ACIP Evidence to Recommendation User's Guide

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Introduction

In 2010, the Advisory Committee on Immunization Practice (ACIP) formally adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the evidence and developing evidence-based recommendations. Since then, an assessment of the certainty of available evidence using GRADE has been an integral part of ACIP recommendation development. In addition to assessing the certainty of evidence, guideline panels consider other domains when making a recommendation (e.g., the balance of benefits and harms, patient's values and preferences, etc.). This document presents the information that must be considered when making a recommendation. Previous documents/publications provide information on assessing the certainty of the evidence (Ahmed 2011).

During the process of recommendation formulation, panels consider a range of factors in addition to the certainty in the evidence. Elucidation of these factors and the judgments behind them facilitates transparency, consistency, and communication of recommendations to healthcare providers, partner organizations, and the public (Alonso-Cuello 2017a & b). To structure the discussion of these additional factors and to make the judgments transparent, an evidence to decision-making (EtD) framework is used.

The EtD structures decision-making by:

- Informing panel members' judgments about the pros and cons of each intervention under consideration;
- Ensuring the important factors that determine a decision (criteria) are considered;
- Providing a concise summary of the best available evidence to inform judgements about each criterion;
- Helping structure discussion and identify reasons for disagreements when they occur; and
- Making the basis for decisions transparent to guideline users or those affected by a policy decision.

The ACIP has continued to follow and build upon the methodological advances in the GRADE approach and, as a result, has developed a modified Evidence to Recommendation (EtR) framework tailored to the needs of ACIP (Appendix 1). The purpose of EtR framework is to help panels making recommendations move from evidence to decisions, and to provide transparency around the impact of additional factors on deliberations when considering a recommendation.

How to Use This Guide

The following supplementary information is intended to guide ACIP work groups while they complete the EtR framework, as they address specific policy questions and develop policy options for ACIP's consideration.

ACIP's EtR frameworks are prepared by ACIP work groups for presentation to ACIP. As such, the EtR frameworks represent the information reviewed and considered by the ACIP work group in developing policy options for ACIP's consideration. The ACIP's final recommendation and any additional considerations of ACIP during its deliberations are captured in a separate table titled 'Final deliberation and decision by ACIP' at the bottom of the EtR framework (Appendix 1).

The ACIP's EtR frameworks and accompanying GRADE evidence profiles are posted on the ACIP website (https://www.cdc.gov/vaccines/acip/recs/index.html), and are referenced with links in the MMWR *Policy Note* or *Recommendations and Reports* documents, upon publication in MMWR.

The EtR Framework

The EtR frameworks are designed to include key **background** information, **criteria** for making a decision, and **conclusions**.

The **background** section of the EtR is intended to provide details of the policy question that is the topic of the framework. In the EtR framework table, this section is opened by a statement of the policy question and the PICO (Population, Intervention, Comparator, Outcome), followed by a brief summary of information needed to understand the question and why a recommendation is needed. Specific items that should be addressed include whether the recommendation would be for "off-label" use (i.e., an indication not specified in the FDA approved label) or a preferential recommendation.

The second part of the framework is composed of rows delineating the factors or **criteria** considered during recommendation development, which are grouped into "domains." These questions are intended to frame the discussions and guide literature searches and collection of relevant data.

The following columns are included for each criterion:

- **Judgments** that the work group members must make in relation to each criterion are summarized in the first column of the framework as checkboxes. In most cases, it is anticipated that the framework will be developed with judgments for each criterion suggested by the work group and subject matter experts (SMEs) who have prepared the framework. The judgments should be a result of the work group reaching a consensus; however, minority opinions expressed during the discussion should be captured in the "additional considerations" section (see below).
- **Evidence** to inform each of those judgments is presented in the second column of the table. Evidence refers to facts used to inform the work group's judgments that are derived from studies that used systematic and explicit methods.[1] If published evidence is available, a paragraph or bulleted list summarizing the important considerations is sufficient, with mention of the most critical references or links to more detailed summaries of the evidence such as the GRADE evidence profile[1]. If no peer-reviewed body of evidence is available, this should be simply stated and any additional information used to inform the judgment indicated. The intent is to be transparent about the information that was used to make the judgment, not to imply the need for the development of evidence when it is not available.
- **Additional information** that informs or justifies each judgment may be provided in the final, right-hand column of the table. Additional information can include other data, assumptions, and logic used to make a judgment. Work groups may make different judgments for one or more subgroups (such as patients who are older or who have more severe disease) in relation to some or all of the criteria. When relevant, they may also report additional details, such as dissenting views of work group members or the results of voting on judgments where there was disagreement. Minority opinions voiced during discussions should be presented to increase transparency around the deliberation process. In addition, interpretations of the evidence may be presented here.

[1] If using GRADEpro Guideline Development Tool software (https://gradepro.org/), a GRADE evidence profile can be automatically inserted into the EtR framework.

Organization of this Guide

This document provides additional information for each domain and criterion, including the criterion question as presented in the EtR framework, related questions that expand on the issues to consider for each criterion (adapted from the GRADE Handbook), and completion guidance. A Discussion section is also included to provide further information and clarification on issues specific to each criterion/question. This additional information is intended to assist work groups and the ACIP in providing the relevant information to populate the framework.

Overarching Framework Completion Guidance

Despite availability of a framework, individuals and groups will need to continue to make judgments at several points, especially when data are minimal or absent. One purpose of the framework is to make those judgments explicit. Therefore, when evidence is not available, this should be stated and a summary of the discussion included. It is also anticipated that there will be differences of opinion within the work group, and the framework should be used to reflect these differences, particularly with regard to the final recommendation. Since one goal of the framework is to enhance transparency and communication of deliberations, significant differences of opinion or discussion points should be captured within each domain when relevant.

Specific Criteria

Domain 1: The Problem

Criterion: Public Health Priority

Criterion question: Is the problem of public health importance?

Related questions:

- *Are the consequences of the problem serious (i.e. severe or important in terms of the potential benefits or savings)?*
- *Is the problem urgent?*
- *Are a large number of people affected by the problem?*
- *Is the problem related to emerging diseases, antimicrobial resistance, or epidemic potential?*
- *Are there disadvantaged groups or populations disproportionately/differentially affected by this problem?*

Completion Guidance: Provide a short summary of the background and significant elements of the problem, including a description of epidemiology, clinical features, and sequelae of the disease/condition in terms of public health consequences. This may be excerpted or summary information from presentations to the full ACIP. Specific items to consider may include:

- Frequency of the disease/condition (e.g., incidence, prevalence, secular trends)
- Severity of the disease/condition (e.g., mortality, morbidity)
- Social impact of the disease/condition (e.g., hospitalization rate, sickness absenteeism, effects on high-risk groups and vulnerable populations, clinical features, perception of importance, and the existence of other preventive measures)

Any additional considerations regarding the public health priority may also be included.

Domain 2: Benefits & Harms of the Options

Criterion 1: Magnitude of desirable anticipated effects

Criterion question: How substantial are the desirable anticipated effects?

Related question:

- *How substantial is the anticipated effect for each main outcome for which there is a desirable effect?*

Completion Guidance: Across the critical outcomes (as specified in the PICO question and elaborated in the evidence profiles), evaluate the magnitude of the anticipated effect. The anticipated direct and indirect (e.g., herd immunity) benefits of vaccination or other interventions, should then be listed in the framework in terms of specified outcomes with a description of how substantial the effects are. For effectiveness or efficacy, specific items that may be considered are immunogenicity, strain coverage, capacity to reduce the disease incidence, capacity to disrupt carriage, duration of protection, and/or serotype replacements.

The range of effectiveness/efficacy estimates should be included here, but specific information regarding the confidence in point estimates should be presented in the certainty of evidence section (Criterion 4) below as part of the GRADE evidence profile. Describe any differences in

effectiveness/efficacy estimates for special populations (e.g., immunocompromised, specific age groups, etc.) and disadvantaged groups or settings (i.e. baseline risk). Work groups should also consider the uncertainties (if any) related to benefit with regard to durability of effectiveness, and effect on serious health outcomes (e.g., death and hospitalization), which are not often measured pre-licensure because such studies would require a sample size too large to be feasible. The numbers of illnesses, hospitalizations and deaths that can be averted by use of the vaccine may be presented here but is not required.

In addition, information may be included in the "additional considerations" section to highlight where evidence may be lacking (e.g., subgroups where additional data are needed to assess the benefits).

Discussion

Additional considerations here can include quality of life, acute and chronic pain, and functional status, among those who receive the vaccine and those who do not, including those who suffer the condition that could be prevented or ameliorated by vaccination. Work groups are encouraged to perform a number needed to vaccinate (NNV) analysis. If a number needed to vaccinate (NNV) analysis is performed, any important uncertainty or assumptions should be included. There are no defined thresholds for an "acceptable" NNV.

Guidance surrounding the use of immunogenicity data as a surrogate for efficacy or effectiveness can be found in the GRADE Handbook (Schünemann 2013). It is important to use the same language around judgments (e.g., "minimal," "small," "moderate," "large") as included in the framework. The framework requires that the work group check one box and rationale should be provided for the judgment selected by the work group. However, any differences in opinions on the judgement selected should be reflected in the additional Information section to ensure transparency.

Criterion 2: Magnitude of undesirable anticipated effects

Criterion question: How substantial are the undesirable anticipated effects?

Related question:

- *How substantial is the anticipated effect for each main outcome for which there is an undesirable effect (taking into account the severity or importance of the adverse effects and the number of people affected)?*

Completion Guidance: For each of the critical outcomes (as specified in the PICO question and elaborated in the evidence profiles), evaluate the magnitude of the undesirable anticipated effect. List the anticipated harms of vaccination, in terms of chosen outcomes and describe how substantial those effects are. Specific items to consider may include reactogenicity, adverse events, and interactions with other vaccines. Describe any differences in harms for disadvantaged groups or settings. As above, information may be included in the Additional Information section to highlight where evidence may be lacking.

Discussion

When answering this question, work groups should consider the size and strength of the pre-licensure safety database to sufficiently examine safety outcomes of interest. Groups can also discuss safety experience with vaccines from the same product class, and any uncertainties related to the safety of the

product based on limitations of study design, limitations of size of safety database for rare outcomes, and duration of follow up. Work groups should consider "risk of harm" (e.g., unknown long-term effects of new adjuvants, having only clinical trial data vs. long-term real-world experience).

Just as for the benefits section, it is important to use the same language around judgments (e.g., "minimal," "small," "moderate," "large") as included in the framework. Only one box should be checked, but differences in opinions should be reflected in the Additional Information section to ensure transparency.

Similar to the previous criterion, work groups should consider the existing safety information for both the product under consideration, as well as similar products (e.g., vaccines in the same class). Any uncertainties related to safety should be clearly articulated and discussed.

Criterion 3: Balance of desirable versus undesirable anticipated effects

Criterion question: Do the desirable effects outweigh the undesirable effects?
Related question:

- *What is the balance between the desirable effects relative to the undesirable effects?*

Completion Guidance: The work group should describe the deliberations on this topic, ensuring that any minority opinions are included. If specific subgroups have a different benefit to harm balance than the general population, describe those considerations here (especially if those groups are not included in the recommendation on the basis of this altered balance).

Discussion

When the comparator is "no vaccination," this section is focused on comparing the balance of risks and benefits of the **same** vaccine. Comparison of the adverse events profile of this vaccine to other vaccine(s) available to prevent the same disease can be addressed in the implementation section (e.g., communication with providers and patients to ensure recipients are counseled about severity of adverse events) or in the 'Additional Considerations' section. Since it may be difficult to compare benefits and risks, as measures are inherently different, judgment must be exercised.

Criterion 4: Certainty of evidence for outcomes

Criterion question: What is the overall certainty of this evidence for the critical outcomes?
Related question:

- *What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision?*

Completion Guidance: For most situations, the overall certainty of the evidence is the lowest certainty of the critical outcomes. See the ACIP GRADE Handbook regarding the process of making detailed judgments about the quality of evidence or certainty in estimates of effects and preparation of evidence profiles. The GRADE evidence profiles and associated documents should be referenced here. If there is uncertainty about whether to prepare evidence profiles, please follow the "When to GRADE" algorithm (Appendix 2) and consult the ACIP Secretariat. If evidence profiles are not prepared, a rationale and summary of any alternative methods should be provided.

Discussion

It is expected that the overall certainty of the evidence will be informed by the GRADE evidence profiles used to inform Criteria 2 and 3 (benefits and harms). If evidence profiles are not prepared, a rationale and summary of any alternative methods should be provided.

Domain 3: Values and Preferences

Criterion 1: Target population perception of value

Criterion question: Does the target population feel that the desirable effects are large relative to undesirable effects?

Related questions:

- *How does the target population (i.e., those affected or potentially affected by the disease) view the balance of desirable effects versus undesirable effects?*
- *Would patients and caregivers feel that the benefits outweigh the harms and burden?*
- *Does the population appreciate and value the vaccination?*

Completion Guidance: Provide information regarding the perspectives and perceptions of potential recipients about the disease and the vaccine. Describe the source of target population values and preferences for critical outcomes (e.g., targeted research, questionnaires). Discussion and evidence regarding the possible value to the population due to herd immunity may also be included, where applicable.

Discussion

Work groups may want to consider the following topics:

- How much less people value outcomes that occur in the future versus outcomes that occur now
- Potential recipient attitudes to undesirable effects (i.e. how risk averse they are)
- Risk perception – whether some segment of the population is inclined to view itself as not at risk for the disease

If the evidence is limited, work group deliberations can be used. If evaluation of values is desirable and there is sufficient time to conduct research, there are existing survey mechanisms that may be used when funding and space are available. Work groups interested in this should consult with the ACIP Secretariat.

Criterion 2: Uncertainty around target population perception of value

Criterion question: Is there important uncertainty about, or variability in, how much people value the main outcomes?

Related questions:

- *How much do individuals value each of the outcomes in relation to the other outcomes (i.e., what is the relative importance of the outcomes)?*
- *Is there evidence to support those value judgements, or is there evidence that the variability in those values is large enough to lead to different decisions?*

Completion Guidance: It is not anticipated that there will be a need to routinely gather evidence if none is currently available; rather, any paucity of information should be indicated here. However, if the

variability is estimated to be so significant that this factor alone could lead to a different decision, this should be indicated and consideration given to obtaining additional evidence. The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority from both an individual and public health perspective and the more important it is to obtain evidence of the values of those potentially affected by the disease.

Domain 4: Acceptability

Criterion: Acceptability to key stakeholders

Criterion question: Is the option acceptable to key stakeholders?

Related question:

- *Are there key stakeholders that would not accept the distribution of benefits, harms, and costs?*
- *Are there key stakeholders that would not accept the costs or undesirable effects in the short term for the desirable effects (benefits) in the future?*

Completion Guidance: This will often represent the opinion of the work group. Input from ACIP members may also be obtained through commentary and discussion at meetings and incorporated into the final framework. Stakeholders may include professional societies, liaison organizations, providers, pharmaceutical companies, advocacy groups, and the general public. Acceptability may vary across stakeholder groups and any such variability, and the rationale for it, should be captured here. Similar to other domains, the work group consensus opinion on whether it would be acceptable to the majority of stakeholders will be the basis for the final judgment; there is not a specified "threshold" to determine the answer.

Discussion

Work groups should carefully consider and define which specific stakeholders (e.g., providers in healthcare settings, providers in community settings, providers in public health settings, healthcare delivery systems, and the public) are considered in their discussions. Critical stakeholders for each circumstance may differ and therefore there is no pre-specified list of stakeholders that should always be considered, rather work groups should determine those groups that are relevant for their given situation. Liaison members on work groups can often provide perspective for their organizations that may be useful in deliberations.

Domain 5: Resource Use

Criterion: Resource allocation

Criterion question: Is the option a reasonable and efficient allocation of resources?

Related questions:

- *What is the cost-effectiveness of the vaccination?*
- *How does the cost-effectiveness of the vaccination vary in any sensitivity analyses?*
- *How does the cost-effectiveness change in response to changes in context, assumptions, model structure, across different studies, etc.?*

Completion Guidance: The objective of this section is to describe the available evidence from cost-effectiveness analyses (CEAs) as well as any major factors that could affect the cost-effectiveness profile

of the vaccine. Identify the cost-effectiveness results, including the base-case and a sensitivity range, from any available cost-effectiveness studies. When possible, indicate which assumptions cause the greatest change in results by examining the sensitivity analyses of a study. If there are two or more studies, identify any major differences between the studies. Identify any other important factors that may affect the cost-effectiveness profile of the vaccination. For example, issues identified in other domains of the EtR framework regarding the overall certainty of the evidence for critical outcomes may also be important factors that affect vaccination cost-effectiveness.

Discussion

Work groups should assemble economic evidence on the study question and the intervention strategies being evaluated. It may be helpful for the health economic evidence to be assembled in consultation with the ACIP Economics Lead and/or the NCIRD Lead Economist. The evidence collected can include analyses conducted by independent researchers, the vaccine industry and CDC economists. The work group lead and the ACIP Secretariat will determine if an internal CDC CEA should be conducted. This will generally be needed for new vaccines and new recommendations with major programmatic economic impact.

The findings from the health economic analyses should be reviewed and presented in accordance with ACIP guidance on economic studies (https://www.cdc.gov/vaccines/acip/committee/guidance/economic-studies.html). The work group should consider the quality of the CEAs as described by the Second Panel on Cost-Effectiveness in Health and Medicine. [4] This may include review of the model design and inputs to determine if the estimates are reasonable in terms of disease transmission, intervention effects, vaccine costs, implementation costs, disease outcome costs, and community vs. patient preferences. It may be important to understand and articulate whether there is variability in local epidemiology, infrastructure, or costs that influence impact of the intervention.

Domain 6: Equity

Criterion: Health equity

Criterion question: What would be the impact on health equity?

Related questions:

- *Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?*
- *Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?*
- *Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings?*
- *Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?*

Completion Guidance: Clinical and public health guidelines need to explicitly consider health equity (Welch et al, 2017). Health inequities are differences in health considered unfair or unjust and could have been avoided. This domain facilitates transparent and explicit consideration of the impact of the intervention when compared with the alternative option on the target population, specifically to identify if any persons would be disadvantaged as a result of the intervention. The identification of factors that

may lead to health inequities may lead to modified recommendations that apply to the target population or separate recommendations tailored to disadvantaged groups. Work groups may conduct a high-level search to identify any publications reporting on issues of health equity or inequity on the topic under consideration. Relevant publications may be qualitative or quantitative. If no evidence is identified, then the work group should provide additional considerations addressing the related questions to the best of their ability.

Domain 7: Feasibility

Criterion: Implementation feasibility

Criterion question: Is the option feasible to implement?

Related questions:

- *Is the intervention sustainable?*
- *Are there important barriers that are likely to limit the feasibility of implementing the intervention or require consideration when implementing it?*
- *Is access to the vaccine an important concern?*
- *Would the vaccine recommendation have any impact on health equity?*
- *Are there important considerations when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?*

Completion Guidance: The Implementation Checklist tool (Appendix 3) summarizes potential barriers to implementation and can be used to guide these discussions. Impact on health equity is a component that factors into several areas of the tool, but any outstanding concerns can be explicitly described. Information regarding barriers that would be difficult to overcome should be provided. Implementation issues are not expected to drive the recommendation, but it is possible that implementation considerations may change the type of recommendation, influence the wording of the recommendation or only inform the guidance that accompanies the recommendation. If there are specific factors that influence the ultimate decision regarding the recommendation or its wording, the rationale would be important to include here. As with other areas of the framework, if data are lacking this should be stated. Factors that may impact guidance accompanying the recommendation may be briefly listed here, with additional information included in the "Additional Considerations" section of the framework.

Conclusions and Additional Considerations

Finally, the **conclusions** that the work group reaches and any additional considerations that the work group would like to present regarding the policy question or recommendation are presented in the last four rows of the EtR framework (Appendix 1).

The type of recommendation and actual text of the recommendation are based on the judgments made for all of the criteria and relate directly to the summary "Balance of Consequences" judgement presented in the first row of the conclusions section. The specific wording of each of the three recommendation types will stand alone. The three recommendation options include: ACIP recommends the intervention; ACIP recommends the intervention for individuals based on shared clinical decision-making; and, ACIP does not recommend the intervention (Even though the Intervention may be used within FDA licensed indications).

The final row of the EtR framework table provides space to emphasize any additional considerations that are pertinent to the recommendation, including suggestions for overcoming implementation barriers, proposed monitoring and evaluation needs, and/or areas requiring additional research to inform future decisions.

Summary of the ACIP's deliberations and final recommendations

A summary of the ACIP discussions regarding the work group recommendations and the final wording approved should be included in the table 'Final deliberation and decision by the ACIP.' This should include a brief description of the rationale supporting any ACIP modification of, or disagreement with, the work group recommendation. This section will be completed by the ACIP work group lead and the ACIP work group chair collaboratively.

Additional Resources

1. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. bmj. 2016 Jun 28;353:i2016.
2. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Vandvik PO, Meerpohl J, Guyatt GH. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. bmj. 2016 Jun 30;353:i2089.
3. Ahmed, F., Temte, J.L., Campos-Outcalt, D., Schünemann, H.J. and ACIP Evidence Based Recommendations Work Group (EBRWG, 2011. Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC). *Vaccine*, *29*(49), pp.9171-9176.
4. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook. 2013.
5. Welch, V. A., Akl, E. A., Guyatt, G., Pottie, K., Eslava-Schmalbach, J., Ansari, M. T., ... & Hultcrantz, M. (2017). GRADE equity guidelines 1: considering health equity in GRADE guideline development: introduction and rationale. *Journal of clinical epidemiology*, *90*, 59-67.

Appendix 1: ACIP Evidence to Recommendations Framework

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework. The question should be precise and identify the specific intervention, comparison, and outcome, as well as the target population and the setting (specific subpopulations) in PICO format.
Population: Target population for vaccine (e.g., age range, sex, immune status, pregnancy)
Intervention: Vaccination (if applicable, dosage and schedule)
Comparison(s): No Vaccination/Standard of care/An existing vaccine/Other prevention option
Outcome: Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)

Background: The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided. If a recommendation is preferential or represents off-label use, this should be indicated.
Include sample language: Additional background information supporting the ACIP recommendations on the use of xxx vaccine can be found in the relevant publication of the recommendation referenced on the ACIP website.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem of public health importance?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Provide available scientific evidence on burden of disease, preferably within the target population for the recommendation. If no published evidence is available, provide expert judgment on the public health priority considerations.	Identify any additional public health priority considerations, including consideration of disparities.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	**How substantial are the desirable anticipated effects?** ○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.	Take into consideration: Is the baseline benefit similar across subgroups (by age, gender, pregnancy or lactation status, occupation [i.e., healthcare workers], immune status, race, SES, and other groups)? Are there indirect effects that should be considered (e.g., herd immunity)?
	How substantial are the undesirable anticipated effects? ○ Minimal ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Are there undesirable effects of the vaccine, either on the individual (e.g., adverse events following immunization) or population (e.g., age-shift of disease, serotype replacement) levels?	Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms?
	Do the desirable effects outweigh the undesirable effects? ○ Favors interventionl ○ Favors comparison ○ Favors both ○ Favors neither ○ Varies ○ Don't know	Describe the balance of benefits of the vaccine with possible harms (individual and population level).	

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	What is the overall certainty of this evidence for the critical outcomes? *Effectiveness of the intervention* ○ No studies found ○ 4 (very low) ○ 3 (low) ○ 2 (moderate) ○ 1 (high) *Safety of the intervention* ○ No studies found ○ 4 (very low) ○ 3 (low) ○ 2 (moderate) ○ 1 (high)	Please refer to GRADE evidence profiles for detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence-Based Recommendations.	If GRADE was not used to evaluate the certainty of evidence, please provide justification and the method and outcome of any other tools used to evaluate the body of evidence relevant to the critical outcomes.
VALUES	**Does the target population feel that the desirable effects are large relative to undesirable effects?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Provide any available evidence on target population values & preferences related to vaccination and comparative health benefits and risks. Describe the source of these estimates.	Are values and preferences for relevant outcomes measured? Are the benefits, harms and costs of vaccination valued differently by different subgroups? If the target group doesn't value the intervention, or attributes little value to the harms and benefits, consider whether potential education measures are needed.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes? O Important uncertainty or variability O Probably important uncertainty or variability O Probabl not important uncertainty or variability O No important uncertainty or variability O No known undesireable outcomes	Please provide available data used to determine the relative importance that the target population attributes to the desirable and the undesirable outcomes related to the intervention as well as the comparison.	Describe the source of variability, if any. Are there methods for determining values satisfactory for this recommendation? If not, systematic assessment of values and preferences of target group may be considered.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** O No O Probably no O Probably yes O Yes O Varies O Don't know	Provide assessment of whether intervention would be acceptable to stakeholders (ethically, programmatically, financially, etc.)	
RESOURCE USE	**Is the intervention a reasonable and efficient allocation of resources?** O No O Probably no O Probably yes O Yes O Varies O Don't know	Provide summary of cost-effectiveness analyses (CEAs) of the vaccine in the target population. Include base case results and a sensitivity range. Include any other notable findings, for example, specific policy-relevant scenarios.	Overall findings: Summarize the findings from available CEAs, including major differences in baseline assumptions. Uncertainty: Does the analysis capture the full range of uncertainty? For example, are the findings from the uncertainty of evidence analysis, identified earlier in this document (the EtR Framework), appropriately represented in the methods of the CEAs? Multiple assessments: Are there multiple CEAs? If so, what are the major differences in methods and results?

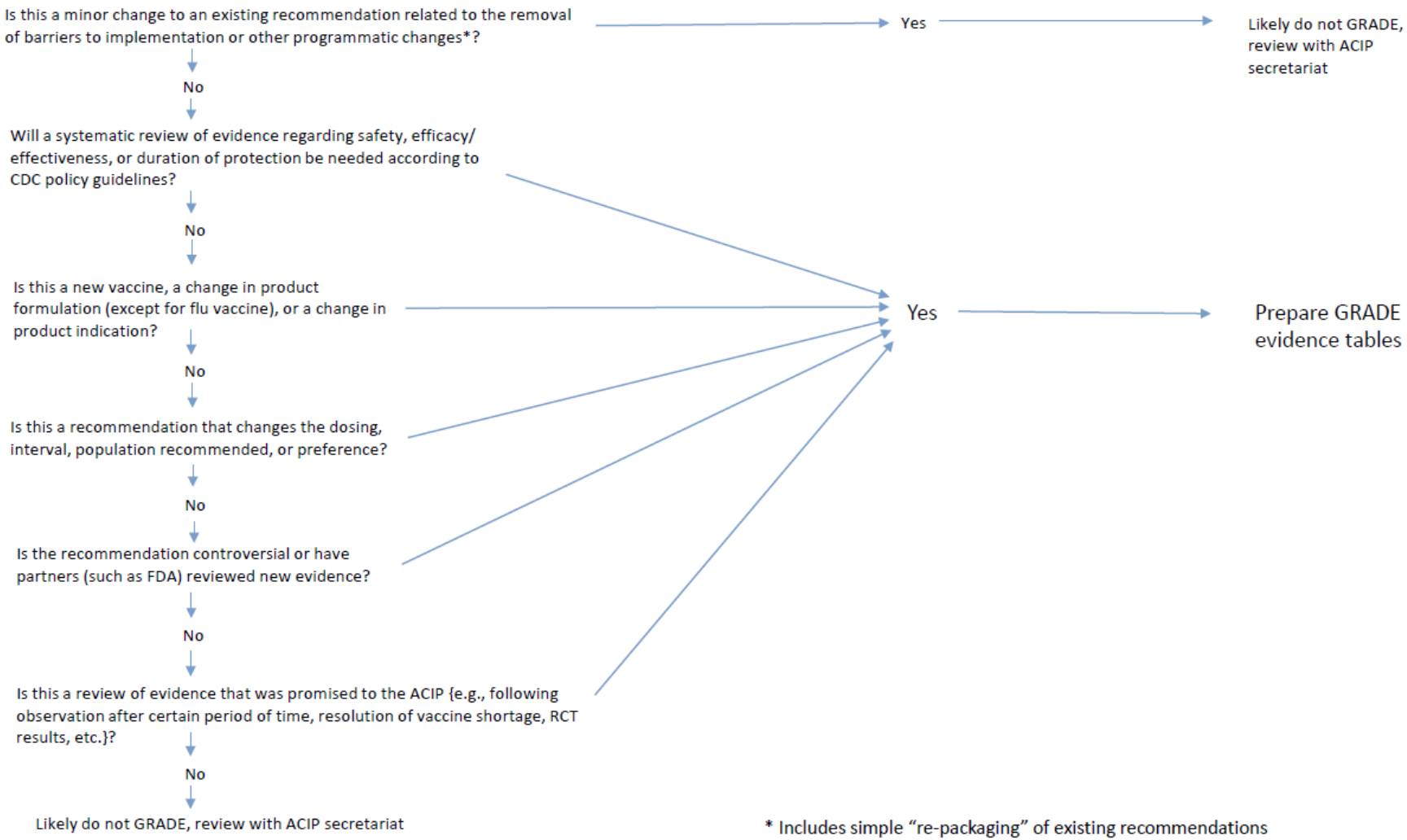
	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Summarize the findings from a review of the literature addressing issues of health inequities or groups who may be disadvantaged.	Consider from the evidence or guideline panel: • Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered? • Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings? • Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? • Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Are there any barriers to implementation?	Please refer to the Implementation Considerations checklist.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings O	Undesirable consequences *probably outweigh* desirable consequences in most settings O	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* O	Desirable consequences *probably outweigh* undesirable consequences in most settings O	Desirable consequences *clearly outweigh* undesirable consequences in most settings O	There is insufficient evidence to determine the balance of consequences O
Is there sufficient information to move forward with a recommendation? Yes O No O						
Policy options for ACIP consideration	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications O	ACIP recommends the intervention for individuals based on shared clinical decision-making O	ACIP recommends the intervention O			
Draft recommendation (text)	Please provide the draft recommendations proposed to ACIP.					
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.).					

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications ○	ACIP recommends the intervention for individuals based on shared clinical decision-making ○	ACIP recommends the intervention ○
Additional ACIP considerations	Wording as accepted in the guide		

Appendix 2 When to Prepare GRADE Evidence Profile Algorithm



Appendix 3 Implementation Considerations Checklist

Considerations for the Assessment of the Feasibility of Implementing Proposed Vaccine Recommendations

The checklist below was developed to supplement the framework for assessing new vaccine recommendations under consideration by the Advisory Committee on Immunization Practices (ACIP). The checklist may be used to inform recommendations for new vaccines as well as changes to existing recommendations regarding factors that can influence the feasibility of implementing vaccine recommendations. This checklist is intended to be an aid for working groups that are weighing different options and for recommendations where data may be less strong and feasibility issues can be considered. The checklist may also help identify where implementation challenges may be anticipated for a new recommendation. Immunization programs, vaccine providers, and other stakeholders can utilize this information to prepare for and mitigate anticipated barriers to implementation of a new vaccine recommendation.

Items in this checklist are not intended to be scored, but will inform the feasibility category recommendation that is part of framework.

Feasibility Considerations for Assessment of Proposed Vaccine Recommendation Implementation				
Purpose: Use the checklist below to assess the feasibility of proposed vaccine recommendations based on factors known to impact vaccine use. **Population:** Target population for vaccine (e.g. age group, sex, pregnancy, high-risk medical condition, occupation, travel) **Vaccine:** (If applicable, dosage and schedule) **Comparator:** (If applicable, dosage and schedule)				
	CRITERIA	JUDGEMENT	SUMMARY OF EVIDENCE*	ADDITIONAL CONSIDERATIONS
FINANCIAL BARRIERS	**Are challenges with insurance coverage likely barriers to patients receiving the new vaccine?** Consider uninsured persons, other vulnerable populations, and insurance type by age group.	◻ No ◻ Probably no ◻ Probably yes ◻ Yes ◻ Varies ◻ Unknown		
FINANCIAL BARRIERS	**Are there substantial financial burdens for providers or health systems?** Consider practice costs, such as high vaccine purchase costs, insurance payment/reimbursement concerns, and burdensome storage and handling requirements.	◻ No ◻ Probably no ◻ Probably yes ◻ Yes ◻ Varies ◻ Unknown		
SIMPLICITY AND INTEGRATION	**How easily can the vaccine be integrated into providers' practices?** Consider timing and sequencing of doses, target populations, and ease of integration into practice flow (e.g. can the recommendation be added to routine patient preventive care visits?).	◻ Very easily ◻ Somewhat easily ◻ With some difficulty ◻ With great difficulty ◻ Unknown		
SIMPLICITY AND INTEGRATION	**How complex is the vaccine recommendation?** Consider how readily the recommendation can be programmed into preexisting clinical decision support tools such as Standing Orders Protocols, EHR alerts, and/or Immunization Information Systems.	◻ Not at all ◻ Slightly ◻ Moderately ◻ Very ◻ Unknown		
ACCESS	**Are a wide range of vaccination providers (e.g. pharmacists and medical specialists) able to stock and administer the vaccine?** Consider, for example, laws and regulations for pharmacist vaccination, insurance coverage for vaccines given by obstetricians and other non-primary care providers, out-of-network providers, etc.	◻ No ◻ Probably no ◻ Probably yes ◻ Yes ◻ Varies ◻ Unknown		
ACCESS	**Are health systems and providers incentivized to adopt the vaccine recommendation?** Consider whether quality measures are in place and health system priorities.	◻ No ◻ Yes ◻ Unknown		

JUDGEMENT	Is the vaccine recommendation feasible to implement?	◻ No	◻ Probably no	◻ Probably yes	◻ Yes
JUSTIFICATION (TEXT)†					

*Provide available evidence (including expert opinion of work group members) to support judgement (e.g., there is a high disease burden, illness is severe, etc.).

†Include any accompanying information and/or support for how the judgment was determined.