



Review

Clinical and economic assessment of different general population strategies of pertussis vaccine booster regarding number of doses and age of application for reducing whooping cough disease burden: A systematic review

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ABSTRACT

Pertussis continues to be an important cause of morbidity and mortality in children too young to be fully protected despite high vaccination coverage. This has been attributed to waning immunity in older people, leading to the development of strategies to increase levels of immunity. A systematic review was conducted to assess the clinical and cost effectiveness of four population-based strategies for pertussis booster vaccination: single booster at 12–24 months old, single pre-school booster, single adolescent booster and multiple boosters in adulthood every 10 years. Electronic databases and Internet resources were searched to June 2006. Nine observational studies, four mathematical models and eight economic evaluations were included, evaluating four different strategies. Strong evidence to recommend any of these strategies was not found.

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1. Introduction

Pertussis (also known as ‘whooping cough’) remains one of the least well-controlled vaccine-preventable diseases for which routine vaccination exists.

The majority of cases of clinically recognisable pertussis occur in children aged 1–5 years, however, severe disease and death occur mainly in infants under 6 months who have either not been vaccinated or are incompletely immunised [1].

An increase in incidence since the early-1990s has been noted in developed countries despite high vaccination coverage [2,3]. Non-immunised children and older individuals with waning immunity may serve as reservoir for the infection and increase the risk of transmission of *Bordetella pertussis* to vulnerable infants [1,4]. Several different strategies for booster vaccination have been considered, with substantial variation in both the number of doses given and the age of administration [5].

In most countries three primary doses of pertussis vaccine are administered to infants aged 2–6 months. One or two booster doses are commonly offered between 1 and 7 years later. A first booster dose may be given at 12–24 months of age or pre-school at age 3–6

years. Adolescent boosters may be used, with or without previous boosters [6–8]. Some experts advocate a booster every 10 years throughout life [9].

The most robust evidence regarding the efficacy of pertussis vaccine boosters comes from randomised controlled trials (RCTs). However, these studies have compared different types of booster vaccine rather than booster strategies. In addition, while the safety and immunogenicity of pertussis vaccine boosters have already been demonstrated in these trials [10–12] the effectiveness of specific booster strategies in reducing morbidity and mortality at population level cannot be inferred from serological outcomes. This systematic review provides evidence regarding the clinical and cost effectiveness of different pertussis vaccine booster strategies.

2. Materials and methods

2.1. Search strategy

Searches were carried out in Medline (1966–2006); Embase (1980–2006); the Cochrane Library and internet resources related to communicable disease and vaccination including those of

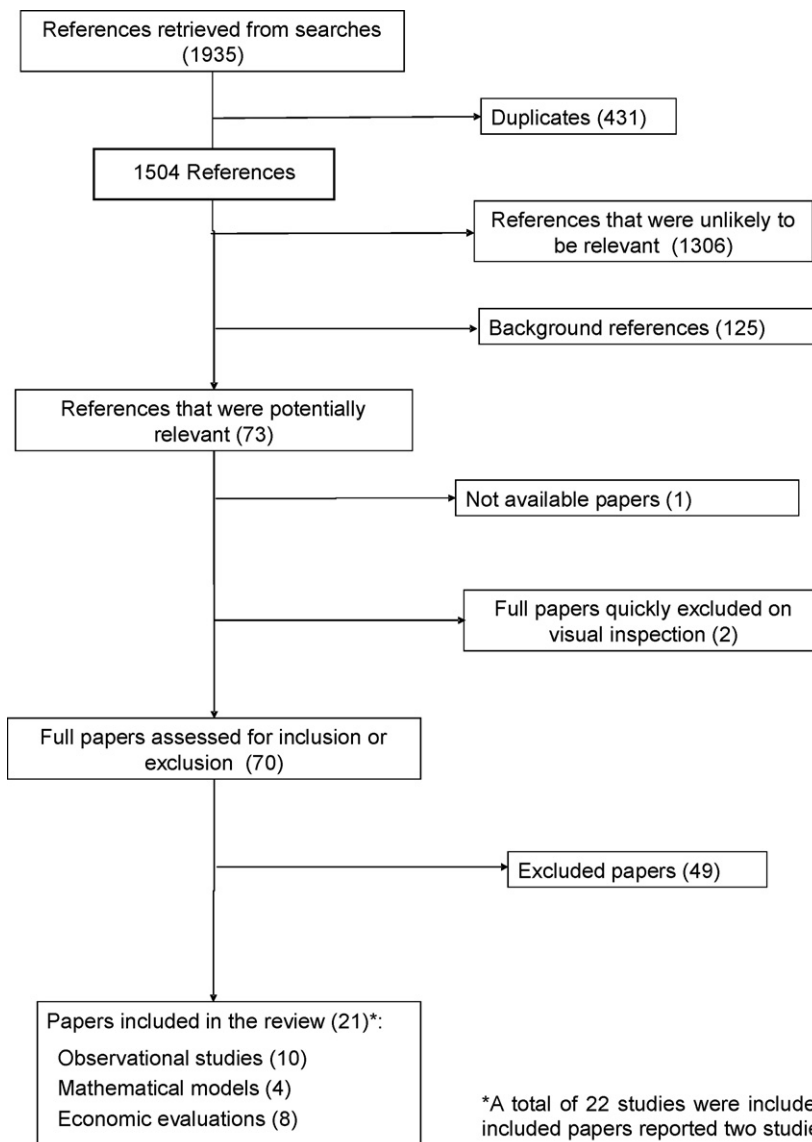


Fig. 1. Flow chart of selection process.

Table 1a
Characteristics of descriptive studies.

	Country/region	Dates	Source of data	Evaluated booster	Previous vaccination	Estimated Coverage	Quality
Hamed (1995) [16]	France (<i>Indre et Loire</i> region)	1993	Survey of 490 doctors (suspected cases)	5–6 years old voluntary booster (type of vaccine not reported)	3 primary doses + first booster at 18 months	89% in 1991 for priming doses and first booster	Low response rate 45.5%; voluntary booster ^a
Andrews (1997) [17]	Australia	1991–1997	Notification rates (crude and age-specific)	4–5 years old introduced 1994 (whole-cell)	3 primary doses + first booster at 18 months	77% in 1997 for primary doses; unknown for boosters	Limitations of reported data ^b
Torvaldsen (2003) [18]	Australia	1993–2001	Notification rates (crude and age-specific)	4–5 years old introduced 1994 (acellular and whole-cell)	3 primary doses + first booster at 18 months	90% in 2000 for primary doses; 75% for evaluated booster (fifth dose)	Limitations of reported data ^b
De Greeff (2005) [19]	Netherlands	1996–2003	Notification rates (crude and age-specific)	4 years old introduced 2001 (acellular)	3 primary doses	85% for primary doses in 1996; unknown for booster	Limitations of reported data ^b

^a Based on survey of doctors using different local booster policies; this approach may be particularly susceptible to confounding.

^b Limitations for studies based on notification data include variation in diagnostic and surveillance methods over time, reliance on limited information available from notification forms, and potential underreporting of cases.

Table 1b
Characteristics of case–control studies.

	Country/region	Dates	Population	Number of cases/controls	Evaluated booster	Previous vaccination	Estimated coverage
De Serres (2001) ^a [20]	Canada (Quebec)	1 January 1998–15 January 1999	11 months–3 years old	120 cases 4 controls per case (469 + 11 excluded)	18 months old (acellular and whole-cell)	3 primary doses	94.5% primary vaccination (coverage in controls)
De Serres (2001) ^a [20]	Canada (Quebec)	1 January 1998–15 January 1999	4–7 years old	197 cases 4 controls per case (776 + 12 excluded)	5–6 years old (acellular and whole-cell)	3 primary doses + 18 months old booster	96% primary vaccination (coverage in controls)
Gonzalez (2002) [21]	Spain (Castellón)	6 February–29 July 2000	7–12 years (studied during an outbreak; controls were contacts)	94 cases (44 excluded) 36 controls (18 excluded)	18 months old (whole-cell)	3 primary doses	95% primary vaccination

^a De Serres 2001 includes two case–control studies.

Centers for Diseases Control; Health Protection Agency; World Health Organization; Centro Nacional de Epidemiología; Euro-surveillance; Asociación Española de Vacunología; Advisory Committee on Immunization Practices and Asociación Española de Pediatría. All databases were searched up to June 2006. Key words used were: pertussis; *Bordetella pertussis*; pertussis vaccine; diphtheria-tetanus acellular pertussis vaccine; whooping cough; vaccines; secondary immunisation and booster. The reference lists of articles identified from these sources were examined for additional studies not obtained through the electronic databases. No language restriction was applied.

2.2. Inclusion criteria

Full copies of relevant papers were retrieved and the inclusion criteria were applied to them independently by two assessors. Discrepancies were resolved through a third independent assessor. Studies were selected for inclusion if they met the following criteria.

2.2.1. Design

RCTs or observational studies (including cohort studies, case-control studies and descriptive studies), mathematical predictive models and economic evaluations.

2.2.2. Population

General population (children, adolescents and adults) in developed countries who have already received primary pertussis vaccination.

2.2.3. Intervention

Pertussis vaccine booster administered to a whole age group; studies of booster vaccination targeted at specific population subgroups were excluded.

2.2.4. Comparator

Any alternative population-based vaccination strategies for pertussis vaccine booster (including no booster dose).

2.2.5. Outcomes

For clinical studies, the primary outcome of interest was mortality and fatality rate from whooping cough. Secondary outcomes of interest were any kind of morbidity indicators (incidence, notified cases, consultations or hospitalisations) associated with whooping cough. Economic evaluations which considered costs, cost per life-year gained (LYG), cost per death avoided, cost per case of whooping cough prevented or cost per quality adjusted life-year (QALY) gained were included.

2.3. Data extraction, quality assesment and synthesis of results

A data extraction form was developed by adapting those used in previously published studies [13–15] and was piloted in a repre-

sentative sample of included studies. Data was extracted from each paper by the main reviewer and independently checked by a second reviewer. Two reviewers independently carried out quality assessment for each included study using the checklists included in the data extraction form. Disagreements were resolved by discussion.

Results were tabulated and described. Meta-analyses were considered inappropriate because of heterogeneity in quality and design of the included studies.

3. Results

Altogether 1504 references were identified, 73 of which were considered potentially relevant to the review question. Twenty-one articles were finally included (Fig. 1): 9 observational papers including 10 observational studies [16–24] (Tables 1a–1c), 4 mathematical models [25–28] (Table 2) and 8 economic evaluations [29–35] (Table 3).

Four different pertussis booster strategies were identified for evaluation: single booster at 12–24 months old, single pre-school booster, single adolescent booster and multiple boosters in adulthood every 10 years. The outcome of each booster strategy was divided into *direct effect* (protection given in the eligible age group) and *herd immunity* (indirect protection given by the booster in other age groups). The most relevant herd immunity effect to our systematic review is that which refers to the most vulnerable age group (infants, especially those up to 6 months).

3.1. Booster at 12–24 months old

Four observational studies (2 case-control and 2 cohort studies, Table 4) assessed the direct effect of this booster. One of the studies did not provide numerical estimate as no pertussis case was reported during the study [22]. Results from the remaining studies were consistent despite variations in study design and quality, with reported odds ratios or relative risk of contracting pertussis ranging from 2.8 to 3.0 for no booster compared to booster at 12–24 months. Both De Serres et al. [20] and González et al. [21] estimated booster effectiveness of 66% based on reported clinical cases. This is lower than estimates of between 85 and 95% based on immunological responses observed in RCTs [29–32].

Hethcote HW et al. [28] (Tables 2 and 7) also investigated this booster strategy by modelling the potential effect of eliminating it from the Australian schedule. The model predicted a large increase (83%) in pertussis incidence in children from 2 to 10 years old and a moderate increase in infants up to 2 years old (27%).

None of the economic evaluations look at the 12–24 months old booster dose strategy.

3.2. Pre-school booster strategy

Focusing on the direct effect, three descriptive studies (Table 5) compared national surveillance data before and after the intro-

Table 1c
Characteristics of cohort studies.

	Country	Follow-up	Dates	Population	Number of subjects	Evaluated booster	Estimated coverage
Blennow (1990) [22]	Sweden	Retrospective 4 years (2 years for pertussis exposure)	1984–1988	Subjects previously participated in a clinical trial	201 (of 304 in original trial)	17 or 24 months old (acellular)	100% at least 2 doses of primary vaccination
Tindberg (1999) [23]	Sweden	Retrospective 10 years (2 years for pertussis exposure)	1984–1994	Subjects previously participated in a clinical trial	207 (of 304 in original trial)	17 or 24 months old (acellular)	100% at least 2 doses of primary vaccination
Hviid (2006) [24]	Denmark	Retrospective 24 years	1977–2001	All children born in Denmark 1977–2001	1,540,832	4, 5 or 6 years old	98% at least 1 dose of primary vaccination

Table 2
Characteristics of mathematical models and main results.

Model	Country	Time horizon	Sources of data	Ages	Evaluated Booster strategy	Previous doses	Assumed coverage	Main results ^a
Agua (2006) [25]	No location specified	No time period specified	Literature	0–70 years	Adolescents and adults every 10 years (type not specified)	Not specified	95%	27% for severe disease (all ages)
Van Rie (2004) [26]	USA	1940–2040	Literature, historical statistical data	All ages	Two strategies: 12 years (adolescents) adults every 10 years (acellular)	3 primary doses + 2 boosters	75% adolescents 60% adults	Adolescent booster: 37% adolescents 18% infants ^b Adult booster: 50% adults 39% adolescents 33% infants ^b
Hethcote (1999) [27]	USA	1940–2040	Literature, historical statistical data	All ages	Adults every 10 years from age 10 (acellular)	3 primary doses + 2 boosters	100% for booster doses in base-case scenario	24/40% ^c adults 21/34% ^c adolesc. 18–27% ^c infants ^d
Hethcote (2004) [28]	Australia	1950–2050	Literature, historical statistical data	All ages	Two strategies: ^e 18 months ^f 12 years (adolescents) (acellular)	3 primary doses + 2 boosters	90% 18 months 80% adolescents	18 months booster: 83% children ^f 27% infants ^b Adolescent booster: 64% adolescents 22% infants ^b

^a Predicted percentage decrease in incidence of pertussis by age-group for all disease degrees (severe, mild and weak disease).

^b Infants up to 2 years old.

^c Results from the two different reported models (see Table 7).

^d Infants up to 1 year old.

^e Analysis estimates the effect of eliminating the 18 month booster dose and also the substitution of the 18 month booster by the adolescent one

^f Children from 2 to 10 years old.

duction of this booster dose in the vaccine schedule [17–19]. Each reported downward trends and observed reduction in pertussis incidence in the eligible age groups ranged from 35 to 55%.

A case–control study (Table 5) found that the risk of pertussis among the children who had received no booster dose was 1.7 times higher compared to children who received a pre-school booster dose, equivalent to an effectiveness of 41% [20]. However, an ecological study based on a survey of 490 doctors in France found no effect for this booster strategy [16].

It was possible to assess the estimated indirect effect in the descriptive studies and these varied from 0% in Torvaldsen et al. [18] to 38% in De Greeff et al. [19]. In contrast with Torvaldsen et al. [18], Andrews et al. [17] found 22% herd immunity in the same population and using the same notification data but using different time periods for data both before and after the introduction of booster vaccination (Table 1a). A further study by Hvidt et al. [24] in Denmark estimates herd immunity at around 18% (plausible range 7–33%) in children 0–1 years old.

This booster strategy was considered in two economic evaluations [31,32] (Table 3). Both of them were carried out for England and Wales. Stevenson et al. [31] presents the results for two scenarios, one more conservative than the other. The reported incremental cost-effectiveness ratios are £35,000/QALY and £14,500/QALY for each of the scenarios, respectively, from the Health Care Provider (HCP) perspective. Discount was applied to costs but not benefits in this study (Table 6).

The study by Edmund et al. [32] presents cost-effectiveness estimates based on herd immunity achieved (Table 6). Using the higher estimate of herd immunity reported by Hviid (33%), the cost per LYG was estimated at £25,800. A more conservative estimate of herd immunity of around 20% gave a cost per LYG of £49,500 from the HCP perspective.

3.3. Adolescent booster strategy

There are no observational studies regarding this strategy. However, two mathematical models (Tables 2 and 7) have considered it and predict a decrease in the disease incidence of 64 and 37%, respectively, in the adolescent population and 22 and 18% in the infant population [26,28]. Both studies are based in the same model and make reasonable assumptions (Table 7). Differences may be due mainly to the differences in the assumed vaccine coverage.

Six economic evaluations [29,30,32–35] addressed the adolescent booster strategy but some of them have important limitations on quality (Table 6). Important factors such as herd immunity are ignored by some of the studies, others assume unrealistically high coverage in this population and sensitivity analyses were frequently not reported for some key assumptions. The study reported by Edmunds et al. [32] appears to be subject to least bias. Results of this study were reported according to the level of herd immunity that was achieved. Assuming a reduction of 14.4% in pertussis incidence among children aged 0–14 years according to the modelling results reported by Van Rie et al. [26], the estimated cost per life-year gained for adolescent booster strategy compared to no booster would be in excess of £55,900 from HCP perspective [32].

3.4. Adolescent and adult booster every 10 years

This booster strategy is taken into account by three of the included mathematical models [25–27] (Tables 2 and 7) and two economic evaluations [34,8] (Tables 3 and 6). The mathematical model from Aguas et al. [25] predicts a 27% decrease in pertussis incidence for severe disease in all ages with this strategy but they did not specify this decrease by age-group.

Table 3
Characteristics of economic evaluations studies and main results.

	Evaluated booster	Country/region	Study type	Type of analysis/model used	Perspective	Data sources	Cost year	Currency	Sensitivity analysis	Time horizon	Comments	Main results
Iskedjian (2005) [29]	Adolescents (14 years)	Canada (Quebec)	Cost-effectiveness and cost-benefit	Decision analytic spread sheet analysis	Health care provider and societal	Literature, national statistical sources, experts opinion	2003	CAD\$	Univariate, multivariate and probabilistic	10 year period from 2004	Conflicts of interest	\$ CAN 527/case avoided
Iskedjian (2004) [30]	Adolescents (12 years)	Canada (Ontario)	Cost-effectiveness and cost-benefit	Decision analytic spread sheet analysis	Health care provider and societal	Literature, national statistical sources, experts opinion	2003	CAD\$	Univariate, multivariate and probabilistic	10 year period from 2003	Conflicts of interest	\$CAN 188/case avoided
Stevenson (2002) [31]	Pre-school (4–5 years)	England and Wales	Cost-benefit, cost-effectiveness and cost-utility	Markov model	Health care provider	Literature, national statistical sources, experts opinion	2000	UK£	Univariate	5 years period	Conflicts of interest	£35,000/14,500/QALY
Edmunds (2002) [32]	Pre-school Adolescents	England and Wales	Cost-effectiveness	Deterministic transmission dynamic model	Health care provider and societal	Literature, national statistical sources	2001	UK£	Univariate, multivariate and probabilistic	Lifetime	–	£49,500/25,800/LYG, £55,900/LYG
Caro (2005) [33]	Adolescents (11–18 years)	USA	Cost-effectiveness	Cohort simulation	Health care provider and societal	Literature, experts opinion	2002	USA\$	Univariate	Lifetime (10 years for results)	–	£22,000/LYG
Lee (2005) [34]	Adolescent and adult booster every 10 years, adolescent (11 years old)	USA	Cost-effectiveness and cost-utility	Markov model	Health care provider and societal	Literature, experts opinion	2004	USA\$	Univariate	Lifetime	–	\$1.5 million/QALY ^a , \$23,000/QALY
Purdy (2004) [35]	Adolescents and adults every 10 years from 10 years old	USA	Cost-benefit	Estimations from trials and literature review	Societal	Literature, national statistical sources	2002	USA\$	Univariate, multivariate	10 year period from 2001	Conflicts of interest	\$32 break even cost/vaccination
Lee (2000) [36]	Adolescents	USA	Cost-benefit	Simple estimation from survey data of costs	Societal	Literature, national statistical sources	1995–1996	USA\$	No	–	–	\$101,000 saved

^a Compared with adolescent booster alone.

Table 4
Results of observational studies assessing 12–24 months old booster.

	Study type	Estimator	Estimate (95% CI) ^a	Booster dose effectiveness ^a
De Serres (2001) [20]	Case-control	OR	2.9 (1.7, 4.9)	66%
Gonzalez (2002) [21]	Case-control	OR	3 (0.4, 23)	66%
Blennow (1990) [22]	Cohort	RR	–	–
Tindberg (1999) [23]	Cohort	RR	2.8 ^b	–

^a Comparing no booster dose versus acellular or whole-cell booster dose for the odds/risk of contracting clinically diagnosed pertussis.

^b Calculated from information given in the paper.

Table 5
Results of observational studies assessing pre-school booster.

	Country	Design	Type of analysis	Outcome measure	Direct effect	Indirect effect
Andrews (1997) [17]	Australia	Descriptive (national data)	Before and after	Notified pertussis cases	35% decrease	22% decrease in infants < 1 year old
Torvaldsen (2003) [18]	Australia	Descriptive (national data)	Before and after	Notified pertussis cases	36% decrease	No herd immunity effect was seen
De Greeff (2005) [19]	Netherlands	Descriptive (national data)	Before and after	Notified pertussis cases	55% decrease	38% decrease in infants < 1 year old
Hamed (1995) [16]	France	Descriptive (survey data)	Ecological	Pertussis cases suspected by doctors	No effect was found	Not evaluated
De Serres (2001) [20]	Canada	Case-control	Odds ratio	Odds of contracting clinically diagnosed pertussis	OR 1.7 (1.2–2.4)	Not evaluated
Hviid (2006) [24]	Denmark	Historical cohort	Modelling	Avoided pertussis hospitalisations	Not evaluated	18% (7–33%) in infants < 1 year old

Table 6
Main base-case assumptions in the economic evaluation studies^a.

	Herd immunity	Booster coverage	Under-reporting factor	Vaccine effectiveness	Duration of protection	Discounting
Iskedjian (2005) [29]	<i>Not taken into account</i>	85%	9	85%	10 years	3% costs and benefits
Iskedjian (2004) [30]	<i>Not taken into account</i>	95%	9	85%	10 years	3% costs and benefits
Stevenson (2002) [31]	Age-related (from 31 to 69%)	84.5%	Age-related (from 0.06 to 20)	94–88%	Age-related	0–6% costs only
Edmunds (2002) [32]	All the results are presented in terms of this parameter	84%	2.5	95%	Average lasting 5 years (decline at a constant rate)	3% costs and benefits
Caro (2005) [33]	20%	80%	7.6	85%	10 years	3% costs and benefits
Lee (2005) [34]	Not taken into account in base-case scenario	Age-related (from 5 to 76%)	<i>Not taken into account</i>	87%	<i>Gradually decreasing over 15 years</i>	3% costs and benefits
Purdy (2004) [35]	40%	40%	2	88%	<i>Gradually decreasing over 10 years</i>	3% costs and benefits
Lee (2000) [36]	<i>Unclear</i>	100%	<i>Not taken into account</i>	<i>Not taken into account</i>	<i>Not taken into account</i>	<i>Not taken into account</i>

^a Cells in *italics* indicate that no sensitivity analysis was carried out for this parameter.

Hethcote et al. [27] found a decrease in disease incidence of 24% in adults, 21% in adolescents and 18% in infants with the more conservative model and 40, 34 and 27%, respectively, with less stringent assumptions. This study assumed 100% vaccine coverage which is unlikely to be achievable, particularly in the adult population. More reliable coverage was assumed by Van Rie et al. [26] (Tables 2 and 7).

They predict, for all degrees of disease severity, a 50% reduction in adults, 39% in adolescents and 33% in infants.

Two economic evaluations modelled this strategy. Purdy et al. [8] reported \$32 break-even cost per vaccination. The herd immunity level assumed, however, is very high (40%). Lee et al. [34] took herd immunity data from Van Rie et al. [26] in the sensitiv-

Table 7
Sensitivity analysis of the included mathematical models (bold text indicates parameters to which the results are most sensitive).

	Aguas (2006) [25]	Van Rie (2004) [26]	Hethcote (1999) [27]	Hethcote (2004) [28]
Transmission Level/force of infection	Yes	Yes	Yes	Yes
Relative infectiousness of severe, mild and weak disease	No	Yes	Yes	Yes
Duration of the infection-acquired and vaccine-induced immunity	No	Yes	Yes	Yes
Distribution of the severity of disease	No	Yes	No	No
Vaccination coverage	No	Yes	Yes	Yes
Vaccine effectiveness	No	No	Yes	No
Fraction of children infected by parents and siblings	No	Yes	No	No
Different models	No	Yes ^a	Yes ^b	Yes^c

^a Waning immunity assumptions are changed from the original model.

^b Two models are implemented, adult vaccinations cause a larger boost in the immunity level in the second model than in the first model.

^c Immunity levels achieved with different doses are changed from the original model.

Table 8
Summary of results.

	Study design	12–24 months old	Pre-school	Adolescents	Adolescents and adults
Direct effect ^a					
OR/RR	Observational	~3	1.7	–	–
Case–control method ^b	Observational	66%	41%	–	–
Incidence decrease	Observational; modelling	83%	35–55%	37–64%	39–50%
Indirect effect ^a					
Incidence decrease	Observational; modelling	27%	(0–38%)18%	18–22%	33%
Cost-effectiveness (comparator: no booster dose)	Economic evaluations; modelling	–	£49,511 per LYG	>£55,884 per LYG	\$1.5 million per QALY

^a Direct effect: protection given by the booster in the eligible group; indirect effect: herd immunity given by the booster in infants.

^b Method to calculate vaccine effectiveness: $1 - [(Vc \times UVc) / (Vc \times UVc)] \times 100$; Vc: vaccinated cases; UVc: unvaccinated cases; Vcon: vaccinated controls; UVCon: unvaccinated controls.

ity analysis and they concluded that the cost per QALY from the HCP perspective is \$ 1.5 million.

4. Discussion

This review identified 21 studies that assessed the clinical effectiveness and/or cost-effectiveness of four different population strategies for pertussis vaccine booster. The type of evidence and quality of studies vary substantially between the strategies. The best evidence level of this systematic review is rather low (category III of evidence [36]) derived from observational studies (cohort and case–control studies but also descriptive studies). Nevertheless the evidence may shed some light on comparing one booster policy to another.

Table 8 summarises the evidence that is considered most robust in terms of study design, quality and underlying assumptions (where applicable) for each of the strategies. The reduction in morbidity in those vaccinated (direct effect) was substantially lower than estimates based on immunological status reported in efficacy trials (around 90%). Also in terms of direct effect, booster vaccination at 12–24 months old seems to be more effective than in older groups and this result is consistent across the different study designs (Table 8).

The estimated indirect effect of reduction in morbidity in infants too young to be completely vaccinated (herd immunity) ranged from 18 to 38%. It is not possible to conclude from the available evidence whether any of the population booster strategies is more effective than the other strategies in increasing herd immunity among the vulnerable infants, but results from various studies suggest that a high level of herd immunity, over 40%, is unlikely to be achievable by any of the strategies. Although a booster strategy employing multiple doses during a person's lifetime might provide some additional herd immunity if sufficient coverage rate can be achieved, it will do so at substantially greater cost and thus is unlikely to be cost-effective.

Incompletely vaccinated infants are at greatest risk of severe infection and death from this disease, so the level of herd immunity achieved by booster strategies is a decisive factor in their cost-effectiveness. Existing evidence suggests that population-based booster strategies seem to be able to achieve only modest herd immunity in infants. Considering the substantial costs required to implement these strategies, they do not appear to be cost-effective.

Non-universal booster strategies, for example vaccination of parents, health care workers and others in close contact with young children or expectant parents, were not considered in this review. These strategies may also be worth investigating given the high cost of universal strategies.

Attempts to model the effectiveness and cost-effectiveness of booster vaccination are complicated by a lack of reliable infor-

mation on the real burden of the disease (underreporting factor), duration of protection from the vaccine and infection-acquired protection, transmission level, relative infectiousness of severe, mild and weak disease and achievable coverage levels in the adolescent and adult population. The herd immunity effect of any of the booster dose strategies is particularly important, but also particularly difficult to measure.

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