Discussion: Why selection of a comparator and assumptions on its efficacy are essential

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How does the choice of comparator influence inclusion of studies for decision-making?

- The validity of the consistency assumption is extremely important when considering an active comparator.
- Proper formulation of the NI margin is important
- However, probably the consistency assumption should be actively addressed, especially when conditions change, e.g., appearance of variants, from when the RCT was carried out.
- We should probably try to impute the actual VE in some way
  - Incorporate data from observational studies for the comparator vaccine, e.g., Bayesian hierarchical modeling
Example from influenza vaccines

Superiority randomized trial of live attenuated (EXP) vs inactivated (AC) influenza vaccines

Relative efficacy, any confirmed influenza illness:
\[ VE = (1 - (3.9/8.6))100 = 54.6\%, \ P < 0.001^* \]

The VE for the live vaccine from the pivotal randomized vaccine trial was VE = 93% (95%CI: 88% to 96%)*** from nearly 9 years earlier.

Consistency assumption: The estimated VE during the 2004-05 flu season for inactivated influenza vaccine was 10% (95% CI, -36% to 40%) from test-negative observational study.** Actual VE of the live vaccine was around 50% and not 90%.


Decision-making around evidence for the vaccine

- The comparator and experimental vaccine were from different platforms.
- There was not correlate of protection for the live vaccine.
- Did not notice that the vaccine would have reduced efficacy against mismatched vaccine with circulating strains.
- Failed to notice that repeated vaccination with live vaccines reduced protection over time.