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Acellular pertussis vaccine efficacy: An updated systematic review and meta –analysis

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Abstract

Background: Recent studies indicate an increased incidence of pertussis disease in recent years. The aim of this study was to evaluate the efficacy of the acellular vaccine for children (as a replacement of current whole cell vaccine in the Expanded Program on Immunization) and for high-risk adults in Iran through updating current best available evidence.

Methods: We performed a systematic literature review in relevant databases we focused on previously published systematic reviews to select those that address our questions. The AMSTAR (assessing the methodological quality of systematic reviews) tool was used for screening available reviews. Then search in databases was done until Feb 2014 to update the evidence. We pooled results using meta-analysis methods by Stata statistical package.

Results: Eleven systematic review articles were included in the initial evaluation. In the end, two systematic reviews on acellular vaccine booster doses and the acellular vaccine in children were selected as the baseline evidence. In the update phase, new clinical trials were screened, and the results were updated. Overall pooled estimate of relative efficacy of acellular to whole cell was 0.68 (95% CI, 0.55–0.81) for children immunization Pooled estimates for the efficacy of acellular versus placebo were 0.70 (95% CI, 0.60–0.80). Overall pooled estimate of efficacy of booster dose of acellular was 0.87(95% CI, 0.85–0.88) compared to placebo. In addition pooled estimate of acellular vaccine efficacy based on response to antigen was 0.78(95% CI, 0.64–0.93) in high-risk group.

Conclusion: The results show higher performance and safety of the acellular vaccine in the prevention of pertussis in children versus the whole cell vaccine. Moreover, the efficacy of the acellular vaccine in high-risk adult groups is acceptable. This study provides evidence in favor of the introduction of an acellular vaccine to the national program of immunization. Studies on cost effectiveness and aspects of policy analysis are recommended.

Keywords: Whooping cough, Acellular vaccine, Whole cell vaccine.

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Introduction

Whooping cough is an acute bacterial respiratory disease, caused by *Bordetella pertussis*. It can be transmitted through nasal and pharyngeal discharges. This disease has a high degree of virulence. Also the

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bacteria has a high attack rate (80-100%) (1). Immunization against whooping cough is widely coverage by whole-cell vaccine which was developed in the 1940s (2). Most of the whole-cell vaccines are mixed with Diphtheria and Tetanus toxoids, undesired chemicals like endotoxins which are side products of whole cell vaccines cause side effects for this kind of vaccines. Due to growing concerns about the neurologic disorders related to whole-cell vaccines, Acellular vaccines were produced and tested in 1970 and were used in 1980 in Japan (3,4). Increasing in the incidence of pertussis in adolescents suggesting that the immunity by the acellular vaccine may be more efficient than whole-cell vaccine (5), although according to the technical advisory group on vaccine-preventable diseases (TAG), countries that are using whole-cell vaccine should not switch to an acellular vaccine. Similarly, countries currently using acellular should not switch back to the use of whole-cell until more evidence is available to support changes in vaccination strategies for pertussis (5). In Iran, in spite of vaccination program covering more than 90% of the population, reports show an increasing trend of incidence rate in some years which may be due to lack of control in adults (6). This study was designed and performed in order to reach the best estimation of vaccine efficacy and also as an introduction to cost-effectiveness analysis of acellular vaccination in Iran for providing strong evidence for health policy makers.

Methods

We tried to systematically answer three questions in this study:

What is the relative efficacy of acellular pertussis vaccine compared to the whole cell vaccine in children of fewer than five years old?

What is the efficacy of an additional booster dose of acellular pertussis vaccine compared to placebo in fully immunized children with whole cell pertussis?

What is the efficacy of a booster dose of acellular pertussis vaccine compared to placebo in high-risk adults (healthcare staff and pregnant women)?

First, we performed a systematic review on review studies of acellular vaccine efficacy in: 1. children, 2. Health care worker, 3. pregnant women and 4. Booster dose of acellular pertussis vaccine. We selected a core systematic review for each of the above-mentioned groups, considering quality factors of AMSTAR (assessing the methodological quality of systematic reviews) and publication time of the review. Then we performed a systematic review of clinical trials of the acellular vaccine in order to update core reviews.

Search strategy

In order to retrieve related studies we used Pertussis Vaccine/ Whooping Cough/ whoop/ *Bordetella pertussis*/ Vaccines, Acellular/ Meta-analysis/ review/ systematic review

Keywords in relevant evidence base medicine database via Ovid S.P.

To arrange the search strategy, since there was a related systematic review in Cochrane (8) we used a searching method in this review as a guidance to develop a final search strategy. For the secondary studies in MEDLINE, we used CRD which is a very precise strategy (9). Also, we used Cochrane recommended methods of systematic searching (10). Also, we used PUBMED recommended strategy for systematic review and for the secondary studies in another database. We used Lee et al. method (11-13). Search in databases was done in August 2012 by a clinical librarian (FSH) and we did not limit our search to a certain language or time period.

Search resources

We conducted a search strategy in Medline via Ovid, EMBASE via Ovid, EBM Reviews via Ovid, CINAHL and PUBMED via EBSCOhost. Other references such as CEA Registry, Pediatric Economic Database Evaluation, EURONHEEDs and Google Scholar were used for covering gray literature and to increase the sensitivi-

ty of the search. We did a manual reference checking and citation tracking of related papers. In every step of searching, we were considered PRISMA statement (14). First, as our objective was finding relevant systematic reviews and updating them, we updated our search in February 2013, in case to recheck are the references of the systematic reviews which have been chosen as core review. For updating the research we used Cochrane updating protocol. We used a combination of the following words in the updating step of our research:

Pertussis Vaccine/ Whooping Cough/ *Bordetella pertussis*/ Vaccines, Acellular/ ("Quantitative Studies"/ ("Placebos") random* or AB random* (single* blind* or double* blind* or triple* blind* or treble* blind* or single* mask* or double* mask* or triple* mask* or treble* mask*) or AB (single* blind* or double*)

The following references have been used in the updating step: Biological Abstracts, EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>, CINAHL with Full Text, EMBASE<1974 to 2014 February 06>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>.

Inclusion criteria

In the first phase of screening, all of the systematic reviews with or without meta-analysis were included. In the updating phase all the RCTs (randomized clinical trial), quasi-RCTs and immunogenicity studies were included. The study population included children less than 6 years old from the general population, adolescent and high-risk groups including pregnant women and health care workers. The interventions were evaluated with four different analytical strategies. The first strategy was assessing acellular vaccine for children compared to placebo, the second strategy was assessing acellular vaccine for children compared to whole cell vaccine, the third one was assessing the booster dose of acellular vaccine (booster vaccination after 10 years) compared to no-booster and the fourth one was acellular vaccine to the high-risk group compared to placebo or unrelated vaccines.

Exclusion criteria

Laboratory studies conducted on animals were excluded. Also, studies using non-standardized methods were excluded from this study.

Study selection

Full-texts of the relevant studies were critically appraised for eligibility criteria by two researchers independently (MY and SSH). Flow diagram of articles included in the systematic review is shown in (Fig. 1).

Outcome Assessment

The primary outcome was the clinical efficacy of the vaccine to prevent disease during the follow-up period, and the secondary outcome was the immunity in that period. Disease had been defined in two different ways in clinical trials. Based on the first definition whooping cough is a disease with 21 days long lasting continues coughs by Bordetella pertussis which has been proved with positive cell culture, positive serological tests or having contact with a known case of disease which had been proved with two positive cultures (WHO 1991). In the other definition, the disease is having 7 days of continues coughs with a positive cell culture or serologic test (8).

Data extraction

Data extraction was carried out by two researchers (MY, SSH). Year of publication, year of study, location of study, study design, number of patients in the study, number of patients in each group, age range and type of vaccine synchronizing with other vaccines administered, duration of follow-up, number of doses and study phase were extracted., Outcome indicators such as relative risk, odds ratio, and response rates (percent) to the antigen for high-risk group were extracted from the studies as well.

Quality assessment

The systematic review studies were assessed with AMSTAR (A program that assesses the quality of the articles in 11 different areas.), and the clinical trials were assessed with CASP (Critical Appraisal Skills Programme (CASP) tool) (15,16).

Data Synthesis

The statistical analyses were done via STATA version 11. Indicators for assessing the clinical trials were risk ratio (RR) or odds ratio (OR). For the high-risk group, we did not find enough studies to assess clinical outcomes through RR or OR, so, we assessed the vaccine immunogenicity and analysis was performed on the response rate to the antigen. For calculating the vaccine efficacy, we used RR-1 formula (17). Moreover, publication biases of the studies were assessed via Funnel-plot with regression asymmetry test (Egger's test). Heterogeneity of the studies was assessed with Cochrane Q-test. All pooled estimates were calculated by random effect model (except the cases of no significant heterogeneity). Subgroups were determined based on four strategies for the vaccination program.

Results

Study selection

The electronic searching identified 1026 abstract from databases. After the initial screening of title/abstract by two researchers (MY, SSH), 853 abstracts were excluded from the analysis and a total of 173 studies were selected for further investigation and extracting data from full texts. Finally, 11 review studies (8,18-26) in the initial evaluation were criticized with the AMSTAR tool by three researchers (MY, SSH, MML) (Table 1). Finally, we selected ---

Table 1. Specifications of systematic review of acellular vaccine efficacy

No	First Author	Year	Country	Study Type	Reference
1	Tinnion ON.	2000	Australia	Systematic Review	18
2	Zhang	2012	Brazil	Systematic Review	8
4	Rodriguez	2012	UK	Systematic Review	19
5	Johns T.L	2011	USA	Systematic Review	20
6	Plosker G.L.	2009	New Zealand	Systematic Review	21
7	de Carvalho	2006	Brazil	Systematic Review	22
8	Jefferson T	2003	Italy	Systematic Review	23
9	Wintermeyer S.M	1994	USA	Systematic Review	24
10	Gil A.	1996	Spain	Systematic review and Meta-analysis	25
11	Tinnion O	2011	Australia	Systematic Review	26

Table 2. Specifications of clinical trials that estimated acellular vaccine efficacy

No	First Author	Year	Intervention	Population	Age	Efficacy (95% CI)	Reference
1.	Gustafsson	1996	DTaP vs placebo	2566	Children <6	0.59(0.50–0.65)	27
2.	Trollfors	1995	DTaP vs placebo	96	Children <6	0.63(0.52–0.71)	28
3.	Greco	1996	DTaP vs placebo	37	Children <6	0.84(0.75–0.89)	29
4.	Ahgspv	1997	DTaP vs placebo	1428	Children <6	0.41(0.21–0.60)	30
5.	PVSG	1998	DTaP vs placebo	4273	Children <6	0.72(0.62–0.79)	31
6.	Joel I. Ward	2005	DTaP vs placebo	1391	Children <6	0.92(0.32–0.99)	32
7.	Salmaso	2012	DTaP vs placebo	126	Children <6	0.81(0.74–0.85)	33
8.	De Serres G	2001	DTaP –Booster	25	Adult	0.87(0.60–0.90)	34
9.	González Morán F	2002	DTaP -Booster	130	Adult	0.66(0.54–0.73)	35
10.	Iskedjian	2005	DTaP -Booster	90929	Adult	0.85(0.69–0.89)	36
11.	Stevenson	2002	DTaP -Booster	14332	Adult	0.88(0.71–0.90)	37
12.	Edmunds	2002	DTaP -Booster	1165	Adult	0.95(0.61–0.99)	38
13.	Caro	2005	DTaP -Booster	68000	Adult	0.85(0.56–0.89)	39
14.	Lee	2004	DTaP -Booster	69	Adult	0.87(0.65–0.91)	40
15.	Gustafsson	1996	DTaP vs DTwp	2587	Children <6	0.85(0.80–0.88)	27
16.	Greco	1996	DtaP vs DTwp	36	Children <6	0.84(0.76–0.89)	29
17.	Simondon	1997	DtaP vs DTwp	1772	Children <6	0.85(0.66–0.93)	41
18.	Ahgspv	1997	DtaP vs DTwp	1419	Children <6	0.58(0.35–0.73)	30
19.	Patrick Olin	1997	DtaP vs DTwp	20728	Children <6	0.5(0.36–0.71)	42
20.	Patrick Olin	1997	DtaP vs DTwp	20747	Children <6	0.38(0.26–0.56)	42

systematic reviews to be used as a base (core systematic review) for answering each of the four questions of this study: the Zhang et al. (9) review article (2012) for acellular vaccine in children, the Rodriguez et al. (19) review article for booster vaccine were obtained as core reviews for analyzing data about vaccine safety and efficacy. We updated these reviews through our protocol for finding new clinical trials through a systematic review. We classified new trials in the four subgroups; then Meta-analyses were performed to create pooled estimates for vaccine efficacy. In the updating phase, clinical trial studies were screened, and a total of 2 clinical studies out of 20 studies were added to the core systematic review (32,33). Finally, we obtained 15 studies (27-42) from core systematic reviews and clinical trials extracted from updating phase, among them we included 7 interventions for the efficacy of acellular vaccine versus placebo, 6 interventions for the efficacy of acellular vaccine versus whole cell, 7 interventions for the efficacy of acellular vaccine booster dose (Table 2). In addition, two review articles were analyzed for assessing the vaccine efficacy in the high-risk group as an immunological response in pregnant women and health workers (42,43).

Meta-analysis results

Six studies on 51,548 children less than 6 years old had assessed the relative efficacy of acellular vaccine compared to the whole

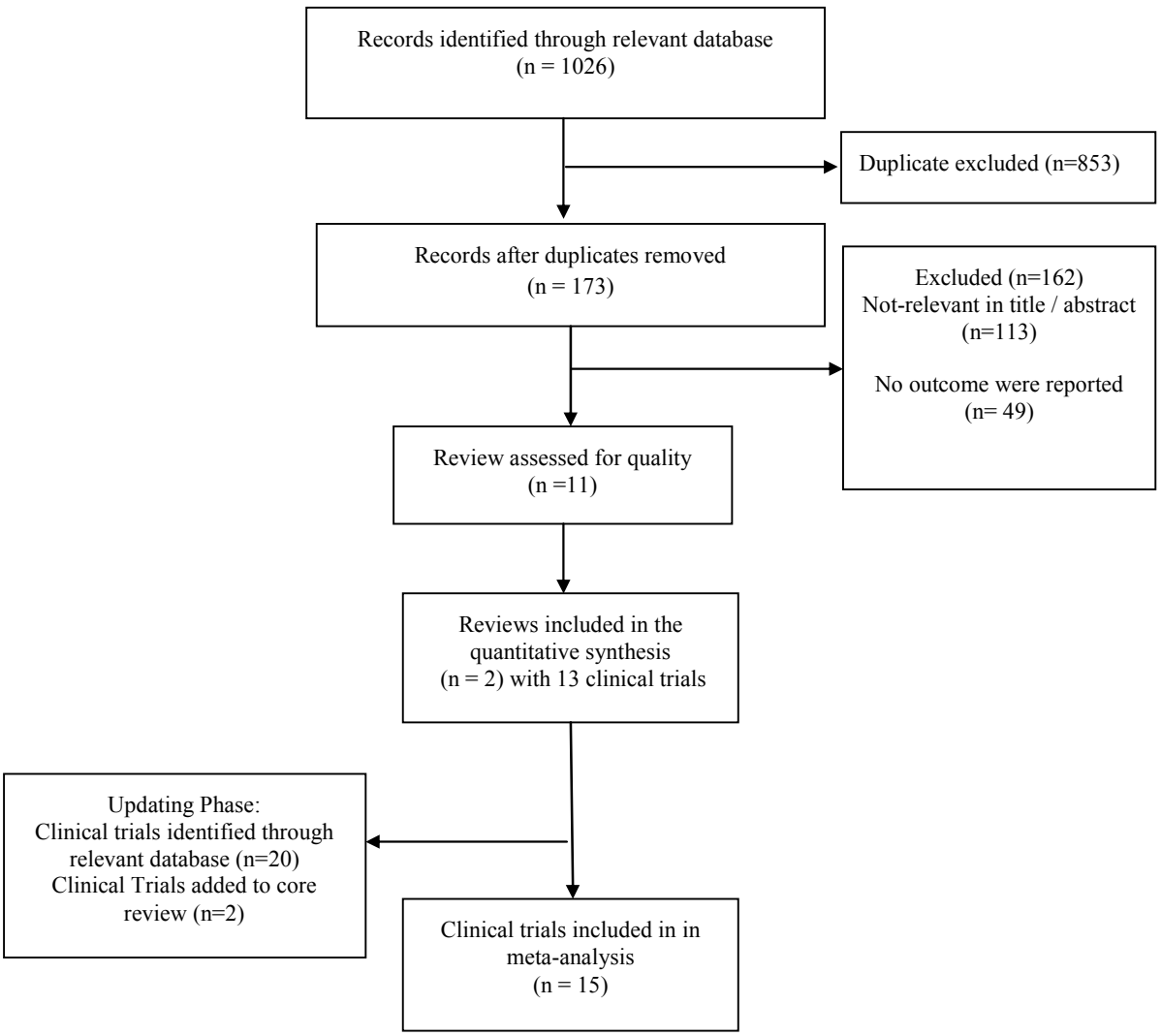

Fig.1. Flow of studies through the review process

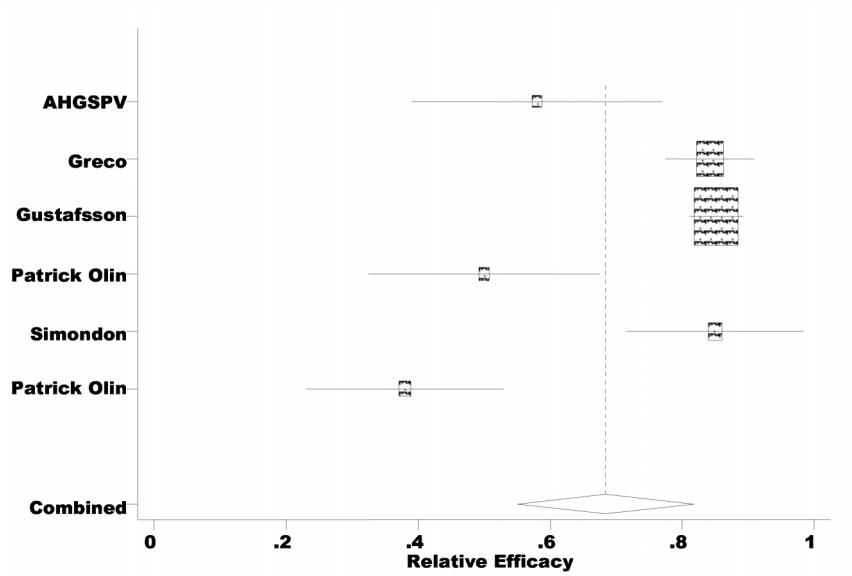

Fig. 2. Funnel-plot for overall pooled estimate of relative efficacy of acellular vaccine versus whole cell

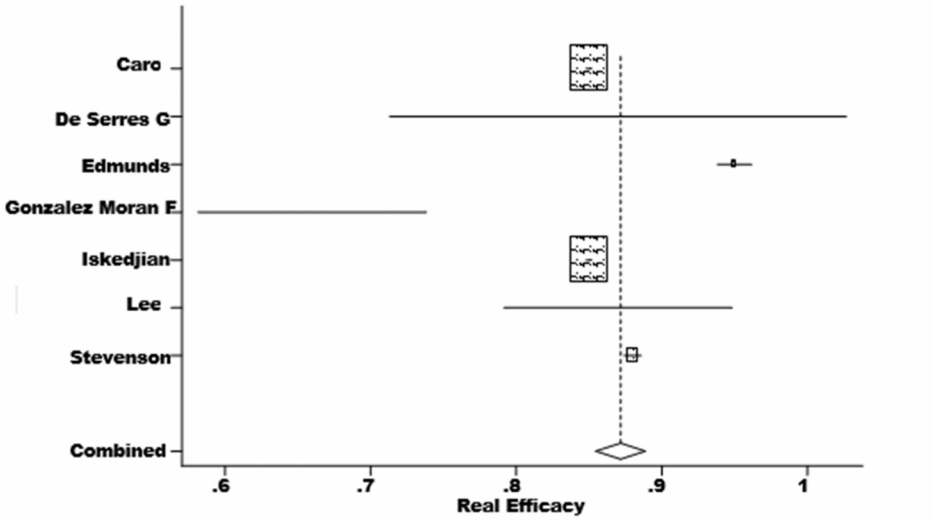

Fig. 3. Funnel-plot for overall pooled estimate of relative efficacy of acellular vaccine versus placebo

cell. There was considerable heterogeneity between results of the studies (Q=54.4, p<0.001, I^2=91%), and pooled estimate of relative efficacy of acellular vaccine to the whole cell in random model was 0.68 (95% CI: 0.55-0.81) (Table 4 and Fig. 2) Seven studies on 9,971 children less than 6 years old had assessed relative efficacy of acellular vaccine compared to placebo. There was considerable heterogeneity between results of the studies (Q=43.6, p<0.001, I^2=86%), and pooled estimate of relative efficacy of the acellular vaccine to placebo in the random model was 0.70 (95% CI: 0.60-0.80) (Table 4 and Fig. 3).

Seven studies on 176,650 adults had assessed the efficacy of acellular vaccine booster dose. There was a considerable heterogeneity between results of the studies (Q=383.7, p<0.001, I^2=98%), and pooled estimate of efficacy of acellular vaccine booster dose in the random model was 0.87 (95% CI: 0.85-0.88) (Table 4 and Fig. 4).

Two studies on 69,285 in adults had assessed the efficacy of the acellular vaccine in high-risk population. There was considerable heterogeneity between results of the studies (Q=51.3, p<0.001, I^2=92%), Pooled

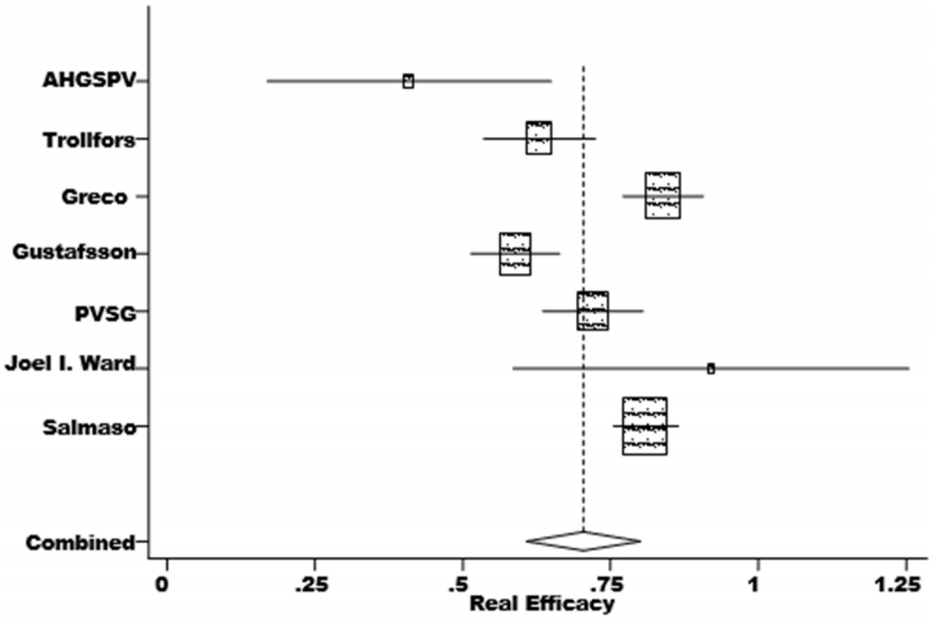

Fig. 4. Funnel-plot graph for overall pooled estimate of relative efficiency of acellular vaccine booster doses

estimate of antigen response rate to the acellular vaccine in high-risk group in random model was 0.78 (95%CI: 0.64-0.93)

Publication bias on assessment of the efficacy of acellular vaccine versus the whole cell vaccine, as well as the efficacy of acellular vaccine versus placebo with Egger & Begg test were examined, which indicates no bias. Summary of efficacy results is shown in Table 3.

Safety result

Evaluating the complications of the acellular and the whole cell vaccine with the data exerted from the systematic review articles indicate that the pooled estimate of relative risk of all complications after vaccination with acellular vaccine against whole cell vaccine is 1.02(95%CI: 0.99-1.05). Moreover, according to studies, the incidence of seizure complication following whole-cell vaccine was 1 in 1,750 cases.

Table 3. Specifications of studies estimated response to antigen in high-risk group

No	First Author	Year	Population	Antibody	Response rate	SE
1.	Gall SA,	2011	8334	PT-IgG	0.833	7.42
2.	Gall SA,	2011	8334	PT-IgA	0.1	6.22
3.	Gall SA,	2011	8334	FHA-IgG	0.9	6.22
4.	Gall SA,	2011	8334	FHA -IgA	0.633	9.23
5.	Gall SA,	2011	8334	PRN-IgG	0.833	7.42
6.	Gall SA,	2011	8334	PRN- IgA	0.8	7.88
7.	Gall SA,	2011	2996	PT-IgG	0.872	5.89
8.	Gall SA,	2011	2996	PT-IgA	0.436	8.32
9.	Gall SA,	2011	2996	FHA-IgG	0.9	6.17
10.	Gall SA,	2011	2996	FHA -IgA	0.769	7.19
11.	Gall SA,	2011	2996	PRN- IgA	0.821	6.63
12.	Gall SA,	2011	2996	PRN-IgG	1	2.30
13.	Littmanna	2008	261	PT-IgG	0.97	7.42
14.	Littmanna	2008	261	PT-IgA	0.634	7.88
15.	Littmanna	2008	261	FHA-IgG	0.992	5.89
16.	Littmanna	2008	261	FHA-IgA	0.963	8.32
17.	Littmanna	2008	261	PRN-IgG	0.972	6.17

Table 4. Results of subgroup Meta analyses

Subgroup	No. of Studies	Heterogeneity			Pooled Estimate	
		X^2	p	I^2	Random (95%CI)	Fixed (95%CI)
DTap vs DTwP	6	54.4	<0.001	91	0.68 (0.55-0.81)	0.80 (0.77-0.84)
DTaP vs Placebo	7	43.6	<0.001	86	0.70 (0.60-0.80)	0.73 (0.70-0.77)
DTaP booster dose vs. no booster	6	373.7	<0.001	98	0.87 (0.85-0.88)	0.853 (0.851-0.854)
DTap in high risk groups vs. no vaccine	2	51.3	<0.001	92	0.78 (0.64-0.93)	0.766 (0.764, 0.768)

Discussion

Results of the current review in order to estimate the pooled estimate of efficacy of acellular whooping cough vaccine when used with multiple strategies as vaccination of children and booster doses for adults and high-risk groups (pregnant women and health care worker), illustrates that application of acellular vaccine in children reduces the incidence of disease by 60-80%. The estimated efficacy compared with whole-cell vaccine is 55-81%. Efficacy of acellular vaccine in booster doses in adults averted disease in this age group by 85-88%. In high-risk groups after investigating the immune response, the cases averted has been estimated 64-93% in a random model. A review study conducted with Cochrane by Zhang et al. (8) in 2012 in order to determine the efficacy and safety of acellular vaccine in children less than 6 years old. In that review study, the efficacy of the vaccine was shown in 6 clinical trials designed for the defined consequences. Efficacy of vaccines with more than 3 particles to prevent typical whooping cough disease is 84-85% and efficacy to prevent mild whooping cough disease is 71-78%. In the current study according to the updates performed, pooled estimate of efficacy of the acellular vaccine was 71-77%.

Vaccine safety is one of the first issues in this field that is studied in Zhang's review article, and because of that, we didn't discuss it in the present study. In the mentioned review study, major and minor side effects were studied in 52 clinical trials in 136541 children and cumulative efficacy of the acellular and whole-cell vaccines were compared in various doses. Study indicated that risk ratio (RR) of major side effects as death, encephalopathy, seizures and hypotonic posture in the first dose of acellular vaccine compared to the whole cell vaccine were 0.97 , 0.00 , 0.47 , 0.26 respectively and risk ratio in minor side effects like anorexia, prolong crying and high fever were estimated 0.43, 0.17, 0.15 respectively. These numbers increased slightly in the next doses (8). Assessing acellular vaccine was considered because of fewer side effects than whole cell vaccine, especially neurologic side effects. On the other hand, the limitations of using whole cell vaccine in adults as well as not making a lifetime security by using whole cell vaccine in children causing poor control of the disease, incidence of disease in adults and transmission of it to other groups in a society are known. There are studies in this field , for example, Pertussis incidence rates in two decades in the United States has increased steadily while during the process that vaccination rates among children were high. During the years 1997 to 2000, most of the cases, according to the Center for Disease Control and Prevention (CDC) were infants (55.5%) and patients of 10 to 19 years old (29%). But in 2005, 60% of the reported cases were among adolescents of 10 to 18 years old (46) from the reasons of increasing in this disease reports, upgrade of diagnostic procedures and increase awareness about the disease was noted. However, many studies have shown that immunity after vaccination decreases over time and protection may only be 10 to 15 years which this can increase the number of susceptible individuals among adolescents and adults. The study conducted by Nikbin et al. (6) in the ministry of health in Iran indicated that the number of susceptible and diagnosed whooping cough patients is recently increasing. The reasons for this

increase in the article were the same as we mentioned here. It has been described that most cases have been confirmed among children due to the less attention of the disease among adults. In a review study by Rodriguez (19) in 2012, the clinical efficacy of direct and indirect (herd immunity) of vaccine booster dose with different strategies was evaluated and calculated. Twenty one observational studies entered into the analysis and were estimated using mathematical modeling. Direct result of the vaccination (reduction of the incidence was 37-64% in adolescents and 39-50% in adults vaccinated) was estimated, and indirect effects or community immunity (18-22% reduction in the incidence of disease in adolescents and 33% in adults) was calculated. Highlights from a study conducted by Rodriguez, is computing the community immunity, which is an explanation for the epidemiologic process change and the use of booster doses (19).

Control of disease in high-risk groups such as pregnant women to maintain safety in infants and employees of the health system as a factor for infection and transmission also had been considered. This point makes us remember the importance of booster dose in adults. In most cases, the disease incidence in adults is directly related to epidemiology in health care workers (21,22) .In a study conducted by Wright et al. in 1992 among emergency room staff, a serological survey showed that despite high immunization coverage in children, antibody levels were low in the majority of employees. This caused this group to be at high risk for infection and subsequent transmission of pertussis to susceptible individuals. The incidence of Bordetella pertussis among health professionals was 3.1% at 95% confidence level (CI) (5.3%-0.00) among 106 physicians, 6.3% at 95% CI (6.9%-0.00) among the physicians and nurses of emergency department (19).

On the positive side, this review performs an integrate search of the information and estimates the pooled efficacy rates and compiles different kinds of strategies. To conclude, to demonstrate the efficacy and safety of acellular vaccines, considering the widespread use of vaccines in children with higher safety and booster doses among adults especially high-risk groups to promote safety in this group to eliminate or reduce the transmission cycle is recommended. In addition, performing cost-effectiveness analysis for implementing acellular vaccine in national immunization program in Iran seems necessary.

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Conflict of Interest

Authors declare they have no conflict of interests.

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