Assessing the Feasibility of Indirect Comparisons of Seasonal Vaccines: A Framework for Network Meta-analysis

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Background

- Comparing the efficacy or effectiveness of vaccines using network meta-analysis (NMA) presents challenges that can impact the relevance and validity of findings.
- While basic frameworks have been established to guide feasibility assessments of NMAs comparing treatments,[1-3] limited guidance is available for comparisons of vaccines.
- NMAs of seasonal vaccines (i.e., vaccines against circulating virus strains that fluctuate over time) such as influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), require additional considerations beyond those typically considered in feasibility assessments for treatments or routine vaccines. There is also limited information provided in published NMAs of seasonal vaccines on the process by which feasibility was assessed.

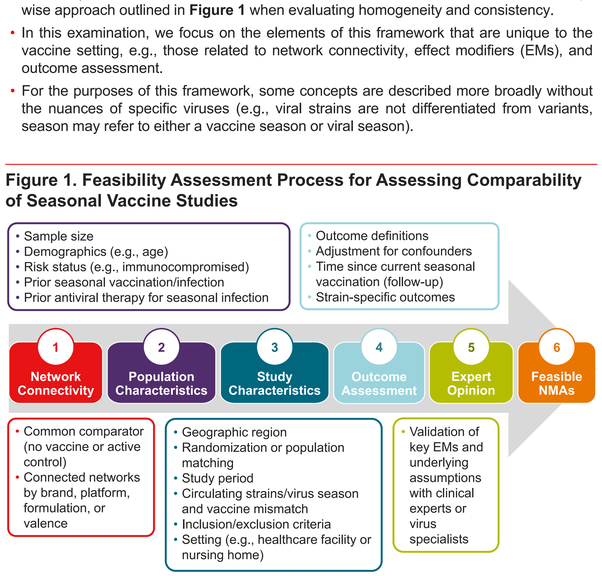
Objectives

- **To produce a framework for assessing the feasibility of a valid NMA that compares the vaccine efficacy/effectiveness (VE) of seasonal vaccines, considering evidence from randomized controlled trials (RCTs) or comparative observational studies.**

Feasibility Framework

- Feasibility assessments of seasonal vaccines should consider all elements in the step-wise approach outlined in **Figure 1** when evaluating homogeneity and consistency.
- In this examination, we focus on the elements of this framework that are unique to the vaccine setting, e.g., those related to network connectivity, effect modifiers (EMs), and outcome assessment.
- For the purposes of this framework, some concepts are described more broadly without the nuances of specific viruses (e.g., viral strains are not differentiated from variants, season may refer to either a vaccine season or viral season).

Figure 1. Feasibility Assessment Process for Assessing Comparability of Seasonal Vaccine Studies



Note that the order in which each component is evaluated may vary depending on your research question or set of studies being considered for feasibility of NMA.
Abbreviations: EM = effect modifier; NMA = network meta-analysis

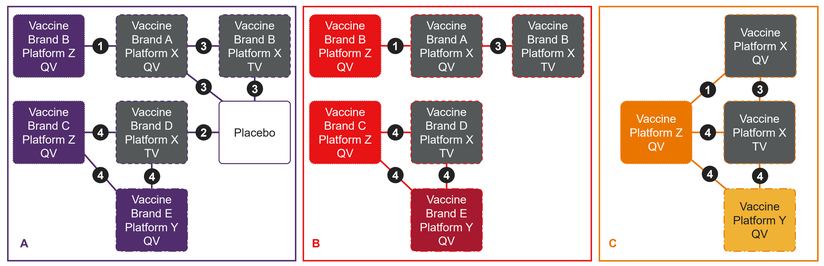
Identification of the Evidence Base

- Studies to be considered in a feasibility assessment should be identified via a systematic literature review. The review protocol should describe the proposed process for the feasibility assessment, including a comprehensive list of potential EMs based on a priori knowledge.[1]
- Depending on the objective of the NMA, careful consideration is needed regarding the study design(s) of interest. While RCTs are the gold standard, VE trials are rarely conducted for seasonal vaccine adaptations, making RCT evidence less relevant for current decision-making. In these cases, high-quality, comparative observational studies (e.g., case-control, cohort designs) with adequate adjustment for potential confounding variables should be considered.[4] Other well-known limitations of NMAs of non-RCT evidence must also be considered.

Network Connectivity

- The feasibility of an NMA first depends on whether the identified studies can form a connected network of evidence through common comparators. Differences in vaccine characteristics, including brand, platform, formulation, and/or valence, must be carefully considered.
- To estimate the relative effects between different influenza vaccine brands, placebo arms are often required to form a single network of all studies (**Figure 2A**). However, the inclusion of placebo-controlled studies requires important considerations for potential bias (see **Effect Modifiers** below).
  - Limiting to active-controlled studies reduces this bias but may result in disconnected networks (**Figure 2B**). Collapsing nodes by platform (e.g., egg-based, cell-based, or recombinant), valence (e.g., trivalent, quadrivalent), and/or dose (e.g., standard dose, high dose) rather than brand may provide greater opportunity for comparisons of key vaccine groups (**Figure 2C**). The assumptions required to combine vaccines into a single node should be based on input by clinical experts.

Figure 2. Considerations for Network Connectivity of Influenza Vaccines



A) Network (including placebo) by brand, platform, and valence
- **Pros**: Maximizes available evidence to include all studies in the network
- **Cons**: Inclusion of a placebo group introduces effect modification by season resulting in high risk of bias

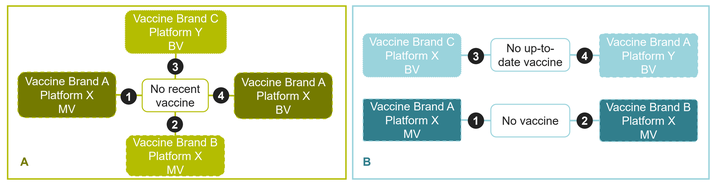
B) Network (active comparators only) by brand, platform, and valence
- **Pros:** Minimizes bias in relative effect estimates by removing the placebo group
- **Cons:** Limits ability to compare to other vaccines of interest

C) Network (active comparators only) by platform and valence
- **Pros**: Minimizes bias in relative effect estimates by removing the placebo group while maintaining network connections to key vaccine comparators
- **Cons**: Assumes equivalence by brand, which does not allow for between-brand comparisons

● Indicates study number
Note: Platforms may refer to "egg-based," "cell-based," "recombinant," etc.
Abbreviations: QV = quadrivalent; TV = trivalent

- Networks of seasonal vaccines may also need to consider studies with a "no recent vaccine" group representing a mix of unvaccinated individuals and those previously vaccinated in a prior season (no up-to-date vaccine) (**Figure 3A**).
  - As the vaccine landscape evolves, fewer individuals remain fully unvaccinated, resulting in comparator groups of unvaccinated for past seasons and of no up-to-date vaccine for more current seasons. Therefore, separate networks may need to be considered by common comparator (**Figure 3B**).
- Observational studies do not always report the brand or include a mix of brands. In these situations, brand-specific vaccine comparisons may also require the use of a threshold to assign a brand to a given study arm.

Figure 3. Considerations for Network Connectivity of COVID-19 Vaccines



A) Network (no recent vaccine [no up-to-date vaccine / no vaccine] comparator) by brand, platform, and valence
- **Pros**: Maximizes available evidence to include all studies in the network and allows connections to key vaccine comparators
- **Cons**: Increased risk of bias by introducing effect modification with a no [recent] vaccine comparator, which also assumes equivalence among placebo, no vaccine, and no recent vaccine

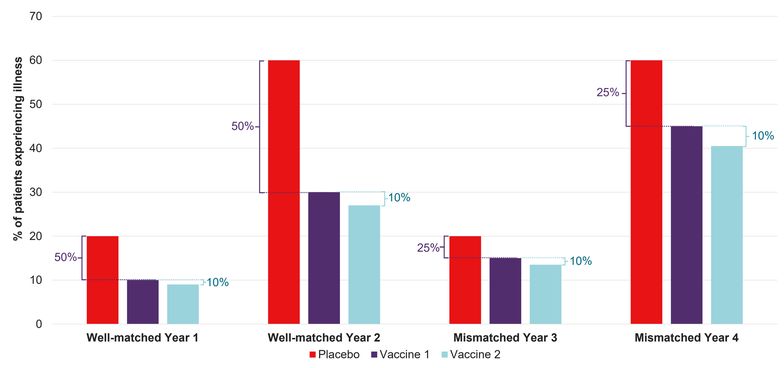
B) Networks by comparator, brand, platform, and valence
- **Pros**: Minimizes bias by separating vaccines/seasons and limiting to same common comparator
- **Cons**: Limits ability to compare to vaccines of interest

Note: Platforms may refer "mRNA-based," "protein-based," etc. MV and BV may refer to a specific strain, e.g., "monovalent wildtype vaccines," "monovalent XBB.1.5-adapted vaccines," and "bivalent BA.4/5-adapted vaccines."
Abbreviations: BV = bivalent; MV = monovalent; ● Indicates study number

Effect Modifiers

- For seasonal vaccine studies, evidence of effect modification should be assessed for additional variables beyond standard population characteristics, including geography, study period, vaccine mismatch, and prior vaccination, infection, and antiviral therapy (timing and rates).
- Optimal vaccine protection depends on the viral strains included in the vaccine and whether those strains are circulating and causing infections during the time of the study.[5] Therefore, major differences in circulating strains/vaccine season may affect VE and introduce bias in an NMA, particularly for comparisons with 1) studies directly comparing two vaccines with different valencies or 2) placebo or no (recent) vaccine groups.
  - Head-to-head vaccine studies wherein both vaccines are adapted to the same strains and administered in the same season are less prone to effect modification, as relative effects are expected to be similar regardless of strain match.
  - For placebo- or "no recent vaccine"-controlled studies, the season that the study was conducted and match of the vaccine to circulating strains are important EMs (**Figure 4**).
    - Comparisons including placebo or "no recent vaccine" should consider the study year and potential impact of "mismatched" years as a potential EM.

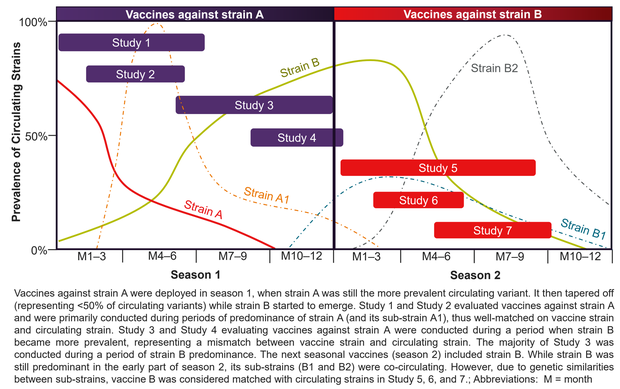
Figure 4. Evidence of Effect Modification Based on Influenza Season when the Comparator is Placebo



Note: The percentages shown are the ratios among the groups, in this hypothetical scenario. For example, in the study conducted in a well-matched influenza season (Year 1), the percent of patients receiving Vaccine 1 is 50% lower than patients who received placebo; the percent of patients receiving Vaccine 2 is 10% lower than those receiving Vaccine 1.

- In these cases, methodological heterogeneity between vaccine studies may exist when 1) studies of the same vaccines are not conducted within the timeframes where circulating strains would be similar and/or 2) strain-specific outcomes are not reported (**Figure 5**).
  - The prevalence of circulating strains for each study should be considered, but information varies by country and can be difficult to identify; any assumptions should be vetted with clinical experts and/or virus specialists to ensure studies are appropriately grouped.
- Residual immunity from a recent infection or vaccination should also be considered when assessing comparability of populations and imbalances in EMs.
- Data permitting, subgroup or sensitivity analyses should be explored to potentially minimize bias resulting from differences in these EMs.

Figure 5. Comparability of Studies based on Seasonal Vaccine, Study Period, and Prevalence of Circulating Virus



Vaccines against strain A were deployed in season 1, when strain A was still the more prevalent circulating variant. It then tapered off (representing <50% of circulating variants) while strain B started to emerge. Study 1 and Study 2 evaluated vaccines against strain A and were primarily conducted during periods of predominance of strain A (and its sub-strain A1), thus well-matched on vaccine strain and circulating strain. Study 3 and Study 4 evaluating vaccines against strain A were conducted during a period when strain B became more prevalent, representing a mismatch between vaccine strain and circulating strain. The majority of Study 3 was conducted during a period of strain B predominance. The next seasonal vaccines (season 2) included strain B. While strain B was still predominant in the early part of season 2, its sub-strains (B1 and B2) were co-circulating. However, due to genetic similarities between sub-strains, vaccine B was considered matched with circulating strains in Study 5, 6, and 7.; Abbreviations: M = month

Outcomes

- While not specific to seasonal vaccines, several challenges relate to variability in timing of outcome assessment, event rates, and adjustment for confounding factors when conducting NMAs of vaccine studies.
  - VE is highly susceptible to waning of effect over time,[6] particularly among special target populations such as older adults or immunocompromised individuals. Therefore, aligning the timing of outcome assessment following vaccination across studies is critical to reduce potential bias.
    - Special populations are often evaluated as subgroups and lack reporting of unique baseline characteristics, resulting in the inability to effectively evaluate imbalances in EMs, which should be emphasized as a limitation.
  - RCTs of vaccines are often small and lack the power to detect differences in key efficacy outcomes beyond infection rates (e.g., severe infections, hospitalizations, deaths), which often occur as rare events.
  - It is also important to consider how and whether relative effects from observational studies are adjusted and for which set of potential confounders, as this varies across studies and is often based on data availability and the degree of overlap in characteristics across groups.[7]
  - Analyses based on unadjusted events rates from observational studies should be approached with extreme caution.[8]

Conclusions

- **This framework highlights some of the key challenges with assessing the feasibility of NMAs for seasonal vaccines and offers clear and transparent considerations to ensure a valid approach. Improved reporting of feasibility assessment methods and findings, particularly key assumptions, is needed to assess the relevance and reliability of NMA findings.**
- **Adjustments to this framework may be needed for future vaccines or virus seasons, given the evolving landscape of seasonal viruses and rapid mutation of circulating strains.**

References

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