Development and Evaluation of a Clinical Practice Guideline to Promote an Evidence-based Approach to Vaccine Hesitancy in Primary Care

DEVELOPMENT AND EVALUATION OF A CLINICAL PRACTICE GUIDELINE TO PROMOTE AN EVIDENCE-BASED APPROACH TO VACCINE HESITANCY IN PRIMARY CARE

by

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As members of the DNP Project Committee, we certify that we have read the DNP project prepared by Jocelyn R. Smith entitled "Development and Evaluation of a Clinical Practice Guideline to Promote an Evidence-Based Approach to Vaccine Hesitancy in Primary Care" and recommend that it be accepted as fulfilling the DNP project requirement for the Degree of Doctor of Nursing Practice.

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Final approval and acceptance of this DNP project is contingent upon the candidate's submission of the final copies of the DNP project to the Graduate College.

I hereby certify that I have read this DNP project prepared under my direction and recommend that it be accepted as fulfilling the DNP project requirement.

DNP Project Chair: Gloanna Peek, PhD, RN, CPNP — Date: November 13, 2017

STATEMENT BY AUTHOR

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SIGNED: __Jocelyn R. Rivera_____

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DEDICATION

This project is dedicated to my Grandma Z. I am who I am because of you. I love you to the moon and back.

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ABSTRACT

The purpose of this project is to develop a clinical practice guideline with recommendations for vaccination and vaccine hesitancy in the pediatric setting. Routine vaccinations are given to children at recommended ages to decrease the incidence of, and prevent infectious disease. These vaccinations prevent diseases such as rotavirus, diphtheria, pertussis, tetanus, hepatitis B, haemophilus influenza type B, pneumococcal disease, polio, influenza, measles, mumps, rubella, varicella and hepatitis A. There are currently no guidelines that combine evidence-based interventions to increase vaccination rates, the recommended vaccine schedule, specific information on each vaccination, its side effects, and ingredients of each vaccination.

By developing this guideline, it is hoped that pediatric providers will be able to effectively approach the caregivers of vaccine-aged children with evidence based information about vaccination, and be able to address specific concerns regarding vaccines. The available literature was formally evaluated using GRADEpro software. These results were put into the BRIDGE-Wiz (Building Recommendations in a Developer 's Guideline Editor) software to create clear, concise, key action statements for the guideline.

There were five recommendations that were created based on the literature review which include assessing parental concerns regarding vaccination at each visit, educating parents on vaccination, each vaccine, at each visit and when concerns arise, recommending vaccinations during each visit and when the opportunity arises, recommending pre-scheduling vaccination appointments, and implementing a reminder/recall system when vaccinations are due or past due. There were also informational tables created for provider reference that include important

information regarding vaccines. The first table includes each vaccination, the disease it prevents, and the risk of the disease vs the risk of the vaccination. The second table includes the vaccine ingredients that commonly cause concern, and information to address those concerns.

The guideline can be used in pediatric primary care to guide interventions to increase the uptake of vaccinations, and as a tool for providers to use while educating parents on specific vaccinations. The guideline was formally evaluated using the AGREE II tool by three experts in the field of pediatric primary care. All three of the reviewers stated that they would recommend the guideline for use in the pediatric setting.

INTRODUCTION

Background Knowledge

Vaccination is considered one of the highest achievements of public health to date (Dube et al., 2013). Per the World Health Organization (WHO) (2012), immunizations prevent between 2-3 million deaths a year from diphtheria, tetanus, pertussis, and measles; making vaccination one of the most successful and cost effective public health interventions. Although vaccinations have been proven effective, many parents are hesitant to vaccinate their children. Evidence suggests that refusal to vaccinate has led to multiple outbreaks of vaccine-preventable diseases, such as measles (Lee, Rosenthal, & Scheffler, 2013).

The most recent measles outbreak occurred from January to October of 2017 and 120 people from 15 states, including Arizona, were reported to have measles (Center for Disease Control and Prevention [CDC], 2017a). Pertussis is another common vaccine preventable disease in Arizona and the United States, with peaks in reported disease every few years and frequent outbreaks (CDC, 2017b). The most recent peak year was 2012, and there were 48,277 reported cases of pertussis in the United States (CDC, 2017b). In the late 1940s polio was widespread in the United Stated, crippled an average of 35,000 people each year, and was one of the most feared diseases (CDC, 2017c). The United States has been free from polio outbreaks since 1979, but it is still prevalent in other countries which could spread through traveling making vaccination very important (CDC, 2017c).

There have been positive gains in vaccine coverage due to state mandated vaccination but there has also been a shift in perception of disease experience and heightened concerns regarding vaccine safety. Although vaccination programs have led to a significant decline in mortality and

morbidity of infectious diseases, parental vaccine hesitancy is thought to be responsible for decreased vaccine coverage (Dube et al., 2013). Decreased vaccine coverage is increasing the risk of vaccine-preventable outbreaks and epidemics (Dube et al., 2013). Not only is the direct protection for unvaccinated children in jeopardy but the indirect protection, or herd immunity, of children who are not able to receive vaccinations suffers as well. Increased efforts are required to improve and maintain public confidence in vaccines (Siddiqui, Salmon, & Omer, 2013).

There is limited data available on the rate of vaccine refusal. Many children who are not vaccinated do not attend public schools or regularly see physicians. The CDC does have an interactive map that shows vaccine coverage by state specific to each vaccine. For example, based on the national immunization survey from 2015, 85% of children received the DTap vaccination, 90.6% received the MMR vaccine, 83% received the polio vaccine, 82% received the HIB vaccine, and 94% received the Hepatitis B vaccine (CDC, 2017). These results do not account for the families who did not fill out the survey.

Significance to Health Care

Vaccination coverage directly relates to Pediatric Nurse Practitioners working in Arizona, as stated above there has been recent outbreaks of vaccine preventable diseases in Arizona. It is important to understand the distinct determinants of the decision not to vaccinate, to establish strategies to address the issues (Betsch, Böhm, & Chapman, 2015). Refusing vaccination can result from inconvenience, complacency, a lack of confidence and knowledge, and a rational calculation of pros and cons (Betsch et al., 2015). The significance of vaccine refusal is immense in pediatric primary care. In the clinical setting, the pediatric nurse practitioner is able to approach parents, understand their specific concerns regarding vaccination, and use evidence

based tools to address those concerns. Evidence based interventions to reduce vaccine hesitancy need to be developed and rigorously evaluated. Per Siddqui et al. (2013) tools to assist clinicians in effectively working with parents who have vaccine concerns would be particularly useful.

Purpose

The purpose of this DNP project is to develop an evidenced based clinical practice guideline (CPG) for pediatric nurse practitioners to use when approaching parents about vaccination, and when educating vaccine hesitant parents. The CPG presented in this DNP project will outline evidence-based practice to approach parents of vaccine-aged children. The components of this CPG will be based on the current standards for immunization in pediatric patients including the following: current recommended vaccine schedule and catch-up schedule, evidence on utilizing all clinical encounters to assess the immunization status of patients, administering all immunizations as per schedule, educating patients/parents regarding the importance of immunizations and the recommended schedule, documenting reasons for not immunizing, report immunizations, and providing information sheets (Nordin et al., 2012). By developing a clinical guideline, it is hoped that vaccinations rates will increase, which in turn will decrease vaccine preventable outbreaks.

Aim

- Develop and evaluate a CPG based on evidence for pediatric providers to utilize when recommending vaccinations in pediatric patients, and when addressing vaccine refusal.

Objective

The overall objective of the CPG is to provide practitioners with best practice evidence regarding immunizations, immunization schedules, barriers to vaccination, and strategies to increase vaccination rates.

Study Question

What are the evidence-based recommendations for vaccination and for increasing vaccination compliance in the pediatric setting?

Concepts and Definitions

Pediatric provider is described as any provider in the acute or outpatient setting that cares for pediatric patients up to 21 years of age. Pediatric patient is defined as infants, children, and adolescents. The American Academy of Pediatrics (AAP) (2017), recommends people be under pediatric care up to the age of 21. Herd immunity is the resistance to the spread of a contagious disease within a population that results if a sufficiently high proportion of individuals are immune to the disease, especially through vaccination (WHO, 2014). Vaccine hesitancy is described as delay in acceptance or refusal of vaccines despite availability of vaccination services (WHO, 2014). A clinical practice guideline is a statement that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options (American Academy of Family Physicians, 2017).

FRAMEWORK AND SYNTHESIS OF EVIDENCE

Johns Hopkins Nursing Evidence-Based Practice Model

This DNP project was to developed to create a clinical practice guideline that will outline the current recommendations for vaccinating, and interventions to address vaccine hesitancy. The Johns Hopkin's Nursing Evidence-Based Practice (JHNEBP) Model was used as a framework for development of this clinical practice guideline. The JHNEBP model pays detailed attention to identifying practice questions and evaluating evidence (Schaffer, Sandau, & Diedrick, 2012). This model offers tools for rating evidence, includes an action plan for implementation, and is useful in a variety of settings (Schafffer et al., 2012).

There are three main components of the JHNEBP model: the practice question, evidence, and translation into practice (Schaffer et al., 2012). The problem that is identified is vaccine hesitancy, and overall knowledge regarding vaccinations. The second step is to review the literature and rate the strength of evidence (Schaffer et al., 2012). The evidence was collected, appraised, and is discussed later in the project. The final step is to incorporate the evidence from the literature into the CPG for the pediatric provider to use in the clinical setting, which was done by creating a CPG for provider use.

The literature collected was evaluated and organized using the Grades of Recommendation Assessment, Development and Evaluation (GRADEpro) and Building Recommendations in a Developer's Guideline Editor (BRIDGE-Wiz) programs, these are both available online and provide a formal evaluation of the current literature. After the CPG was developed it was officially evaluated using the AGREE II framework. Data was collected from this evaluation and is presented in the result section of this project.

Preliminary Review of Literature

Understanding the Determinants of Vaccine Hesitancy

Complacency, inconvenience, lack of confidence, weighing pros and cons are all determinants of vaccine hesitancy and refusal (Betsch et al., 2015). Reasons for vaccine hesitancy are best understood when placed in the appropriate historical, political, and socio-cultural contexts (Kestenbaum & Feemster, 2015). Social science research has shown that vaccination decision-making should be understood in a broader socio-cultural context (Dube et al., 2013). Parental reasoning for vaccine refusal should be discussed at length to effectively address the concerns. Many parents have concerns about the safety of vaccinations, the efficacy of vaccinations, and perceive a low risk of their child getting the disease if not vaccinated (Harmsen, Mollema, Ruiter, Paulussen, & Melker, 2013).

Strategies to Increase Vaccination

Informational Interventions

Informational interventions provide necessary, evidence based information to the patient and their family. A meta-analysis determined that health messages creating strong fear in the receiver and, at the same time, providing advice that increases self-efficacy were most successful in changing behavior (Betsch et al., 2015). One study found that the largest proportion of parents who changed their minds about delaying, or not getting a vaccination for their child, listed "information or assurances from health care provider" as the main reason (Gust, Darling, Kennedy, & Schwartz, 2007). Examples of informational interventions include any information that is provided to the caregiver regarding vaccination including verbal education, written information, or providing evidence based resources online to review vaccine information.

Debunking Myths

Interventions that provide an alternative account of the myth have been proven successful in eliminating misinformation (Betsch et al., 2015). Storytelling as a method of disseminating messages can be used, as parents and patients may be more motivated by stories than scientific communication (Kestenbaum et al., 2015). For example, providers need to have material that contains evidence showing the safety of vaccinations and that they do not correlate with autism.

Pre-Scheduling

It is important to vaccinate whenever possible, and the provider should be sure to check for overdue vaccinations (AAP, 2017). To avoid overdue vaccinations pre-scheduling appointments for patients for vaccination is an effective strategy. People pre-scheduled for a flu shot appointment (which they can cancel if they do not want it) are more likely to get vaccinated than those who are not pre- scheduled, but who can make an appointment if they want one (Betsch et al., 2015).

Mandated Vaccination

In the United States, public school districts and private schools routinely mandate that children be current on vaccinations as a precondition for school registration (Betsch et al., 2015). The mandated vaccinations vary by state. The Arizona Department of Health Services (ADHS) (2016) requires DTap, Td, Tdap, Meningococcal, Polio, MMR, Hep B, and Varicella, per to entry into kindergarten in the public-school system. Although these are required for school entry in Arizona, there are exceptions that are made for various reasons including: medical reasons, lab evidence of immunity, and personal beliefs (ADHS, 2016). The top medical reasons that states allow exemption for are immune compromised patients and allergic reactions to vaccine

components (McKee & Bohannon, 2016). An example of a personal belief for exemption is that some parents believe that the natural immunity that the child develops from getting an illness is better for their child than vaccination, this is not allowed by all states as a valid exemption (McKee et al., 2016).

Reminder/Recall

Per the AAP (2017), immunization reminder-recall systems are cost-effective and are a powerful way to ensure optimal vaccination rates. There is large support for the effectiveness of reminders/recall on vaccine uptake (Betsch et al., 2015). Examples of effective reminders include mailed reminders to schedule appointments, emailed reminders of appointment date, text, and phone calls (Betsch et al., 2015). Each different type of reminder/recall system targets a different population. For example, text-message reminders were proven effective when trying to reach low-income, urban population more effectively than through email (Betsch et al., 2015).

Provider Recommendation

A lack of physician recommendation is among the most common reasons for non-vaccination (Johnson, Nichol, & Lipczynski, 2008). Studies show that recommendations increase uptake of vaccination (Betsch et al., 2015). Despite the availability of information from a wide range of resources, providers remain the most important predictor of vaccine acceptance. Recent studies have emphasized the importance of a strong recommendation (Kestenbaum et al., 2015). A large proportion of parents who changed their minds about delaying, or not getting a vaccination for their child listed “information or assurances from health care provider” as the main reason (Dube et al., 2013, p. 1768).

Strengths, Weaknesses, Gaps and Limitations

Multiple studies state that there needs to be more research done on pro-vaccine messaging and effective interventions to increase vaccination rates, (Nyhan et al., 2014) & (Sadaf, Richards, Glanz, Salmon, & Omer, 2013). Based on the available evidence parents are concerned about side effects of vaccine, and the efficacy of vaccines. There are multiple interventions that can be implemented but the most important aspect is that a trusted provider is recommending vaccinations as best practice, and addressing specific parental concerns. See Table 1 for a full appraisal of evidence table.

METHODS

To address vaccine hesitancy, refusal, and increase of vaccine preventable disease outbreak a clinical practice guideline needed to be developed. After performing the initial synthesis of evidence there was no clinical practice guideline identified that adequately addressed this issue, and presented evidence for practitioners to use when approaching vaccine hesitancy and vaccination in general.

Guideline Development

The guideline addresses the following question: What are the evidence-based recommendations for vaccination and for increasing vaccination compliance in the pediatric setting? The guideline was developed using Johns Hopkins Nursing Evidence-Based Practice Model framework, the GRADEpro guideline development tool, and Building Recommendations in Developers Guideline Editor software (BRIDGE-Wiz). The guideline was then evaluated using The Appraisal of Guidelines for Research & Evaluation instrument (AGREE).

The GRADEpro guideline development tool is a way to formally assess the quality of the evidence found to support the clinical practice guideline. The tool was developed to be a transparent system for grading quality of evidence and strength of recommendation (Schunemann, Ahmed, & Morgan, 2011). The purpose of this software is to create a summary of literature, and structure this evidence into recommendations that can be placed in the CPG (Schunemann et al., 2011). A literature review was done and clinical questions were formed, the clinical questions were then entered into the software program. The software prompts the user to enter supporting evidence for each question and subsequently builds an evidence table based on the input (Schunemann et al., 2011). Once the grading was complete the final recommendations were put into the BRIDGE-Wiz program, which turned them into key action statement to insert into the formal guideline.

BRIDGE-Wiz organizes the knowledge that is essential to creating guideline recommendations in a systematic, methodical, manner using a specialized software (Shiffman, Michel, Rosenfeld, & Davidson, 2011). When using the BRIDGE-Wiz software the user is prompted to answer a series of questions about the actions that are to be outlined in the guideline (Shiffman et al., 2011). The answers to these questions were formed into a recommendation to be placed into the guideline. The program uses a controlled natural language approach, which creates statements that are highly expressive, understandable and require no learning effort (Shiffman et al., 2011). Once the guideline was complete with the recommendations it was externally reviewed using the AGREE II framework to ensure there are no biases.

Appraisal of Guideline for Research and Evaluation (AGREE II Framework)

The AGREE II framework was used as a guide to evaluate this clinical practice guideline. The appraisal of guidelines for research & evaluation instrument (AGREE) was developed to address variability in guideline quality (Brouwers et al., 2009). The AGREE II tool is a 23-item tool, that involves six domains. The AGREE II tool was utilized to evaluate the clinical practice guideline. The purpose of the AGREE II instrument is to systematically develop a clinical practice guideline to assist the practitioner, and patient decisions, about evidence based health care topics, such as vaccination (Brouwers et al., 2009). The AGREE II tool is useful in evaluating the quality of a clinical practice guideline. The purpose of the AGREE II tool is to provide a framework to: assess the quality of guidelines, provide a methodological strategy for the development of guidelines, and inform what information and how information ought to be reported in guidelines (Brouwers et al., 2009).

The AGREE II tool is generic and can help to develop and evaluate any guideline developed for health care including health promotion, public health, screening, diagnosis, interventions or treatments (Brouwers et al., 2009). This instrument can be used by various stakeholders including practitioners that want to evaluate an existing guideline before adaptation of it, guideline developers who need a structured and rigorous methodology, policy makers who need help in deciding which guidelines to recommend, and educators (Brouwers et al, 2009).There are six domains outlined in the tool: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence (Brouwers et al., 2009).

Domain 1 Scope and Purpose

Within this domain the overall objective of the guideline is specifically described. The health question that is being addressed is described. The population and patients who the guideline is meant to apply to is described in detail (Brouwers et al., 2009).

Domain 2 Stakeholder Involvement

The guideline development/evaluation group includes individuals from relevant professional groups. The target users of the guideline are distinctly identified (Brouwers et al., 2009).

Domain 3 Rigor of Development

Systematic methods are used to search for and appraise relevant evidence, and the criteria for selecting evidence is described. The strengths and limitations of the evidence are outlined. Processes for formulating recommendations are described. The health benefits, side effects, and risks of the guideline recommendations are considered (Brouwers et al., 2009).

Domain 4 Clarity of Presentation

The recommendations in the guideline must be unambiguous and specific. The options for managing the clinical issue or health issue are clearly outlined in the guideline. Fundamental recommendations are clearly identified in the guideline (Brouwers et al., 2009).

Domain 5 Applicability

The guideline must provide advice on how to evidence can be put into clinical practice and describe the barriers to application. The possible resource implications of utilizing the recommendations within the guideline have been considered. The guideline includes monitoring criteria (Brouwers et al., 2009)

Domain 6 Editorial Independence

The views of the funding body must not influence the content of the guideline and competing interests of group members must be identified and addressed (Brouwers et al., 2009).

Ethical Considerations

The three most relevant ethical principles that apply to research with human subjects are respect for persons, beneficence, and justice.

Respect for Persons

Respect for persons outlines two principles: that everyone should be treated as an autonomous agent and that people who have diminished autonomy are entitled to protection (Belmont Report, 1979). Since this project involves development of a guideline, the expert reviewers are the subjects of my research study. These subjects will all have the right to act independently and have the freedom to choose to participate or not participate in the study.

Beneficence

Beneficence ensures that people are treated in an ethical manner, this is done by respecting their decisions and protecting subjects from harm. Beneficence is an obligation that the researcher has to the subjects of the study to do no harm and maximize benefits (Belmont Report, 1979). In this study, there is minimal harm to the participants. The CPG that will be presented is intended to increase the knowledge of the provider and given them tools and confidence when approaching vaccine hesitant parents.

Justice

Justice in terms of ethical principles means selecting participants based on the study requirements and to make sure not to discriminate against certain participants (Polit & Beck,

2012). The big question is who receives the benefits of the research and who does not (Belmont Report, 1979). There are many people who will benefit from this research study, the first are the subjects who will gain increased knowledge to apply in the clinical setting. The next are the pediatric patients whose parents will deiced to vaccinate, which will protect those children from harmful disease. Lastly the general population benefits from increased herd immunity.

Setting

The CPG was developed using the GRADEpro and BRIDGE-Wiz programs to formally evaluate the current literature. After the CPG was developed it was presented to expert reviewers to be evaluated using the AGREE II tool. The expert reviewers were chosen based on their specialty and experience.

Data Collection Using the AGREE II Tool

There are six domains within the AGREE II instrument which were discussed above. Each of the AGREE II domains are rated on a seven-point scale (1-strongly disagree to 7-strongly agree), and there is a user manual to guide the evaluator in using the instrument (Brouwers et al., 2009). The user manual also provides three additional sections to aide in the facilitation if the users assessment.

To calculate the domain scores each individual item is scored, summed up and then scaled to the total as a percentile of the maximum possible score for that domain (Brouwers et al., 2009). For example, if there are four appraisers the maximum possible score for an individual domain is 84, and the minimum score is 12 (Brouwers et al., 2009).

Data Analysis

To interpret the domain scores there is no specific minimum score that needs to be met to determine if the CPG is high quality. This decision is made by the user, who is guided by the context of the evaluation. After completing initial evaluation using the scoring, the AGREE II evaluator will provide 2 overall assessments of the guideline (Brouwers et al., 2009). This requires the evaluator to discern the quality of the guideline, considering the criteria measured in the assessment process and the evaluator is asked whether he/she would recommend use of the guideline (Brouwers et al., 2009). The reviewer can choose to recommend the CPG, not recommend the CPG, or recommend the CPG with modifications. There is also a section in the evaluation for additional comments from the evaluator.

External Review

An external review by clinical experts was done to decrease internal biases and provide feedback to the developer. The reviewers were chosen based on their clinical expertise, and their experience with the pediatric population. The criteria to be an expert reviewer was to be in the pediatric specialty for more than four years. The reviewers were identified and invited to participate through email via an electronic invitation. The email included an invitation to review the guideline using the AGREE II tool, a copy of the guideline, the AGREE II manual, and an appraisal form to be completed and returned to the developer. Three expert reviewers were invited to evaluated to guideline and three reviewers completed the evaluation. The reviewers scores and comments were tallied using the AGREE II software instructions.

Data Collection

The project proposal was reviewed and approved by the International Review Board (IRB) prior to collecting the data. All the data collected was kept on a designated hard drive. The hard drive was locked in a cabinet when not in use. The review of literature, guideline development and the appraisal process took approximately five months.

RESULTS

Results of Literature Analysis and Evidence Recommendations

After the literature analysis was formally evaluated using the GRADEpro software, the BRIDGE-Wiz software was used to create key action statements to insert into the guideline. The follow key action statements were used in the guideline along with evidence based information regarding vaccinations. View full proposed CPG in Appendix B.

1. *It is recommended that pediatric providers assess parental concerns regarding vaccination during each visit. (Evidence Quality: Moderate, Rec. Strength: Strong Recommendation For)*

Parental reasoning for vaccine refusal should be discussed at length to effectively address the concerns. Common parental concerns are related to the safety of the vaccinations, the efficacy of the vaccination, and perceive a low risk of their child getting the disease (Harmsen, Mollema, Ruiter, Paulussen, & Melker, 2013). Understanding a parent's unique concerns enables the health care provider to effectively communicate with the vaccine-hesitant parent (Healy & Pickering, 2010). Establishing an open, non-judgmental dialogue early on and providing easily comprehensible answers about vaccine side effects and providing accurate information is recommended (Healy et al., 2010). Reasons for vaccine hesitancy are best understood when

placed in the appropriate historical, political, and socio-cultural contexts (Kestenbaum & Feemster, 2015).

2. *It is recommended that Pediatric providers educate parents on vaccination and each vaccine (Evidence quality: High; Recommendation strength: Strong Recommendation For) AND it is recommended that Pediatric providers recommend vaccinations (Evidence quality: High; Recommendation strength: Strong Recommendation For) during each visit AND when parents have concerns/questions about vaccination*.

Health care providers have the greatest influence on a parent's decision to vaccinate (Healy et al., 2010). A lack of physician recommendations is among the most common reasons for non-vaccination (Johnson, Nichol, & Lipczynski, 2008). Health care providers should always provide necessary, evidence based information. A meta-analysis determined that health messages creating strong fear in the receiver and, at the same time, providing advice that increases self-efficacy were most successful in changing behavior (Betsch et al., 2015). One study found that the largest proportion of parents who changed their minds about delaying or not getting a vaccination for their child listed "information or assurances from health care provider" as the main reason (Gust, Darling, Kennedy, & Schwartz, 2007, p.). It is important to reassure parents that although there are side effects related to vaccination the research shows that the benefits outweigh the risks of getting the disease.

Interventions that provide an alternative account of the myth have been proven successful in eliminating misinformation (Betsch et al., 2015). Having specific examples and educational materials that disprove myths is important to address this concern.

Studies show that recommendations increase uptake (Betsch et al., 2015). Despite the availability of information from a wide range of resources, providers remain the most important predictor of vaccine acceptance. Recent studies have emphasized the importance of a strong recommendation (Kestenbaum & Feemster, 2015). A large proportion of parents who changed their minds about delaying or not getting a vaccination for their child listed "information or assurances from health care provider" as the main reason (Dube et al., 2013, p.).

3. *It is recommended that Pediatric providers implement reminder/recall systems whenever vaccinations are due or past-due. (Evidence Quality: High, Rec. Strength: Strong Recommendation For)*

There is large support for the effectiveness of reminders/recall on vaccine uptake (Betsch et al., 2015). Reminders and recalls allow clients to know when vaccinations are due or overdue (Briss et al., 2000). Various methods can be used and call have been proven effective. The type of reminder/recall system used may be based on the population that is being targeted. Reminder/recall systems that have been proven to increase vaccination rates include phone call, post-card, letter, text message, and email. The reminders can be specific or general (Briss et al., 2000). Per the evidence presented in the literature review there is strong scientific evidence supporting client reminder/recall systems to improve vaccine coverage. All types of reminders are effective with telephone being the most effective but also the costliest (Szilagyi & Jacobson, 2009).

4. *It is recommended that Pediatric providers recommend pre-scheduling vaccination appointments at each visit. (Evidence Quality: Moderate, Rec. Strength: Strong Recommendation For)*

To increase vaccination coverage providers should pre-schedule appointments for well-visits or vaccination visits. People pre-scheduled for a flu shot appointment (which they can cancel if they do not want it) are more likely to get vaccinated than those who are not pre-scheduled but who can make an appointment if they want one (Betsch et al., 2015).

External Review Results

The individual external evaluation results are listed in Table 1. The total graded scores for each domain are illustrated in Table 2. When looking at the AGREE II Tool results the developer should compare domain totals to identify which domains need revision, revisions are also based on individual comments. The AGREE II tool does not provide an interpretation of the results; rather, the developer should compare domain totals to understand which domains are strongest and which domains need revision. The domain totals are tabulated by the below AGREE II formula. All three of the expert reviewers stated that they would recommend the CPG for use.

TABLE 1. *External Appraisal Results*

Questions	Reviewer 1	Reviewer 2	Reviewer 3	Reviewer Comments
1	7	7	7	
2	7	7	7	
3	7	7	7	
4	7	7	7	
5	7	7	7	
6	7	7	7	
7	7	7	7	
8	7	7	7	
9	7	7	7	
10	7	7	7	
11	7	7	7	
12	7	7	7	
13	7	7	7	
14	7	7	7	
15	7	7	7	
16	7	7	5	Discussion of what to do with parents who still opt to not vaccinate or who choose to delay vaccines is lacking.

TABLE 1 – *Continued*

Questions	Reviewer 1	Reviewer 2	Reviewer 3	Reviewer Comments
17	7	7	7	
18	7	7	7	
19	7	6	7	Something else to consider when trying to improve vaccine rates is having a walk-in clinic for shots.
20	7	6	7	
21	4	7	3	No monitoring criteria as stated in CPG.
22	7	7	7	
23	4	7	1	NA
24	7	7	5	
I would recommend this guideline for use	Yes, with modifications Yes Yes, with modifications			
Additional comments:	The appendices were very helpful, especially the specific info on vaccine ingredients and Appendix C which addresses many common parental concerns. Loved the anecdotes you gave as examples to use in addressing parental concerns. The risk of disease vs risk of vaccination (Appendix A) very clear and informative. The common vaccine ingredient that cause parental concern so very clear and concise. I have printed this guideline to use with my patients, I think it will be very helpful. I would recommend this guideline for use after minor grammatical errors are fixed.			

TABLE 2. *Domain Totals*

Domain	Total
1. Scope and Purpose	100%
2. Stakeholder Involvement	100%
3. Rigor of Development	100%
4. Clarity of Presentation	96%
5. Applicability	88%
6. Editorial Independence	75%

The domain score totals were calculated using the formula provided by the AGREE II tool which is as follows: Obtained score (sum of review scores) minus the minimum possible score divided by the maximum possible score minus the minimum possible score (Brouwers et al., 2010). After the total score for each domain was calculated and the comments for each

question were reviewed the developer made changes to the guideline. The post appraisal changes included: Grammatical changes, adding a statement to the editorial independence portion of the guideline, and adding in suggested common side effects of different vaccinations.

DISCUSSION

Summary

The CPG presented in this DNP project outlines evidence-based practice to approach parents of vaccine-aged children. The components of this CPG is based on the current standards for immunization in pediatric patients including the current evidence on utilizing all clinical encounters to assess the immunization status of patients, administering all immunizations as per schedule, educating patients/parents regarding the importance of immunizations and the recommended schedule, documenting reasons for not immunizing, report immunizations, and providing information sheets (Nordin et al., 2012). To ensure that the evidence is of good quality the GRADEpro software was be used. The recommendations were completed and BRIDGE-Wiz was used to organize the recommendations in a transparent fashion. Using the AGREE II instrument for evaluation ensures that this guideline is of good quality, and will make a positive impact in pediatric primary care. Educating parents on immunizations is extremely important, and it is at times hard to approach parents who have preconceived notions that vaccines are harmful to their children. By developing this clinical guideline, it is hoped that vaccinations rates will increase, which in turn will decrease vaccine preventable outbreaks. It is also hoped that providers will form open, honest relationships with their patients and continue to care for the children despite their parents refusing vaccination.

Implications for Practice

There are numerous practice implications for the CPG. If implemented into daily practice, the provider will be able to establish an open relationship with the parents/patients, better understand the specific needs of each family regarding vaccination, and effectively educate them based on those needs. The provider will be able to approach families using evidence-based interventions to increase vaccination and address vaccine hesitancy. The literature demonstrates that these interventions, recommendations, and education, are likely to promote increased vaccination rates. Providers are encouraged to review the guideline and decide whether it is a good fit for their practice and the population of patients that they care for.

Future Research and Limitations

There is still a large need for investigation on vaccine hesitancy and interventions to address vaccination and vaccination refusal. There is a large percentage of evidence that supports multi-component interventions but there is a need for research on specific education interventions. There is a lack of randomized control trials using educational interventions to increase vaccination rates. There will continue to be vaccine hesitancy in the United States, which leads to outbreaks of vaccine-preventable disease, and this is an important topic that needs to be addressed in pediatric primary care. The limitations of the project include referral sampling of evaluators, recommendations were developed by one person versus a committee, lack of randomized controlled trials, and the AGREE II is not a reflection of potential or actual patient outcomes.

APPENDIX A:

APPRAISAL OF EVIDENCE

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Betsch, Böhm, & Chapman, 2015	Importance of understanding the determinants of individual vaccination decisions to establish effective health policies	Literature review	NA	NA	-Motivating the complacent -Removing barriers for those for whom vaccination is inconvenient -Adding incentives and additional utility for the calculating
Dube, Laberge, Guay, Bramadat, Roy & Bettinger, 2013	An overview of vaccine hesitancy	Literature review	NA	NA	-Increasing trend towards vaccine hesitancy is being seen in primary care -Factors effecting decision to vaccinate include-socioeconomic, moral/religious, past experiences, Health professional recommendations, trust, and risk perceptions

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Gust, Darling, Kennedy & Schwartz, 2007	Qualitative immunization survey to assess parental reasons for delaying or refusing vaccination	Qualitative	3924 parents	Survey was used to collect data	-Vaccine safety concern was a predictor for unsure, refused, and delayed vaccination -The largest proportion of parents who changed their minds about delaying or not getting a vaccination for their child listed "information or assurances from health care provider" as the main reason
Harmsen, Mollema, Ruiter, Paulussen, & Melker, 2013	Why parents refuse childhood vaccination	Qualitative	8 online focus groups: total sample size-60	Online focus groups	Reasons for refusing vaccination: -Life style -Risk perceived -Immune system -Perceived advantage of having the disease -Negative experience with vaccination -Perceptions about side effects -Social environment -Perceived vaccine efficacy

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Healy & Pickering, 2010	How to communicate with vaccine hesitant parents	Literature review	NA	NA	-Establishing an ongoing, no confrontational dialogue with parents - Evidence based data can be used to address the specific fears and concerns of parents -Information should be communicated by using unambiguous, easily understood language. -The serious consequences of not vaccinating should be highlighted both by data showing that vaccine-preventable diseases are a constant threat and by using the experience and stories of patients and parents affected by these diseases

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Kempe et al., 2011	To assess among pediatricians and family medicine physicians the prevalence of parental requests to deviate from recommended vaccine schedules, their responses to such requests and attitudes about the burden and success of communication	Qualitative	696	Survey of nationally representative samples of pediatricians and family medicine physicians	The problem of communicating with parents about vaccines is high, especially among pediatricians. Physicians report the greatest success convincing skeptical parents using messages that rely on their personal choices and experiences
Leask, Kinnersley, Jackson, Cheater, Bedford & Rowles, 2012	Communicating with parents about vaccination	Literature review	NA	NA	-Health professionals should build rapport -Accept questions and concerns -Facilitate valid consent -Try to elicit the parent's own motivations to vaccinate while, avoiding excessive persuasion and adversarial debates

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Leib, Liberatos & Edwards, 2011	Pediatricians experiences with vaccine refusal	Quantitative survey: Variables examined included number of parental vaccine concerns and refusals seen by each physician, physicians' response to parental vaccine concerns and refusals, the personal impact of parental vaccine safety refusals on pediatricians, and respondent estimates of socioeconomic characteristics of families seen in their practices. (Lieb et al., 2011)	133 pediatricians	Survey	-The majority of responding pediatricians reported an increase in parental vaccine safety concerns and refusals -30% of responding pediatricians have dismissed families because of their refusal to immunize. -Suburban physicians caring for wealthier, better educated families experience more vaccine concerns and/or refusals and are more likely to dismiss families for vaccine refusal. -Vaccine refusals have a negative personal impact on one- third of physician respondents

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Nyhan, Reifler, Richey & Freed, 2014	Effective messages in vaccine promotion	Randomized control trial	1759 Parents	Web-based 2-wave survey experiment	-Debunking claims of an MMR/autism link successfully reduced misperceptions that vaccines cause autism -Images of sick children increased expressed belief in a vaccine/autism link -Dramatic narrative about an infant in danger increased self- reported belief in serious vaccine side effects -Current public health communications may not be effective

Author / Article	Qual: Concepts or Phenomena Quan: Key Variables Hypothesis Research Question	Design	Sample (N)	Data Collection (Instruments/Tools)	Findings
Omer, Salmon, Orenstein, DeHart & Halsey, 2009	Vaccine Refusal, Mandatory Immunization, and the Risks of Vaccine-Preventable Diseases	Literature review	NA	NA	-Health care providers are cited by parents, including parents of unvaccinated children, as the most frequent source of information about vaccination - Those providers providing care for un-vaccinated children were less likely to have confidence in vaccine safety
Sadef, Richards, Glanz, Salmon & Omer, 2013	A systematic review of interventions for reducing parental vaccine refusal and vaccine hesitancy	Systematic review	NA	Systematic review done using in four databases: PubMed, CENTRAL, EMBASE and PsychInfo.	-Passage of state laws had appositive effect on vaccination rates -Parent centered information and education was important -reminder recall systems

APPENDIX B:

PROPOSED CLINICAL PRACTICE GUIDELINE

PROPOSED CLINICAL PRACTICE GUIDELINE

RECOMMENDATIONS FOR VACCINATION AND VACCINE HESISTANCY IN PEDIATRIC PRIMARY CARE

Author and Guideline Developer

Jocelyn R. Smith, MS-RN

Qualifying Statements

- This guideline is meant to supplement current vaccination guidelines. It is not meant to replace or disagree with current practice guideline recommendations.
- The guideline is not meant to substitute clinical judgement.

Introduction

Vaccination is considered one of the highest achievements of public health to date (Dube, Laberge, Guay, Bramada, Roy & Bettinger, 2013). According to the World Health Organization (2012), immunizations prevent between 2-3 million deaths a year from diphtheria, tetanus, pertussis, and measles; making vaccination one of the most successful and cost effective public health interventions. Although vaccinations have been proven effective, many parents are hesitant to vaccinate their children. Refusal to vaccinate has led to multiple outbreaks of vaccine-preventable diseases such as measles. The most recent outbreak occurred from January to July of this year and 48 people from 13 states, including Arizona, were reported to have measles (Center for Disease Control and Prevention, 2016).

Although vaccination programs have led to a significant decline in mortality and morbidity of infectious diseases, parental vaccine hesitancy is thought to be responsible for decreased vaccine coverage which is increasing the risk of vaccine-preventable outbreaks and epidemics (Dube et al., 2013). Not only is the direct protection for unvaccinated children in jeopardy, but the indirect protection, or herd immunity, for children who are not able to receive vaccinations suffers also.

Vaccination coverage directly relates to Pediatric providers working in Arizona, as stated above there have been recent outbreaks of vaccine preventable diseases in Arizona. It is important to understand the distinct determinants of the decision not to vaccinate to establish strategies to address the issues (Betsch, Böhm, & Chapman, 2015). Refusing vaccination can result from inconvenience, complacency, a lack of confidence and knowledge, and a calculation of pros and cons (Betsch et al., 2015). The significance of vaccine refusal is immense in Pediatric primary care. The Pediatric provider is able to approach parents, understand their specific concerns regarding vaccination, and use evidence-based tools to address the concerns.

The recommendations in this guideline are based on the best research available regarding vaccination. The individual interventions provided in this guideline are effective in increasing vaccination, but overall multiple interventions utilized together have been proven to be most effective in increasing vaccination uptake (Briss et al., 2000). Addressing specific parental concerns and educational interventions should be implemented at every visit along with the other

interventions. Since provider education and recommendation have been proven to be an enormous influence on the decision to vaccinate, the guideline will also present details about each disease, each vaccination, possible side effects, and the recommended vaccine schedule as a clinical resource for providers to reference in practice.

Scope and Purpose

Purpose

To create a statement that includes recommendations based on the best available evidence regarding vaccination and vaccine hesitancy in the pediatric setting.

Objective

The overall objective of the CPG is to provide practitioners with best practice evidence regarding immunizations, barriers to vaccination, and strategies to increase vaccination rates.

Health Question

What are the evidence-based recommendations for vaccination and for increasing vaccination compliance in the pediatric setting?

Target Population

The patient population includes parents or legal guardians of vaccine-aged children, adolescents, and young adults.

Stakeholder Involvement

Group membership

The guideline was developed by a doctoral student with the guidance of a doctoral committee. The committee was composed of a project chair and two committee members. The project chair is a Pediatric Nurse Practitioner and faculty for the College of Nursing at the University of Arizona. The two chair members are also pediatric providers and faculty at the University of Arizona.

Target population preferences and views

An extensive literature search was done to capture the preferences and views of the target population. The views of the target population varied based on their acceptance of vaccines. The information gathered was used to create the key action statements. The key action statements are based on best practice evidence to tailor the response of the provider to the patient population's specific concerns regarding vaccination.

Target users

Any providers who see pediatric patients (0-21 years of age) in the inpatient or outpatient setting to inform them of evidence-based practice regarding vaccination schedules, vaccination education, and how to increase vaccination rates.

Rigor of Development

Search Methods

Searches of Electronic Databases including PubMed, CINHAL and searches through other literature using Google Scholar.

Inclusion Criteria:
Subjects: Parents or care givers of vaccine aged children
Research articles examining: Effective vaccine messages, vaccine hesitancy, interventions to increase vaccination rates, parental concerns regarding vaccination.

Exclusion Criteria:
Findings not applicable to pediatrics
Non-English publications

Evidence selection criteria:

Searches occurred between August 2016-August 2017. The date of publication was not specified due to limited research on the subject. There were 16 articles included in the synthesis of literature.

Key words included:
Vaccination recommendations
Vaccine hesitancy
Vaccination concerns
Interventions to increase vaccination
Vaccination rates
Vaccination adverse reactions
Vaccine refusal

Strengths and limitations of the evidence

The GRADEpro (Grades of Recommendation Assessment, Development and Evaluation) guideline development tool was used to formally assess the quality of the evidence found to support the clinical practice guideline. The tool was developed to be a transparent system for grading quality of evidence and strength of recommendation (Schunemann, Ahmed & Morgan, 2011). The purpose of this software was to create a summary of literature and systematize this evidence into recommendations that were placed into this CPG (Schunemann et al., 2011).

Limitations of evidence include limited randomized control trials. Multiple studies state that there needs to be more research done on pro-vaccine messaging and effective interventions to increase vaccination rates. (Nyhan et al., 2014) & (Sadaf, Richards, Glanz, Salmon, & Omer, 2013).

An appraisal of all of the available evidence was done, and the evidence was formally evaluated using the GRADEpro software. **See Appendix D** for the grade of evidence tables, these evidence tables helped form the key action statements but the key action statements were formed using the BRIDGE-Wiz software. Some key action statements are based on literature reviews and research that did not include randomized control trials. This evidence was graded using an appraisal of research table during the initial search for evidence.

Formulations of Recommendations

BRIDGE-Wiz (Building Recommendations in a Developer 's Guideline Editor) organizes the knowledge that is essential to creating guideline recommendations in a systematic, methodical, manner using a specialized software (Shiffman, Michel, Rosenfeld & Davidson, 2011). When using the BRIDGE-Wiz software the user is prompted to answer a series of questions about the actions that are to be outlined in the guideline (Shiffman et al., 2011). The answers to these questions are formed into a recommendation to be placed into the guideline. The program uses a controlled natural language approach, which creates statements that are highly expressive, understandable and require no learning effort (Shiffman et al., 2011). After the review of evidence was completed, the results were put into the BRIDGE-Wiz software and this is how each key action statement was formulated.

Considerations of benefits and harms

The benefits and harms were considered when formulating this guideline. Benefits include developing a trusting, open relationship with patients, being able to effectively address caregiver concerns, and increase the number of children that are vaccinated. Harm is related to possibly damaging the provider/patient relationship and adverse reactions to vaccinations given.

Link Between Recommendations and Evidence

The recommendations are based on evidence presented in this guideline.

External Review

External review will be done using the AGREE II framework to evaluate this clinical practice guideline. The appraisal of guidelines for research & evaluation instrument (AGREE) was developed to address variability in guideline quality (Brouwers et al., 2009).

Updating Procedure

The guideline will be updated based on the feedback from the expert reviewers using the AGREE II framework.

Major Recommendations

1. Assess parental concerns regarding vaccination during each visit.
2. Educate parents on vaccination, and each vaccine at every visit and when parents have concerns/questions about vaccination.
3. Recommend vaccinations during each visit and when any opportunity arises.
4. Recommend pre-scheduling vaccination appointments at each visit.
5. Implement reminder/recall systems whenever vaccinations are due or past-due.

Key Action Statement

It is recommended that Pediatric providers assess parental concerns regarding vaccination during each visit. (Evidence Quality: Moderate, Rec. Strength: Strong Recommendation For)

Quality of evidence: The recommendation was based on randomized control studies, expert opinion and literature reviews.

Benefits:

- Address specific concerns and vaccinate child

Risk, Harm, Cost:

- Discontinuation of care with that provider and decreased vaccination rates

Benefit-Harm Assessment: Preponderance of Benefit

Evidence/Recommendation

Parental reasoning for vaccine refusal should be discussed at length to effectively address the concerns. Common parental concerns are related to the safety of the vaccinations, the efficacy of the vaccination, and the perceived low risk of their child getting the disease (Harmsen, Mollema, Ruiter, Paulussen, & Melker, 2013). Understanding a parent's unique concerns enables the health care provider to effectively communicate with the vaccine-hesitant parent (Healy & Pickering, 2010). Establishing an open, non-judgmental dialogue early on, providing easily comprehensible answers about vaccine side effects and providing accurate information is recommended (Healy & Pickering, 2010). Reasons for vaccine hesitancy are best understood when placed in the appropriate historical, political, and socio-cultural contexts (Kestenbaum & Feemster, 2015).

Common Concerns/Reasons Parents Choose Not to Vaccinate

- Complacency or inconvenience
- Lack of confidence in the provider

- Fear that vaccines are unsafe and cause very bad side effects (allergic reactions, autism, ADHD)
- Fear of vaccine ingredients
- Fear that the vaccine will give the child the disease it is meant to protect against
- Pros vs cons: Getting the natural disease is better or safer for their child then the vaccination
- Concerns about the number of injections at one time and that the immune system will be "overloaded"

(Healy & Pickering, 2010)
(Betsch et al., 2015)

Key Action Statement

It is recommended that Pediatric providers educate parents on vaccination and each vaccine (Evidence quality: High; Recommendation strength: Strong Recommendation For) **AND it is recommended that Pediatric providers recommend vaccinations** (Evidence quality: High; Recommendation strength: Strong Recommendation For) **during each visit AND when parents have concerns/questions about vaccination.**

Action:
Educate on each vaccination and importance of vaccination
Recommend vaccination during each visit

Aggregate Evidence Quality: High

Benefits:

- Address specific parental concerns
- Increase vaccination rates
- Debunk myths regarding vaccination

Risk, Harm, Cost:

- Potential side effects of vaccinations if child is vaccinated at that visit

Benefit-Harm Assessment: Preponderance of Benefit

Evidence/Recommendations:

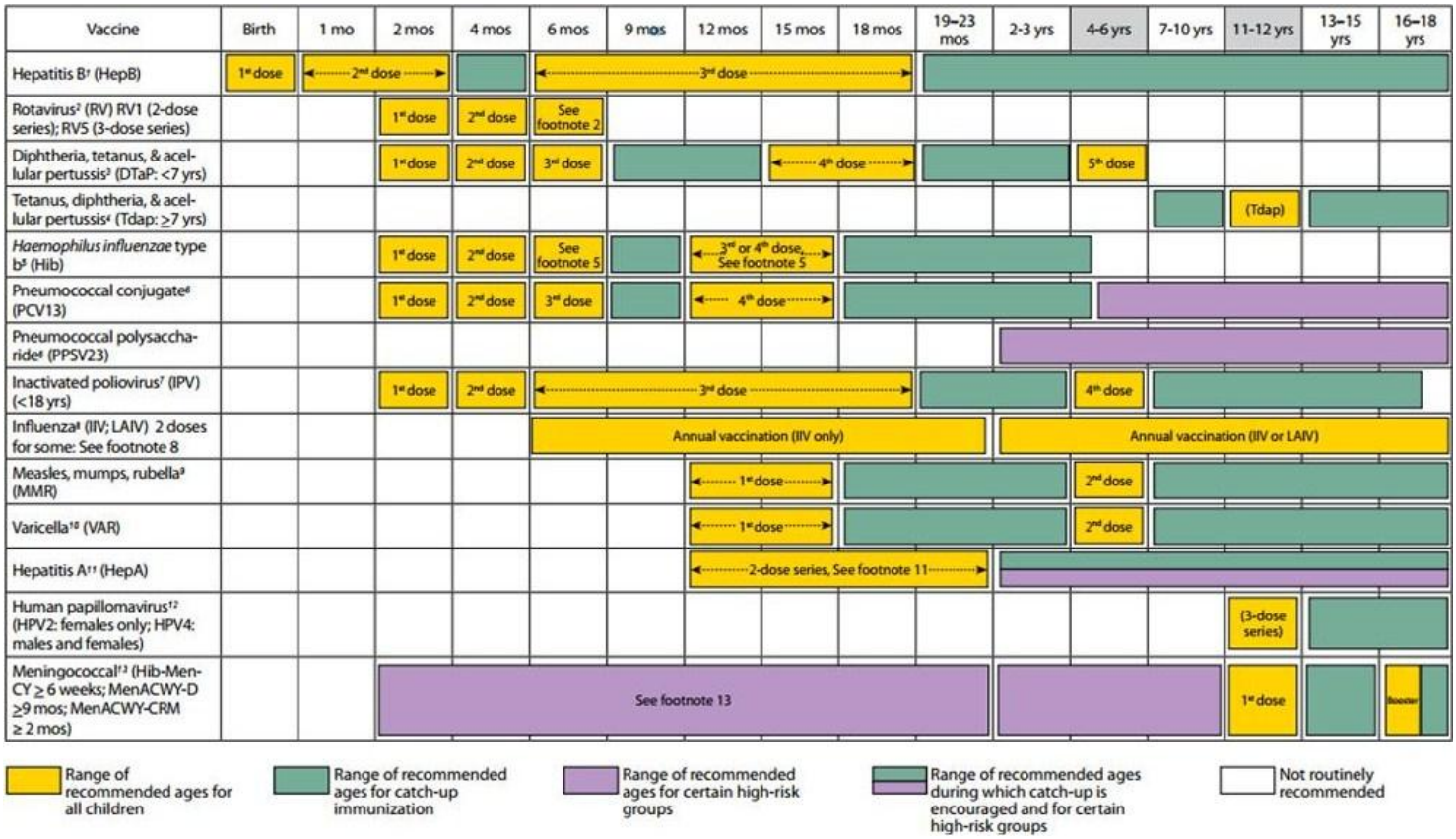
- Establish a non-confrontational relationship regarding immunization from the very first interaction
- Ask the caregiver what their specific concerns are regarding vaccination
- Listen carefully to identify parental beliefs to target education
- Have quick access to credible informational resources for client to take home

- Acknowledge that vaccines are associated with adverse events and balance that with discussing the risks of the disease **(See Appendix A for a full description of each vaccine benefits/risks)**
- Be able to address concerns about vaccine ingredients **(See Appendix B for a full list of ingredients in each vaccine and Appendix C for a list of ingredients that commonly cause concern)**
- Be aware of current vaccine schedule and recommend vaccination at appropriate ages **(See Figure 1 for the Center for Disease Control and Prevention current recommended vaccine schedule)**

Health care providers have the greatest influence on a parent's decision to vaccinate (Healy & Pickering, 2010). A lack of physician recommendations is among the most common reasons for non-vaccination (Johnson, Nichol, & Lipczynski, 2008). Health care providers should always provide necessary, evidence-based information. A meta-analysis determined that health messages creating strong fear in the receiver, and at the same time, providing advice that increases self-efficacy were most successful in changing behavior (Betsch et al., 2015). One study found that the largest proportion of parents who changed their minds about delaying or not getting a vaccination for their child listed "information or assurances from health care provider" as the main reason (Gust, Darling, Kennedy & Schwartz, 2007). It is important to reassure parents that although there are side effects related to vaccination the research shows that the benefits outweigh the risks of getting the disease.

Interventions that provide an alternative account of the myth have been proven successful in eliminating misinformation (Betsch et al., 2015). Having specific examples and educational materials that disprove myths is important to address this concern. Studies show that recommendations increase uptake (Betsch et al., 2015). Despite the availability of information from a wide range of resources, providers remain the most important predictor of vaccine acceptance. Recent studies have emphasized the importance of a strong recommendation (Kestenbaum & Feemster, 2015).

Figure 1. The Center for Disease Control and Prevention 2017 recommended vaccine schedule



Key Action Statement

It is recommended that Pediatric providers implement reminder/recall systems whenever vaccinations are due or past-due. (Evidence Quality: High, Rec. Strength: Strong Recommendation For)

Action: Implement reminder/recall systems

Aggregate Evidence Quality: High

Benefits:

- Increased vaccination

Risk, Harm, Cost:

- Low harm
- Cost varies based on system used

Benefit-Harm Assessment: Preponderance of Benefit

Evidence/Recommendation

- Post-cards
- Letters
- Email
- Phone call (person or automated system)-most effective
- Text-message

There is large support for the effectiveness of reminders/recall on vaccine uptake (Betsch et al., 2015). Reminders and recalls allow clients to know when vaccinations are due or overdue (Briss et al., 2000). Various methods can be used and all have been proven effective. The type of reminder/recall system used may be based on the population that is being targeted. Reminder/recall systems that have been proven to increase vaccination rates include phone call, post-card, letter, text message, and email. The reminders can be specific or general (Briss et al., 2000). Per the evidence presented in the literature review, there is strong scientific evidence supporting client reminder/recall systems to improve vaccine coverage. All types of reminders are effective, with telephone being the most effective but also the costliest (Szilagyi & Jacobson, 2009).

Key Action Statement

It is recommended that Pediatric providers recommend pre-scheduling vaccination appointments at each visit. (Evidence Quality: Moderate, Rec. Strength: Strong Recommendation For)

Action: Recommend pre-scheduling vaccination appointments

Aggregate Evidence Quality: Moderate

Benefits:

- Increased vaccination rates

Risk, Harm, Cost:

- Low risk
- Cancelation of appointments
- Low cost

Benefit-Harm Assessment: Preponderance of Benefit

Evidence/Recommendation

To increase vaccination coverage providers should pre-schedule appointments for well-visits or vaccination visits. People pre-scheduled for a flu shot appointment (which they can cancel if they do not want it) are more likely to get vaccinated than those who are not pre-scheduled but who can make an appointment if they want one (Betsch et al., 2015).

Applicability

Facilitators and barriers to application

The facilitators to application are the providers in pediatric and family practices that care for vaccine-aged patients. Barriers to application include administrative burdens on providers or health care systems, difficulties coordinating interventions, and lack of appropriate vaccination records. Barriers also include parents or care givers who are not open to discussing the topic of vaccination.

Implementation advice/tools

To effectively implement this clinical practice guideline, the provider must have the confidence to approach the parent or caregiver about the topic of vaccination. This tool provides information to help address common parental concerns. The provider should be ready to have an unbiased conversation, inquire about specific concerns, and have the evidence to effectively address those concerns.

Monitoring/Auditing

This guideline is meant to be used as a tool for Pediatric providers during clinical practice. There will be no specific monitoring in regards to the use of the guideline.

Editorial Independence

Funding body

There was no funding body during the creation of this guideline.

Competing interests

No competing interests of guideline development group identified due to guideline being developed by one individual.

Appendix A - Risk of Disease vs Risk of Vaccination			
Vaccine	**Disease**	**Risk of Disease**	**Risks of vaccination**
Diphtheria, tetanus and pertussis (DTAP) 5 shot series: 2 mo, 4 mo, 6 mo, 15-18 mo, 4-6 yo (Tdap is available for 11 years and older who are going to be around infants)	**Diphtheria:** caused by Corynebacterium diphtheria which releases a toxin that makes it difficult for children to breath and swallow. Also, attacks the heart, kidneys and nerves. **Tetanus**: Caused by a toxin-releasing bacterium (Clostridium tetani). The bacteria live in the soil and enters the body from wounds. The toxin causes muscle spasms that can interfere with breathing. **Pertussis:** (whooping cough), highly contagious, 8 out of 10 non-immune people will be infected when exposed to the disease. Older children and adults transmit pertussis to infants and young children. Pertussis can be deadly.	**Diphtheria:** damage to heart, kidneys, and nerves. Can be fatal. **Tetanus:** severe muscle spasms, suffocation, heart damage, death. **Pertussis:** uncontrollable coughing for weeks or months, coughing can cause broken ribs, blood vessels, or hernias. Pneumonia, Seizures, bouts of apnea, can be fatal.	Pain, redness and swelling at the injection site Mild fever Fussiness, fatigue, lack of appetite Nausea, vomiting, diarrhea, stomach ache Extensive swelling of the limb where the shot was given (about 3 in 100 people) Severe reactions (about 1 in 10,000 people): Fever of 105 degrees or higher Fever-associated seizures Inconsolable crying Hypotonic-hyporesponsive syndrome, a condition in which a child can become listless and lethargic with poor muscle tone for several hours.
Hepatitis A 2 shot series given at 12 months and then 6 to 12 months after the first shot	Hepatitis A is a virus that causes inflammation of the liver. Symptoms include yellowing of the skin, nausea, vomiting. Children are less likely to develop symptoms when they are infected with the virus. Hepatitis A can be transmitted though infected feces, sewage, water, and food.	Inflammation of the liver Fever Vomiting Jaundice Nausea	Pain, redness, and tenderness at injection site Headache (5 out of 100)

Hepatitis B 3 dose series given at birth, 1-2 months of age and again between 6-15 months of age	Hepatitis B virus attacks the liver. Individuals can be infected with the virus but not show symptoms until decades later. 2000 people die from hepatitis every year in the united states. The virus is spread through blood-even through casual contact (Sharing washcloths, toothbrushes, razors)	Inflammation of the liver Liver cirrhosis Liver cancer Disease can be fatal	Pain or soreness at the injection site Low-grade fever Severe allergic reaction 1 out of 600,000 doses
Hib Haemophilus influenza type B Given at 2 months and 4 months of age	HIB is a bacterium that infects the lining of the brain causing meningitis. Before the vaccine was created Hib was the most common cause of meningitis. Hib can also cause sepsis, pneumonia, cellulitis, arthritis and epiglottitis.	Meningitis-fever, stiff neck, drowsiness, coma. Sepsis-blood stream infection Epiglottis-severe swelling of a tissue that closes off the windpipe Arthritis-infection of the joints Cellulitis-infection of the skin Pneumonia-infection of the lungs Disease can be fatal	Pain or soreness at the injection site Low-grade fever
HPV Human Papillomavirus All adolescents between 11 & 12 should get the vaccine. If started before 15 years old the patient only needs 2 shots separated by 6-12 months. If older 3 shots are needed-	HPV is a virus that infects the skin, genital area and the lining of the cervix. There are multiple types of HPV the vaccine protects against 9 types of HPV that cause disease (6,11,16,18,31,33,45,52 & 58) 16 & 18 are the most common and cause cervical cancer 6&11 most commonly cause anal and genital warts.	Cervical cancer Genital warts Cancers of the head and neck Cancers of the anus and penis Can be fatal	Pain, redness and tenderness at injection site Low-grade fever Allergic reaction (1 in 1 million recipients)

second shot should be given 1-2 months after first and third shot 6 months after the first.	HPV is the sole cause of cervical cancer. HPV is the most common sexually transmitted disease in the US and world.		
Influenza CDC recommends children get the flu shot every year starting at 6 months of age. Children from 6 months to 8 years of age require two doses separated by 4 weeks if they have never had the shot before. The vaccination is not a live virus; it is inactivated and cannot cause the flu	Influenza virus infects the trachea or bronchi, symptoms include high fever, chills, muscle aches, headache, runny nose, cough. Complications include severe, often fatal, pneumonia. Every year influenza kills 1000-10,000 people.	High fever and chills Severe muscle aches Headache Pneumonia Runny nose and coughing for weeks Disease can be fatal	Side effects are extremely rare and the vaccination cannot cause the flu Pain, redness and swelling at the injection site Fever or muscle aches Guillian-Barre Syndrome
MMR Measles, Mumps, Rubella A live weakened virus is used for the vaccine Given in a 2-dose series at 12-15 months and at 4-6 years of age.	**Measles:** caused by a virus that causes high fever, rash, diarrhea, and possibly death. Spread from person to person and is one of the most contagious diseases, for example if there are 100 susceptible people in a room with a person infected with measles, 90 of them will become infected.	**Measles:** Fever, pink eye, rash on face and body Pneumonia Encephalitis Death **Mumps:** Swollen salivary or parotid glands Meningitis Deafness Orchitis	Soreness at injection site Low grade fever (rarely a fever greater than 103 between 5 and 12 days Rash Decrease platelets temporarily Short lived arthritis (mainly in adults)

	Mumps: caused by a virus that causes swelling of the salivary or parotid glands that lasts for 7-10 days. Before the vaccination was available mumps was the most common cause of meningitis. **Rubella:** known as "German measles". Viral infection that causes a rash, swelling of the face and joints and fevers. Rubella can cause birth defects if a mother gets infected during pregnancy.	Miscarriage during pregnancy **Rubella:** mild rash on face, swelling of glands behind the ear, swelling of small joints Congenital rubella syndrome when women are infected early in pregnancy	
Meningococcal Recommended for: Adolescents and teens between 11-18 years' old Children without a spleen Children with compromised immune systems College freshman Children who are exposed to the disease	About 1 in 20 children with meningitis caused by meningococcus and about 1 in 3 children with bloodstream infections caused by meningococcus will die from the infection. Death from sepsis can occur within 12 hours of the beginning of the illness. Meningococcus is one of the most rapid and overwhelming infectious diseases known to man.	Meningitis-inflammation of the lining of the brain Sepsis-bloodstream infection (fever, shock, coma) Limb amputation, hearing loss, seizures, kidney disease Disease can be fatal	Pain or tenderness where the shot is given, but does not cause any serious side effects. Although a possible association with Guillian-Barre Syndrome (GBS) was investigated, no causal association was found.
Pneumococcal 4 dose series given at 2, 4, 6, & 12 months.	The diseases caused by pneumococcus bacteria include meningitis, bloodstream infections and pneumonia. Before the vaccine, every year pneumococcus caused	Pneumonia Empyema-pus between the lung and chest wall Sepsis Meningitis	Pain and redness at the injection site High fever in 1 of 100 infants Fever and muscle aches (1 in 100 people)

	about 700 cases of meningitis, 17,000 cases of bloodstream infections and 71,000 cases of pneumonia.	Antibiotics don't always work to treat the infection Disease can be fatal	
Polio Inactivated polio vaccine (IPV) Series of four shots at 2 months, 4 months, 6 to 18 months and again at 4 to 6 years of age	Caused by a highly contagious virus that can cause paralysis by replicating attacking the nervous system. Since development of the vaccination polio has been eliminated from the united stated since 1979 but still exists in other parts of the world which makes recurrence a possibility from travel and from individuals who are not immunized.	Sore throat, fever, stomach pain, stiff neck, headache Permanent paralysis Disease can be fatal	Pain, redness and swelling at the injection site
Rotavirus RotaTeq-Give by mouth at 2 months, 4 months, and 6 months of age Rotarix-2 doses by mouth at 2 months and 4 months of age	Rotavirus infects the lining of the intestines causing high fever, persistent and severe vomiting and diarrhea. Before the vaccine rotavirus cause 20-60 deaths each year in the US	Fever Vomiting Diarrhea Dehydration caused by serve vomiting and diarrhea can be fatal	Low grade fever Mild vomiting and diarrhea The rotavirus vaccines have been found to be rare causes of intestinal blockage affecting about 1 in 100,000 children. Of interest, natural rotavirus is also a rare cause of intestinal blockage. Most recent evidence shows that the incidence of intestinal blockage of infants in the United States **has not increased because of rotavirus vaccines.**
Varicella	Varicella is the virus that causes chicken pox and it	Rash (300-500 blisters)	Pain and tenderness at the injection site

A weakened live virus is used to make the vaccine The vaccine is recommended for children between 12-15 months and again between 4-6 years of age	is highly contagious. The virus is characterized by 300-500 blisters covering the entire body. Chickenpox can have severe complications and before the vaccine 1-2 children would die every week from the infection. The virus can also cause birth defects if a pregnant woman is infected.	Pneumonia or encephalitis Birth defects Bacterial co-infections Disease can be fatal	Low-grade fever Rash around the injection site

(Children's Hospital of Philadelphia, 2017)

Appendix B - VACCINE INGREDIENTS FROM THE CENTERS OF DISEASE CONTROL AND PREVENTION	
Vaccine	**Contains**
DT (Sanofi)	aluminum phosphate, isotonic sodium chloride, formaldehyde, casein, 58ehydrat, maltose, uracil, inorganic salts, vitamins, dextrose
DtaP (Daptacel)	aluminum phosphate, formaldehyde, glutaraldehyde, 2-phenoxyethanol, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion, 2-phenoxyethanol
DtaP (Infanrix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, sodium chloride, polysorbate 80 (Tween 80)
DtaP-IPV (Kinrix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, VERO cells, a continuous line of monkey kidney cells, Calf serum, lactalbumin hydrolysate, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B
DtaP-IPV (Quadracel)	modified Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion, formaldehyde, ammonium sulfate aluminum phosphate, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, MRC-5 cells, normal human diploid cells, CMRL 1969 medium supplemented with calf serum, Medium 199 without calf serum, 2-phenoxyethanol, polysorbate 80, glutaraldehyde, neomycin, polymyxin B sulfate
DtaP-HepB-IPV (Pediarix)	Fenton medium containing a bovine extract, modified Latham medium derived from bovine casein, formaldehyde, modified Stainer-Scholte liquid medium, VERO cells, a continuous line of monkey kidney cells, calf serum and lactalbumin hydrolysate, aluminum hydroxide, aluminum phosphate, aluminum salts, sodium chloride, polysorbate 80 (Tween 80), neomycin sulfate, polymyxin B, yeast protein.
DtaP-IPV/Hib (Pentacel)	aluminum phosphate, polysorbate 80, sucrose, formaldehyde, glutaraldehyde, bovine serum albumin, 2-phenoxyethanol, neomycin, polymyxin B sulfate, modified Mueller's growth medium, ammonium sulfate, modified Mueller-Miller casamino acid medium without beef heart infusion, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin. Glutaraldehyde, MRC-5 cells (a line of normal human diploid cells), CMRL 1969 medium supplemented with calf serum, Medium 199 without calf serum, modified Mueller and Miller medium
Hib (ActHIB)	sodium chloride, modified Mueller and Miller medium (the culture medium contains milk-derived raw materials [casein derivatives]), formaldehyde, sucrose
Hib (Hiberix)	saline, synthetic medium, formaldehyde, sodium chloride, lactose
Hib (PedvaxHIB)	complex fermentation media, amorphous aluminum hydroxyphosphate sulfate, sodium chloride
Hib/Mening. CY (MenHibrix)	saline, semi-synthetic media, formaldehyde, sucrose, tris (trometamol)-HCl
Hep A (Havrix)	MRC-5 human diploid cells, formalin, aluminum hydroxide, amino acid supplement, phosphate-buffered saline solution, polysorbate 20, neomycin sulfate, aminoglycoside antibiotic
Hep A (Vaqta)	MRC-5 diploid fibroblasts, amorphous aluminum hydroxyphosphate sulfate, non-viral protein, DNA, bovine albumin, formaldehyde, neomycin, sodium borate, sodium chloride
Hep B (Engerix-B)	aluminum hydroxide, yeast protein, sodium chloride, disodium phosphate 58ehydrate, sodium dihydrogen phosphate 58ehydrate
Hep B (Recombivax)	soy peptone, dextrose, amino acids, mineral salts, phosphate buffer, formaldehyde, potassium aluminum sulfate, amorphous aluminum hydroxyphosphate sulfate, yeast protein

Hep A/Hep B (Twinrix)	MRC-5 human diploid cells, formalin, aluminum phosphate, aluminum hydroxide, amino acids, sodium chloride, phosphate buffer, polysorbate 20, neomycin sulfate, yeast protein
Human Papillomavirus (HPV) (Gardasil)	vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein
Human Papillomavirus (HPV) (Gardasil 9)	vitamins, amino acids, mineral salts, carbohydrates, amorphous aluminum hydroxyphosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein
Influenza (Afluria) Trivalent & Quadrivalent	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, potassium chloride, calcium chloride, sodium taurodeoxycholate, ovalbumin, sucrose, neomycin sulfate, polymyxin B, beta-propiolactone, thimerosal (multi-dose vials)
Influenza (Fluad)	squalene, polysorbate 80, sorbitan trioleate, sodium citrate dehydrate, citric acid monohydrate, neomycin, kanamycin, barium, egg proteins, CTAB (cetyltrimethylammonium bromide), formaldehyde
Influenza (Fluarix) Trivalent & Quadrivalent	octoxynol-10 (TRITON X-100), α-tocopheryl hydrogen succinate, polysorbate 80 (Tween 80), hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde, sodium deoxycholate, sodium phosphate-buffered isotonic sodium chloride
Influenza (Flublok) Trivalent & Quadrivalent	sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, polysorbate 20 (Tween 20), baculovirus and *Spodoptera frugiperda* cell proteins, baculovirus and cellular DNA, Triton X-100, lipids, vitamins, amino acids, mineral salts
Influenza (Flucelvax) Trivalent & Quadrivalent	Madin Darby Canine Kidney (MDCK) cell protein, protein other than HA, MDCK cell DNA, polysorbate 80, cetyltrimethlyammonium bromide, and β-propiolactone
Influenza (Flulaval) Trivalent & Quadrivalent	ovalbumin, formaldehyde, sodium deoxycholate, α-tocopheryl hydrogen succinate, polysorbate 80, thimerosal (multi-dose vials)
Influenza (Fluvirin)	ovalbumin, polymyxin, neomycin, betapropiolactone, nonylphenol ethoxylate, thimerosal
Influenza (Fluzone) Quadrivalent	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, thimerosal (multi-dose vials), sucrose
Influenza (Fluzone) High Dose	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, formaldehyde, sucrose
Influenza (Fluzone) Intradermal	egg protein, octylphenol ethoxylate (Triton X-100), sodium phosphate-buffered isotonic sodium chloride solution, sucrose
Influenza (FluMist) Quadrivalent	monosodium glutamate, hydrolyzed porcine gelatin, arginine, sucrose, dibasic potassium phosphate, monobasic potassium phosphate, ovalbumin, gentamicin sulfate, ethylenediaminetetraacetic acid (EDTA)
Meningococcal (MenACWY-Menactra)	Watson Scherp media containing casamino acid, modified culture medium containing hydrolyzed casein, ammonium sulfate, sodium phosphate, formaldehyde, sodium chloride
Meningococcal (MenACWY-Menveo)	formaldehyde, amino acids, yeast extract, Franz complete medium, CY medium
Meningococcal (MPSV4-Menomune)	Mueller Hinton casein agar, Watson Scherp casamino acid media, thimerosal (multi-dose vials), lactose
Meningococcal (MenB – Bexsero)	aluminum hydroxide, *E. coli*, histidine, sucrose, deoxycholate, kanamycin

Meningococcal (MenB – Trumenba)	defined fermentation growth media, polysorbate 80, histidine buffered saline.
MMR (MMR-II)	chick embryo cell culture, WI-38 human diploid lung fibroblasts, vitamins, amino acids, fetal bovine serum, sucrose, glutamate, recombinant human albumin, neomycin, sorbitol, hydrolyzed gelatin, sodium phosphate, sodium chloride
MMRV (ProQuad) (Frozen)	chick embryo cell culture, WI-38 human diploid lung fibroblasts MRC-5 cells, sucrose, hydrolyzed gelatin, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate dibasic, human albumin, sodium bicarbonate, potassium phosphate monobasic, potassium chloride; potassium phosphate dibasic, neomycin, bovine calf serum
MMRV (ProQuad) (Refrigerator Stable)	chick embryo cell culture, WI-38 human diploid lung fibroblasts, MRC-5 cells, sucrose, hydrolyzed gelatin, urea, sodium chloride, sorbitol, monosodium L-glutamate, sodium phosphate, recombinant human albumin, sodium bicarbonate, potassium phosphate potassium chloride, neomycin, bovine serum albumin
Pneumococcal (PCV13 – Prevnar 13)	soy peptone broth, casamino acids and yeast extract-based medium, CRM197 carrier protein, polysorbate 80, succinate buffer, aluminum phosphate
Pneumococcal (PPSV-23 – Pneumovax)	phenol
Polio (IPV – Ipol)	Eagle MEM modified medium, calf bovine serum, M-199 without calf bovine serum, vero cells (a continuous line of monkey kidney cells), phenoxyethanol, formaldehyde, neomycin, streptomycin, polymyxin B
Rotavirus (RotaTeq)	sucrose, sodium citrate, sodium phosphate monobasic monohydrate, sodium hydroxide, polysorbate 80, cell culture media, fetal bovine serum, vero cells *[DNA from porcine circoviruses (PCV) 1 and 2 has been detected in RotaTeq. PCV-1 and PCV-2 are not known to cause disease in humans.]*
Rotavirus (Rotarix)	amino acids, dextran, Dulbecco's Modified Eagle Medium (sodium chloride, potassium chloride, magnesium sulfate, ferric (III) nitrate, sodium phosphate, sodium pyruvate, D-glucose, concentrated vitamin solution, L-cystine, L-tyrosine, amino acids solution, L-250 glutamine, calcium chloride, sodium hydrogenocarbonate, and phenol red), sorbitol, sucrose, calcium carbonate, sterile water, xanthan *[Porcine circovirus type 1 (PCV-1) is present in Rotarix. PCV-1 is not known to cause disease in humans.]*
Td (Tenivac)	aluminum phosphate, formaldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate
Td (Mass Biologics)	aluminum phosphate, formaldehyde, thimerosal, modified Mueller's media which contains bovine extracts, ammonium sulfate
Tdap (Adacel)	aluminum phosphate, formaldehyde, 2-phenoxyethanol, Stainer-Scholte medium, casamino acids, dimethyl-beta-cyclodextrin, glutaraldehyde, modified Mueller-Miller casamino acid medium without beef heart infusion, ammonium sulfate, modified Mueller's growth medium
Tdap (Boostrix)	modified Latham medium derived from bovine casein, Fenton medium containing a bovine extract, formaldehyde, modified Stainer-Scholte liquid medium, glutaraldehyde, aluminum hydroxide, sodium chloride, polysorbate 80
Varicella (Varivax) *Frozen*	human embryonic lung cell cultures, guinea pig cell cultures, human diploid cell cultures (WI-38), human diploid cell cultures (MRC-5), sucrose, hydrolyzed gelatin, sodium chloride, monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, EDTA (Ethylenediaminetetraacetic acid), neomycin, fetal bovine serum
Varicella (Varivax) *Refrigerator Stable*	human embryonic lung cell cultures, guinea pig cell cultures, human diploid cell cultures (WI-38), human diploid cell cultures (MRC-5), sucrose, hydrolyzed gelatin, urea, sodium chloride,

	monosodium L-glutamate, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride, neomycin, bovine calf serum

Appendix C - Common Vaccine Ingredients that Cause Parental Concern		
Ingredient	Vaccines that contain the ingredient	Information about ingredient
Aluminum	Hepatitis A Hepatitis B Diphtheria-tetanus-containing vaccines Haemophilus influenza type B (HIB) Pneumococcal vaccines	**Parental concern:** safety of aluminum in vaccines. Aluminum is the third most abundant element and is found in plants, soil, water and air. Aluminum is used in food-related products and common health products. Aluminum is used as an adjuvant in vaccines to boost the immune response. This allows for less volume of the vaccine and fewer doses. Tested extensively in clinical trials before being licensed. The aluminum found in vaccines is similar to that in a liter of infant formula, and infants receive more aluminum from their diet than they do from vaccines in the first 6 months of life.
Thimerosal (Ethymercury-containing preservative)	Influenza vaccine	Thimerosal is an ethylmercury-containing preservative. Thimerosal contained in vaccines is not harmful. **Methylmercury** is a form of mercury that at high levels can be toxic in people. **Ethylmercury** is processed differently in the body and excreted much more rapidly than methylmercury making it much less likely to accumulate in the body and cause harm. It is important to educate individuals that Thimerosal is a form of **ethylmercury** NOT **methylmercury.** Thimerosal is no longer used in any childhood vaccinations

		except for the influenza vaccine.
Gelatin	HPV vaccine	**Parental concern:** The gelatin in the HPV vaccine causes infertility. Gelatin (polysorbate 80) is used as a stabilizer for the HPV vaccine. It is important to know that the HPV vaccine does not cause infertility and this gelatin has been used for years as an emulsifier to make ice cream. A typical serving of ice cream may contain about 170,000 micrograms of polysorbate 80. The amount of polysorbate 80 in each dose of the HPV vaccine is 50 micrograms.
Antibiotics	**Measles, mumps, rubella (MMR)-** Neomycin (per dose): 0.025 mg **Measles, mumps, rubella, varicella** (ProQuad)-Neomycin (per dose): .005 mg to < 0.016 mg **Meningococcal B** Vaccine-Kanamycin (per dose): <0.00001 mg **Varicella [chickenpox]** (Varivax)-Neomycin (per dose): Trace quantities Influenza Some **influenza** vaccines contain no antibiotics and others contain one or more of the following: Neomycin (per dose): < 0.00002 mg – 0.000062mg, Polymyxin B (per dose): < 0.011mg, Beta-propiolactone (per dose): < 0.0015 mg, Kanamycin (per dose): < 0.00003 mg, Gentamicin (per dose): < 0.00015 mg **Polio (IPOL)-**Neomycin (per dose): 0.000005 mg, Streptomycin (per dose): 0.0002 mg, Polymyxin B (per dose): 0.000025 mg **Diphtheria, tetanus, pertussis, polio (Kinrix, Pentacel)**	**Parental concern:** Allergic reaction to the antibiotic in the vaccine. Antibiotics are used in vaccines to prevent bacterial contamination. Antibiotics can cause severe allergic reactions in children but the antibiotics that are contained in vaccines are not the usual antibiotics that cause severe allergic reactions. Antibiotics used for vaccines: Neomycin, polymyxin B, streptomycin, and gentamicin. Very small quantities are used and have not been shown to cause severe allergic reactions.

	Kinrix- Neomycin (per dose): ≤ 0.00000005 mg, Polymyxin B (per dose): < 0.00000001 mg **Pentacel and Quadracel-**Neomycin (per dose): < 0.000000004 mg**,** Polymyxin B (per dose): < 0.000000004 mg **Diphtheria, tetanus, pertussis, hepatitis B, polio (Pediarix)-**Neomycin (per dose): 0.00000005 mg**,** Polymyxin B (per dose): < 0.00000001 mg **Hepatitis A**-Neomycin (per dose): < 0.00004 mg **Hepatitis A, hepatitis B** (Twinrix)-Neomycin (per dose): < 0.00002 mg	
DNA	Chickenpox Rubella Hepatitis A	**Parental concern:** Vaccines using human embryo cells could cause harm if the DNA from the embryo cells "mixes" with the child's DNA. The DNA in vaccines is exposed to chemicals which makes it unstable and it is highly fragmented which makes it impossible to create a whole protein.
Egg products	Yellow fever vaccine Influenza vaccine	**Parental concern:** Egg allergies and vaccines Vaccines that are made in eggs contain egg proteins in the final product. Yellow fever vaccine: the amount of egg protein in this vaccine can cause an allergic reaction, this patient should be referred to an allergist if they need the yellow fever vaccine. Influenza vaccine: Individuals with egg allergies can receive this vaccine because the amount of egg protein is very minimal. Individuals with an egg allergy should remain in the clinic or

		office for 30 minutes after the vaccine is given.
Formaldehyde	DTap DTap-Hep B IPV (Pediarix) DTap-IPV (Kinrix & Quadracel) DTap-IPV-HIB (Pentacel) Hepatitis A Hepatitis A-Hepatitis B (Twinrix) Hib Hepatitis B Meningococcal Influenza (not all influenza vaccines)	**Parental Concern:** Safety of ingredient because high concentrations can cause DNA damage and cancer. The quantities in vaccines is not large enough to cause cancer. The average amount of formaldehyde that a child is exposed to at one time may be as high as 0.7 mg but this is considered a safe level because: 1. All individuals have detectable amounts of natural formaldehyde in their blood because it is used for human metabolism. 2. Quantities of formaldehyde 600 times more than the amount in vaccines has been given safely to animals.

Children's Hospital of Philadelphia (2017). Vaccine Ingredients, retrieved from http://www.chop.edu/centers-programs/vaccine-education-center/vaccine-ingredients

Appendix D - GRADEpro Summary of Findings Tables

Summary of findings:

Should reminder/recall systems vs no intervention, be used in pediatric primary care to increase vaccination rates?

Patient or population: vaccine hesistancy
Setting:
Intervention: reminder/recall systems
Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with reminder/recall systems				
post card reminders vs control (Reminder/recall systems)	500 per 1,000	**630 per 1,000** (459 to 774)	**OR 1.70** (0.85 to 3.42)	2968 (3 RCTs)	⨁⨁⨁⨁ HIGH	
letter reminders vs control	500 per 1,000	**613 per 1,000** (558 to 666)	**OR 1.58** (1.26 to 1.99)	2622 (5 RCTs)	⨁⨁⨁⨁ HIGH	
immunization rates (phone reminders vs control)	495 per 1,000	**807 per 1,000** (645 to 905)	**OR 4.25** (1.85 to 9.75)	206 (1 RCT)	⨁⨁⨁⨁ HIGH	
Immunization	479 per 1,000	**527 per 1,000** (512 to 545)	**OR 1.21** (1.14 to 1.30)	5258 (1 RCT)	⨁⨁⨁⨁ HIGH	
immunization	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 24.8** (21.0 to 29.5)	(22 RCTs)	⨁⨁⨁⨁ HIGH	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings:

Should educational interventions be used in pediatric primary care to increase vaccination rates and address vaccine hesitancy?

Patient or population: vaccine promotion
Setting:
Intervention: educational interventions
Comparison: no intervention

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no intervention	**Risk with educational interventions**			
Immunization (multicomponent educational intervention)	517 per 1,000	**718 per 1,000** (548 to 936)	**RR 1.39** (1.06 to 1.81)	356 (1 RCT)	⨁⨁⨁⨁ HIGH
Attitude towards vaccination	411 per 1,000	**448 per 1,000** (427 to 472)	**RR 1.09** (1.04 to 1.15)	18426 (1 RCT)	⨁⨁⨁⨁ HIGH
Vaccine decision making	522 per 1,000	**829 per 1,000** (772 to 976)	**OR 4.43** (3.10 to 37.20)	184 (1 RCT)	⨁⨁⨁⨁ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of findings:

Pre-scheduling compared to not prescheduling for vaccination increase

Patient or population: vaccination increase
Setting:
Intervention: pre-scheduling
Comparison: not prescheduling

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with not prescheduling	Risk with pre-scheduling				
Immunization	502 per 1,000	**978 per 1,000** (975 to 981)	**OR 45** (39 to 52)	960 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	Need more randomized control trials

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

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