomatic adults: 40%	Data from a real outbreak	Not considered	Not considered
Rozenbaum *et al.*[28]	<1 year: 200/100,000 5 years: 100/100,000 ≥15 years: 50/100,000	Surveillance data from 1996 to 2001	Used correction factor of 600	Serological survey
Itatani *et al.*[29]	Incidence rates ranged from 25 to 250/100,000 person-years	Japan's Infectious Disease Surveillance Centre	Range of incidences	Previous studies from USA, Germany and Canada
Meregaglia *et al.*[30]	Infants: 54/100,000 hospitalizations/year	Regional hospital discharge database	Not considered	Not considered
Ding *et al.*[31]	Mothers – 450/100,000. Infants aged <6 months – 71.6/100,000	Mothers: local study. Infants: Surveillance data (California Department of Public Health and Centers for Disease Control and Prevention (CDC)	Not considered	Not considered
Terranella *et al.*[32]	<1 year: 62.6/100,000; Incidence by month of age (/100,000) < 1: 12.4; 1: 18.9; 2: 15.3; 3: 8.9; 4: 5.7; 5: 3.2; 6: 2.4; 7: 1.6; 8: 1.5; 9: 1.4; 10: 1.1; 11: 1.4	National Notifiable Diseases Surveillance System (NNDSS), 2000 – 2007.	Increase of 15%	Authors' assumption

(*Continued*)

Table 3. (Continued).

Study	Incidence rates by age groups	Source of incidence data	Strategies to account for underreporting	Source of correction factor
Lugnér *et al.*[33]	<5 years-old: 130/100,000; 20 – 40 years-old women: 2,606/100,000	Statistics Netherlands	100 x the surveillance data	Serological surveys
McGarry *et al.*[35]	Different incidence rates were considered: 25, 50, 100, 150, and 200/100,000	Centers for Disease Control and Prevention, California Department of Public Health Pertussis Report 2011, Washington State Department of Health (2012)	Different incidence rates were used	Tdap efficacy study; 3 studies of pertussis prevalence among persons with cough
McGarry *et al.*[35]	Incidence rate by age (/100,000) <1 year: 435.00; 1–6 years: 61.8; 7–9 years: 67.3; 10–18 years: 49.0; 19–64 years: 124.15; ≥65 years: 86.08	California Department of Public Health surveillance data; Centers for Disease Control and Prevention (CDC).	For adults ≥65 years, data was inflated, assuming 1% reporting	2009 Centers for Disease Control and Prevention (CDC)
Fernández-Canoa *et al.*[36]	Hospitalization by age-group 0–2 months – 119/100,000; 3–4 months – 26/100,000 ; 5–6 months – 5/100,000; 7–11 months – 4/100,000; <1 year – 153/100,000	Hospitalization data of Spanish Government (MBDS), from 2009 to 2011.	Not considered	Not considered
Kamiya *et al.*[37]	Age-specific; 11–30 years (data not shown)	National Notifiable Diseases Surveillance System – NNDSS 2002–2011	Used correction factor of 20–200 in sensitivity analysis	Several studies and authors' assumptions
Atkins et al.[38]	The model was calibrated to USA incidence data from 2003–2012 (data not shown)	Centers for Disease Control and Prevention (CDC)	The authors combined data of reported case, hospitalization rates, reporting rates for hospitalized cases, and active surveillance of non-hospitalized cases (data not shown)	CDC, Wisconsin Department of Health Services, and local study
Sartori *et al.*[39]	Children aged <1 year-old: 55.407/100,000	National Notifiable Diseases Information System (Sistema de Informação de Agravos de Notificação, SINAN)	Not considered	Not considered
Hoek et al.[40]	Infants aged <3 months: ~ 0.5 to ~ 45/100,000; Women aged 20 – 44 years: 0 to ~ 40/100,000	Number of hospitalization from 2010 to 2012 (NHS)	Not considered	Not considered

explored the impact of including asymptomatic infections in the disease transmission dynamic model.

Cost estimates

The elements of costs considered in the reviewed studies are described in Supplementary Table 2. All studies included direct medical costs and the vaccination program costs, and 23 included indirect costs. Calugar et al. evaluated the health-care workers vaccination from the hospital perspective and included productivity loss as indirect cost. Atkins et al. included indirect costs in the sensitivity analysis. All the studies used local data to estimate direct medical costs, except Itatani et al., who assumed the values.

Eight studies considered public health response as part of the direct medical costs. The studies considered costs of health surveillance, contact tracing and prophylactic measures.

Seven studies that evaluated strategies focused on protecting infants (pregnant women vaccination, maternal postpartum vaccination or cocooning) considered caregivers loss of productivity.

Results of the analyses

Table 4 shows the summary measures presented in the results of the analyses.

Two studies showed that adolescents' vaccination strategy was cost-saving at society perspective. Other seven studies had incremental cost-effectiveness ratio considered cost-effective or highly cost-effective and recommended it as a good strategy. Adolescent vaccination presented unsatisfactory results in only one study.

Among 11 studies that evaluated adults vaccination strategy, the program was considered cost-effective in six and cost-saving in two.

Cocooning strategy performance diverged among studies. It was cost-saving in two studies, and not cost-effective in the other studies, with ICER ranging from U$112,091/QALY to U $2,005,940/QALY.

Seven studies evaluated pregnant women vaccination and the ICER varied from cost-saving to not cost-effective (US$ 439,708.46/QALY). When compared with cocooning, pregnant women vaccination had better economic performance in four of five studies.

Ten studies declared sponsorship by pharmaceutical industry; eleven by public institutions and six did not report sponsorship. All studies sponsored by pharmaceutical industry showed good results for Tdap vaccination, except two that evaluated cocooning, pregnant women and elderly vaccination. All cost-saving studies were in this group.

All studies conducted some Sensitivity Analyses (Supplementary Table 3). The parameters with the greatest impact on the results were pertussis incidence, followed by vaccine efficacy and vaccine price.

Discussion

The first Tdap economic evaluation was published in 2002, when a significant increase in pertussis incidence among

Table 4. Summary measures (Incremental Cost-Effectiveness Ratio, ICER, or Cost-Benefit ratio) presented in results of economic evaluations of pertussis vaccination for adolescents and adults, according to the perspective.

Study	Societal*	Health care provider*	Sponsor
Edmunds *et al.*[14]	9,278.21/LYG	18,047.45/LYG	Medical Research Council
Scuffham e McIntyre[15]	Not considered	1,562,146.18/DALY	Commonwealth Department of Health and Ageing
Purdy *et AL.*[16]	Cost preventable (billions of US$)/ break-even (US$) **Adolescent vaccination**: US$0.4 to 2.1 billons/ US$49.12	Not considered	GlaxoSmithKline
Iskedjian *et al.*[17]	Cost-saving	274.77/case prevented	Sanofi-Pasteur
Caro *et al.*[18]	6,322.19/LYG	29,310.66/ LYG	NR
Iskedjian *et al.*[19]	374.13/ case prevented	476.35/case prevented	Sanofi-Pasteur
Lee *et al.*[20]	**Adolescents vaccination**: 25,244.96/QALY;	**Adolescents vaccination**: 29,031.70/QALY;	National Immunization Program, Centers for Disease Control and Prevention, Association of Teachers of Preventive Medicine, National Vaccine Program Office Agency for Healthcare Research and Quality
Calugar et al.[21]	Not considered	Cost-benefit ratio: 3	Centers for Disease Control and Prevention and St. Luke's Hospital
Lee *et al.*[22]	**Adult vaccination**: 13,539.39/ QALY; **10-year boosters**: 14,770.25/QALY	Not considered	Agency for Healthcare Research and Quality, National Immunization Program, Centers for Disease Control and Prevention Association of Teachers of Preventive Medicine
Lee *et al.*[23]	**Adult vaccination**: 8,796.50/QALY. **10-year boosters**: 10,919.79 /QALY	**Adult vaccination**: 31,919.79 /QALY. **10-year boosters**:40,949.25/QALY	Agency for Healthcare Research and Quality, US Department of Health and Human Services
Coudeville *et al.*[24]	Cost-saving	Not considered	Sanofi-Pasteur
Westra *et al.*[25]	Cost-saving	**Cocooning**: 6,234.84/QALY; **Pregnant women**: 4,743.90/QALY	GlaxoSmithKline
de Vries *et al.*[26]	5,988.16/QALY and 8,635.27/QALY (for duration of protection after vaccination of 8 and 15 years, respectively)	Not considered	GlaxoSmithKline
Greer and Fisman[27]	Cost-saving	Not considered	Ontario Early Researcher Award Sanofi-Pasteur
Rozenbaum *et al.*[28]	**Single (3rd) booster for adolescents or adults**: 7,292.58/QALY; **Adolescent + adult vaccination**: 13,022.47/QALY. **10-year booster**: 21,971.53 /QALY	Not considered	NR
Itatani *et al.*[29]	**Adolescents' vaccination**: 36.24/QALY; **Adolescents + 10-year boosters**: dominated; **Adolescents + cocooning**: 2,432.54/QALY	**Adolescents vaccination**: 51.21/QALY; **Adolescents + 10-year boosters**: dominated; **Adolescents + cocooning**: 2,496.61/QALY	NR
Meregaglia *et al.*[30]	Not considered	32%: 246,490.46/case prevented	NR
Ding *et al.*[31]	Expected Net of Benefit US$61.25/vaccinated mother	Expected Net of Benefit US$37.25/ vaccinated mother	Centers for Disease Control and Prevention, U.S. Dept. of Health and Human Services
Terranella *et al.*[32]	**Pregnant women**: 439,708.46/QALY. **Cocooning**: 2,127,816.28/QALY	Not considered	NR
Lugnér *et al.*[33]	**Cocooning**: 120,828.15/QALY; **Pregnant women**: 171,060.07/QALY.	Not considered	National Institute for PublicHealth and the Environment, Bilthoven, Netherlands
McGarry *et al.*[34]	ICER per disease incidence (/100.000): 25: 369,229.63/QALY; 100: 68,896.32/QALY; 200: 18,675.26/QALY.	"similar results"	GlaxoSmithKline
McGarry et al.[35]	Cost-saving	Cost-saving	GlaxoSmithKline
Fernández-Canoa *et al.*[36]	Not considered	Benefit-to-cost ratio: **Cocooning**: 0.4; **Pregnant women**: 0.15.	NR
Kamiya *et al.*[37]	**Adolescents vaccination**: 21,672,785.63/QALY **Adult vaccination**: 28,752,816.66/QALY	Not considered	Centers for Disease Control and Prevention
Atkins *et al.*[38]	Not considered	**Pregnant women**: 116,902.95/QALY; Both parents: 835,056,23/QALY (antepartum) and dominated (postpartum); Adult vaccination: dominated	Notsew Orm Sands Foundation (Houston, Texas) and Sanofi-Pasteur
Sartori *et al.*[39]	17,217.25/LYG	17,237.13/LYG	Brazilian Ministry of Health/Pan American Health Organization
Hoek *et al.*[40]	Not considered	60,619.60/QALY	National Institute for Health Research Health Protection Research Unit

*Summary measures were adjusted to 2016 values and then converted to international dollar units using Purchasing Power Parity (PPP).
NR: Not reported; LYG: Life years gained; QALY: Quality adjusted life years; DALY: Disability adjusted life year

unvaccinated infants, adolescents and adults became a problem in developed countries and new immunization strategies for older age groups became available.[14,41] Adolescents and adults vaccination were the first strategies introduced in developed countries, such as Australia, Canada, France, Germany and the USA,[2] and also the first economically evaluated.

In general, the studies found favorable cost-effectiveness ratio for adolescents and adults vaccination, particularly for adolescents' vaccination. Assumptions regarding underreporting correction, herd protection and vaccine coverage were crucial to cost-effectiveness results of adolescents and adults vaccination.

In general, pertussis is considered a childhood disease and goes unnoticed among adolescents and adults. Adolescents and adults usually have milder symptoms, similar to viral infections, making pertussis diagnosis difficult.[42,43] Mostly, only culture-positive cases or cases with typical symptoms are reported. Underreporting is an issue since asymptomatic infections are transmissible.[5,43] Most studies on the cost-effectiveness of adolescent and adults vaccination explicitly took underreporting into account, increasing the incidence detected by regular health surveillance from 2.5 to 600 times. Serological surveillance studies, capture-recapture studies, enhanced surveillance data and author assumption were the source for correction factor. Increasing the incidence has a positive impact on the performance of the strategies evaluated.[17,19,20,26,28]

Some studies considered that all pertussis cases used health services resulting in direct costs. Assuming that undiagnosed or unreported cases are just as severe and costly as reported cases probably overestimates pertussis-related health resource utilization and costs. Few studies considered asymptomatic cases and recognized their importance in the transmission of the disease.[24,26,28,34,35]

Eleven studies that evaluated adolescents or adults vaccination considered herd protection.[14,17,19,20,22,24,26,28,29,35,38] Eight of them used dynamic models and three studies used static models and included herd protection as a correction factor. Herd protection refers to protection of susceptible individuals due to decreased transmission of the pathogen, i.e., reduction in the force of infection, when a high proportion of the population is immunized. Dynamic models allow projecting changes in transmission patterns, taking herd protection into account. Adolescents and adults are the main source of pertussis infection for infants.[2,4,44-48] Considering herd protection for adolescents and adults vaccination would result in averted cases among infants. However, recent studies showed the lack of sterilizing mucosal immunity following aP vaccination.[49] The vaccinated could be colonized by *Bordetella pertussis* and transmit the disease, lacking herd protection of adolescents and adults vaccination.[49]

Some economic evaluations of adolescents and adults vaccination overestimated vaccine coverage, reaching 96%, which contributed to the good performance of the program. Vaccination coverage among adolescents and adults is low for many vaccines in most countries. In the USA, Tdap vaccine coverage among adults aged 19–64 years was 24.7%, in 2014–2015.[50] According to the Vaccine European New Integrated Collaboration Effort consortium, adult vaccination coverage for tetanus and diphtheria ranged from 61% to 74%, in 2010–2011.[51] In Brazil, dT coverage among adults is approximately 33% per year (Immunization Division, São Paulo State) and Tdap coverage among pregnant women was 40.3%, in 2015.

The primary objective of the cocooning and pregnant women vaccination is to reduce transmission to infants. The first economic study of cocooning was published in 2004.[15] Cocooning was introduced in developed countries, such as Australia, France, Germany and the USA, in the early 2000s.[2] This review showed that cocooning performance diverges among studies. The economic evaluations with higher effectiveness for cocooning,[23,33] even to the point of cost-saving,[24] assumed that the mother was the only source of pertussis for the infants, overestimating the impact of postpartum maternal vaccination.

Cocooning effectiveness/impact also diverged among different studies, and there is evidence that the strategy is inefficient to reduce hospitalizations and deaths among infants in settings with low pertussis incidence. In Canada, it would be necessary to vaccinate more than 10,000 people to prevent one hospitalization, and vaccinate at least 1 million to prevent one death of infant <1 year of age, in a setting with 57 hospitalizations per 100,000 inhabitants and risk of parents-to-infant transmission of 35%.[52] In the USA, a study of a postpartum vaccination program did not show any beneficial effect.[53]

After a frustrating performance of the previous strategies, pregnant women vaccination was introduced in USA, in 2011, and UK, in 2012. The first economic evaluation was published in 2010, when many countries reported further increase of pertussis incidence in infants.[3,54,55] Pregnant women vaccination was demonstrated efficacious, had good economic performance and became the main strategy of adults' pertussis vaccination to protect infants.

The overall impact and cost-effectiveness of cocooning are likely to be substantially lower than pregnant women vaccination, which requires only one dose, whereas cocooning requires, as a minimum, multiple doses for parents and family members. Implementing an effective cocooning strategy with high coverage has also proved challenging in several countries.[2]

Pertussis incidence was one of the parameters that mostly influenced the results of pregnant women vaccination programs. Westra et al. (2010)[25] reported that ICERs increased 6x and 3x for cocooning and pregnant women vaccination, respectively, when unreported cases were not taken into account in the analysis. Van Hoek et al.[40] show that pregnant women pertussis immunization would be highly cost effective if the peak incidence of infant disease at the time the program was introduced continues (ICER ~ 17,000 during incidence peak). However, the ICER was highly dependent on the future incidence of pertussis in infants under 3 months of age and it will vary over time considering the cyclical pattern of the disease.[40]

The number of vaccinees in cocooning and pregnant women vaccination does not allow the development of herd protection and static models are adequate to evaluate these strategies.[25,39]

Only eight studies included the public health response in the direct costs.[17-19,21,27,32,36,39] In one study in the USA, the epidemiological investigation of household contacts, laboratory testing the symptomatic contacts and antibiotic treatment for contacts positive for *B. pertussis* cost US$2,269/case, being an important component of costs.[32] Another study, in Brazil, estimated that surveillance costs per case were higher than the outpatient care costs per case.[39] Many countries have long-standing surveillance systems for pertussis.[56] The case reporting results in a public health response, including cases interviews, contacts testing (PCR or culture), identification of symptomatic contacts, and treatment of symptomatic contacts or

chemoprophylaxis for all contacts. The U.S. Centers for Disease Control and Prevention recommends post exposure prophylaxis for all household contacts of a pertussis case.[57] In Brazil, the MoH recommends nasopharyngeal swab for diagnostic tests for all domiciliary contacts of pertussis cases.[58] The contact tracing results in costs that should be considered in economic evaluation of pertussis vaccination programs.

Just one study referred to a developing country.[54] Pregnant women vaccination was shown a cost-effective intervention for preventing pertussis cases and deaths in infants in Brazil. Brazil, Argentina and Chile reported significant increase in pertussis incidence rates in recent years, despite pertussis childhood vaccination with whole-cell vaccines and have already introduced pregnant women vaccination with Tdap.[3,54]

This systematic review and synthesis of the results of the articles included in the analysis of economic evaluations of pertussis vaccination strategies in adults presented more challenges than usual in this type of study due the large number of different strategies, and methodological differences of the studies. The strategies performance and economic evaluation conclusions varied considerably among different studies. Variations were due to different assumptions on epidemiological parameters, health service utilization and costs made in the studies from different countries. Understanding the model and all the parameters used in the economic analysis is essential to understand the results, and identify the major issues important to public health decisions.

Methods

Protocol and registration

This systematic review has been conducted based on the Centre for Reviews and Dissemination (CRD) guidelines[12]. A protocol was developed before initiating this review but it was not registered in the international prospective register of systematic reviews (PROSPERO).

Literature search

A search of studies published from January 1st, 2000 to July 15th, 2016 was conducted in four databases: MEDLINE (via PubMed), Excerpta Medica, CRD and Latin-American and Caribbean Health Sciences Literature (LILACS). It was deemed appropriate to narrow the search to this timeframe because Tdap was licensed in 2005.The following terms were used: 'pertussis' and 'pertussis vaccine' in combination with any of the following: 'economics', 'pharmaceutical', 'cost analysis', 'cost of illness', 'cost(-) benefit', 'health care cost", 'cost(-) effectiveness', 'cost(-)utility', 'cost' and/or (pharmaco) economic evaluation. The search was limited to full economic evaluations on pertussis vaccination of adolescents (≥10 years of age) and adults. The Appendix 1 shows the electronic search strategies created for each database.

Searching other sources

The reference lists of all included studies identified in the electronic databases were reviewed to identify further studies.

Eligibility criteria

The eligibility criteria were defined based on the components of the PICOS approach:

- Population: adolescents (≥10 years of age) and adults (including healthcare workers, pregnant women, cocooning and any other vaccination strategies targeting adolescents or adults);
- Intervention: pertussis vaccination;
- Comparators: no vaccination and strategies of pertussis vaccination of adolescents and adults;
- Outcome: incremental cost-effectiveness ratio (ICER) or cost-benefit ratio;
- Study design: full economic evaluation, defined as a comparative analysis of costs and consequences of two alternative healthcare interventions; including cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis.

Study selection

One reviewer (EGF) screened all titles and abstracts of studies retrieved by the search and selected them using the eligibility criteria. Any doubts during this process were resolved by discussion with another reviewer (PCS).

Data extraction

A predefined data extraction form was calibrated amongst the two reviewers (EGF and CCMR) using a random sample of five included studies. After this, data was independently extracted by the two reviewers (EGF and CCMR) and checked by them. The divergences between the data that the reviewers extracted were resolved by discussion or by arbitrage of a third reviewer (PCS).

Data collected

- Methodological characteristics: type of study, perspective, model, herd protection, time horizon, number of cohorts, currency and year of costs, discount rate, sensitivity analysis, and parameters varied in the sensitivity analysis;
- Estimates of key parameters: epidemiological data (pertussis incidence, disease severity, and case fatality rate); vaccine related data (vaccination schedule, coverage, efficacy, adverse events, and waning immunity rate); costs (direct and indirect), and summary measures (incremental cost-effectiveness ratios (ICERs) or cost-benefit ratio);
- Research funding sources.

To improve comparability between studies results, all summary measures presented in different currencies were adjusted to 2016 value (latest price year used in included studies) using consumer price index [59]. Afterwards, they were converted to international dollar units using Purchasing Power Parity (PPP), the exchange-rate equivalent to an identical basket of goods and

services in countries (Organization for Economic Co-operation and Development.[60]

Synthesis of results

The more relevant results were summarized as a narrative synthesis. The methodological characteristics and key variables estimates are shown in summary tables.

Disclosure of potential conflicts of interest

The authors report no conflict of interest.

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Appendix 1. Search strategy per database

Database	Search strategy
MEDLINE	((((((((((((((((((((((((((Economics[MeSH Terms]) OR Economics, Pharmaceutical[MeSH Terms]) OR ((cost and cost analysis[MeSH Terms]))) OR cost of illness [MeSH Terms]) OR cost benefit analyses[MeSH Terms]) OR health care cost[MeSH Terms]) OR analyses, cost benefit[MeSH Terms])) OR ""analysis cost-benefit"") OR ""cost benefit analysis"") OR ""analyses, cost benefit"") OR ""analysis, cost benefit"") OR ""cost benefit analyses"") OR ""cost effectiveness"") OR ""effectiveness, cost"") OR ""cost-utility analysis"") OR ""analysis, cost-utility"") OR ""cost utility analysis"") OR ""economic, evaluation"") OR ""evaluation economic"") OR ""cost benefit"") OR (((""cost and benefit"")))) OR (((""benefit and cost"")))) OR ""cost effectiveness-analysis"") OR ""analysis, cost-effectiveness"") OR ""cost effectiveness analysis"")) AND ("pertussis" OR pertussis[MeSH Terms] OR pertussis vaccine[MeSH Terms] OR "pertussis vaccine" OR "Diphtheria-Tetanus-acellular Pertussis Vaccines" OR ""Diphtheria-Tetanus-acellular Pertussis Vaccines""[MeSH Terms])
EMBASE	('diphtheria pertussis tetanus vaccine' OR 'pertussis' OR 'pertussis vaccination' OR 'pertussis vaccine') AND ('biomedical technology assessment'/exp OR 'cost utility analysis'/exp OR 'cost of illness'/exp OR 'cost minimization analysis'/exp OR 'pharmacoeconomics'/exp OR 'cost benefit analysis'/exp)
CDR	(PERTUSSIS) OR (PERTUSSIS VACCINE) OR (Diphtheria-Tetanus-acellular Pertussis Vaccines) IN DARE, NHSEED, HTA
Lilacs	((tw:(Pertussis Vaccine)) OR (tw:(Diphtheria-Tetanus-Pertussis Vaccine)) OR (tw:(Whooping Cough)) OR (tw:(Diphtheria-Tetanus-acellular Pertussis Vaccines)) AND (tw:(Pharmaceutical Economics)) OR (tw:(Pharmacoeconomics)) OR (tw:(Cost-Benefit Analysis)) OR (tw:(Cost-Effectiveness Evaluation)) OR (tw:(cost effectiveness)))