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Strategies to improve measles-mumps-rubella vaccine coverage in developed countries: a Systematic Review

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ABSTRACT

Background: Concerns regarding the measles-mumps-rubella (MMR) vaccine's safety have led some parents and communities in developed countries to choose not to vaccinate their children. This decrease in vaccination has led to various measles outbreaks, and while determining factors behind poor adherence to this vaccine have been described previously, no study has systematically reviewed all strategies that attempted to improve MMR vaccination coverage in developed countries and their effectiveness.

Objective: To systematically review and analyze which strategies have been effective when aiming to improve either the uptake or the intention to vaccinate with the MMR vaccine in developed countries.

Methods: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. We searched PubMed and Embase, from the year of 2000 until 7th August 2017 and two reviewers independently screened and reached consensus regarding included studies. Inclusion criteria were as follows: population consisted of parents of children <18 years old, or children <18 years old; intervention was any strategy aiming to improve either outcome or vaccine intention for the MMR vaccine; control was usual care, and two outcomes were assessed: vaccine uptake and vaccination intention. Heterogeneity between studies was too high for a quantitative analysis to be conducted.

Results: Of 280 articles identified, 7 were included; risk of bias was generally high (only two studies were low risk, and another unclear). Regarding vaccination uptake, one randomized control trial (RCT) showed that text-message reminders of vaccination

schedule and appointment were effective for participants without a baseline appointment; in another study, the use of a decision-aid was more effective than the use of a leaflet, and the leaflet was less effective than usual care. Regarding vaccination intention, we found one study where both untailored and tailored interventions resulted into a slight but not statistically significant difference in vaccination intention. Another RCT concluded that correcting misinformation regarding MMR vaccine and autism resulted in lower vaccine intentions in children without a baseline appointment, and showing benefits to the society rather than directly to the child, presenting risks of not getting the vaccine, and self-affirmation exercises were not effective strategies.

Conclusions: Emphasizing benefits to the child, as opposed to only the society, seemed to improve intention to vaccinate. Text-message reminders might be useful among children without scheduled appointments to improve vaccination uptake. Correcting misinformation in parents with a baseline negative attitude regarding vaccination decreased intent to vaccinate. Strategies showing effectiveness when conducted in adults deciding on a subject that affects themselves only should be tested before being applied to parents deciding about their child, as the results may not be replicated.

Keywords: measles-mumps-rubella vaccine; MMR; strategies; uptake; intention; parents.

1. INTRODUCTION

Vaccines are perhaps the greatest medical achievement of modern civilization. Ever since their discovery by Edward Jenner with the vaccine for smallpox, there has been a huge decrease in morbidity and mortality caused by vaccine preventable diseases (VPDs)[1,2], such as measles, diphtheria, mumps, pertussis, rubella, among others. However, the measles-mumps-rubella (MMR) vaccine has attracted much attention in recent years, mostly owing to now discredited claims about its safety[3] that circulate as encouragement and ammunition among anti-vaccination activists and Web sites. These anti-vaccination campaigns have caused parents to question their decisions regarding their child's immunization, which results in suboptimal compliance to the MMR vaccine.

In 2017 in Europe, there was a 4-fold increase in measles cases compared to previous year[4], mainly due to a decline in routine immunization schedules and low coverage among marginalized groups. This is a major health problem: even minor declines (5%) in MMR vaccination coverage can result in a several-fold increase in measles cases for children[5]. Therefore, although the high rate of childhood vaccination coverage in most developed countries indicates that vaccination remains a widely accepted public health measure, recent outbreaks of VPDs in several parts of the developed world have been linked mainly to under-vaccinated or non-vaccinated communities[6].

While developing countries were the biggest challenge to increase vaccine coverage before, the anti-vaccination movement and misinformation that result into vaccine hesitancy now occur mostly in developed countries[7]. Perhaps this happens because immunization programs are generally effective in developed countries, therefore parents tend to perceive risks of vaccinating as higher than those of contracting VPDs.

The determining factors behind this vaccine hesitancy are already well documented and extensively investigated[8–10], such as misleading information coming from the Internet, having a large number of children, the targeted child being a second child, and being single, unemployed or self-employed parents.

However, to the best of our knowledge, no previous review has embraced the problem at hand: which strategies aiming to improve MMR vaccine coverage have been studied in developed countries, and which were proven effective? Thus, we performed a systematic review of all available randomized control trials (RCTs) describing interventions performed either in parents or children, aiming to improve MMR vaccine uptake and intention in developed countries, when compared to usual care.

Systematic review registration number in PROSPERO: CRD42018088970

2. METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines for systematic reviews and meta-analysis (Appendix 1 - PRISMA 2009 Checklist).

2.1 Eligibility criteria

In the present review, we included randomized control trials that met the following inclusion criteria: (1) *design* – randomized control trials conducted in developed countries; (2) *population* – parents/caretakers of children under 18 years old, or children under 18 years old; (3) *intervention* – any strategies aiming to improve either the uptake or intention to vaccinate with the MMR vaccine; (4) *control* – usual care; (5) *predefined outcomes* – MMR vaccination uptake (primary) and intention (secondary). Developed countries were defined as those present in the World Economic Situation and Prospects (WESP) report from 2014[11].

2.2 Information sources and search strategy

Comprehensive systematic online searches were conducted using the following electronic databases and a combination of keywords: the PubMed and Embase databases, from inception to 7th August 2017 to identify potentially relevant studies.

The search strategy for PubMed was: ("Health Promotion"[MAJR]) AND "Measles-Mumps-Rubella Vaccine"[MAJR] OR "Measles-Mumps-Rubella Vaccine"[MAJR]) AND "Parents"[MeSH Terms]. For Embase, the search strategy was: Measles-Mumps-Rubella Vaccine AND (parents OR promotion OR education).

Our research was limited to humans and studies published from the year of 2000 onward, in an attempt to include recent strategies developed after Wakefield's

controversial study[3] was published. The search was restricted to articles written in either English, Portuguese, Spanish or French; no other limits were placed during this phase of the study.

2.3 Data extraction and quality assessment

Two reviewers (LB and IR) independently screened the titles and abstracts identified in the literature search to assess which did not comply with the inclusion criteria, and the union of their selections was retrieved. The researchers then proceeded to review the full-texts of the remaining studies and, after an independent analysis, attempted to reach consensus regarding eligibility. Divergent opinions regarding study inclusion were settled by discussion and consensus was obtained, with no need for the dispute to be settled by a third party.

Quality of included studies was assessed by the same two reviewers using the risk of bias tool provided by the Cochrane Collaboration[12]; this tool assigns a value of high, low or unclear to the following items: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; other sources of bias. Any dispute was resolved through consensus. The level of risk for each study was then classified as *low* (all key domains presenting low risk), *unclear* (one or more key domains with unclear risk), and *high* (high risk for one or more key domains).

Data and records management throughout the review were conducted in Covidence[13], the standard production platform for Cochrane reviews selected by Cochrane.

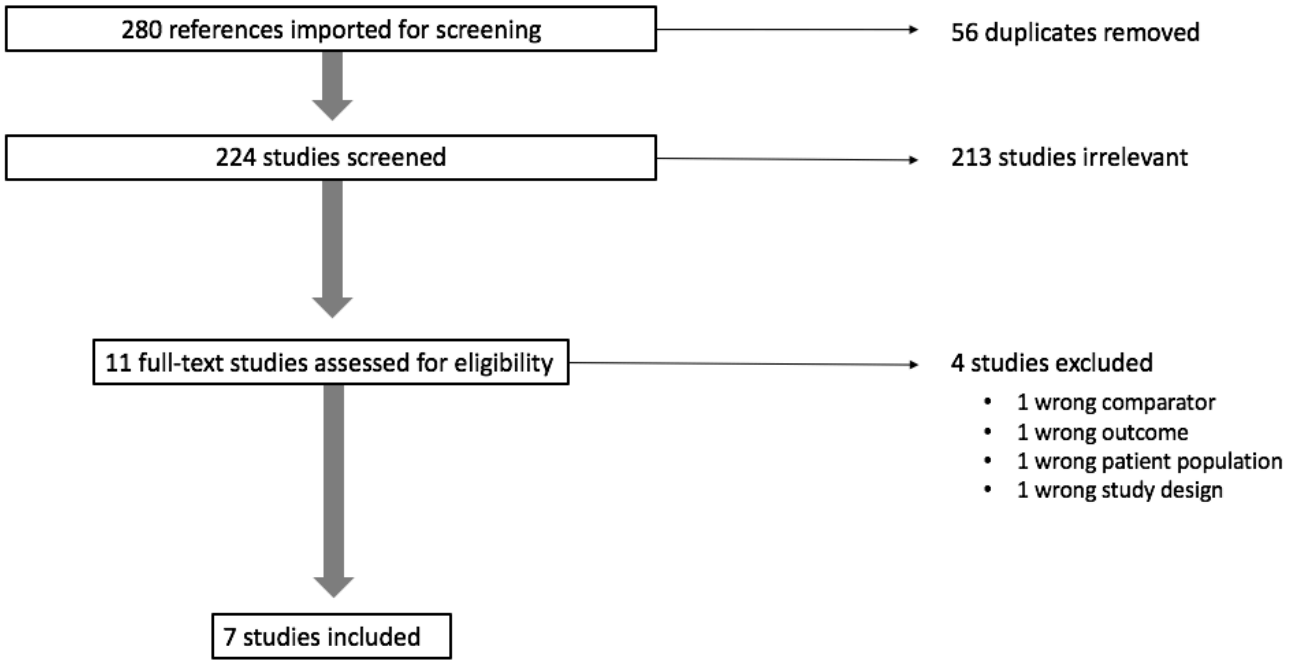
2.4 Outcomes and statistical analysis

The primary outcome assessed was vaccine uptake; the secondary outcome was vaccine intention. Outcomes were described narratively, as due to clinical diversity and disparity of methodology, it was not possible to perform a quantitative analysis (meta-analysis).

3. RESULTS

3.1 Study selection

As presented in **Flowchart 1**, the initial search carried out 280 references (100 in Embase and 180 in PubMed electronic databases). Of these, 56 were found to be duplicates and were therefore excluded, and 213 were found irrelevant based on review of title and abstract. The remaining studies were read in full and assessed for eligibility, and 4 were excluded due to wrong outcome[14], population[15], study design[16], and comparator[17]. In the end, 7 studies were included (one of which, Reavis et al[18], involving two different interventions).



Flowchart 1 – Literature search and selection process for studies included

3.2 Study characteristics and quality

The main characteristics and outcomes of interest of the included studies were extracted for the purpose of this systematic review, and are summarized in **Table 1**.

Authors	Year	Country	Design	Number of participants	Population (inclusion criteria)	Setting	Intervention	Control	Outcomes measured
Hofstetter et al	2015	United States of America	RCT	2054	Parents with a child aged 9.5-10.5 months who had had a participating clinic visit in the past 6 months and had a cellular phone number listed in the hospital records	Pediatric practices in an ambulatory care network affiliated with a large academic medical center	Two interventions: - up to three text message reminders were sent to schedule the one-year appointment plus appointment text message reminder - an appointment text message reminder only	Usual care (routine automated telephone appointment reminder provided directly from the clinic network)	Child's MMR vaccination uptake by 13 months of age
Porter-Jones et al	2008	United Kingdom (Wales)	RCT	974	All children being seen by their Health Visitor at the scheduled 8-month assessment	health visitor visit for the routine 8-month assessment	Usual care + a teddy bear wearing a T-shirt displaying a website address and telephone number providing information about MMR	Usual care	Child's MMR vaccination uptake
Shourie et al	2010	United Kingdom (England)	RCT	203	First-time parents who had an email address and sufficient English language skills to participate with a child aged 3–12 months being offered the first dose of the MMR	General practice	Two interventions: - MMR decision aid plus usual practice; - MMR leaflet plus usual practice	Usual care	First dose MMR vaccine uptake
Nyhan et al	2011	United States of America	RCT	1751	Parents (age 18 years and older), with one or more children aged 17 years or younger	Online panel	Four interventions: - correcting misinformation, - presenting information on disease risks, - using dramatic narratives - displaying visuals to make those risks more salient or accessible.	Usual care (control message)	Intention to vaccinate a future child
Hendrix et al	2012	United States of America	RCT	802	Parents (age 18 years and older) with a child (<12 months)	Online recruitment	Three interventions: Control + additional information either emphasizing the benefits: - to the child receiving the vaccine - to other members of society - to both the child and society members	Usual care (standard information derived directly from the MMR VIRS)	Intention to vaccinate
Gowda et al	2011	United States of America	RCT	77	Parents (age 18 years and older) of children < 6 years old, screened as hesitant to vaccinate against MMR and able to read/converse in English	Pediatric primary care clinics affiliated with the University Health System or via the University's clinical trial recruitment website	Tailored web pages (image, content, experimential and name tailoring) based on each parent's information from a baseline survey	Usual care (untailored information derived directly from the MMR VIS)	Change in intention to vaccinate child
Reavis et al (Study 1)	2014	United States of America	RCT	585	Guardians/parents with at least one child under the age of 18 living in the household	Online recruitment	Three interventions: - information from the CDC refuting the link between autism and the MMR vaccine ("autism correction") + self-affirmation exercise - "autism correction" + standard values exercise ("values control") - Passage about bird feeding ("control passage") + "self affirmation"	Usual care ("control passage" + "values control")	Intention to vaccinate a future child
Reavis et al (Study 2)	2015	United States of America	RCT	576	Guardians/parents with at least one child under the age of 18 living in the household	Online recruitment	Self-affirmation exercise	Usual care (Values control)	Intention to vaccinate a future child

Table 1 – summary of study's characteristics

All included studies were RCTs published between 2008 and 2017, with five being conducted in the United States and the remaining two conducted in the United Kingdom. Sample sizes ranged from 77 to 2054 participants, and in every study population consisted of parents or caretakers, except for one[19], where the sample consisted of children. Two of our included studies were conducted in parents with children 17 years or younger, and the remaining five were conducted in children whose age was comprehended between the ideal range for MMR vaccine doses in their countries.

Various types of interventions were employed, including parents' education, self-affirmation exercises, and reminders. However, in all of them the control group consisted of usual care (either by administration of a placebo intervention, or by actual conventional management). Three RCTs reported MMR vaccine uptake as one of the measured outcomes, and four articles (one of them containing two different studies[18]) measured vaccination intention.

Vaccine uptake was reported in all three studies as vaccination uptake rate. The tool used to evaluate vaccine intention, on the other hand, was heterogeneous among studies, with two studies assessing intention in a 6-point scale, and two studies using an 11-point scale; however, even among studies using the same assessment tool, results were displayed in varied ways: either as calculated odds ratio, as mean scores in the chosen scale, or as mean differences between pre- and post-intervention intention.

The results of quality assessment, performed such as described in Methods, are presented in **Table 2 and 3**. In general, risk of bias for studies that assessed vaccine uptake was high, with two studies out of three with one or more key domains considered 'high risk'. For studies whose outcome was vaccine intention, risk of bias was moderately high, with two studies presenting with high overall risk, two presenting with low risk, and one with unclear risk of bias.

Authors	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall level of risk
Hofstetter et al	+	+	+	+	+	+	+	+
Porter-Jones et al	-	-	-	?	+	+	+	-
Shourie et al	+	+	-	?	-	-	+	-

Table 2 – Risk of bias summary for studies whose outcome was "vaccination uptake": review authors' judgements about each risk-of-bias item. Underlined domains refer to key domains used to assess overall level of risk (see Methods).

Authors	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall level of risk
Nyhan et al	+	+	+	?	?	+	+	?
Hendrix et al	-	?	?	?	+	+	+	-
Gowda et al	-	+	+	?	+	+	+	-
Reavis et al (study 1)	+	+	+	?	+	+	-	+
Reavis et al (study 2)	+	+	+	?	+	+	-	+

Table 3 – Risk of bias summary for studies whose outcome was "vaccination intention": review authors' judgements about each risk-of-bias item. Underlined domains refer to key domains used to assess overall level of risk (see Methods).

3.3 Results of studies

3.3.1 Primary outcome – MMR vaccination uptake

Three authors reported MMR vaccination uptake as a measured outcome[19–21]. The population in two studies consisted of parents/caretakers, and in another it consisted of children (although the child's immunization status would be defined by their parents). However, the interventions and approach to measuring the reported outcome varied among different studies. General results of these studies are summarized in **Table 4**.

In Hofstetter et al[20], text messaging was the elected method to attempt to improve vaccination rate, with one group receiving up to three text message reminders to schedule an appointment plus an appointment text message reminder, another being allocated only the appointment text message reminder, and a control group (where usual care included an automated phone appointment reminder provided from the clinic itself). Results were presented as vaccination rates between 361 days and 13 months of age for each arm, also calculating the relative risk ratio between interventions. There was no significant difference in MMR vaccination by 13 months between arms (with a mean uptake of 62.2%, p=0.3); however, it was also concluded that among children without a baseline appointment (meaning, children without a one-year preventive care visit scheduled before randomization), those in the arm receiving up to three text message reminders to schedule an appointment plus an appointment text reminder were more likely to receive the MMR vaccine than those in other arms. Overall risk of bias for this study was considered low.

In another study (Porter Jones et al[19]), presenting high risk of bias, vaccination uptake was assessed in Flintshire, Wales, where the uptake rate of all childhood immunization was the lowest in Wales. After receiving either standard MMR information alone (considered usual care) or after receiving at the 8-month assessment a teddy bear wearing a T-shirt displaying a website address and telephone number providing

information concerning the vaccine, vaccination uptake was recorded, as was the number of hits to the website address and calls made to the telephone number. There was no significant difference in uptake in children who received the teddy bear (vaccination rate of 87.3%, with a 95% confidence interval (CI) of 84.5-90.1%) and those who did not (88%, 95% CI 84.8-91%), with p=0.744. First-born children had significantly higher uptake rates (90.2%, 95% CI 87.3-93.2%) than those who were not first-born (85.8%, 95% CI 82.9-88.6%) (p=0.041). The total number of hits to the website was 62 (11%, if every hit is regarded as one parent from the intervention arm), and there were no calls to the listed telephone number.

Uptake was also reported by Shourie et al[21], where the elected strategy was the use of a decision-aid, which consists of a different type of information resource that provides information about the benefits and risks of either having *or* not having the MMR vaccine. One intervention arm was randomized to receive a web-link for the MMR decision aid while continuing to receive usual care, and another was allocated to receive a leaflet issued by Health Scotland that answered frequently asked questions about the MMR vaccine; the control arm received usual practice only. Uptake data for 203 children was then collected from general practice records when the child was aged 15 months, showing an uptake rate of 100% for the decision aid arm, 91% for the leaflet and 99% for usual care (control). There was a significant difference in uptake between the leaflet and control arms (8% difference, with a 95% CI of 1-15%, and p=0.04), and between the decision aid and leaflet arms (9% difference, with a 95% CI of 3-16%, and p=0.05), but not between the decision aid and control groups (1% difference, with a 95% CI of -1-4%, with p=0.99). This study presented high risk of bias.

Authors	Assessment method	Number of participants	Intervention	Effects of intervention in MMR vaccine uptake	Authors' conclusions
Hofstetter et al	Vaccination uptake rate between 361 days and 13 months of age, with RRR (95% CI)	2054	Scheduling + appointment text message reminders (all subjects; no baseline appointment)	All subjects - 64.6% (n=686) No baseline appointment - 61.1%	There was no significant difference in MMR vaccination by 13 months between arms (mean uptake = 62.2%, p-value = 0.30). Among subjects without a baseline appointment, those in the scheduling + appointment text message reminders were more likely to receive MMR vaccination by 13 months than those in other arms.
			Appointment text message reminders*	All subjects - 60.9% (n=686); RRR = 1.06 (0.98 - 1.15)* No baseline appointment - 54.9%; RRR = 1.11 (1.00 - 1.24)	
			Usual care (control)	All subjects - 61.1% (n=682); RRR = 1.06 (0.97 - 1.15) No baseline appointment - 55.2%; RRR = 1.11 (1.00 - 1.23)	
Porter-Jones et al	Vaccination uptake rate (95% CI)	974	Usual care + teddy bear	87.3% (84.5 - 90.1) (n=542)	There was no significant difference in uptake between arms (p-value = 0.074)
			Usual care (control)	88% (84.8 - 91) (n=432)	
Shourie et al	Vaccination uptake rate at 15 months of age	203	Decision aid + usual care	100% (n=48)	There is a statistically significant difference (8%, 95% CI: 1-15%; p-value = 0.04) in uptake between the leaflet and control arms, and there is a statistically significant difference (9%, 95% CI: 3-16%; p-value = 0.05) between the decision aid and leaflet arms; but not between the decision aid and the control arms (1%, 95% CI: -1 - 4%; p-value = 0.99)
			Leaflet + usual care	91% (n=85)	
			Usual care (control)	99% (n=70)	

Table 4 – Summarized results of studies whose outcome was MMR vaccine uptake.
P-values were statistically significant when ≤ 0.05; RRR – relative risk ratio; CI – confidence interval

3.3.2 Secondary outcome – MMR vaccination intention

Intention to vaccinate was one outcome reported in four studies[18,22–24], but unlike our designed primary outcome, it was conducted and described differently in each RCT. General results of these studies are summarized in **Table 5**.

In Nyhan et al[24], the authors assessed the effectiveness of four different interventions in the intent to vaccinate: correcting misinformation about autism (refuting the link between autism and the MMR vaccine), presenting information on disease risks (symptoms and adverse events associated with MMR), use of a dramatic narrative (mother describing her child's hospitalization following infection with measles), or the display of visuals to render those risks more accessible (children affected by each disease). The first three interventions mentioned above were adapted word by word from the CDC materials; the control group read a passage on the costs and benefits of bird feeding, considered usual care as it did not interfere with the standard management the sample would otherwise receive. Intention was assessed using a 6-point scale, and the results were presented as adjusted odd ratios (aORs) with 95% CI, describing the effects of each intervention for the full sample, and then separated by baseline vaccine attitude group. Among the full sample, correcting misinformation about autism resulted in lower vaccination intentions (aORs = 0.52; 95% CI of 0.32-0.84). When analyzing intentions between separate vaccine attitude groups (previously defined in a baseline survey), the authors observed that the negative effects of that intervention ('correcting misinformation') were mainly evident in individuals with the least favorable vaccine attitudes (aOR = 0.36, 95% CI 0.20-0.64), and the positive effects were mainly concentrated on those with more favorable attitudes (although not statistically significant). The difference in effects of this intervention between the least and most favorable groups was significant (aOR=8.27, 95% CI 1.19-57.49). None of the other

interventions significantly increased intent to vaccinate, nor was there any statistically significant difference between vaccine attitude groups. The risk of bias was considered unclear in one or more key domains.

Hendrix et al[22] conducted a randomized clinical trial with four arms, where vaccination intention was compared after providing each arm with a different message. The control arm was given only the MMR Vaccine Intervention Statement (VIS), considered standard information from the CDC and therefore usual care; the other three arms received additional information emphasizing the vaccine's benefits either directly to the child, to the child and society, or only to society. Intention was measured in an 11-point scale, and the results were presented on a scale ranging from 0 to 100, as mean and standard deviation. When compared to the control arm (mean intention 86.3, with standard deviation 21), it was concluded that intention to vaccinate was significantly higher when emphasizing benefits to the child directly (91.6, standard deviation of 6.9; p=0.01) or to the child and society (90.8, standard deviation of 18.2; p=0.03), but not when highlighting benefits to society only (mean intention 86.4, standard deviation of 24.9; p = 0.97). Risk of bias was considered high.

Intent to vaccinate was also described by Gowda et al[23], in a RCT presenting high-risk of bias, where intention was assessed before and after either a tailored information (using the information provided from the baseline-survey) or usual care (untailored information derived directly from the MMR VIS - control group), and difference between them was calculated. Intention was measured using an 11-point scale but two analytic approaches: categorization of participants in mutually exclusive vaccine intention categories and then assessing the proportion of parents changing vaccine intention categories; and a second approach where the results were appraised as a continuous measure, and the difference in intention pre- and post-intervention was calculated. This

latest approach is the chosen one to be reviewed in our work, as previous studies used a similar continuous scale (and not the above mentioned categorical intentional change), therefore easing the comparison between investigations. The authors concluded that being exposed to both untailored or tailored education ensued a statistically significant increase in intent to vaccinate (from 34% to 52%) in subjects with a positive baseline intention. The difference in intention was larger among the tailored information (mean difference 1.08, standard deviation 1.68) compared to the untailored information group (mean difference 0.49, standard deviation 2.39), however that difference was not statistically significant (p=0.22). When analyzing results by baseline intention, differences between categories were found not to be statistically significant either.

In Reavis et al[18], two studies investigated vaccine intention, measured in a 6-point scale, after a self-affirmation exercise. Self-affirmation consists of expressing one's core values in the hope that it will reduce the impact of a threat to their beliefs by focusing on and affirming their competence in some other area. In Study 1, participants were first randomly assigned to a self-affirmation exercise ("self-affirmation"), or a standard values affirmation procedure ("values control"); then, they read one of two reading passages: either information derived from the CDC refuting the link between MMR vaccine and autism ("autism correction"), or a passage about bird-feeding ("control passage"). Therefore, we have a total of four conditions for which mean vaccine intention was described: self-affirmation exercise and autism correction (mean intention 4.98, standard deviation (SD) 1.38); values control and autism correction (mean intention 5.12, SD 1.33); control passage and self-affirmation (mean intention 5.09, SD 1.36); and the control arm, defined as control passage and values control (mean intention 5.05, SD 1.48). There was no significant main effect of passage condition (autism correction or control passage) or affirmation condition (self-affirmation or values control) on vaccination

intention. The authors analyzed also the interaction between both conditions and pre-intervention vaccine attitudes (measured using 10 questions from Freed et al[25] on a 5-point scale), concluding that for participants with initially positive vaccine attitudes, there was no statistically significant difference between conditions; however, for participants with baseline negative vaccine attitudes, values affirmation decreased intent to vaccinate when combined with the control passage condition, and had no effect in the presence of it. In the face of these findings, the authors conducted another study (Study 2), to attempt to reproduce the previous result: that with no correcting information, self-affirmation exercises might decrease intent to vaccinate when compared with baseline intentions. Consequently, a new sample was assembled, and affirmation conditions ("self-affirmation" and "values control") were randomly allocated to participants, this time without the "autism correction" or "control passage" arms; intention was assessed one more time, and mean intention for self-affirmation arms (5.11, SD 1.50) and values control arm (5.19, SD 1.36) were found, as in Study 1, to have no main effect on intention to vaccinate; however, unlike Study 1, there was no interaction between affirmation condition and baseline vaccine attitudes. Both interventions presented low risk of bias.

Authors	Assessment method	Number of participants	Intervention	Effects of intervention in MMR vaccine intention	Authors' conclusions
Nyhan et al	6-point scale and calculated Odds Ratio (95% CI)	1751	Misinformation correction	0.52 (0.32 – 0.84), p<0.05 (n not reported)	"Misinformation correction" resulted in parents reporting they would be less likely to vaccinate, specially among parents with negative vaccine atitudes. No intervention significantly increased intent to vaccinate
			Disease risks	0.98 (0.54 – 1.77) (n not reported)	
			Disease narrative	1.09 (0.62 – 1.94) (n not reported)	
			Disease visuals	1.29 (0.73-2.26) (n not reported)	
			Control	(n not reported)	
Hendrix et al	11-point scale, with results presented on a scale ranging from 0-100, as mean and SD	802	VIS only (control arm)	mean = 86.3, SD = 21 (n=200)	Interventions mentioning the vaccine's benefits to the child (P=0.01) and to the child + society (P=0.03) resulted in higher vaccination intentions when compared to the control arm; emphasizing the vaccine's benefits to society did not produce greater vaccine intention
			VIS + benefits to child	mean = 91.6, SD = 16.9 (P = 0.01) (n=201)	
			VIS + benefits to child and society members	mean = 90.8, SD = 18.2 (P = 0.03) (n=200)	
			VIS + benefits to society	mean = 86.4, SD = 24.9 (P = 0.97) (n=201)	
Gowda et al	11-point scale; Mean difference between post-intervention and baseline vaccination intention scores presented in a scale from 1-10	77	Tailored information	mean difference = 1.08, SD = 1.68 (P = 0.22) (n=36)	Larger difference in vaccine intention reported among the tailored versus the untailored group, but the result was not statistically significant, nor was there any significant change in intention in parents stratified by baseline intention
			Untailored information (control arm)	mean difference = 0.49, SD = 2.39 (P = 0.22) (n=41)	
Reavis et al (Study 1)	6-point scale, presented as mean and SD	585	Autism correction + self-affirmation	mean = 4.98, SD = 1.38 (n=156)	No significant main effect of reading passage or affirmation condition in the intent to vaccinate; for participants with baseline negative vaccine attitudes, self affirmation decreased intent to vaccinate when combined with the control passage condition
			Autism correction + Values control	mean = 5.12, SD = 1.33 (n=139)	
			Control passage + self-affirmation	mean = 5.09, SD = 1.36 (n=138)	
			Control passage + values control (control arm)	mean = 5.05, SD = 1.48 (n=152)	
Reavis et al (Study 2)	6-point scale, presented as mean and SD	576	Self-affirmation	mean = 5.11 SD = 1.50 (n not reported)	No significant main effect of affirmation condition on intent to vaccinate
			Values control	mean = 5.19, SD = 1.36 (n not reported)	

Table 5 – Summarized results of studies whose outcome was 'MMR vaccine intention'.
P-values ≤ 0.05 were statistically significant; aORs – adjusted Odds Ratio; CI – confidence interval; SD – standard deviation; VIS – Vaccine Information Sheet

4. DISCUSSION

Despite heterogeneity among included studies concerning strategies to improve MMR vaccination coverage, this systematic review allowed us to conduct a qualitative analysis of all strategies that attempted to improve either vaccination uptake or intention, and conclude which were effective. We also became aware of the fact that out of 8 studies, 6 resorted to strategies that revolved around parents' education, with one study employing reminding strategies, and yet another experimenting with a self-affirmation exercise.

Primary outcome – uptake

Among the three included studies that addressed this outcome, the strategies used were all different: use of a decision aid[21], teddy bears with information about the vaccine[19] (both strategies relying upon parents' education) and text message reminders[20].

In one study's[21] effectiveness assessment of a decision aid, the authors concluded that among all arms (decision aid, leaflet, or usual care) uptake was very high, with the decision-aid intervention accounting for 100% vaccination rate. However, it is curious how the uptake rate in the control arm was so high (99%), and not so different from the uptake registered by the decision aid arm (100%). To explain this finding, the authors hypothesize that although the uptake was similar among arms, in the intervention arms parents made *informed* decisions about their child's vaccination, while in the control arm parents may have adopted a stance of "unquestionable acceptance". This seems to further dissipate some concerns that, by making parents deliberate about their decision when confronted with both risks and benefits of having *and* not having the MMR vaccine, their motivation to vaccinate might be affected in a negative way. Thus, this RCT suggests informed decision making, particularly with decision aid resources, doesn't seem to decrease vaccination uptake when compared to usual care.

In the investigation conducted by Porter-Jones et al[19], teddy bears with a phone number or web address providing information about the MMR vaccine did not improve the uptake of the vaccine. The authors attempt to explain this finding by hypothesizing that the teddy bears may have been given to children too far in advance of the expected first dose for the vaccine (12-13 months), or that perhaps the chosen teddy bear was not considered sufficiently charismatic.

Text message reminders, used in another study by Hofstetter et al[20], resulted in higher MMR vaccine uptake rate among children without a scheduled one-year preventive care visit before the start of the study. It may be that this strategy is beneficial especially when targeted towards this high-risk group (children without a scheduled one-year appointment), which supports other studies[26] that consider text-messaging an effective reminding method, at least as much as the telephone.

Secondary outcome – intention

Among the five included RCTs[18,22–24] that studied the effect of various interventions in vaccination intention, the strategies employed were different, however the common ground between them was that they focused on parents' education, except for one, that consisted of a self-affirmation exercise (study 2 by Reavis[18]).

Message framing was the strategy used by one study[22], and the results show that emphasizing benefits of the MMR vaccine to the society resulted into lower intent to vaccinate, unlike emphasizing benefits to the child only or the child and society. This is a singular finding, as it does not comply with other studies conducted on adults' vaccine intentions for themselves[27,28]. There has been some discussion surrounding this fact, with general consensus suggesting that parents or caretakers do not make the same decisions for their child that they would make for themselves, possibly because of a parental focus

on the child's wellbeing that overcomes concerns on general population's health they might have had for themselves.

This effect is somewhat replicated in another included study[18]. Here, the chosen method to improve vaccination intention was the use of self-affirmation strategies, which according to previous studies seemed to increase the acceptance of health messages (on realms such as smoking or vegetable consumption) by reaffirming a person's sense of self. However, in this study they showed no significant effect on changing the intention to vaccinate. When discussing this finding, the authors hypothesized that while self-affirmation studies have been conducted in adults with positive results, no study had ever assessed its intervention when deciding for one's child. Therefore, this suggests that these two strategies (message framing and self-affirmation), while effective when making a decision for oneself, may not be as effective when deciding on behalf of their child.

One other explanation for the self-affirmation exercise to not have had any change in vaccine intention (and even demonstrate lower intentions for participants with negative baseline intention) is that parents with negative vaccination attitudes may have deeply ingrained beliefs that vaccines are harmful, while it is unlikely participants in these previous studies may have had such strong beliefs regarding subjects like smoking (e.g. strongly believing smoking is actually good for your health). Thus, the authors conjecture that it may be that self-affirmation messages will actually strengthen such negative attitudes.

Regarding other interventions that actually *decreased* vaccination intention in subjects with baseline negative attitudes, Nyhan et al[24] describe a similar phenomenon. After allocating interventions that underline the risks of not vaccinating against MMR, the authors concluded that correcting information about the MMR vaccine and autism actually resulted in *lower* vaccination intentions, and this negative effect was more

evident in groups whose baseline vaccine attitude was negative. This may happen because when faced with correcting information about their negative beliefs regarding the vaccine, it is possible that participants recollect other worries they may have to attempt to justify their belief. This finding, although seemingly striking, is supported by other studies[29] that report the same result. In addition, the authors discuss that basing an intervention on showing the risks of not taking the vaccine, rather than the benefits of taking it, do not appear effective, as none of the other interventions increased intent to vaccinate. This supports other evidence[30] that states that health interventions that induce fear are less effective on changing beliefs and attitudes.

In Gowda et al[23], both tailored and untailored information seem to slightly improve vaccination intention, with a larger difference in the tailored group (although not statistically significant), which may signify that vaccine hesitancy may come from a lack of information in general to make a decision.

Limitations

As is the case for any systematic-review, ours also presents with some limitations. First, overall risk of bias was high in four studies, conditioned by high risk of bias in domains considered by this review's authors as important towards determining the intervention's outcome, such as sequence generation, in three[19,22,23] out of four studies presenting with overall high risk.

Secondly, although the studies have the same outcome (either vaccination uptake or vaccination intention), the strategies used were different among them, making it difficult to compare them on the same ground and to perform a quantitative analysis. Furthermore, population varied among studies regarding ethnicity, social status, annual

income, degree of education, among others, but establishing a comparison, although desirable, could not happen, as not all studies reported the same population data.

Thirdly, intention was one of two outcomes analyzed, and although it is considered a relatively strong predictor of vaccine uptake[31], it is not certain whether parents followed through with it by vaccinating their children or not. Besides, for both analyzed outcomes, not all included studies were performed in parents whose children's age was necessarily within range for vaccination (either first or second MMR-vaccine dose), with two studies[18,24] being conducted in parents of children 17 years or younger, and thus possibly out of their countries' age range for vaccination. This might interfere with parents' attitudes towards vaccinations, as making decisions on a subject might be different when that decision still has the power to affect your child's vaccination status.

Finally, seen as this systematic review attempted to provide evidence on effective strategies to combat vaccine hesitancy and anti-vaccination groups, ideally all strategies should have been conducted in populations previously screened as unsure or with negative attitudes towards vaccination, and this did not happen in all studies, as restricting our inclusion criteria would further reduce the number of studies included.

5. CONCLUSIONS

Regarding strategies that were effective on MMR vaccination *uptake*, informed decision making through the use of decision aids resulted in high vaccination uptakes, but not statistically significant when compared to control. Using text-message reminders appeared to improve vaccine uptake among children who did not have a one-year appointment scheduled.

Intention to vaccinate was higher with strategies reporting the benefits to the child directly (and not to the society only) and with strategies utilizing personalized or tailored intervention, although this last finding was not statistically significant.

Strategies showing effectiveness when conducted in adults deciding on a matter that affects only themselves should be previously tested to confirm it replicates the effect on parents deciding for their child.

Fear inducing approaches emphasizing risks of not vaccinating rather than benefits of vaccinating do not seem to be effective either in changing vaccination intention. Also, in a population with baseline negative vaccination intentions, correcting information might be misinterpreted or lead participants to attempt to defend their anti-vaccination attitudes by bringing to mind other concerns, further decreasing intent to vaccinate.

Thus, we conclude by noting that not all strategies focusing on parents' education were effective, although that was the type of strategy used by most interventions included in this systematic review, and further studies are needed to compare the effectiveness of a same strategy in various populations, in order to allow a more homogenous analysis of the data.

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APPENDIX 1 - PRISMA 2009 Checklist; *Strategies to improve MMR vaccine coverage in developed countries: A Systematic Review*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-23
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23-24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

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