REVIEW DERLEME

The Effect of Interventions on the Prevention of Parental Vaccine Refusal and Hesitancy: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Ebeveyn Aşı Red ve Tereddütünün Önlenmesine Yönelik Girişimlerin Etkisi: Randomize Kontrollü Çalışmaların Sistematik Bir İncelemesi ve Meta-analizi

Mustafa Volkan Düzgün (0000-0001-7461-7319), Ayşegül İşler Dalgıç (0000-0001-8448-0483)

Akdeniz University Faculty of Nursing, Department of Pediatric Nursing, Antalya, Turkey

Abstract

Vaccination is an effective way to prevent infectious diseases. However, parental resistance to childhood immunizations has recently been a growing trend due to various factors. This systematic review and meta-analysis study focused on randomized controlled trials to investigate interventions for preventing parental vaccine refusal/hesitancy. This study was conducted according to the preferred reporting items for systematic review and Meta-analysis Protocols. PubMed, Science Direct, Web of Science, MEDLINE, Cochrane Library, Ovid, CINAHL, and ProQuest databases were screened with no year restriction. Two researchers each used the Cochrane risk-of-bias tool to determine the quality of the trials. Data were synthesized using a meta-analysis package. The study population consisted of 3,302 articles. The sample consisted of 22 randomized controlled trials, which implemented the interventions of text message reminders, digital training in vaccination, training in physician communication, training in parental decision-making, web-based activities, perinatal training in vaccination, immunization reminder and follow-up bracelets, and mother-daughter training. The results showed that slightly more parents agreed to get their children vaccinated after the interventions. The trials were moderately heterogeneous due to differences in sample size, country, and year. This paper investigated the effect of interventions on parental vaccine refusal/hesitancy and provided level-A evidence to suggest such interventions can be used to change parents' vaccination comprehension and decisions.

Keywords
Vaccine hesitancy, vaccine refusal, child, systematic review, meta-analysis

Öz

Aşılama bulaşıcı hastalıkları önlemenin etkili bir yoludur. Bununla birlikte, çocukluk çağı bağışıklamalarına karşı ebeveyn direnci son zamanlarda çeşitli faktörler nedeniyle büyüyen bir eğilim olmuştur. Bu sistematik derleme ve meta-analiz çalışması, ebeveyn aşısı reddini ve tereddütünü önlemeye yönelik müdahaleleri araştırmak için randomize kontrollü çalışmalara odaklandı. Bu çalışma, sistematik derleme ve meta-analiz protokolleri için tercih edilen raporlama maddelerine göre yapıldı. PubMed, Science Direct, Web of Science, MEDLINE, Cochrane Library, Ovid, CINAHL ve ProQuest veritabanları yıl kısıtlaması olmadan tarandı. İki araştırmacı da denemelerin kalitesini belirlemek için Cochrane ön yargı riski aracını kullandı. Veriler bir meta-analiz paketi kullanılarak sentezlendi. Çalışmada 3.302 makale tarandı. Örneklem, kısa mesaj hatırlatmaları, aşılamada dijital eğitim, hekim iletişimi eğitimi, ebeveyn karar verme eğitimi, web tabanlı faaliyetler, aşılamada perinatal eğitim, bağışıklama hatırlatıcısı ve takip bilezikleri ile anne-kız eğitiminin uygulandığı 22 randomize

Anahtar kelimeler
Aşı tereddütü, aşı reddi, çocuk, sistematik derleme, meta-analiz

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Address for Correspondence/Yazışma Adresi: Mustafa Volkan Düzgün MD, Akdeniz University Faculty of Nursing, Department of Pediatric Nursing, Antalya, Turkey
Phone: +90 242 227 61 30
E-mail: mvduzgun@akdeniz.edu.tr

kontrollü denemeden oluştu. Sonuçlar, müdahalelerden sonra biraz daha fazla ebeveynin çocuklarına aşı yaptırmayı kabul ettiğini gösterdi. Denemeler, örneklem büyüklüğü, ülke ve yıldaki farklılıklar nedeniyle orta derecede heterojendi. Bu makale, girişimlerin ebeveyn aşısı red ve tereddütü üzerindeki etkisini araştırmış ve bu tür müdahalelerin ebeveynlerin aşı anlayışını ve kararlarını değiştirmek için kullanılabileceğini düşündürecek seviye-A kanıtları sağlamıştır.

Introduction

Vaccination has proven to be a cost-effective method for reducing mortality and morbidity rates caused by infectious diseases. However, recently, global childhood vaccination rates have declined. Sociocultural, environmental, economic, and individual factors play a role in parental vaccine refusal/hesitancy (1-3).

Recent outbreaks of vaccine-preventable diseases, such as measles and pertussis, demonstrate the dangers of low vaccination rates (4,5). For instance, Europe observed an eightfold increase in measles cases in 2018 (41,000 cases) compared to 2016 (5,000 cases; (6), and 87% of cases are attributed to those who refuse to be vaccinated (3,7). Diphtheria-tetanus-pertussis immunization rates have dropped to 92% and 91% in Europe and the United States, respectively. Therefore, the World Health Organization (WHO) identified vaccine refusal/hesitancy as one of the 10 threats to global health in 2019 (8,9). Moreover, the anti-vaccination trend has extended beyond childhood immunizations to campaigns against COVID-19 vaccines, a virus that has claimed millions of lives worldwide (10).

Many researchers have devoted their efforts to understanding and preventing parental refusal of childhood vaccinations (11-18). Specifically, some researchers have investigated interventions for the prevention of parental vaccine refusal/hesitancy. For example, some researchers sent vaccine-hesitant parents short texts a few days or more before a vaccination program to persuade them to get their children vaccinated (19-26). Other researchers implemented training-focused interventions, such as digital training in vaccination (27), training in physician communication (28), web-based interventions (29,30), and perinatal training in vaccination (31).

However, no comprehensive meta-analysis research exists assessing the overall effectiveness of interventions tailored to the prevention of parental vaccine refusal/hesitancy and identification of standards to inform further research on this topic. We aimed to fill this gap in the literature by determining the best intervention(s) against vaccine refusal/hesitancy so that healthcare professionals can use them to increase immunization rates.

Aims

This systematic review and meta-analysis focused on randomized controlled trials to determine the effectiveness of interventions for increasing parental vaccine acceptance rates.

The research questions were as follows:

-What kind of interventions are implemented to prevent parental vaccine refusal/hesitancy?

-Which interventions can help persuade parents to get their children vaccinated?

-How effective are interventions for increasing vaccine acceptance rates?

Methods

Search Strategy and Outcomes

The study followed the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). Figure 1 shows the flow diagram. This study satisfied all items recommended by the PRISMA-P checklist (32) and was recorded in the International Prospective Register of Systematic Reviews (PROSPERO; code: CRD42020157785).

Two researchers each searched the Science Direct, Web of Science, Springer Link, Ovid, CINAHL, PubMed, Cochrane Library, and ProQuest databases (August 2020) with no year restriction based on the four elements of PICOS (patient/population, intervention, comparison, outcome and study design). They screened the databases using the keywords of "vaccine," "refusal," "hesitancy," "parent," "intervention," and "clinical trials" alone or in combination. They also used keywords/MeSH terms within articles from search alerts in PubMed. They compared the articles they accessed independently. They discussed the articles and reached a consensus on which articles to include in the study.

The literature review based on the search strategy yielded 3,302 articles, which were transferred to the EndNote 9 package. First, duplicates were removed (n=228), after which irrelevant articles by title or abstract were removed (n=2,899). The remaining 175 articles were reviewed based on the inclusion and exclusion criteria (Table 1), and 143 were removed. The full texts of the remaining 32 articles were reviewed and 10 were removed. One of the remaining 22 articles was regarded as two different articles because it involved two different interventions. Therefore, some sections and tables include 23 articles.

Risk of Bias and Quality Appraisal

The researchers each used the Cochrane risk-of-bias assessment tool (RoB 2) to evaluate the risk of

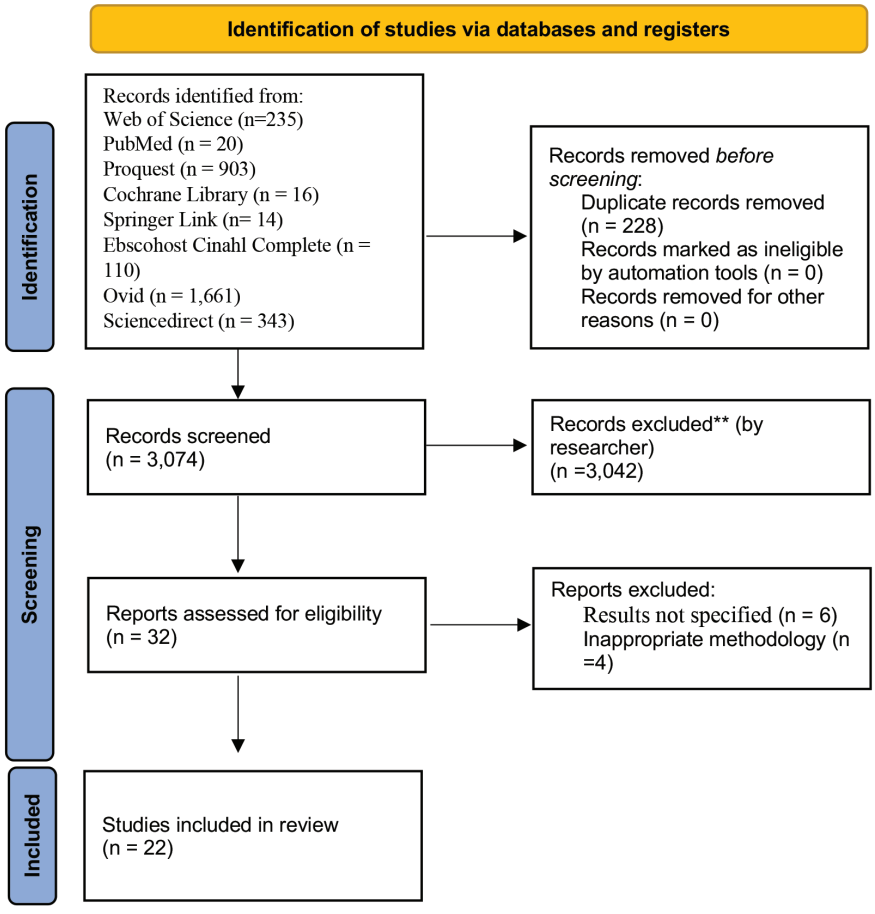

Figure 1. Flowchart of study identification.

Table 1. Inclusion and exclusion criteria	
The inclusion criteria	The exclusion criteria
Population: Parents with children aged 0-18.	Population: Participant ≤18 years old.
Interventions: All attempts to prevent vaccine refusal and vaccine hesitancy.	Intervention: Interventions that do not directly affect vaccination.
Comparison: We will compare the interventions with each other and with the group that has never been intervened.	Comparison: No comparison within or with any groups.
Outcomes: Effects of interventions on vaccination rates.	Outcomes: Outcome not measured, or data results not specified.
Study design: Randomized controlled trials.	Study design: Non-randomized trials or mixed method studies without randomized controlled trials.

bias of the articles based on the following bias domains (33) (Figure 2ab). GRADE was used to grading quality of evidence and the strength of recommendation of studies.

Data Extraction and Analysis

The researchers each extracted the data based on (a) author, year, country, (b) participant characteristics, (c) intervention, (d) intervention details, (e) control group, (f) outcome measures, (g) results, and (h) certainty of the evidence (GRADE).

The data were analyzed using the Comprehensive Meta-analysis (version 2.0). The main outcome was pre- and postintervention vaccine acceptance rates. The data were prepared for meta-analysis using Microsoft Excel. The effect size (ES) was calculated using Borenstein and Hedges (34), which were rated as small (d=0.20), medium (d=0.50), and large effects (d=0.80) between the intervention and control groups (35). Cochran's Q test and I^2 statistics were employed to determine heterogeneity (36). A significance level of less than <.05 indicated heterogeneity for Cochran's Q test. I^2 of 25%, 50%, and 75% were classified as low, moderate, and high heterogeneity, respectively (37). The random-effects model was used to show the average difference and to calculate the weighted average difference (38). Publication bias was determined using Egger's test, Begg and Mazumdar's test for rank correlation, and Duval and Tweedie's Trim-and-Fill test (39,40). Analog ANOVA and meta-regression analysis were performed to identify the cause of heterogeneity (41-44).

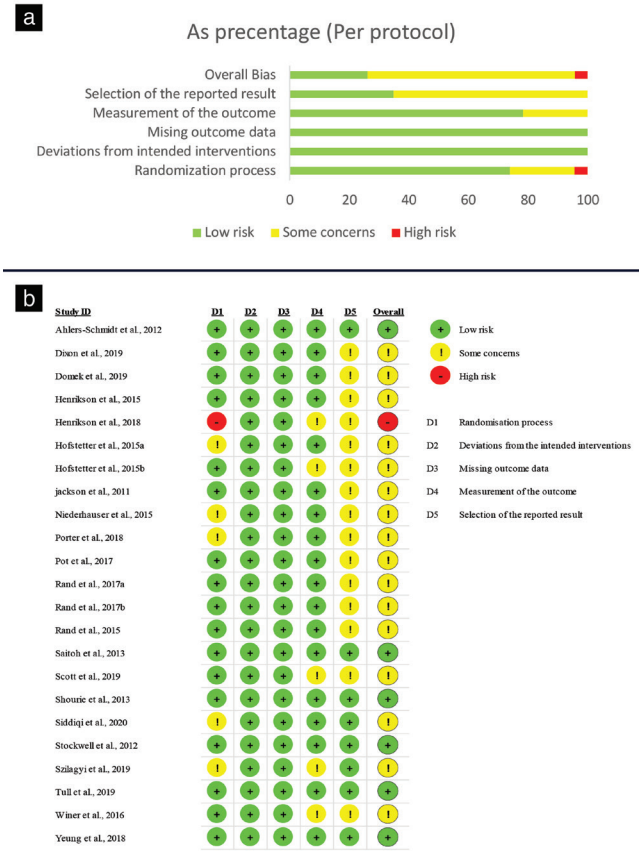

Figure 2. a) Risk of bias graph b) Risk of bias summary.

Results

Research Characteristics

The sample consisted of 22 randomized controlled trials, with a sample size of 57 to 15,786 (n=55,138). The trials were conducted between 2011 and 2020 in the United States (n=14), the United Kingdom (n=2), China (n=1), Australia (n=1), the Netherlands (n=1), Japan (n=1), Pakistan (n=1), and Guatemala (n=1).

Most trials implemented the intervention of sending parents short reminder messages (SMS alerts) before scheduled immunization visits for their children (19-26,45-49). The other trials provided digital training in vaccination [DTV; n=1; (27)], training in physician communication [TPC; n=1; (28)], training in parental decision-making [TPDM; n=1; (50)], perinatal training in vaccination [PTV; n=1; (31)], web-based interventions [WBI; n=2; (29,30], office-based educational brochure [OBEB; n=1; (51)], immunization reminder and follow-up bracelets [IRFB; n=1; (52)], and mother-daughter training [MDT; n=1; (53)].

The details of the interventions differed among trials. The SMS trials (19-26,45-49) involved sending parents short reminder messages just before scheduled immunization visits, or 4 days, 1 week, 4 weeks, 1 month, 2 months, or 4 months before the visits. The frequency of the SMS alerts depended on the dose of vaccination. The DTV trial (27) used only reinforcement messages depending on the parents' views or administered training in vaccination within the scope of a program. The TPC trial (28) administered physicians 45-minute training and examined its effect on parental vaccine hesitancy. The TPDM trial (50) provided training to parents eight times for 2 months.

One WBI trial (30) provided online training (via email) only once, while the other WBI trial (29) administered intervention six times with intervals of 2, 4, and 6 weeks. The PTV trial (31) presented two sessions (10 minutes per session) of training to parents in the perinatal period. The OBEB trial (51) used brochures laid out in the waiting room for visitors to take. The 1-year IRFB trial provided vaccinated children with bracelets that had a symbol for each vaccination (52). The MDT trial held 11 dinner meetings for mother-daughter training (53). The control groups in all trials received standard procedures (Table 2).

Risk of Bias

In the domain of randomization process, 16 trials were at low risk of bias (19,23,25-31,45,47-51,53), five trials raised some concerns (21,22,24,46,52), and the remaining one was at high risk (20). All trials were at low risk of bias for deviations from intended interventions and missing outcome data. Five trials raised some concerns in the domain of bias in the measurement of the outcome (20,24,47,51,53), while the others were at low risk. Eight trials were at low risk in the domain of bias in the selection of the reported result, while the others raised some concerns. Six trials were at low risk in the domain of general bias, 16 raised some concerns, and one was at high risk (Figure 2b).

Study Outcomes

This paper focused on 22 trials to investigate the effect of interventions on vaccine acceptance rates. Meta-analysis results showed that interventions for vaccine acceptance were effective [p<0.001, Hedge's g=0.10, 95% CI (0.06, 0.14)]. The Cochran's Q test results showed a moderate level of heterogeneity (Q=61.26, p<.001, I^2=64.09%; Figure 3). The moderating variables of intervention type (Q=11.114, df=9, p=0.268) and vaccine type (Q=4.467, df=4, p=0.347) had no significant effect on the effect size between subgroups. The moderating variable of country significantly affected the heterogeneity (Q=32.891, df=7, p<0.001). The meta-regression analysis showed that sample size significantly affected the ES (Q=61.26, df=22, p<0.001), suggesting a negative correlation between sample size and ES. The variable of year also significantly affected the heterogeneity (Q=61.26, df=22, p<0.001).

Publication bias was determined using a funnel plot, Begg and Mazumdar's test, and Egger's test. The funnel plot presents the standard error for the Y-axis and the ES for the X-axis (Figure 4). The Begg and Mazumdar's tau with continuity (tau=0.34, Z=2.32 p=0.02) and Egger's regression test results indicated publication bias. Therefore, Duval and Tweedie's Trim-and-Fill test was used to calculate publication

Study name	Time point	Statistics for each study						
		Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Ahlers-Schmidt et al., 2012	fourth month	0,185	0,244	0,060	-0,294	0,663	0,757	0,449
Dixon et al., 2019	Blank	0,175	0,053	0,003	0,071	0,279	3,291	0,001
Domek et al., 2019	Visit 2	0,415	0,126	0,016	0,168	0,662	3,294	0,001
Henrikson et al., 2015	Blank	0,028	0,101	0,010	-0,170	0,226	0,279	0,780
Henrikson et al., 2018	Blank	0,051	0,054	0,003	-0,056	0,157	0,935	0,350
Hofstetter et al. (2015a)	Blank	0,049	0,047	0,002	-0,043	0,141	1,037	0,300
Hofstetter et al. (2015b)	Blank	0,046	0,030	0,001	-0,012	0,105	1,555	0,120
Jackson et al. (2011)	Blank	0,355	0,173	0,030	0,017	0,693	2,058	0,040
Niederhauser et al. (2015)	Blank	0,401	0,264	0,070	-0,117	0,919	1,517	0,129
Porter et al. (2018)	Blank	0,119	0,088	0,008	-0,055	0,292	1,341	0,180
Pot et al. (2017)	Blank	0,012	0,022	0,000	-0,032	0,055	0,524	0,600
Rand et al. (2015)	Blank	0,067	0,032	0,001	0,003	0,130	2,054	0,040
Rand et al. (2017a)	Blank	0,335	0,102	0,010	0,136	0,534	3,293	0,001
Rand et al. (2017b)	Blank	0,101	0,106	0,011	-0,106	0,308	0,955	0,340
Saitoh et al. (2013)	Blank	0,584	0,208	0,043	0,177	0,991	2,814	0,005
Scott et al. (2019)	Blank	0,200	0,106	0,011	-0,008	0,408	1,882	0,060
Shourie et al. (2013)	Blank	0,330	0,142	0,020	0,052	0,608	2,329	0,020
Siddiqi et al. (2020)	Blank	0,095	0,056	0,003	-0,015	0,204	1,696	0,090
Stockwell et al. (2012)	Blank	0,076	0,023	0,001	0,031	0,121	3,291	0,001
Szilagyi et al. (2019)	Blank	0,006	0,016	0,000	-0,025	0,037	0,385	0,700
Tull et al. (2019)	Blank	0,082	0,032	0,001	0,020	0,144	2,576	0,010
Winer et al. (2016)	Blank	0,164	0,203	0,041	-0,234	0,562	0,809	0,419
Yeung et al. (2018)	Blank	0,264	0,080	0,006	0,107	0,421	3,292	0,001
		0,054	0,009	0,000	0,037	0,071	6,236	0,000

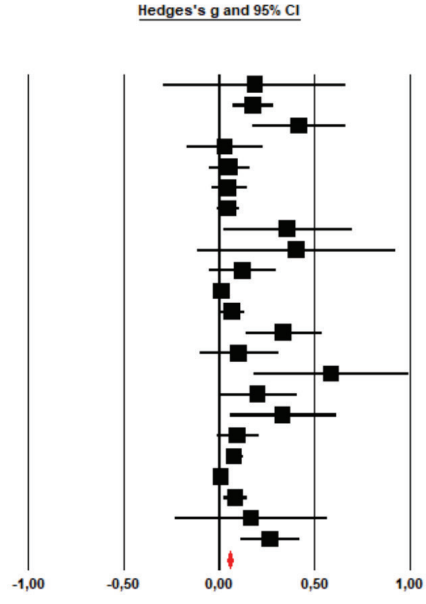

Figure 3. Meta-analysis results of the effect of interventions on vaccine acceptance.
Heterogeneity: Q=61.26, df=22 (p<0.001), I^2=64.09% test for overall effect: Z=5.34 (p<0.001)

Table 2. Characteristics of The Included Studies

Author, year, country	Participants	Type of intervention	Intervention details	Control group	Outcome criteria	Results	Certainty of the evidence (GRADE)
Ahlers-Schmidt et al. (45) United States	68 Newborn Parents Intervention Group: 28 Control Group: 40	Text messages reminder	-Detail: 7 days before their child's immunizations -Frequency: 3 times	Standard notification of immunizations	-Immunization rates	There was no significant difference in immunization rates between the intervention and control groups.	⊗⊗⊗⊗ High
Dixon et al. (27) United States	1596 Parents Intervention Group: 537 Control Group: 1059	A digital vaccine educational intervention	-Detail: The program is message or information oriented according to parents' opinions -Frequency: 1 time (more than one if needed)	Standard care	-Vaccine intake rate	The vaccine intake in the educated group was significantly higher than in the control group (p=0.001).	⊗⊗⊗◯ Moderate
Domek et al. (19) Guatemala	464 Parents Intervention Group: 263 Control Group: 201	Text message reminders	-Detail: Before the visit for immunization -Frequency: 3 times	Standard care	-Vaccination rate	The rate of going to the vaccination appointment in the intervention group was significantly higher than the control group (p=0.001).	⊗⊗⊗◯ Moderate
Henrikson et al. (28) United State	391 Mothers Intervention Group: 193 Control Group: 198	Physician Communication Training	-Detail:45 minutes -Frequency: Unspecified	Standard care	-Vaccine hesitancy rate	There was no significant difference in hesitancy rate between the intervention and control groups (p=0.780).	⊗⊗◯◯ Low
Henrikson et al. (20) United State	1805 Mothers Intervention Group: 1354 Control Group: 451	Telephone/ text reminder components	-Detail: At 6st weeks for 1st dose, 2nd dose 6 weeks after first dose, 4 months after last dose -Frequency: 3 times	Standard care	-Vaccine series completion	The vaccine series in the intervention group was significantly higher than in the control group (p=0.035).	⊗⊗◯◯ Low
Hofstetter et al. (46) United State	2054 Parents Intervention Group: 1382 Control Group: 672	Text message reminders	-Detail: Once a week for the first 3 weeks and 1 and 2 day before the first year appointment -Frequency: 5 times	Standard care	-MMR vaccination	There was no significant difference in MMR vaccination rate between the intervention and control groups (p=0.30).	⊗⊗◯◯ Low

Table 2. Continued

Author, year, country	Participants	Type of intervention	Intervention details	Control group	Outcome criteria	Results	Certainty of the evidence (GRADE)
Hofstetter et al. (47) United State	4818 Parents Intervention Group: 3054 Control Group: 1764	Text message reminders	-Detail: Five weekly automated text message influenza vaccination reminders in November-December and two booster text messages in January. -Frequency: 42 times	Standard care	-Influenza vaccination	There was no significant difference in influenza vaccination rate between the intervention and control groups (p=0.12).	⊗⊗⊗◯ Moderate
Jackson et al. (50) United Kingdom	135 Parents Intervention Group: 68 Control Group: 67	Informed parental decision-making	-Detail: Four daytime and four evening meetings. -Frequency: Eight times during July and August	Standard care	-MMR vaccination	The MMR vaccine intake in the intervention group was significantly higher than in the control group (p=0.04).	⊗⊗◯◯ Low
Niederhauser et al. (21) United State	57 Parents Intervention Group: 30 Control Group: 27	Text message reminders	-Detail: Immunization reminders were sent 4 weeks prior and 2 weeks prior to the due date for the infant's 2, 4, and 6 month vaccinations -Frequency: 2 times	Standard care	-Immunization rate	There was no significant difference in immunization rates between the intervention and control groups (p=0.131).	⊗⊗◯◯ Low
Porter et al. (22) United State	512 Parents Intervention Group: 271 Control Group: 241	Message	-Detail: Followed for 2 weeks -Frequency: 2 times	Standard care	-Intent to vaccinate	There was no significant difference intent to vaccinate between the intervention and control groups (p=0.18).	⊗⊗◯◯ Low
Pot et al. (29) Holland	8062 Parents Intervention Group: 3995 Control Group: 4067	Web-based tailored intervention	-Detail: At one, two and four week intervals -Frequency: 6 times	Standard care	-HPV vaccine uptake	There was no significant difference vaccination uptake between the intervention and control groups (p=0.6).	⊗⊗⊗◯ Moderate
Rand et al. (48) United State	3812 Parents Intervention Group: 1893 Control Group: 1919	Text message reminders	-Detail: Before the three HPV vaccines -Frequency: 4 times	Standard care	-HPV vaccination	There was significant difference HPV vaccination between the intervention and control groups (p=0.04).	⊗⊗⊗◯ Moderate

Table 2. Continued

Author, year, country	Participants	Type of intervention	Intervention details	Control group	Outcome criteria	Results	Certainty of the evidence (GRADE)
Rand et al. (23) (2017a), United State	391 Parent Intervention Group:191 Control Group: 200	Text message reminder	-Detail: Reminder for each dose that is due (1 week apart) -Frequency: 3 times	Standard care	-HPV vaccination	There was significant difference HPV vaccination between the intervention and control groups (p=0.001).	⊗⊗⊗◯ Moderate
Rand et al. (23) (2017b), United State	358 Parent Intervention Group:178 Control Group: 180	Phone message reminder	-Detail: Reminder for each dose that is due (1 week apart) -Frequency: 3 times	Standard care	-HPV vaccination	There was no significant difference HPV vaccination between the intervention and control groups (p=0.34).	⊗⊗⊗◯ Moderate
Saitoh et al. (31) Japan	106 Mothers Intervention Group: 70 Control Group: 36	Perinatal immunization education	-Detail: 10 minutes each session -Frequency: 2 times	Routine care	-Vaccination rate	There was significant difference vaccination rate between the intervention and control groups (p=0.005).	⊗⊗⊗⊗ High
Scott et al. (51), United State	400 Parents Intervention Group: 267 Control Group: 133	Office-Based educational handout	-Detail: Education was given in the waiting room before the clinic visit -Frequency: 1 time	Standard care	-Vaccine hesitancy	Parents who received an educational intervention versus usual care had greater odds of having their child vaccinated against by the end of the season.	⊗⊗◯◯ Low
Shourie et al. (30) United Kingdom	220 Parents Intervention Group: 143 Control Group: 77	Web based decision	-Detail: Link to join via email before vaccination -Frequency: 1 time	Standard care	-MMR vaccination decision	There was significant difference vaccination decision between the intervention and control groups (p=0.02).	⊗⊗⊗⊗ High
Siddiqi et al. (52) Pakistan	1445 Parents Intervention Group: 964 Control Group: 481	Vaccine reminder and tracker bracelets	-Detail: Each time the child arrives for immunization, a sign is left on the bracelets of vaccination. -Frequency: Up to 12 months before each vaccination	Standard care	-Routine childhood immunization coverage	There was no significant difference immunization coverage between the intervention and control groups (p>0.05).	⊗⊗⊗◯ Moderate
Rand et al. (23) (2017a), United State	391 Parent Intervention Group:191 Control Group: 200	Text message reminder	-Detail: Reminder for each dose that is due (1 week apart) -Frequency: 3 times	Standard care	-HPV vaccination	There was significant difference HPV vaccination between the intervention and control groups (p=0.001).	⊗⊗⊗◯ Moderate

Table 2. Continued

Author, year, country	Participants	Type of intervention	Intervention details	Control group	Outcome criteria	Results	Certainty of the evidence (GRADE)
Rand et al. (23) (2017b), United State	358 Parent Intervention Group:178 Control Group: 180	Phone message reminder	-Detail: Reminder for each dose that is due (1 week apart) -Frequency: 3 times	Standard care	-HPV vaccination	There was no significant difference HPV vaccination between the intervention and control groups (p=0.34).	⊗⊗⊗◯ Moderate
Saitoh et al. (31) Japan	106 Mothers Intervention Group: 70 Control Group: 36	Perinatal immunization education	-Detail: 10 minutes each session -Frequency: 2 times	Routine care	-Vaccination rate	There was significant difference vaccination rate between the intervention and control groups (p=0.005).	⊗⊗⊗⊗ High
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Stockwell et al. (49) United State	7574 Parent Intervention Group: 3790 Control Group: 3784	Text messaging intervention	-Detail: A series of 5 weekly, automated text message influenza vaccine reminders -Frequency: 5 times	Usual care	-Influenza vaccination rate	There was significant difference vaccination rate between the intervention and control groups (p=0.001).	⊗⊗⊗⊗ High
Szilagyi et al. (24) United State	15786 Parents Intervention Group: 7893 Control Group: 7875	Text message reminders	-Detail: Three text messages were sent to the household phone number -Frequency: 3 times	Standard care	-Influenza vaccination rate	There was no significant difference vaccination rate between the intervention and control groups (p=0.70).	⊗⊗◯◯ Low

Table 2. Continued

Author, year, country	Participants	Type of intervention	Intervention details	Control group	Outcome criteria	Results	Certainty of the evidence (GRADE)
Tull et al. (25) Australia	4386 parents Intervention Group: 2860 Control Group: 1526	Short message reminders	-Detail: Reminder 2 days before the vaccination schedule -Frequency: 1 time	Standard procedure	-HPV vaccination rate	There was significant difference HPV vaccination rate between the intervention and control groups (p=0.01).	⊗⊗⊗⊗ High
Winer et al. (53) United State	97 Mothers Intervention Group: 43 Control Group: 54	A mother-daughter dyadic educational intervention	-Detail: Organization of dinner for dyadic education -Frequency: 11 times	Standard procedure	-HPV vaccination rate	There was no significant difference vaccination rate between the intervention and control groups (p=0.42).	⊗⊗◯◯ Low
Yeung et al. (26) China	625 Mothers Intervention Group: 313 Control Group: 312	Text message reminders	-Detail: One week and 1-2 months after the information package was provided -Frequency: 2 times	Standard care	-Influenza vaccine uptake	There was significant difference influenza vaccination rate between the intervention and control groups (p<0.001).	⊗⊗⊗⊗ High

bias again. The results indicated that nine studies be added to avoid publication bias, which would result in a general ES of 0.04 [95% CI (0.04, 0.11); Figure 4].

Discussion

This systematic review and meta-analysis focused on 22 randomized controlled trials to examine the effectiveness of interventions for promoting vaccine acceptance rates. The results indicated that interventions helped reduce vaccine refusal/hesitancy and increase vaccine acceptance rates, albeit insignificantly (Hedge's g=0.10). We believe the difference in sample size, intervention, and outcome across the trials affected the ES of the interventions. Twelve trials showed interventions resulted in increased vaccine acceptance rates (19,20,23,25-27,30,31,48-51), while the remaining 11 found no significant difference in vaccine acceptance rates between the intervention and control groups (21-24,28,29,45-47,52,53).

The results showed that the trials had moderate heterogeneity, which was affected by sample size, intervention, and outcome (54,55). The ANOVA and meta-regression analysis results showed that the difference in sample size, year, and country caused the heterogeneity. The trials with large samples had insignificant ESs, adversely affecting both overall ES and heterogeneity. We suggest researchers employ the right statistical methods and consider missing data and errors when determining the right number of participants for accurate results in terms of ES and effectiveness. Differences in the country also affected the heterogeneity of the trials. Hofstede et al. (56) attributed cultural differences to vertical-collectivism

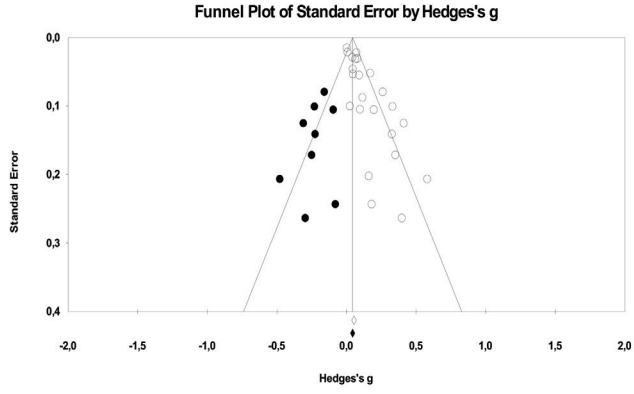

Figure 4. Effect of interventions on vaccine acceptance rates: Funnel plot.

and horizontal-individualism. They argued that horizontally individualistic cultures are the source of heterogeneity because they have loose social ties, resulting in high heterogeneity.

Most trials implemented the intervention of SMS alerts. Their results indicate that texting reminder messages to parents before their scheduled visits for their children's vaccination reduces their vaccine refusal/hesitancy (19,23,26,48,49). However, texting messages sent too early before the scheduled visits or texting multiple messages did not affect vaccine acceptance rates. Face-to-face training, decision-making processes (30,31,50,51), and tech-based interventions (27) were most effective, increasing the overall ES. Given recent advances in technology and low health literacy rates, we believe it is of paramount importance to provide tech-based training in vaccination to the public. However, the training should be short and occasional given that trials of long (28) and frequent training (29,52,53) found no difference in vaccine acceptance rates between the intervention and control groups. If an intervention should be administered more than once, it should be implemented in multiple sessions over an extended period rather than short intervals (50).

The trials had a low or uncertain risk of bias, which was affected by differences in the number of samples and research content. We can state that the trials addressed the risk of methodological thinking and bias and met standards for randomizing and blinding. Most trials generated CONSORT flow charts, which should be used for accurate randomization, low risk of bias, and high research quality (57).

Although the trials reported different results, researchers and practitioners should take interventions as a whole and set standards regarding the frequency, duration, and application of interventions tailored to reduce vaccine refusal/hesitancy and increase vaccine acceptance rates. Such interventions should be short and occasional with tech-based interventions administered face to face right before visits for vaccinations. Researchers should be more careful when determining the right sample size. Future studies should consider these suggestions when it comes to designing interventions tailored to reduce parental vaccine refusal/hesitancy rates.

Strengths and Limitations

This research has several strengths. First, it is a comprehensive systematic review and meta-analysis on vaccine hesitancy in children. Second, a protocol based on Cochrane principles was followed. Another strength was that databases were scrupulously scanned and the Cochrane tools manual was followed to minimize bias. Further, the review was conducted by two authors independent of screenings and bias controls.

Concerning limitations, gray literature, such as conference papers, research, and committee reports, was not included. We wanted to keep the evidence to the highest level. Gray literature can be added to future studies, considering the risks of lowering the level of evidence.

Conclusion

This systematic review and meta-analysis focused on 22 randomized controlled trials to determine the effect of interventions on the reduction of parental vaccine refusal/hesitancy rates. The results show that interventions can be used to persuade parents to get their children vaccinated. Our results will be of considerable value to physicians, nurses, academics, primary healthcare staff, and the public. Overall, the results indicate that interventions should be short tech-based interventions administered face to face. We believe that the results can help primary healthcare staff develop new interventions to reduce parental vaccine refusal/hesitancy rates and provide high-quality care. The results introduce Level-A evidence that can pave the way for further research on the topic. We recommend that more researchers undertake more detailed and specific national and international trials concerning the effectiveness of interventions for promoting parental vaccine acceptance rates.

Ethics

Conflict of Interest: No conflict of interest was declared by the authors.

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